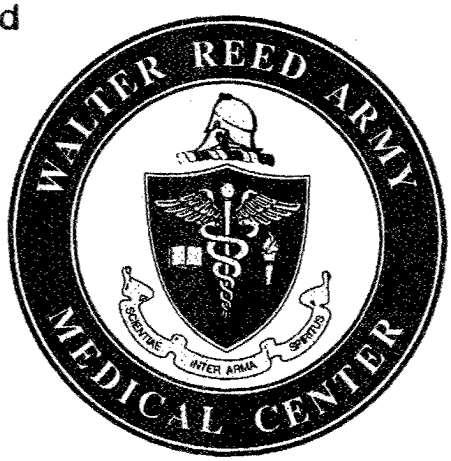
DEPARTMENT OF CLINICAL INVESTIGATION (DCI)

# ANNUAL RESEARCH PROGRESS REPORT

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# FISCAL YEAR 2002

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WALTER REED ARMY MEDICAL CENTER, WASHINGTON, DC

# REPORT DOCUMENTATION PAGE

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Chief
Department of Clinical Investigation

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**13. ABSTRACT** *(Maximum 200 words)*

The Annual Progress Report documents all research protocols, both new and continuing, reviewed during FY 02 by the Clinical Investigation Committee (CIC) and the Human Use Committee/Institutional Review Board (HUC/IRB) of Walter Reed Army Medical Center (WRAMC). Continuing research review is administered by the Research Review Service (RRS), Department of Clinical Investigation (DCI), WRAMC. A detail summary sheet of each protocol giving the objective, technical approach, and progress is presented. Personnel rosters, DCI accomplishments, funding information, and known publications and presentations by the WRAMC professional staff are listed for FY 02.

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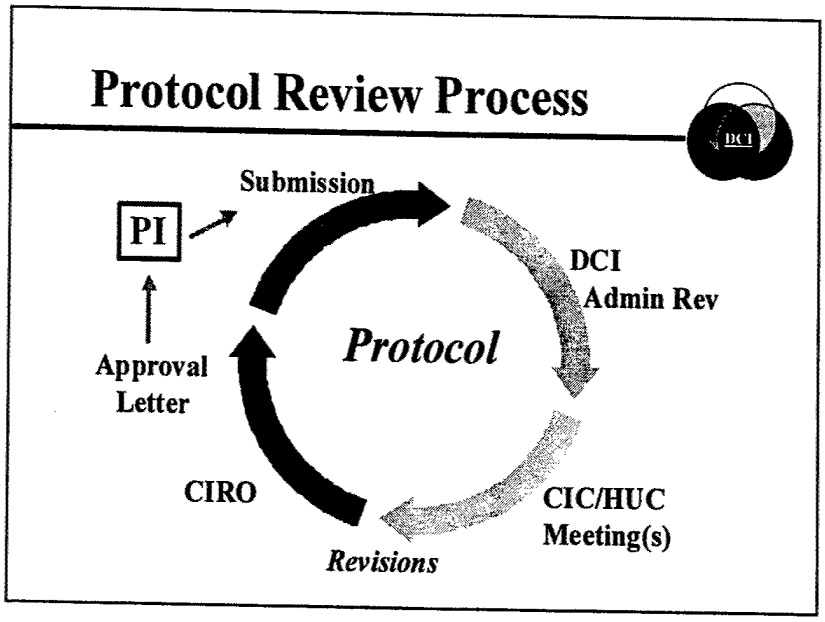
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# TABLE OF CONTENTS

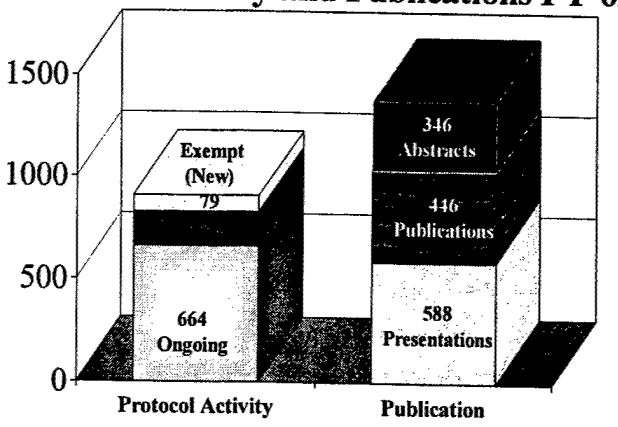

| | | VOL # | PAGE # |
|---|---|---|---|
| I. | **UNIT SUMMARY** | | |
| | A. Objective | I | 1 |
| | B. Technical Approach | I | 1 |
| | C. Organization Scheme | I | 2 |
| | D. Staffing | I | 2 |
| | E. Funding and Protocol Expenses | I | 4 |
| | F. Research Activity Accomplished in FY 02 | I | 11 |
| | G. Research Activity Planned for FY 03 | I | 21 |
| | H. The Bailey K. Ashford Clinical Research Awards | I | 22 |
| II. | **INDEX OF PROTOCOLS BY DEPARTMENT AND SERVICE** | I | 23 |
| III. | **LIST OF PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS BY DEPARTMENT** | I | 80 |
| IV. | **DETAIL SUMMARY SHEETS BY PROTOCOL NUMBER** | II | 1 |

# DEPARTMENT OF CLINICAL INVESTIGATION

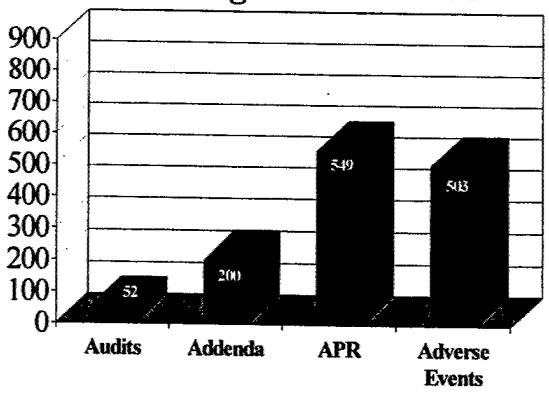
# ANNUAL RESEARCH PROGRESS REPORT




**Protocol Activity and Publications FY-02**




**Continuing Review FY-02**




## FISCAL YEAR 2002 VOLUME I

## WALTER REED ARMY MEDICAL CENTER, WASHINGTON DC

A. OBJECTIVE

The Department of Clinical Investigation (DCI) of the Walter Reed Army Medical Center is headed by COL Maria H. Sjogren, MC. The mission of the DCI is to implement and manage the Clinical Investigation program at Walter Reed Army Medical Center (WRAMC) by promoting, supporting, coordinating, planning, conducting, and publishing ethical, scientific inquiry into clinical health problems of beneficiaries of the military health care system, to include studies in humans and animals. The motto of the Department of Clinical Investigation (DCI) is SHARPP: Striving to Help All Researchers from Planning to Publication.

B. TECHNICAL APPROACH

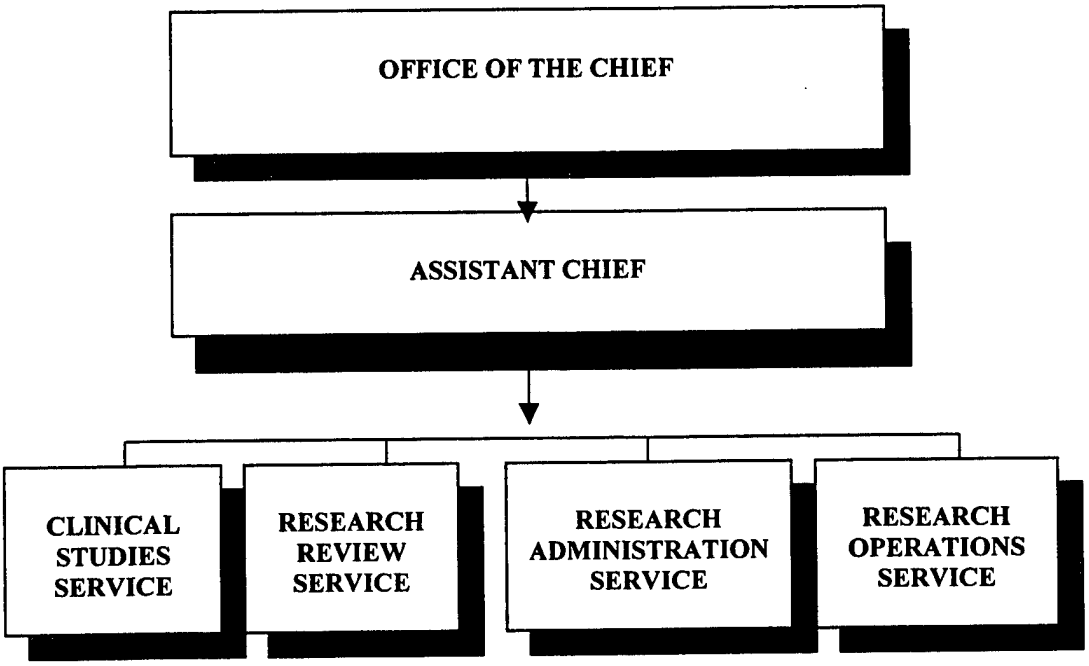
The clinical investigation program at WRAMC is conducted in accordance with the following regulations:

| | |
|---|---|
| AR 40-7 | Use of Investigational Drugs in Humans and the Use of Schedule I Controlled Drug Substances |
| AR 40-38 | Clinical Investigation Program |
| AR 70-18 | The Use of Animals in DOD Programs |
| TB MED 525 | Control of Hazards to Health from Ionizing Radiation Used by the Army Medical Department |
| HSC 40-23 | Management of Clinical Investigation Protocols and Reports |
| WRAMC 70-1 | Clinical Investigation Program, WRAMC Research Activities |
| 45 CFR 46 | Protection of Human Subjects |
| 32 CFR 219 | Protection of Human Subjects |
| 21 CFR 50, 56 | Food and Drug Administration |

NIH Guidelines For Research Involving Recombinant DNA Molecules

| | |
|---|---|
| AR 70-25 | Use of Volunteers as Subjects of Research |
| DoD 3216.1 | Use of Laboratory Animals in DOD Programs |
| DoD 3216.2 | Protection of Human Subjects and Adherence to Ethical Standards in DOD Supported Research |
| DoD 6000.8 | Funding and Administration of Clinical Investigation Programs |

C. ORGANIZATION SCHEME




D. STAFFING

| DESCRIPTION | GRADE | MOS | BRANCH | NAME | ACTIVITY |
|---|---|---|---|---|---|
| **OFFICE OF THE CHIEF** | | | | | |
| Chief | 06 | 61F00 | MC | Sjogren, MH | DCI |
| NCOIC | E6 | 91K40 | NC | Thomas, L | DCI |
| Secretary | 07 | 0318 | GS | Rosen, D | DCI |
| **RESEARCH REVIEW SERVICE** | | | | | |
| Chief | 14 | 1530 | GM | Chang, AS | DCI |
| IRB Admin | 13 | 0601 | GS | Bartlett, E | DCI |
| Statistician | 12 | 1530 | GS | Howard, RS | DCI |
| Statistician | 12 | 1530 | GS | Tuamokumo, F | DCI |
| Clinical Nurse Spec | 12 | 0610 | GS | Porter, MD | DCI |

| | | | | | |
|---|---|---|---|---|---|
| Clinical Nurse Spec | 12 | 0610 | GS | Kessler, DD | DCI |
| Tech Writer-Ed Med/Sci | 11 | 1083 | GS | Miskovsky, VJ | DCI |
| Clinical Studies Spec | 09 | 0301 | GS | Green, IL | DCI |
| Clinical Studies Tech | 07 | 0303 | GS | Vacant | DCI |
| Editorial Asst | 07 | 1087 | GS | Beltz, K | DCI |
| Editorial Asst | 07 | 1087 | GS | Vacant | |
| Clinical Studies Spec | | | | Stowe, G | HMJF |
| Med Lab NCO | E5 | 9K20 | NC | Johnson, C | DCI |

**RESEARCH ADMINISTRATION SERVICE**

| | | | | | |
|---|---|---|---|---|---|
| Chief/ Resch Admin | 12 | 0670 | GS | Word, D | DCI |
| Computer Spec | 12 | 2210 | GS | Rose, JG | DCI |
| Computer Spec | | | | Durant, G | Contract |
| Resch Protocol Coord | 12 | 0610 | GS | Vacant | |
| DCI Grant Manager | 11 | 1101 | GS | Brunson, R | DCI |
| Administrative Coord | 08 | 0303 | GS | Johnson, D | DCI |
| Supply Technician | 06 | 2005 | GS | Shelton, W | DCI |
| Office Clerk | 04 | 0326 | GS | Franklin, AF | DCI |

**RESEARCH OPERATIONS SERVICE**

| | | | | | |
|---|---|---|---|---|---|
| Chief, Res Ops Svc | 13 | 1320 | GS | Abdel-Rahim, M | DCI |
| Immunologist | 13 | 0401 | GS | Vacant | DCI |
| Bio Sci Lab Tech | O5 | 0404 | GS | Martin, JL | DCI |
| Biochemist | O3 | 71B67 | MS | Capps, KB | DCI |
| Resch Biologist | 12 | 0401 | GS | Vacant | DCI |
| Microbiologist | 12 | 0403 | GS | Vacant | DCI |
| Resch Physiologist | 12 | 0413 | GS | Lukes, YD | DCI |
| Resch Chemist | 12 | 1320 | GS | Nicholson, DE | DCI |
| Chemist | 12 | 1320 | GS | Vacant | DCI |

| | | | | | |
|---|---|---|---|---|---|
| Resch Chemist | 11 | 1320 | GS | Bednarek, JM | DCI |
| Med Technologist | 11 | 0644 | GS | Kapur, JJ | DCI |
| Med Technologist | 11 | 0644 | GS | Morris, E | DCI |
| Med Technologist | 11 | 0644 | GS | Barnes, SG | DCI |
| Med Technologist | 11 | 0644 | GS | Anderson, JS | DCI |
| Med Technologist | 11 | 0644 | GS | Fileta, B | DCI |
| Bio Lab Tech | 09 | 0404 | GS | Vacant | DCI |
| Bio Lab Tech | 09 | 0404 | GS | Vacant | DCI |
| Lab Assistant | E5 | 91K10 | NC | Reinhardt, B | DCI |
| Med Lab Spec | E4 | 91K10 | NC | Rich, T | DCI |
| Med Lab Spec | E4 | 91K10 | NC | Hoch, D | DCI |
| **CLINICAL STUDIES SERVICE** | | | | | |
| Chief | O5 | 61P00 | MC | Marin, R | DCI |
| Resch Chemist | 12 | 1320 | GS | Maydonovitch | Gastroenterology |
| Nurse Specialist | 12 | 0610 | GS | Parchment, VA | DCI |
| Nurse Specialist | 12 | 0610 | GS | Bicknell, E | DCI |

E. FUNDING

| | FY 98 | FY99 | FY 00 | FY 01 | FY 02 |
|---|---|---|---|---|---|
| **Appropriated Funding** | | | | | |
| Civilian Personnel | $1,681,000 | $1,827,069 | $2,177,569 | $2,292,958 | $2,102,400 |
| Military Personnel | $452,000 | $352,000 | $418,699 | $419,691 | $516,194 |
| Consumable Supplies | $303,439 | $425,644 | $256,972 | $257,780 | $212,000 |
| Civilian Contracts | $160,000 | $180,000 | $319,200 | $332,000 | $417,683 |
| TDY | $56,654 | $45,728 | $47,727 | $47,000 | $47,000 |
| Capital Expense Equipment Program (CEEP) | $70,000 | $126,500 | $0 | $0 | $0 |

| | FY 98 | FY99 | FY 00 | FY 01 | FY 02 |
|---|---|---|---|---|---|
| MEDCASE | $106,450 | $0 | $236,660 | $0 | $0 |
| Operations | $0 | $0 | $0 | $589,700 | $0 |
| Infra-Structure Program | $0 | $0 | $13,100 | $0 | $0 |
| Subtotal | $2,829,543 | $2,956,941 | $3,469,927 | $3,939,129 | $3,295,277 |
| **Extramural Funding** | | | | | |
| GOG | $30,000 | $0 | $251,621 | $8,800 | $0 |
| CALGB | $82,700 | $55,000 | $99,188 | $24,253 | $23,945 |
| VA | $0 | $0 | $426,394 | $32,214 | $0 |
| USUHS/DoD/MRMC | $0 | $331,913 | $15,330,466 | $6,481,100 | $3,900,214 |
| NIH/NCI | $1,362,000 | $957,438 | $755,713 | $335,246 | $982,223 |
| USUAMRMC | $0 | $0 | $15,426 | $0 | $2,645,279 |
| Partners Health Care System | $0 | $0 | $8,320 | $0 | $0 |
| Tri-Svc Nursing | $0 | $141,733 | $445,781 | $409,924 | $0 |
| Travel (non-federal sources) | $15,000 | $34,508 | $21,626 | $38,292 | $0 |
| Gifts (managed by DCI) | $44,358 | $252,525 | $169,022 | $4,200 | $0 |
| CRDAs (managed by DCI) | $76,059 | $333,798 | $277,722 | $315,106 | $2,553,931 |
| Royalty | $6,721 | $91,079 | $14,400 | $0 | $0 |
| SWOG | $0 | $0 | $0 | $0 | $4,288 |
| **TOTAL** | $4,446,381 | $5,154,935 | $21,285,606 | $11,588,264 | $13,405,157 |

FINANCIAL REPORT ON PROTOCOLS IN FY 02 BY DEPARTMENT AND SERVICE

| Department | Service | Protocol | Carry-In | Authorized | Expenses | Carry-Over |
|---|---|---|---|---|---|---|
| *Department of Allergy-Immunology* | | | | | | |
| | | 01-33001 | $0 | $8,500 | $7,230 | $1,000 |
| | | 02-33003 | $0 | $3,973 | $0 | $1,000 |
| | | 02-33005E | $0 | $1,000 | $0 | $1,000 |
| | | 02-33006E | $0 | $1,000 | $0 | $1,000 |
| **DEPARTMENT TOTAL** | | | $0 | $14,473 | $7,230 | $4,000 |
| *Department of Clinical Investigation* | | | | | | |
| | | 01-9201 | $1,000 | $0 | $821 | $0 |
| **DEPARTMENT TOTAL** | | | $1,000 | $0 | $821 | $0 |
| *Department of Medicine* | | | | | | |
| | | 02-14008E | $0 | $1,000 | $0 | $1,000 |
| | Critical Care Medicine Service | | | | | |
| | | 00-17001E | $1,000 | $0 | $1,004 | $0 |
| | **Service Total** | | $1,000 | $0 | $1,004 | $0 |
| | Endocrine Service | | | | | |
| | | 00-13004E | $1,000 | $0 | $214 | $0 |
| | | 00-13006E | $1,000 | $0 | $844 | $0 |
| | | 00-1304 | $1,000 | $0 | $520 | $0 |
| | | 01-13004 | $0 | $1,000 | $0 | $1,000 |
| | | 01-13005 | $0 | $1,000 | $0 | $1,000 |
| | | 01-13007E | $1,000 | $0 | $995 | $0 |
| | | 02-13006 | $0 | $6,220 | $6,220 | $0 |
| | | 02-13008 | $0 | $1,000 | $0 | $1,000 |
| | | 02-13009E | $0 | $1,000 | $0 | $1,000 |
| | **Service Total** | | $4,000 | $10,220 | $8,793 | $4,000 |
| | Gastroenterology Service | | | | | |
| | | 00-1403 | $1,000 | $0 | $990 | $0 |
| | | 01-14004 | $0 | $6,969 | $1,333 | $1,000 |
| | | 01-14004E | $1,000 | $0 | $874 | $0 |
| | | 01-14006 | $0 | $1,000 | $0 | $1,000 |
| | | 02-14007 | $0 | $2,850 | $861 | $1,000 |
| | | 02-14008 | $0 | $1,000 | $0 | $1,000 |
| | | 02-14009 | $0 | $1,000 | $522 | $0 |
| | | 02-14010 | $0 | $1,000 | $522 | $0 |
| | | 02-14011 | $0 | $2,178 | $2,037 | $0 |
| | | 02-14012 | $0 | $1,780 | $558 | $1,000 |
| | **Service Total** | | $2,000 | $17,777 | $7,697 | $5,000 |

FINANCIAL REPORT ON PROTOCOLS IN FY 02 BY DEPARTMENT AND SERVICE

| Department | Service | Protocol | Carry-In | Authorized | Expenses | Carry-Over |
|---|---|---|---|---|---|---|
| | General Medicine Service | | | | | |
| | | 00-10003E | $1,000 | $0 | $1,000 | $0 |
| | | 01-10004E | $0 | $1,000 | $1,000 | $0 |
| | **Service Total** | | $1,000 | $1,000 | $2,000 | $0 |
| | Hematology-Oncology Service | | | | | |
| | | 01-16004 | $0 | $3,800 | $2,744 | $0 |
| | | 1615-98 | $1,000 | $0 | $842 | $0 |
| | **Service Total** | | $1,000 | $3,800 | $3,586 | $0 |
| | Infectious Disease Service | | | | | |
| | | 1978 | $1,000 | $0 | $1,000 | $0 |
| | | 1993 | $0 | $1,000 | $0 | $0 |
| | **Service Total** | | $1,000 | $1,000 | $1,000 | $0 |
| | Nephrology Service | | | | | |
| | | 00-11010E | $1,000 | $0 | $772 | $0 |
| | | 01-11012E | $1,000 | $0 | $866 | $0 |
| | | 02-11003 | $0 | $9,706 | $6,848 | $0 |
| | | 02-11004 | $0 | $6,561 | $4,928 | $1,000 |
| | | 02-11005 | $0 | $1,268 | $0 | $1,000 |
| | | 02-11013E | $0 | $1,000 | $925 | $0 |
| | | 1199-99 | $0 | $3,150 | $957 | $1,000 |
| | **Service Total** | | $2,000 | $21,685 | $15,296 | $3,000 |
| | Pulmonary & Critical Care Medicine Service | | | | | |
| | | 00-17003E | $1,000 | $0 | $1,035 | $0 |
| | | 00-17004E | $1,000 | $0 | $945 | $0 |
| | | 01-17005 | $0 | $1,000 | $0 | $1,000 |
| | | 01-17005E | $1,000 | $0 | $1,071 | $0 |
| | | 01-17006 | $0 | $1,000 | $0 | $1,000 |
| | | 01-17008E | $1,000 | $0 | $944 | $0 |
| | | 01-17011E | $1,000 | $0 | $927 | $0 |
| | | 01-17012E | $1,000 | $0 | $932 | $0 |
| | | 01-17013E | $0 | $1,000 | $0 | $1,000 |
| | | 01-17014E | $0 | $1,000 | $0 | $1,000 |
| | | 02-17008 | $0 | $1,000 | $0 | $1,000 |
| | | 02-17009 | $0 | $7,180 | $0 | $0 |
| | | 02-17016E | $0 | $1,000 | $0 | $1,000 |
| | | 02-17016EX | $0 | $1,000 | $0 | $1,000 |
| | | 02-17017E | $0 | $1,000 | $238 | $0 |
| | | 02-17018E | $0 | $1,000 | $0 | $1,000 |
| | | 02-17019E | $0 | $1,000 | $987 | $0 |
| | **Service Total** | | $6,000 | $17,180 | $7,079 | $8,000 |
| **DEPARTMENT TOTAL** | | | $18,000 | $73,662 | $46,455 | $21,000 |
| *Department of Neurology* | | | | | | |
| | | 01-71001 | $0 | $1,000 | $0 | $1,000 |
| | | 01-71003 | $0 | $7,500 | $5,094 | $0 |
| | | 02-71006 | $0 | $1,000 | $0 | $1,000 |
| **DEPARTMENT TOTAL** | | | $0 | $9,500 | $5,094 | $2,000 |

FINANCIAL REPORT ON PROTOCOLS IN FY 02 BY DEPARTMENT AND SERVICE

| Department | Service | Protocol | Carry-In | Authorized | Expenses | Carry-Over |
|---|---|---|---|---|---|---|
| *Department of Nursing* | | | | | | |
| | | 02-75014E | $0 | $1,000 | $0 | $1,000 |
| **DEPARTMENT TOTAL** | | | $0 | $1,000 | $0 | $1,000 |
| *Department of Obstetrics and Gynecology* | | | | | | |
| | | 01-44005 | $0 | $1,000 | $0 | $1,000 |
| **DEPARTMENT TOTAL** | | | $0 | $1,000 | $0 | $1,000 |
| *Department of Orthopaedics and Rehabilitation* | | | | | | |
| | Orthopedics Surgery Service | | | | | |
| | | 00-2401 | $1,000 | $0 | $1,081 | $0 |
| | | 00-2403 | $1,000 | $0 | $799 | $0 |
| | | 00-2406 | $0 | $2,000 | $0 | $1,000 |
| | | 01-24009 | $0 | $22,257 | $12,267 | $1,000 |
| | | 01-2401 | $1,000 | $0 | $998 | $0 |
| | | 01-24010 | $0 | $2,450 | $1,450 | $1,000 |
| | | 01-24011 | $0 | $3,800 | $3,498 | $0 |
| | | 02-24012 | $0 | $1,000 | $0 | $1,000 |
| | | 02-24013 | $0 | $7,367 | $6,766 | $0 |
| | | 02-24014 | $0 | $1,000 | $0 | $1,000 |
| | | 02-24015 | $0 | $6,370 | $5,385 | $1,000 |
| | | 02-24017E | $0 | $1,000 | $0 | $1,000 |
| | | 02-24020E | $0 | $1,000 | $565 | $0 |
| | | 02-24021E | $0 | $1,000 | $0 | $1,000 |
| | | 02-24022EX | $0 | $1,000 | $565 | $0 |
| | | 2410-99 | $1,000 | $0 | $923 | $0 |
| | **Service Total** | | $4,000 | $50,244 | $34,297 | $8,000 |
| | Physical Medicine & Rehabilitation Service | | | | | |
| | | 01-96007E | $1,000 | $0 | $1,069 | $0 |
| | | 01-96009E | $0 | $1,000 | $0 | $1,000 |
| | | 02-96010E | $0 | $1,000 | $0 | $1,000 |
| | **Service Total** | | $1,000 | $2,000 | $1,069 | $2,000 |
| **DEPARTMENT TOTAL** | | | $5,000 | $52,244 | $35,366 | $10,000 |
| *Department of Pathology and Area Laboratories* | | | | | | |
| | | 01-48004 | $0 | $7,500 | $7,155 | $0 |
| **DEPARTMENT TOTAL** | | | $0 | $7,500 | $7,155 | $0 |

FINANCIAL REPORT ON PROTOCOLS IN FY 02 BY DEPARTMENT AND SERVICE

| Department | Service | Protocol | Carry-In | Authorized | Expenses | Carry-Over |
|---|---|---|---|---|---|---|
| *Department of Pediatrics* | | | | | | |
| | | 01-65001a | $0 | $7,000 | $6,088 | $1,000 |
| | | 01-65002 | $0 | $1,000 | $0 | $1,000 |
| | | 02-65001d | $0 | $2,000 | $1,992 | $0 |
| | | 02-65001EX | $0 | $1,000 | $0 | $1,000 |
| | | 02-65005 | $0 | $2,350 | $2,400 | $0 |
| **DEPARTMENT TOTAL** | | | $0 | $13,350 | $10,480 | $3,000 |
| *Department of Psychiatry* | | | | | | |
| | | 02-72007E | $0 | $1,000 | $0 | $1,000 |
| **DEPARTMENT TOTAL** | | | $0 | $2,000 | $0 | $2,000 |
| *Department of Psychology* | | | | | | |
| | | 02-73003E | $0 | $1,000 | $0 | $1,000 |
| | | 02-73005E | $0 | $1,000 | $0 | $1,000 |
| **DEPARTMENT TOTAL** | | | $0 | $2,000 | $0 | $2,000 |
| *Department of Radiology* | | | | | | |
| | Diagnostic Radiology | | | | | |
| | | 01-47002 | $0 | $1,000 | $0 | $1,000 |
| | **Service Total** | | $0 | $1,000 | $0 | $1,000 |
| **DEPARTMENT TOTAL** | | | $0 | $1,000 | $0 | $1,000 |
| *Department of Surgery* | | | | | | |
| | Anesthesia-Operative Service | | | | | |
| | | 01-20002A | $0 | $1,000 | $0 | $1,000 |
| | | 01-31001E | $0 | $1,000 | $0 | $1,000 |
| | **Service Total** | | $0 | $2,000 | $0 | $2,000 |
| | Critical Care Medicine Service | | | | | |
| | | 02-30000E | $0 | $1,000 | $0 | $1,000 |
| | | 02-30001E | $0 | $1,000 | $908 | $0 |
| | | 02-30003 | $0 | $1,000 | $0 | $1,000 |
| | **Service Total** | | $0 | $3,000 | $908 | $2,000 |
| | General Surgery Service | | | | | |
| | | 02-27000E | $0 | $1,000 | $0 | $1,000 |
| | | 02-31002E | $0 | $1,000 | $0 | $1,000 |
| | **Service Total** | | $0 | $2,000 | $0 | $2,000 |
| | Ophthalmology Service | | | | | |
| | | 00-2302 | $1,000 | $7,000 | $0 | $1,000 |
| | **Service Total** | | $1,000 | $7,000 | $0 | $1,000 |
| | Orthopaedics Surgery Service | | | | | |
| | | 02-24019E | $0 | $1,000 | $0 | $1,000 |
| | **Service Total** | | $0 | $1,000 | $0 | $1,000 |

FINANCIAL REPORT ON PROTOCOLS IN FY 02 BY DEPARTMENT AND SERVICE

| Department | Service | Protocol | Carry-In | Authorized | Expenses | Carry-Over |
|---|---|---|---|---|---|---|
| | Otolaryngology-Head & Neck Service | | | | | |
| | | 00-2509 | $0 | $1,000 | $0 | $1,000 |
| | | 01-3201 | $0 | $1,060 | $0 | $0 |
| | | 02-32009 | $0 | $1,000 | $0 | $1,000 |
| | **Service Total** | | $0 | $3,060 | $0 | $2,000 |
| | Otolaryngology-Head & Neck Surgery Service | | | | | |
| | | 02-25002E | $0 | $1,000 | $0 | $1,000 |
| | | 02-25003E | $0 | $1,000 | $0 | $1,000 |
| | **Service Total** | | $0 | $2,000 | $0 | $2,000 |
| | Peripheral Vascular Surgery Service | | | | | |
| | | 00-2102 | $0 | $7,696 | $5,399 | $1,000 |
| | | 01-2101 | $0 | $7,250 | $1,000 | $0 |
| | | 02-21001E | $0 | $1,000 | $0 | $1,000 |
| | | 02-21002 | $0 | $5,000 | $3,500 | $0 |
| | **Service Total** | | $0 | $20,946 | $9,899 | $2,000 |
| | Urology Service | | | | | |
| | | 00-28005E | $1,000 | $0 | $1,016 | $0 |
| | **Service Total** | | $1,000 | $0 | $1,016 | $0 |
| **DEPARTMENT TOTAL** | | | $2,000 | $41,006 | $11,823 | $14,000 |
| **GRAND TOTAL** | | | **$26,000** | **$218,735** | **$124,424** | **$61,000** |

F. RESEARCH ACTIVITY ACCOMPLISHED IN FY 02

With the mission to empower WRAMC researchers from planning to publication, the Department of Clinical Investigation (DCI) supported a total of 906 active protocols this year (see Table I). Two hundred forty-two of these studies were newly approved during the fiscal year; the remaining 664 studies were ongoing during the fiscal year 2002.

**TABLE I. WRAMC Protocol Activity**

| PROTOCOLS | FY98 | FY99 | FY00 | FY01 | FY02 |
|---|---|---|---|---|---|
| ONGOING at beginning of FY | 537 | 621 | 646 | *671 | 664 |
| NEWLY APPROVED (+) | 226 | 230 | 187 | 220 | 242 |
| (Full protocols) | (226) | (152) | (124) | (153) | (163) |
| (Exempt protocols) | | (78) | (63) | (67) | (79) |
| TOTAL ACTIVE During FY | 763 | 851 | ♦833 | 891 | 906 |
| CLOSED (-) | 128 | 184 | 145 | 216 | 215 |
| (Full protocols) | (128) | (184) | (145) | (138) | (152) |
| (Exempt protocols) | | | | (78) | (63) |
| TERMINATED (-) | 14 | 21 | 8 | 6 | 2 |
| WITHDRAWN (-) | | | 10 | 5 | 6 |
| ONGOING AT END OF FY | 621 | 646 | 670 | 664 | 683 |

♦ includes one protocol with status change from FY 99 Publication

* includes one protocol with status change

Of 294 new and exempt protocols submitted in FY 2002, the Human Use Committee (HUC) and/or the Clinical Investigation Committee (CIC) approved a total of 242 new protocols, including the exempt protocols. The CIC reviews all protocols for scientific merit and funding with the exception of those studies being submitted for funding through an outside agency (such as National Institutes of Health or Medical Research and Materiel Command) where critical review will be provided. Some protocols are reviewed by both the

HUC and the CIC; all greater than minimal risk protocols are reviewed for approval by the HUC. The procedure established for exempt category protocols was continued, whereby research that does not fall within the purview of the Institutional Review Board (IRB) is reviewed within DCI to determine if it meets exempt criteria, continued to work well. One hundred two new protocols were submitted under the Exempt category in FY 02 and 79 of these were granted exempt status.

In addition to administering the initial review and approval of new protocols, the continuing review of the ongoing protocols is also administrated by the Department of Clinical Investigation (DCI), Research Review Service (RRS). Continuing review of ongoing approved protocols was conducted prior to or during the anniversary month of the original approval of the protocols. In order to ensure timely completion, a request is sent to the principal investigator for submission of an annual progress report (APR) two months preceding the month the APR is actually due. The completed report consists of a detail summary sheet (DSS), a list of publications using data obtained as a result of the protocol, a copy of the approved consent form, a questionnaire regarding the maintenance of research records, and the continuing review of human subject participation or animal use. Human Use Committee/Institutional Review Board (HUC/IRB) members serve as primary reviewers for the annual progress reports throughout the year. The primary reviewers recommend approval for continuation of the study for one year, study closure, or study continuation or closure pending additional information. These recommendations are presented monthly to the HUC/IRB for their final review and vote. A total of 549 annual progress reports were reviewed and approved. The detail summary sheets of the protocols ongoing in FY 02 comprise Volume II of this document. Failure to submit an APR within sixty days after the anniversary date of the protocol results in administrative termination by the HUC, and investigators are informed that no research may be published.

The RRS also performs and coordinates other protocol regulatory activities. A total of 200 protocol addenda were reviewed and approved by the WRAMC HUC/IRB, and 52 internal protocol audits were conducted by the DCI this year. A total of 503 adverse events were reviewed and reported to the HUC (see Table II).

**TABLE II. WRAMC Other Research Review Activity**

| | FY99 | FY00 | FY01 | FY02 |
|---|---|---|---|---|
| Addenda Reviewed | 307 | 266 | 217 | 200 |
| Audits Conducted | 17 | 33 | 37 | 52 |
| Adverse Events Reported | 893 | 539 | 329 | 503 |
| Continuing Review and Approval of Annual Progress Reports | 568 | 539 | 516 | 549 |

Publication and presentation productivity by WRAMC staff totaled 1,380 items. This included 446 publications, 588 presentations and 346 abstracts (see Table III).

**TABLE III. WRAMC Publications, Abstracts and Presentations**

| | FY99 | FY00 | FY01 | FY02 |
|---|---|---|---|---|
| Publications | 322 | 349 | 370 | 446 |
| Abstracts | 151 | 121 | 99 | 346 |
| Presentations | 599 | 584 | 564 | 588 |
| TOTAL | 1,072 | 1,054 | 1,033 | 1,380 |

The RRS maintained and updated the "Principal Investigator's Guide" which explains the research review process, details research resources available at WRAMC, and provides checklists, formats, and guidelines for principal investigators. The "Principal Investigator's Guide" and the routine forms and instructions necessary for preparation of a protocol application are available through the DCI website at www.wramc.amedd.army.mil/department/dci.

The Biometrics Section of the RRS continued to provide a wide range of statistical support to investigators including research design, sample size estimation, data analysis, and general troubleshooting. Three levels of statistical courses were offered to the investigators regarding how to conduct data analyses using the SPSS program. Course contents included data coding, data entry, common statistical methods for data analysis, and non-parametric statistics. The Biometrics Section remained vital in facilitating and enhancing the functions and capabilities of research data analysis at WRAMC.

The Research Operations Service (ROS), under the direction of Mr. Maged Abdel-Rahim, continued to carry out the DCI Master Plan by continuing the renovation of Building 7. The ROS maintained its support to the research initiative at WRAMC and the graduate medical education by providing technical expertise in the areas of immunology, molecular biology, biochemistry, and experimental pathology. The ROS supported a total of forty DCI-approved protocols and twenty-eight scientific publications.

The Research Administration Service (RAS), under the direction of Ms. Daisy Word, provided administrative support for the Department and all WRAMC investigators. Extramural funding included support from the U.S. Army Medical Research and Materiel Command, Tri Service Nursing, the National Institutes of Health, the Gynecology Oncology Group, the Southwest Oncology Group, the Uniformed Services University of the Health Sciences, and the Cancer and Leukemia Group B. There were also industry awards through Cooperative Research and Development Agreements (CRDA) managed by intermediary agencies including the Henry M. Jackson Foundation for the Advancement of Military Medicine (HMJF), the TRUE Foundation, and the Geneva Foundation. Extramural funding for WRAMC researchers totaled over $10,000,000 and is shown in Volume I.

The Computer Operations Section of RAS continued to provide comprehensive automation support and services to staff and investigators through its on-site and web resources. (Website is located at http://www.wramc.amedd.army.mil/departments/dci/.) The major focus over the year was to further develop the comprehensive relational database for protocol oversight, transition more resources to the web interface, and standardize operations and security with requirements and changes within AKO, MEDCOM, and AMEDDNA.

The Clinical Studies Service (CSS), under the direction of LTC Raul Marin MC, continued to serve as the conduit of educational efforts to the WRAMC investigator community regarding all aspects of research. Among the educational courses offered were the DCI Research Course (web-based and live), the DCI Research Refresher Course (web-based), the Research in Clinical Medicine Course (live), the HIPAA and Research Lecture Series, and numerous other individual lectures that can be found in the DCI web page. The CSS was also responsible for the DCI Protocol Audit Program, the management of adverse events reported to the WRAMC HUC, publication clearance, and the administration of the Bailey K. Ashford Clinical and Laboratory Research Awards.

Under the auspices of the WRAMC Professional Education and Training Committee, DCI continued to provide training for WRAMC personnel regarding research regulations and the conduct of research at WRAMC. A total of 122 investigators participated in the FY 02 live research course. A total of 80 investigators participated

in the FY 02 web-based version of the WRAMC research course. This on-line option facilitated timely completion of the required course for researchers who come to WRAMC throughout the year or who are billeted at facilities other than WRAMC. Twelve investigators completed the Research In Clinical Medicine Course in the spring. A course in microbiology limited to twelve participants was given in March of 2002.

The 28th Annual Bailey K. Ashford Clinical and Laboratory Research Awards were bestowed on members of the 2002 graduating class whose research accomplishments excelled during training. The selection committee chose eight finalists from the record number of forty-three nominations. The finalists presented their research results at a symposium on 2 May 2002 sponsored by Department of Clinical Investigation. The winners in the clinical and laboratory categories and the finalists along with their presentation topics appear in Volume I. A poster session was held the morning of the symposium to allow the other nominees an opportunity to present their work to the WRAMC community.

The Department of Clinical Investigation received the active support of many WRAMC staff members via their participation on the Human Use Committee/Institutional Review Board (HUC/IRB) {Tables IV and V}, the Clinical Investigation Committee (CIC) {Tables VI and VII}, and the Institutional Biosafety Committee (IBC) {Table VIII}. The research expertise of these individuals contributed significantly to the scientific rigor of the WRAMC clinical investigation program.

**TABLE IV: Human Use Committee/Institutional Review Board Primary Members for FY 2002**

| | |
|---|---|
| **Chairpersons HUC** | |
| COL James Kikendall, MC+ | Gastroenterology Service DOM, Rep DCCS |
| LTC (P) Christina Yuan, MC+ | Nephrology Service DOM, Rep DCCS |
| LTC Raul Marin, MC | Co-Chairperson, HUC<br>Assistant Chief, DCI |
| +Alternate chairing of the HUC meetings | |
| **WRAMC Members** | |
| David Gillespie, LTC, MC | (Rep) Department of Surgery |
| Teresa Kemmer, LTC, SP | (Rep) Chief, Nutrition Care Directorate |
| E. Wayne Combs, LTC, AN | (Rep) Department of Nursing |
| Aubrey Waddell, LTC, MS | (Rep) Chief, Department of Pharmacy |
| Geoffrey Grammer, MAJ, MC | (Rep) Department of Psychiatry |
| William A. Sager, MAJ, CH | (Rep) Chief, Dept of Ministry and Pastoral Care |
| Laurel Meaney, DAC | Patients' Rights Representative |
| Scott Murdoch, JD, DAC | (Rep) Center Judge Advocate |
| Edward E. Bartlett, Ph.D, DAC | IRB Administrator<br>Department of Clinical Investigation |
| Vicki Miskovsky, DAC | Recorder, HUC<br>Department of Clinical Investigation |
| **Non-Affiliated Members** | |
| Thomas M. Herndon, MAJ, MC<br>with<br>George C. Tsokos, COL, MC (alternate) | Director, Department of Rheumatology, USUHS<br><br>Chief, Physiology Service, Division of Medicine, WRAIR |
| Richard Conran, COL, MC<br>with<br>Eric Marks, M.D., DoD (alternate) | Department of Pathology, USUHS<br><br>Nephrology Service, USUHS |
| Janice Agazio, DScN, DoD<br>with<br>Ruth Ellen Bulger, Ph.D., DoD (alternate) | Department of Nursing, USUHS<br><br>Department of Anatomy, USUHS |

**TABLE V: Human Use Committee/Institutional Review Board Alternate Members for FY 2002**

| | |
|---|---|
| Audrey Chang, Ph.D., DAC | Chief, Research Review Service, DCI<br>Co-Chairperson HUC |
| Alexander Stojadinovic, MAJ, MC | General Surgery Service<br>(Rep) Department of Surgery |
| Patricia A. Patrician, LTC, AN | (Rep) Chief, Nursing Research Service |
| Abdull R. Muhammad, CPT, CH | (Rep) Chief, Department of Ministry & Pastoral Care |
| Dean Inouye, LTC, MC | (Rep) Chief, Department of Psychiatry |
| Melanie Craig, MAJ, SP | (Rep) Chief, Nutrition Care Directorate |
| Richard J. Relyea, DAC, JD | (Rep) Center Judge Advocate |
| Verna Parchment, RN, MS, DAC | Research Review Service, DCI |
| Irone Green, DAC | Recorder, Department of Clinical Investigation |

**TABLE VI: Clinical Investigation Committee Primary Members for FY 2002**

| | |
|---|---|
| LTC Raul Marin, MC | Chairperson, CIC<br>Asst. Chief, Department of Clinical Investigation |
| Thomas Burklow, LTC, MC | (Rep) Chief, Department of Pediatrics |
| George Peoples, LTC, MC | (Rep) Department of Surgery |
| Patrick O'Malley, MAJ, MC | (Rep) Chief, Department of Medicine |
| Patricia A. Patrician, LTC, AN | (Rep) Chief, Nursing Research Service |
| Laurie Ryan, Ph.D., DAC | (Rep) Chief, Department of Neurology |
| Kenneth Grant, Ph.D., DAC | Army Audiology & Speech Center<br>Rotating Senior Investigator |
| Scott Murdoch, JD, DAC | (Rep) Center Judge Advocate |
| Al Szkutnik, DAC (non-voting) | (Rep) Department of Pharmacy (consultant) |
| Audrey Chang, Ph.D., DAC | Chief, Research Review Service, DCI |
| Edward E. Bartlett, Ph.D, DAC | IRB Administrator<br>Department of Clinical Investigation |
| Daisy Word, MHSA, DAC | Chief, Research Administration Service, DCI |
| Vicki Miskovsky, DAC (non-voting) | Recorder, CIC |

**TABLE VII: Clinical Investigation Committee Alternate Members for FY 2002**

| | |
|---|---|
| Allen Taylor, LTC, MC | Acting Chairperson, CIC |
| Glenn Edwards, LTC, MC | (Rep) Chief, Department of Pediatrics |
| Oleh Hnatiuk, LTC, MC | (Rep) Chief, Department of Medicine |
| Noah S. Schenkman, LTC, MC | (Rep) Chief, Department of Surgery |
| Andrew Eiseman, MAJ, MC | (Rep) Chief, Department of Surgery |
| John Choi, MAJ, MC | (Rep) Chief, Dept of Neurology |
| Brian Walden, Ph.D., DAC | Rotating Senior Investigators |
| Daniel Winand, JD, DAC | (Rep) Center Judge Advocate |
| Ms. Robin Howard, MS, DAC | (Rep) Chief, Research Review Service, DCI |
| Roscoe Brunson, DAC | (Rep) Chief, Research Administrations, DCI |
| Pending<br>(Non-voting) | Recorder, CIC |

**TABLE VIII: Institutional Biosafety Committee Board Members for FY 2002**

| | |
|---|---|
| **WRAMC Affiliated Members** | |
| COL Craig D. Shriver, MC | Assistant Chair, General Surgery |
| LTC Thomas R. Burklow, MC | Pediatric Cardiology |
| LTC Raul Marin, MC | Physical Medicine & Rehab/Research Admin. |
| COL Bryan L. Martin, MC | Allergy/Immunology |
| Dr. Diarmuid Nicholson (PhD) | Biochemistry/Molecular Biology |
| MAJ Paula Doulaveris, MS | Pharmacology |
| **Non-Affiliated Members** | |
| LTC Ken E. Kester, MC | Chair, Infectious Disease, WRAIR |
| COL Naomi E. Aronson, MC | Infectious Disease, USUHS |
| COL Judd W. Moul, MC | Urology, USUHS |
| Dr. Kuan-Teh Jeang (MD, PhD) | Molecular Virology, NIH |
| Dr. Shyh-Ching Lo, (MD, PhD) | Molecular Pathobiology, AFIP |
| Ms. Donna J. Mateski (MS, RD) | Research Administration, Kaiser |
| LTC Jerome Kim | Infectious Disease |
| **DCI Administration (non-voting)** | |
| COL Maria H. Sjogren, MC | Chief, Dept. of Clinical Investigation |
| Dr. Audrey Chang (PhD) | Chief, Research Review Service, DCI |
| CPT Ken Capps, MS | Clinical Studies Service, DCI |
| Ms. Deborah Kessler (RN, MSN) | Nurse Specialist |
| Dr. Edward Bartlett (PhD) | Asst. Chief, Research Review Service, DCI |

G. RESEARCH ACTIVITY PLANNED FOR FY 03

During FY 03 we will continue training all new principal investigators at WRAMC concerning the conduct of good clinical research through a one-day live research course or a six-hour self-taught web-based course. The Professional and Education Training Committee at Walter Reed advises that all researchers are required to take a web-based refresher course after three years following the initial training course. We continue to participate in the establishment of multi-institution oncology trials in the National Capital Area sponsored by the United States Military Cancer Institute (USMCI). The institutions involved are National Navy Medical Center, Bethesda, MD, Malcolm Grow Medical Center, Andrews AFB, Uniformed Services University of Health Sciences, Bethesda, MD, and Walter Reed Army Medical Center, Washington, DC. A memorandum of understanding has been signed by the Commanders of Walter Reed Army Medical Center, National Navy Medical Center, Malcolm Grow Air Force Medical Center, and the President of USUHS that outlines the principles of collaboration between these entities. Efforts towards developing the Standard Operating Procedures for the Institutional Review Board (IRB) of the USMCI are being successful. The principal investigators may submit their protocols to the USMCI when the research studies involve more than Walter Reed Army Medical Center as a study site.

A major focus in FY 03 will be Health Insurance Portability and Accountability Act (HIPAA) compliance for WRAMC research protocols. The HIPAA regulations will apply to all ongoing protocols that are still enrolling research participants and to all applicable new protocols approved after 14 April 2003. DCI will identify the existing ongoing protocols, including the exempt protocols, for which HIPAA will be applicable and develop forms for authorization for the use of protected health information (PHI) for research, business agreements, etc.

Research is an ever growing and challenging enterprise. For FY03, we will continue to develop Tissue Banking Policy and Guidelines and implement (or adapt) other new requirements, particularly with respect to gene therapy regulations. We will continue to train members of the Institutional Review Boards, both CIC and HUC, and the members of the Institutional Biosafety Committee (IBC). Our IBC continues to actively review and oversee the biosafety issues of two existing gene therapy protocols. Of the two ongoing gene therapy studies, one is closed to the enrollment and the principal investigator voluntarily suspended the other one until the FDA resolves the safety of the use of retroviral vectors in blood stem cells. We will continue to update and guide WRAMC investigations so that the best protection program for research volunteers is implemented.

# The Bailey K. Ashford Clinical Research Awards
# 2002

## First Place - Laboratory Award Category

*MAJ Andrew J. Bauer MC*
*Fellow, Pediatric Endocrinology Service*
*"Blockade of Angiogenesis: A Novel Treatment for Anaplastic Thyroid Cancer*

## First Place - Clinical Research Category

*CPT Scott E. Brietzke MC*
*Resident, Otolaryngology – Head and Neck Surgery*
*"Injection Snoreplasty: Scientific Journey from Problem to Solution"*

## First Place - Laboratory Poster Award Category

*LT David Allen USNR*
*Fellow, Nephrology*
*"Rat Model for Hemodialysis During Hemorrhagic Shock"*

## First Place - Clinical Research Poster Category

*CPT A. Hiroshi Andrews MC*
*Resident, Internal Medicine*
*"Utility of Routine Abdominal Radiography in Patients with Gastrointestinal Hemorrhage Admitted to the Intensive Care Unit"*

## Research Presentation Finalists

*CPT Christopher Cote MC (Resident, Otolaryngology – Head and Neck Surgery)*

*CPT Peter Dunaway MC (Fellow, Gastroenterology Service)*

*MAJ Edmond Paquette MC (Resident, Urology Service)*

*MAJ Benjamin Starnes MC (Fellow, Vascular Surgery)*

*MAJ E. Darrin Cox MC (Resident, Internal Medicine Service)*

*CPT (P) Joseph Flynn MC (Fellow, Hematology-Oncology Service)*

# III. LIST OF PROTOCOLS BY DEPARTMENT AND SERVICE

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| ***Aberdeen Proving Ground*** | | |
| 01-86001 | Walsworth, Matthew, CPT SP. Efficacy of Stretching and Mobilization with Neutral Wrist Splinting Versus Neutral Wrist Splinting Alone in Patients with Carpal Tunnel Syndrome: A Randomized Trial. (1/16/2001) | 600 |
| 02-86002 | Knapik, Joseph, Ph.D. DAC. Injury Control and Running Footwear. (3/12/2002) | New |
| ***CHPPM*** | | |
| 02-98001E | Piotrowski, Mark, MAJ DE. USACHPPM Dental Mouthguard Study. (12/19/2001) | Exempt |
| ***DENTAC*** | | |
| 02-94000E | Trebus, Daniel M., MAJ DE. Prevalence of Soft Tissue Injuries with Use of Commercial Endotracheal Tube Holders. (9/25/2002) | Exempt |
| 02-94001 | Trebus, Daniel M., MAJ DE. The Effect of Platelet Rich Plasma on Postoperative Pain, Edema, and Ecchymosis in Cervicofacial Rhytidectomy: A Pilot Study. (1/15/2002) | New |
| 9400-99 | Theberge, Daniel M., COL DE. Absorption Rate a New Bioabsorbable Membrane - A Pilot Study. (2/2/1999) | 631 |
| ***Department of Allergy-Immunology*** | | |
| 01-33001 | Kim, Theodore, MAJ MC. In Vitro Gamma-Interferon Response to MTB Antigens in BCG-Vaccinated Individuals and Those with Equivocal PPD Skin Test Compared to Negative and Positive Control Subjects. (2/13/2001) | 388 |
| 01-33002 | Waibel, Kirk H., CPT MC. Suppression of Ragweed Wheal Response by Montelukast: A Double-blind Study. (3/20/2001) | 389 |
| 02-33003 | Katial, Rohit, MAJ MC. Comparing the Rate of Return of the Wheal-and-Flare Responses in Skin Prick Testing to Both Histamine Control and Aeroallergens after Discontinuing Two Weeks of Therapeutic Daily Dose Fexofendadine. (2/26/2002) | New |
| 02-33005E | Martin, Bryan L., LTC MC. Vaccine Temp Associated Adverse Events: Review of Clinical Cases Referred To A Tertiary Medical Center. (12/19/2001) | Exempt |
| 02-33006E | Nelson, Michael R., LTC MC. The role of skin testing and RAST in the evaluation of bee sting allergy. (1/30/2002) | Exempt |
| 3369 | Kosisky, Susan, DAC. Survey of Prevalent Pollen and Fungal Aeroallergens in the Washington DC Area. (5/11/1993) | 390 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 3372 | Engler, Renata J.M., COL MC. Mosquito Hypersensitivity: Immunology and Value of Skin Testing with Whole Body Mosquito Extracts. (12/21/1993) | 391 |
| 3385 | Engler, Renata J.M., COL MC. Adverse Reactions with Intravenous Immunoglobulin Therapy. (12/10/1996) | 392 |
| 3390-99 | Nelson, Michael R., LTC MC. A Phase 3 Study to Determine the Efficacy and Safety of C1-Inhibitor (HUMAN) Vapor Heated, Immuno in Subjects with Hereditary Angioedema (HAE). (5/25/1999) | 393 |
| ***Department of Clinical Investigation*** | | |
| 00-9201 | Francis, Gary L., COL MC. Role of Focal Adhesion Kinase and E-Cadherin in Differentiated Thyroid Cancer. (10/5/1999) | 613 |
| 00-9202AD | Sjogren, Maria H., COL MC. Efficacy of Therapy with Interferon (interferon alfa-2b or Pegylated Interferon alfa-2b) in Combination with Ribavirin for Chronic Hepatitis C Infections in Egypt. (1/27/2000) | Admin |
| 01-92002 | Sjogren, Maria H., COL MC. A Prospective, Randomized, Multicenter, Open-Label, Comparative Safety Study of Pegasy® vs. Pegasys® Plus Ribavirin Treatment vs. A Twelve-Week Treatment Delay in Patients with Chronic Hepatitis C. (1/23/2001) | 614 |
| 01-92003 | Sjogren, Maria H., COL MC. Hepatitis C Virus Infection: Mechanism of Disease Progression. (2/20/2001) | 617 |
| 01-92004 | Rojkind, Marcos, M.D.. Interleukin-6 and Tumor Necrosis Factor-Alpha Role In Alcoholic Liver Cirrhosis. (9/11/2001) | 618 |
| 01-92005 | Rojkind, Marcos, M.D.. The Role of the Acute Phase Response in Alcoholic Liver Cirrhosis. (9/14/2001) | 619 |
| 01-92006 | Rojkind, Marcos, M.D.. Alcohol-Induced Liver Fibrosis: An In Vitro Model. (9/14/2001) | 620 |
| 01-9201 | Bednarek, Jana, Ph.D. DAC. Hepatitis G Virus and Aplastic Anemia. (12/5/2000) | 621 |
| 02-92007 | Sjogren, Maria H., COL MC. A Multicenter Double-Blinded Study in Patients with Compensated Cirrhosis Due to Chronic Hepatitis C Who are Non-Responders to Prior Interferon Alfa or Interferon Alfa + Ribavirin Therapy, Comparing Treatment with Thymosin Alpha 1 + Peginterferon Alfa-2a With Peginterferon Alfa-2a + Placebo. (10/23/2001) | New |
| 02-92007E | Fileta, Bader, DAC. Analysis of Malaria Recombinant Protein Vaccines. (10/2/2001) | Exempt |
| 02-92008 | Sjogren, Maria H., COL MC. A Phase II, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study of the Safety and Anti-Fibrotic Efficacy of Interferon Gamma-1b (IFN-y 1b) in Patients with Severe Liver Fibrosis or Compensated Cirrhosis Due to Hepatitis C. (11/20/2001) | New |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-92009 | Sjogren, Maria H., COL MC. A Multicenter Double-Blinded Study in Non-Cirrhotic Patients with Chronic Hepatitis C Who Are Non-Responders to Prior Interferon Alfa or Interferon Alfa + Peginterferon Alfa-2a with Peginterferon Alfa-2a + Placebo. (3/26/2002) | New |
| 02-92010 | Sjogren, Maria H., COL MC. A Phase III Open label Study to Evaluate the Safety and Efficacy of RU-8811, in Patients with Types 3 or 4 Non-Alcoholic Fatty Liver Disease (NAFL). (4/23/2002) | New |
| 02-92012 | Sjogren, Maria H., COL MC. Combination of Ribavirin with Interferon Alfacon-1 or with Pegylated Interferon Alfa 2b as Initial Treatment for Difficult to Treat Subjects Chronically Infected with Hepatitis C Virus - Genotype 1. (6/25/2002) | New |
| 9206 | Yuan, Christina M., LTC MC. Are Heat Shock Proteins Target Antigens of the Immune System in Renal Allograft Recipients?. (4/9/1996) | 623 |
| 9212 | Lukes, Yvonne D., DAC. Hormonal Regulation of the Vitamin D Receptor. (12/9/1997) | 624 |
| 9219-99 | Francis, Gary L., COL MC. Molecular Marker of Radiation Induced Thyroid Disease Developing in Subjects Who lived Downwind of the Hanford Nuclear Power Plant During Childhood. (11/17/1998) | 625 |
| 9220-99 | Francis, Gary L., COL MC. Molecular Markers of Radiation Induced Thyroid Disease Developing in Subjects Treated with External Beam Irradiation for Tinea Capitus as Children. (11/17/1998) | 626 |
| 9221-99 | Sjogren, Maria H., COL MC. Combination of Ribavirin with Interferon Alfacon-1 or With Interferon Alfa 2b as Initial Treatment for Chronic Hepatitis C. (12/15/1998) | 627 |
| 9222-99 | Ramirez, Raul R., LTC MC. Role of Tyrosine Kinases in Differentiated Thyroid Cancer. (3/2/1999) | 629 |
| 9223-99 | Burch, Henry B., LTC MC. An Investigation of Oxidative Damage to Proteins in Thyroid Autoimmunity. (4/6/1999) | 630 |
| ***Department of Medicine*** | | |
| ***Cardiology Service*** | | |
| 00-1201 | Taylor, Allen J., LTC MC. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol - A Randomized Trial Comparing the Effects of Atorvastatin and Pravastatin on Carotid Intima-Media Thickness. (10/26/1999) | 22 |
| 00-1202 | Taylor, Allen J., LTC MC. SWITCH: Statins at WRAMC: Interventions for the Treatment of Cholesterol-An Observational Study of the Formulary Switch to HMG-coA Reductase Inhibitors Mandated by the Department of Defense Pharmacoeconomic Center. (11/30/1999) | 23 |
| 01-12001 | Gorman, Patrick, LTC MC. Acetylysteine for the Prevention of Contrast Associated Nephropathy in Diabetic Patients Undergoing Coronary Angiography. (1/23/2001) | 24 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 01-12002 | Malik, Anwar K., MAJ MC. Remote Echocardiographic Consults - Diagnostic Concordance - Intra and Inter Consults. (6/5/2001) | 25 |
| 01-12003 | Taylor, Allen J., LTC MC. ARBITER II: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol - A Randomized, Placebo-controlled, Double-Blind Study. (7/31/2001) | 26 |
| 02-12004 | Gentlesk, Phillip J., CPT MC. The Effects of Simvastatin on Heart Rate Variability in Dilated Cardiomyopathy. (10/16/2001) | New |
| 02-12005 | Wiley, Thomas A., LTC MC. Ventricular Resynchronization Therapy Randomized Trial (VecToR). (11/29/2001) | New |
| 02-12006NR | Hudak, Craig, MAJ MC. Review of a Humanitarian Device Document. (3/26/2002) | New |
| 02-12007 | Isenbarger, Daniel W., MAJ MC. Utility of the Pace-ECG for Diagnosis of Cardiac Hypertrophy. (8/20/2002) | New |
| 02-12008 | Sullenberger, Lance, CPT MC. The Accuracy of Physical Examination for the Diagnosis of Aortic Valvular Sclerosis. (8/27/2002) | New |
| 1215 | Taylor, Allen J., LTC MC. The Utility of Electron Beam Computed Tomography (EBCT) as a Screening Test for Coronary Artery Disease, and as an Intervention for Risk Factor Modification Among Over 40 Active Duty Personnel. (11/25/1997) | 27 |
| 1217 | Taylor, Allen J., LTC MC. Use of Electron Beam Computed Tomography in the Preoperative Evaluation of Noncardiac Vascular Surgery Patients. (12/16/1997) | 28 |
| 1218-98 | Calagan, Jennifer L., LTC MC. Assessment of Clinical Outcome Using Prothrombin Time Patient Self Testing (PST) to Monitor Long Term Antocoagulation Therapy. (6/16/1998) | 29 |
| 1223-99 | Taylor, Allen J., LTC MC. Multinational, Multi-Center, Double-Blind, Randomized, Active Controlled, Parallel Group Study Comparing the Efficacy and Safety of Long-Term Treatment with Valsartan, Captropril and Their Combination in High Risk Patients After Myocardial Infarction. (5/25/1999) | 31 |
| 1224-99 | Vernalis, Marina, COL MC. Non-Invasive Coronary Artery Disease Reversal. (9/21/1999) | 32 |
| ***Dermatology Service*** | | |
| 1828 | Bessinger, Glenn, CPT MC. Light Microscopic Immunohistochemistry to Identify Leishmania on Formalin Fixed Human Tissues. (1/7/1997) | 184 |
| ***Endocrine Service*** | | |
| 00-1301 | Burch, Henry B., LTC MC. The Effect of Retinols, Tamoxifen and Octreotide on Cellular Proliferation and Control of Thyroglobulin, TSH Receptor and, Sodium-Iodide Symporter mRNA Expression in Thyroid Cancer Tumor Cell Lines. (10/5/1999) | 35 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 00-1302 | Baquero, Jeannie A., CPT MC. The Effect of Omeprazole Therapy on Serum Calcitonin (CT). (2/1/2000) | 36 |
| 00-1303 | Bernet, Victor J., LTC MC. Galectin-3 Levels as a Marker of Thyroid Cancer in Fine-Needle Aspiration (FNA) Samples. (2/8/2000) | 37 |
| 00-1304 | Vaishnav, Yashesh N., Ph.D. DAC. Investigations of Activation of BAG-1 and p73 Genes in Thyroid Cancer in Tissue. (6/13/2000) | 39 |
| 00-1305 | Vigersky, Robert A., COL MC. A 20 Week Multicenter, Double-Blind, Randomized Parallel-Group Fixed Dose Study to...Monotherapy (120 mg), Compared to Oral Rosiglitazone Monotherapy (8mg) in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise Alone. (7/18/2000) | 41 |
| 01-13001 | Stocker, Derek J., CPT MC. A Comparison of the Effects of Rosiglitazone and Metformin on Markers of Inflammation and Carotid Plaque Burden in Patients with Type 2 Diabetes Mellitus. Cardiovascular Effects of Hypoglycemic Medications in Diabetes - CHD Study. (1/23/2001) | 44 |
| 01-13002 | Vigersky, Robert A., COL MC. Using Telemedicine and Wireless Technology to Improve Diabetic Outcomes in Poorly Controlled Patients. (3/20/2001) | 45 |
| 01-13003 | Vigersky, Robert A., COL MC. The Avandia Worldwide Awareness Registry (AWARe): Comparison of Avandia and Actos in "Real World" Medical Practice. (3/27/2001) | 48 |
| 01-13004 | Bernet, Victor J., LTC MC. Pilot Study: Recombinant TSH Stimulation of Radioactive Iodine Uptake in Hyperthyroidism. (5/15/2001) | 49 |
| 01-13005 | Langely, Roy W., MAJ MC. Determination of Thyroid Nodule Malignancy with 18F-FDG Coincidence Imaging and Tc-99m Depreotide Scintigraphy. (6/19/2001) | 50 |
| 02-13006 | Vaishnav, Yashesh N., Ph.D. DAC. Investigations on Y-Ray-Induced Alterations in Gene Expression Profiles in wt-FRTL-5 and Ret/PTC-3 Oncogene Expressing FRTL-5 Thyroid Cell Lines Utilizing cDNA Expression Array. (11/13/2001) | New |
| 02-13007 | Vigersky, Robert A., COL MC. The Use of Heart Rate Variation to Determine the Prevalence and Prognostic Significance of Autonomic Neuropathy in Patients with Either Diabetes Mellitus or Cardiovascular Disease. (2/26/2002) | New |
| 02-13008 | Gaitonde, David Y., CPT MC. Effect of A Single Intra-Articular Steroid Injection on Serum Glucose Levels in Patients with Type 2 Diabetes Mellitus. (3/12/2002) | New |
| 02-13009 | Vigersky, Robert A., COL MC. An Assessment of Ocular Lens Fluorescence Measurements for the Detection of Diabetes: A Joint Joslin Diabetes Center, Tripler Army Medical Center and Walter Reed Army Medical Center Study. (4/23/2002) | New |
| 02-13009E | Burch, Henry B., LTC MC. Comparison of Total Hyperthyroid Time in Patients Previously Pre-treated or Not-pre-treated with Antithyroid Drugs Before Ablation With Radioiodine for Graves' Disease: A Retrospective Analysis. (1/30/2002) | Exempt |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-13010 | Glister, Babette C., CPT MC. Home Fructosamine Testing as a Cost-Effective Adjunctive Tool for Improving Glucose Control in Inadequately Controlled Type 2 Diabetes Mellitus. (5/28/2002) | New |
| 02-13010EX | Vigersky, Robert A., COL MC. The Sensitivity and Specificity of Stereoscopic Non-Mydriatic Digital Retinal Photography in Detecting Diabetic Retinopathy. (9/30/2002) | Exempt |
| 02-13011 | Glister, Babette C., CPT MC. The Effects of Variations in Diet Composition on Body Mass. (8/6/2002) | New |
| 02-13012 | Vigersky, Robert A., COL MC. Continuous Glucose Monitoring in Patients with Type 2 Diabetes Mellitus. (9/17/2002) | New |
| 1392-98 | Francis, Gary L., COL MC. Circulating Micro-Metastasis in Patients with Thyroid Neoplasia. (10/28/1997) | 51 |
| 1395-98 | Burch, Henry B., LTC MC. Establishment of a Thyroid Patient Serum Bank. (4/21/1998) | 52 |
| 1396-98 | Burch, Henry B., LTC MC. Establishment of a Thyroid Tissue Bank. (4/21/1998) | 53 |
| 1399-99 | Bernet, Victor J., LTC MC. The Effect of Retinoic Acid on Sodium-Iodide Symporter mRNA Expression in Thyrocytes Circulating in the Blood Stream - A Pilot Study. (2/16/1999) | 54 |
| ***Gastroenterology Service*** | | |
| 00-1401 | Kikendall, James W., COL MC. Exploration of Genome-Wide Gene Expression Profiles in Subtypes of Colorectal Neoplasia - A Pilot Study. (12/14/1999) | 55 |
| 00-1403 | Mulhall, Brian P., MAJ MC. The Effect of Helicobacter pylori Eradication on the Severity of Gastro-esophageal Acid Reflux as Determined by 24-hours pH Measurement. (1/18/2000) | 56 |
| 00-1404 | Cumings, Mark D., MAJ MC. A Comparison of Pediatric and Adult Colonoscopes in Adult Patients Presenting for Routine Colonoscopy. (3/21/2000) | 58 |
| 00-1405 | Holtzmuller, Kent, COL MC. Phase II Study of Long Term PEG Intron for Patients Who Have Failed to Respond to Rebetron/Interferon with Advanced Fibrosis and Cirrhosis Secondary to Hepatitis C. (3/21/2000) | 59 |
| 00-1406 | Cumings, Mark D., MAJ MC. Screening for Barrett's in Patients With and Without Heartburn. A Multi-Center Trial. (3/21/2000) | 60 |
| 00-1407 | Hwang, Inku, MAJ MC. Tele-Hepatitis Phase I: Validation of desktop Video Teleconferencing (VTC) System at 384 kb ISDN for Evaluation of Patients with Hepatitis. (5/16/2000) | 61 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 00-1408 | Holtzmuller, Kent, COL MC. A Randomized Multicenter Trial Comparing Induction PEG Intron-A Plus Ribavirin Versus PEG Intron-A Plus Ribavirin in Patients…Not Responded or Have Relapsed..Based Therapy for Chronic Hepatitis C, With Maintenance … Who Continue to Remain Non-Responsive. (7/18/2000) | 62 |
| 01-14001 | Duncan, Marten, CPT MC. Association of Helicobacter pylori Infection with Coronary Heart Disease Detected by Electron Beam CT. (1/9/2001) | 63 |
| 01-14002 | Baroni, Darren S., MAJ MC. An Efficacy and Safety Study of Intravenous Pantoprazole in the Prevention of Recurrent Peptic Ulcer Bleeding After Successful Hemostasis (Sponsored Study by Wyeth-Ayerst Research). (4/17/2001) | 64 |
| 01-14003 | Dunaway, Peter M., CPT MC. Effect of Complete Intraesophageal Acid Ablation Upon Cellular Markers of Proliferation, Differentiation, and Apoptosis in Long-Segment Barrett's Esophagus. (4/24/2001) | 65 |
| 01-14004 | Holtzmuller, Kent, COL MC. The Timing of Liver Enzyme Elevation and Hepatitis C Seroconversion in a Cohort of United States Military Gulf War Veterans. (5/1/2001) | 66 |
| 01-14005 | Holtzmuller, Kent, COL MC. Tele-Hepatitis Phase I: Validation of Desktop Video Teleconferencing for Evaluation of Patients with Hepatitis C. (5/29/2001) | 67 |
| 01-14006 | Holtzmuller, Kent, COL MC. B-Catenin Mutations and Nuclear Accumulation are Early Events in Hepatic Carcinogenesis: Role as a Marker to Determine Risk for Hepatocellular Carcinoma in Hepatitis C and Hepatitis B Patients. (6/12/2001) | 68 |
| 02-14007 | Mulhall, Brian P., MAJ MC. The Role of Gastroesophageal Reflux Disease (GERD) in Upper Airway Reactivity Syndrome (UARS). (10/16/2001) | New |
| 02-14007E | Hwang, Inku, MAJ MC. InVivo Localization of Glandular Dysplasia in the Esophagus: Identification of Differentially Expressed Molecules in Dysplasic Barrett's Esophagus Using Archived Tissue. (10/26/2001) | Exempt |
| 02-14008 | Mulhall, Brian P., MAJ MC. The Effect of Interferon Therapy on Hearing in Adult Patients with Chronic Hepatitis C. (10/16/2001) | New |
| 02-14008E | Andrews, Allen, CPT MC. Utility of Colonoscopy in the Evaluation of Acute Lower Gastrointestinal Hemorrhage. (11/16/2001) | Exempt |
| 02-14009 | Mulhall, Brian P., MAJ MC. The Clinical Impact of Gastroesophageal Reflux in Adult Patients with Obstructive Sleep Apnea. (3/26/2002) | New |
| 02-14009E | Cumings, Mark D., MAJ MC. The Significance of Belching in Upright Reflux Disease. (3/20/2002) | Exempt |
| 02-14010 | Wong, Roy K.H., COL MC. A Multicenter, Double-Blind, Three-way Crossover Intraesophageal and Intragastric pH Study of Three Esomeprazole Treatment Regimens in Documented Barrett's Esophagus Patients. (3/26/2002) | New |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-14010E | Cumings, Mark D., MAJ MC. The Significance of Postprandial Reflux in Upright Reflux Disease. (3/20/2002) | Exempt |
| 02-14011 | Cossentino, Mark J., CPT MC. The Effect of Baclofen on Patients with Gastroesophageal Reflux and Normal Lower Esophageal Sphincter Pressures: A Randomized Prospective Study. (4/23/2002) | New |
| 02-14011E | Hwang, Inku, MAJ MC. Cytokeratin 7/20 Staining Patterns and Cellular Proliferation in Long-Segment Barrett Esophagus (LSBE), Short-Segment Barrett Esophagus (SSBE), and Endoscopically Normal Esophagogastric Junction with Specialized Intestinal Metaplasia (EGJ-SIM). (3/20/2002) | Exempt |
| 02-14012 | Duncan, Marten, CPT MC. Use of a Hyperspectral Imaging System for Dysplasia Screening in Patients with Long Segment Barrett's Esophagus - A Pilot Study. (5/28/2002) | New |
| 02-14012E | Napierkowski, John, MAJ MC. Wireless Capsule Endoscopy (WCE): A Multicenter Retrospective Review. (7/10/2002) | Exempt |
| 02-14013 | Duncan, Marten, CPT MC. Twenty-Four Hour pH Mntng and Histologic Evaluation in Patients with Tongues in the Distal Esophagus: Are These Findings Clinically Relevant?. (9/17/2002) | New |
| 1432 | Wong, Roy K.H., COL MC. Short Segment Barrett's Esophagus: Prevalence, Clinical Characteristics and Response to Long-Term Antisecretory Therapy. (11/29/1994) | 69 |
| 1439 | Osgard, Eric, CPT MC. A Questionnaire for Gastroesophageal Reflux: Development of a Diagnostic and Research Tool Applicable to the General Population. (10/29/1996) | 70 |
| 1443 | Dunaway, Peter M., CPT MC. The Effects of Lamivudine on Renal Function in Patients with Chronic Active Hepatitis B and Proteinuria. (1/27/1998) | 71 |
| 1446-98 | Cumings, Mark D., MAJ MC. Hypnosis Versus Omeprazole for the Treatment of Upright Gastroesophageal Reflux, A Randomized Blinded Placebo Controlled Trial. (4/28/1998) | 72 |
| 1451-98 | Mulhall, Brian P., MAJ MC. The Use of a Nutritional Supplement as an Antimicrobial in Helicobacter pylori Eradication. (9/22/1998) | 73 |
| 1454-99 | Sjogren, Maria H., COL MC. Efficacy of Infergen (15 mcg) for Chronic Hepatitis C in Patients Who are Non-Responders and Relapsers to Combination Therapy with Intron-A + Ribavirin. A Multicenter Trial. (11/24/1998) | 74 |
| 1456-99 | Wong, Roy K.H., COL MC. Long-Term Prevention of Recurrent Peptic Ulcer Hemorrhage in Patients Infected with Helicobacter Pylori: A Multi-Center, NIH Funded, Prospective Randomized Double-Blind Study. (3/23/1999) | 75 |
| 1457-99 | Eastone, John, LCDR MC. Colorectal Neoplasia Screening with Colonoscopy in Asymptomatic Women at Regional Navy/Army medical centers: The CONCeRN Trial. (5/25/1999) | 76 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| ***General Medicine Service*** | | |
| 00-1001 | Jackson, Jeffrey L., LTC MC. The Stability of Physical Symptoms and Psychiatric Illness Among Primary Care Patients. (2/1/2000) | 1 |
| 00-1002 | Helman, Donald, CPT MC. Myositis-Specific Antibodies in Subjects with Idiopathic Interstital Lung Disease. (2/8/2000) | 2 |
| 00-1003 | Salerno, Stephen M., MAJ MC. Can Ambulatory Teaching Seminars Improve Amount and Quality of Feedback to Medical Students in the Outpatient Setting?. (2/22/2000) | 3 |
| 02-10004 | Duncan, William, COL MC. A Prospective Randomized Trial of Post-Exposure Prophylaxis for Anthrax. (10/30/2001) | New |
| 02-10009E | Cassimatis, Dimitri, CPT MC. Evaluation of Knowledge and Practices of Internal Medicine Residents for Chronic Hepatitis C Infection. (2/27/2002) | Exempt |
| 02-10010E | Lott, David A., SFC (P). A Study of Soldiers Assigned to the Medical Holding Company, WRAMC Before and After September, 2001. (5/10/2002) | Exempt |
| 02-10011E | Peckham, Russell M., CPT MC. Evaluation of Interobserver Variability in the Radiographic Diagnosis of Idiopathic Pulmonary Fibrosis. (7/31/2002) | Exempt |
| 02-10012E | Klote, Mary M., CPT MC. Practice Variations and Trends Among Government Physicians in the Prescribing of Allergy Immunotherapy. (8/26/2002) | Exempt |
| 1044 | O'Malley, Patrick, LTC MC. Improving Teaching in the Ambulatory Setting: A Study Using Observed Teaching Sessions and Participant Evaluations. (8/2/1996) | 5 |
| 1051 | Shorr, Andrew F., MAJ MC. The Yield of Endobronchial Biopsy in the Diagnosis of Sarcoidosis. (4/24/1997) | 6 |
| 1053 | O'Malley, Patrick, LTC MC. Adrenal Supression Following Short-Term Use of Corticosteroids: Results of a Prospective Study. (11/5/1997) | 7 |
| 1054-98 | Roy, Michael, MAJ MC. Retrospective Analysis of CCEP Phase II Results from the Walter Reed Gulf War Health Center, 1994-96. (5/6/1998) | 8 |
| 1056-98 | Dunaway, Peter M., CPT MC. Characterization of the Esophageal Striated Muscle in Patients with Achalasia: A Prospective Study. (6/16/1998) | 9 |
| 1060-99 | Daniels, Jasmine T., CPT MC. Diagnostic Accuracy of Pleural Fluid Cholesterol and Lactate Dehydrogenase in Identifying Exudates vs. Transudates. (1/12/1999) | 10 |
| ***Hematology-Oncology Service*** | | |
| 00-1501 | Willis, Carl R., MAJ MC. CALGB 89804: A Randomized Phase III Trial of Combinations of Oxaliplatin (OXAL), 5-Fluorouracil (5-FU) and Irinotecan (CPT-11) as Initial Treatment of Patients with Advanced Adenocarcinoma of the Colon and Rectum. (10/19/1999) | 77 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 00-1502 | Drabick, Joseph J., COL MC. CALGB 49906: A Phase III Study of Doxorubicin-Cyclophosphamide Therapy Followed by Paclitaxel or Docetaxel Given Weekly or Every 3 Weeks in Patients with Axillary Node-Positive Breast Cancer. (1/25/2000) | 78 |
| 00-1503 | Drabick, Joseph J., COL MC. CALGB 159806: ERBB-2 and P53 in Response and Outcome After Paclitaxel Chemotherapy for Mestastatic Breast Cancer. (5/9/2000) | 79 |
| 00-1504 | Drabick, Joseph J., COL MC. CALGB 89803: A Phase III Intergroup Trial of Irinotecan (CPT-11) (NSC #6163480 Plus Flourouracil/Leukovorin (5-FU/LV) Versus Flourouracil/Leukovorin Alone After Curative Resection for Patients with Stage III Colon Cancer. (7/25/2000) | 80 |
| 00-1505 | Drabick, Joseph J., COL MC. CALGB 19901: Phase II Study of Fludarabine Inductin Followed by Campath-1H Consolidation in Unteated Patients with Chronic Lymphocytic Leukemia. (7/25/2000) | 81 |
| 00-1506 | Drabick, Joseph J., COL MC. CALGB 99208: Docetaxel and Estramustine Versus Mitoxantrone and Prednisone for Advanced, Hormone Refractory Prostate Cancer, Phase III. (9/19/2000) | 82 |
| 00-1507 | Drabick, Joseph J., COL MC. CALGB 9764: Genetic Changes in Diffuse Aggressive Non-Hodgkin;s Lymphoma. (9/19/2000) | 83 |
| 00-1601 | Drabick, Joseph J., COL MC. A Feasibility Study of Campath-1H and GM-CSF Combination in Patients with Chronic Lymphocytic Leukema and Small Lymphocytic Lymphoma. (10/26/1999) | 84 |
| 00-1603 | Drabick, Joseph J., COL MC. A Multicenter Phase 2 Study of Oral N-Acetyl Dinaline (CI-994) in the Treatment of Patients with Chronic Lymphocytic Leukemia (Protocol 994-05). (12/14/1999) | 85 |
| 00-1605 | Ales, Noel C., CPT MC. Prospective Evaluation of Fatigue in Patients with B-Cell Chronic Lymphocytic Leukemia. (1/18/2000) | 86 |
| 00-1606 | Drabick, Joseph J., COL MC. A Phase II Evaluation of Rubitecan, A Novel Oral Topoisomerase I Inhibitor, in Newly Diagnosed, Recurrent and Refractory Multiple Myeloma. (2/15/2000) | 87 |
| 01-15005 | Drabick, Joseph J., COL MC. CALGB 79804: Issues of Survivorship Among Breast Cancer Survivors. (2/27/2001) | 88 |
| 01-15006 | Drabick, Joseph J., COL MC. CALGB 89904: A Randomized Phase II Study of Gemcitabine/Cisplatin, Gemcitabine/Docetaxel, Gemcitabine/Irinotecan, or Fixed Dose Rate Infusion Gemcitabine in Patients with Metastatic Pancreatic Cancer. (3/20/2001) | 89 |
| 01-15007 | Flynn, Joseph M., CPT MC. CALGB 99903: A Phase II Study of Arsenic Trioxide (NSC #706363), IND # 57974) in Urothelial Cancer. (4/17/2001) | 90 |
| 01-15008 | Drabick, Joseph J., COL MC. CALGB 80001: Feasibility Study of Sentinel Lymph Node Staging for Colon Cancer. (6/26/2001) | 91 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 01-15009 | Drabick, Joseph J., COL MC. CALGB 49805: A Phase III Randomized Double Blind Study of Letrozole Versus Placebo in Women with Primary Breast Cancer Completing 5 or More Years of Adjuvant Taxmoxifen. (7/24/2001) | 92 |
| 01-1501 | Flynn, Joseph M., CPT MC. CALGB 99901: A Phase II Study of 9 Nitrocamptothecin (9-NC, IND # 60,162) for Hormone Refractory Prostate Cancer. (11/21/2000) | 93 |
| 01-15010 | Ketchum, Lloyd, CPT MC. CALGB 49801: Phase III Trial of Tamoxifen Alone Vs. Tamoxifen Plus Radiation for Good Risk Duct Carcinoma In-Situ (DCIS) of the Female Breast. (8/31/2001) | 94 |
| 01-15011 | Drabick, Joseph J., COL MC. CALGB 159902: Molecular Markers of Pleural Involvement in Resected Non-Small Cell Lung Cancer. (8/28/2001) | 95 |
| 01-15012 | Gorak, Edward J., MAJ MC. CALGB 509901: Phase II Study of Melanoma Vaccine (NSC #683472/675756, IND 6123) and Low-Dose, Subcutaneous Interkeukin-2 in Advanced Melanoma. (9/18/2001) | 96 |
| 01-1502 | Drabick, Joseph J., COL MC. CALGB 59906: A Phase II Study of Sequential Doxorubicin and Topotecan in Relapsed or Refractory Intermediated-or-High Grade Non-Hodgkin's Lymphoma. (11/21/2000) | 97 |
| 01-1503 | Drabick, Joseph J., COL MC. CALGB 59804: A Phase I/II Study of Gemcitabine/Vinorelbine/Liposomal Doxorubicin in Relapsed/Refractory Hodgkin's Disease. (11/30/2000) | 98 |
| 01-1504 | Drabick, Joseph J., COL MC. CALGB 59901: A Phase II Study of 506U78 in Patients with Previously Systemically Untreated Cutaneous T-Cell Lymphoma or With Refractory or Relapsed Non-Cutaneous Peripheral T-Cell Lymphoma. (12/12/2000) | 99 |
| 01-16002 | McGrail, Lisa H., CPT MC. Microarray Analysis of Breast Cancer: A Pilot Feasibility Study. (1/9/2001) | 100 |
| 01-16004 | Flynn, Joseph M., CPT MC. Expression of Human Papilloma Virus in Second Primary Malignancies Associated with Chronic Lymphocytic Leukemia. (3/13/2001) | 103 |
| 01-16005 | Drabick, Joseph J., COL MC. A Phase II, Open-Label, Randomized, Multicenter Trial to Evaluate the Preliminary Efficacy and Safety of Hu1D10 in Patients with Relapsed or Refractory Grades I, II, or III B-Cell Non-Hodgkin's Lymphoma (incliding follicular, small lymphocytic..... (6/19/2001) | 104 |
| 01-16006 | Willis, Carl R., MAJ MC. A Multicenter, Phase III Randomized Trial for Stage IIIB or IV NSCLC Comparing Weekly Taxol (Paclitaxel) and Carboplatin (Paraplatin) Regimen Versus Standard Taxol and Carboplatin Administered Every Three Weeks, Followed by Weekly Taxol. (6/26/2001) | 105 |
| 01-16007 | Willis, Carl R., MAJ MC. An Open-Label, Multicenter, Randomized, Phase III Study Comparing Oral Topotecan/Cisplatin Versus Etoposide/Cisplatin as Treatment for Chemotherapy-Naïve Patients with Extensive Disease-Small Cell Lung Cancer. (7/31/2001) | 106 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 01-1601 | Drabick, Joseph J., COL MC. Epstein-Barr Virus as an Etiologic Agent for Hodgkin's Disease: A Nested Case-Control Study. (12/5/2000) | 107 |
| 02-15013 | Drabick, Joseph J., COL MC. CALGB 79803: Phase III Chemo prevention Trial of Selenium Supplementation in Persons with Resected Stage 1 Non-Small Cell Lung Cancer. (10/23/2001) | New |
| 02-15014 | Drabick, Joseph J., COL MC. CALGB 19808: Phase III Randomized Study of Induction Chemotherapy With or Without MDR-Modulation with PSC-833 (NSC #648265, ind # 41121) Followed by Cytogenetic Risk-Adapted Intensification Therapy Followed by Immunotherapy with rIL-2 (NSC #373364, IND 1969) Vs. Observation in Previously Untreated Patients with AML <60 Years. (11/29/2001) | New |
| 02-15015 | Flynn, Joseph M., CPT MC. CALGB 99904: Adjuvant Androgren Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgren Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III. (1/29/2002) | New |
| 02-15016 | Drabick, Joseph J., COL MC. CALGB 79806: Effects of Dietary Soy on Biomarkers of Prostate Cancer: A Prospective Phase II Study. (5/14/2002) | New |
| 02-15017 | Drabick, Joseph J., COL MC. CALGB 40101/CTSU 40101: Cyclophosphamide and Doxorubicin (CA) (4 VS 6 Cycles) Versus Paclitaxel (12 Weeks vs 18 Weeks) as Adjuvant Therapy for Women with Node-negative Breast Cancer: A 2X2 Factorial Phase III Randomized Study. (8/13/2002) | New |
| 02-15018 | Drabick, Joseph J., COL MC. CALGB 30102: Phase III Comparison of Catheter Based Therapy of Pleural Effusions in Cancer Patients (Optimal Pleural Effusion Control, OPEC). (8/27/2002) | New |
| 02-16000E | Gorak, Edward J., MAJ MC. Autologous Stem Cell Transplantation in Patients with Relapsed or Newly Diagnosed Metastatic Breast Cancer: The Effects of Prior Chemotherapy Regimens and Timing of Transplantation on Transplantation Outcome. (8/1/2002) | Exempt |
| 02-16008 | Myhand, Rickey C., LTC MC. An Open-Label, Randomized Study to Develop a ScreeningTool for Functional Capacity in Anemic Subjects with Nonmyeloid Malignancies Receiving Chemotherapy and Darbepoetin alfa (NESP). (4/23/2002) | New |
| 02-16009 | Waselenko, Jamie K., MAJ MC. Randomized Study of Fludarabine and Cyclophosphamide With or Without Genasense (Bcl-2 Antisense Oligonucleotide) in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia (Protocol GL303). (6/11/2002) | New |
| 02-16010 | Babcock, Janine, COL MC. Collection of Blood Components from Healthy Donors for In Vitro Research. WRAIR Protocol 837. (6/11/2002) | New |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-16011 | Waselenko, Jamie K., MAJ MC. A Phase II Study of the Recombinant Human Monoclonal Anti-Bascular Endothelia Growth Factor Antibody (rhuMAB VEGF) Bevacizumab Administered in Timed Sequential Combination with Cytosine Arabinoside (ara-C) and Mitoxantrone for Adults with Refractory and Relapsed Acute Myelogenous Leukemias (AMLs). (7/16/2002) | New |
| 02-16012 | Myhand, Rickey C., LTC MC. Phase II Randomized Trial of High-Dose Busulfan and Thiotepa 9BT) with Autologous Peripheral Blood Stem Cell (PBSC) Support Versus Standard Dose Docetaxel and Estramustine Regimen for Treatment of Hormone Refractory Metastatic Prostate Cancer. (8/6/2002) | New |
| 02-16013 | Waselenko, Jamie K., MAJ MC. A Phase II Clinical Trial of BMS-247550 (NSC #710428), An Epothiline B Analog in Patients with Breast Carcinoma. (8/13/2002) | New |
| 1500-98 | Drabick, Joseph J., COL MC. CALGB 9633: A Phase III Study of Adjuvant Chemotherapy After Resection for Patients with T2N0 Stage I Non-Small Cell Carcinoma of the Lung. (11/5/1997) | 108 |
| 1501-98 | Drabick, Joseph J., COL MC. CALGB 9741: A Randomized Phase III Trial of Sequential Chemotherapy Using Doxorubicin, Paclitaxel, and Cyclophosphamide or Concurrent Doxorubicin and Cyclophosphamide Followed by Paclitaxel at 14 or 21 Day Intervals in Women with Node Positive Stage II. (12/16/1997) | 109 |
| 1502-98 | Drabick, Joseph J., COL MC. CALGB 9762: Clinical Pharmacology of Paclitaxel in Relation to Patient Age. (1/27/1998) | 110 |
| 1505-98 | Drabick, Joseph J., COL MC. CALGB 9781: A Phase III Trial Comparing Trimodality Therapy (Cisplatin, 5-FU, Radiotherapy and Surgery) to Surgery Alone for Esophageal Cancer. (2/24/1998) | 111 |
| 1506-98 | Drabick, Joseph J., COL MC. CALGB 9720: Phase III Study of MDR Modulation with PSC-833 Followed by Immunotherapy with rIL-2 Vs. No Further Therapy in Previously Untreated Patients with AML > 60 Years. (3/24/1998) | 112 |
| 1507-98 | Drabick, Joseph J., COL MC. CALGB 9730: Single-Agent Versus Combination Chemotherapy in Advanced NSCLC: A CALGB Randomized Trial of Efficacy, Quality of Life, and Cost-Effectiveness. (3/24/1998) | 113 |
| 1509 | Drabick, Joseph J., COL MC. CALGB 9011 A Study of Fludarabine Vs. Chlorambucil Vs. Both Drugs for Chronic Lymphocytic Leukemia. (11/27/1990) | 114 |
| 1509-98 | Drabick, Joseph J., COL MC. CALGB 9793: A Phase III Trial of CHOP Versus CHOP and Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Older Patients with Diffuse Mixed, Diffuse Large Cell and Immunoblastic Large Cell History Non-Hodgkin's Lymphoma. (3/31/1998) | 115 |
| 1510-98 | Drabick, Joseph J., COL MC. CALGB 9712: A Randomized Phase II Study of Concurrent Fludarabine + Chimeric Anti-CD20 Monoclonal Antibody IDEC-C2B8 (Rituximab) [NSC #687451] Induction Followed by Rituximab Consolidation Versus Fludarabine Induction Followed by Rituximab Consolidation. (4/28/1998) | 116 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 1512-98 | Drabick, Joseph J., COL MC. CALGB 9732: A Randomized Phase III Study Comparing Etoposide and Cisplatin with Etoposide, Cisplatin and Paclitaxel in Patients with Extensive Small Cell Lung Cancer Includes update #1-(editorial changes). (7/28/1998) | 117 |
| 1514-99 | Drabick, Joseph J., COL MC. CALGB 39801 Concurrent Carboplatin, Paclitaxel, and Radiation Therapy Vs Induction Carboplatin and Paclitaxel Followed by Concurrent Carboplatin, Paclitaxel, and Radiation Therapy for Patients with Unresectable Stage III Non-Small Cell Lung Cancer: A Phase III Trial. (10/27/1998) | 118 |
| 1515-99 | Drabick, Joseph J., COL MC. CALGB 19805: A Phase II Study of Flavopiridol (NSC #649890) in Patients with Fludarabine Refractory B-Cell Chronic Lymphocytic Leukemia. (11/24/1998) | 119 |
| 1516-84 | Drabick, Joseph J., COL MC. CALGB 8364: Immunological Diagnostic Studies in Adult ALL. (10/25/1983) | 120 |
| 1516-99 | Drabick, Joseph J., COL MC. CALGB 19801: A Phase II Study of 506U78 in Patients with Refractory or Relapsed T-Lineage Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (LBL). (11/24/1998) | 121 |
| 1517-99 | Drabick, Joseph J., COL MC. CALGB 119801: Telephone Monitoring: Early Identification of Psychological Distress in Cancer Patients 65 or More Years Old During Active Treatment. (11/24/1998) | 122 |
| 1518-99 | Drabick, Joseph J., COL MC. CALGB 9865: Tumor Replication Error (RER) Status and Outcome in a Colon Cancer Adjuvant Chemotherapy Trial. (12/15/1998) | 123 |
| 1519 | Drabick, Joseph J., COL MC. CALGB 9192: Comparison of Chemotherapy Vs. Chemohormonotherapy in Premenopausal Women with Stage II Receptor Positive Breast Cancer. (3/26/1991) | 124 |
| 1519-99 | Drabick, Joseph J., COL MC. CALGB 9840: A Phase III Study of Paclitaxel Via Weekly 1 Hour Infusion Versus Standard 3 Hour Infusion Every 3 Weeks in the Treatment of Patients with Metastatic Breast Cancer. (12/15/1998) | 125 |
| 1520-99 | Drabick, Joseph J., COL MC. CALGB 9863: Phase I Study of Irenotecan (CPT-11) in Patients with Abnormal Liver or Renal Function or with Prior Pelvic Radiation Therapy. (2/23/1999) | 126 |
| 1521-91 | Drabick, Joseph J., COL MC. CALGB 9194: Comparison of Adjuvant Chemotherapy with Concurrent or Delayed Tamoxifen vs. Tamoxifen Along in Postmenopausal Patients with Receptor Positive Stage II Breast Cancer. (4/30/1991) | 127 |
| 1522-84 | Drabick, Joseph J., COL MC. CALGB 8461: Cytogenic Studies in Acute Leukemia: A Companion to CALGB 8011, 8323, 8321, and 8411. (9/25/1984) | 128 |
| 1523-91 | Drabick, Joseph J., COL MC. CALGB 9111. A Trial of G-CSF vs Placebo During Remission Induction and Consolidation Chemotherapy for Adult Acute Lymphatic Leukemia. (10/25/1991) | 129 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 1523-99 | Drabick, Joseph J., COL MC. CALGB 9862: Molecular Genetic Features of Acute Lymphoblastic Leukemia. (6/22/1999) | 130 |
| 1524-99 | Drabick, Joseph J., COL MC. CALGB 19802: Phase II Study in Adults with Untreated Lymphoblastic Leukemia Testing Increased Doses of Daunorubicin During Induction, and Cytarabine During Consolidation, Followed by High-Dose Methotrexate and Intrathecal Methotrexate in Place of Crania. (8/31/1999) | 131 |
| 1526-92 | Drabick, Joseph J., COL MC. CALGB 9140: A Phase III Study of CAF-Leucovorin vs. *CAF for Visceral Crisis Breast Cancer. (1/2/1992) | 132 |
| 1527-92 | Drabick, Joseph J., COL MC. CALGB 9190: A Trial of Postoperative Interferon in Resected High Risk Melanoma. (1/2/1992) | 133 |
| 1528-92 | Drabick, Joseph J., COL MC. CALGB 9195: A Trial of Adjuvant Chemoradiation vs. Observation After Gastric Resection of Adenocarcinoma. (1/2/1992) | 134 |
| 1534-92 | Drabick, Joseph J., COL MC. CALGB 9191: A Randomized Study of All-Trans Retinoic Acid vs Standard Induction Therapy for Acute Promyelocytic Leukemia. (11/24/1992) | 135 |
| 1535-92 | Drabick, Joseph J., COL MC. CALGB 9222: A Randomized Study of Intensification Therapy for Patients Under Age 60 with Acute Myelogenous Leukemia. (11/24/1992) | 136 |
| 1541-93 | Drabick, Joseph J., COL MC. CALGB 9153: A Trial of Cladribine in Advance Stage, Low Grade Non-Hodgkin's Lymphoma. (3/30/1993) | 137 |
| 1547-94 | Drabick, Joseph J., COL MC. CALGB 9082: Trial Study of High Dose CPA/CDDP/BCNU and ABMS as Consolidation to Adjuvant CAF for Patients With Operable Stage II or Stage III Breast Cancer Involving > 10 Axillary Lymph Nodes. (1/25/1994) | 138 |
| 1548-94 | Drabick, Joseph J., COL MC. CALGB 9395: Phase III Intergroup Study Prospectively Randomized Trial of Perioperative 5-FU After Curative Resection, Followed by 5-FU/Leucovorin for Patients with Colon Cancer. (1/25/1994) | 139 |
| 1551-94 | Drabick, Joseph J., COL MC. CALGB 8869: Laboratory Studies in Breast Cancer Tissue: A Comparison Study to CALGB 8541, 8642, 8741, 8944. (2/22/1994) | 140 |
| 1554-94 | Drabick, Joseph J., COL MC. CALGB 9391 A Randomized Study of Subtotal Nodal Irradiation vs Irradiation Plus Chemotherapy for Stages I-IIA Hodgkin Disease. (4/26/1994) | 141 |
| 1557-94 | Drabick, Joseph J., COL MC. CALGB 9344: Adjuvant High Dose Vs. Standard Dose Cyclophosphamide, Adriamycin With/Without Taxol for Node Positive Breast Cancer. (6/28/1994) | 142 |
| 1558-94 | Drabick, Joseph J., COL MC. CALGB 9394: A Phase III Comparison of Two Schedules of Cyclophosphamide and Doxorubicin for High-Risk Patients with Breast Cancer Involving 0-3 Axillary Lymph Nodes. (8/30/1994) | 143 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 1559-94 | Drabick, Joseph J., COL MC. CALGB 9351: A Phase II Study of High-Dose Chemotherapy in Previously Untreated Non-Hodgkin's Lymphoma. (9/27/1994) | 144 |
| 1560-87 | Drabick, Joseph J., COL MC. CALGB 8642: A Master Protocol to Study Single Agent Chemotherapy Vs. Standard Chemotherapy for Advanced Breast Cancer. (6/30/1987) | 145 |
| 1560-95 | Drabick, Joseph J., COL MC. CALGB 9491: An Intergroup Study of Rectal Cancer Adjuvant Therapy, Phase III. (10/25/1994) | 146 |
| 1561-95 | Drabick, Joseph J., COL MC. CALGB 9497 Health Status and Qualify of Life (QL) In Patients With Early Stage Hodgkins Disease: A Companion Study to CALGB 9391. (10/25/1994) | 147 |
| 1562-95 | Drabick, Joseph J., COL MC. CALGB 9343: Evaluation of Lumpectomy, Tamoxifen and Irradiation of the Breast Compared with Lupectomy Plus Tamoxifen in Women 70 Years of Age or Older Who Have Carcinoma of the Breast That is Less Than or Equal to 4 cm and Clinically Negative Axillary. (11/29/1994) | 148 |
| 1563-95 | Drabick, Joseph J., COL MC. CALGB 9312 Phase III Comparison of Standard Dose vs Myeloablative Therapy for Previously Untreated Symptomatic Multiple Myeloma. (12/20/1994) | 149 |
| 1564-95 | Drabick, Joseph J., COL MC. CALGB 9498 A Phase III Randomized Trial of 5-FU/Levamisole/Leucovorin vs. 5-FU/Levamisole as Adjuvant Therapy for Colon Cancer. (1/31/1995) | 150 |
| 1567-95 | Drabick, Joseph J., COL MC. CALGB 9511: A Pilot Trial With Limited Pharmacokinetic Monitoring During Remission Induction and Consolidation Chemotherapy for Adult Acute Lymphoblastic Leukemia. (8/29/1995) | 151 |
| 1569-96 | Drabick, Joseph J., COL MC. CALGB 9251: A High Intensity, Brief Duration Phase II Chemotherapy Trial In Small Non-Cleaved Lymphoma And L-3 Acute Lymphoblastic Leukemia (ALL). (11/28/1995) | 152 |
| 1570-96 | Drabick, Joseph J., COL MC. CALGB: Cancer and Leukemia Group B. (1/25/1996) | 153 |
| 1573-87 | Drabick, Joseph J., COL MC. CALGB 8762: Molecular Subtypes in Acute Lymphotic Leukemia with Philadelphia Chromosome. (10/27/1987) | 154 |
| 1573-96 | Drabick, Joseph J., COL MC. CALGB 9334, Sclerosis of Pleural Effusions by Talc Thoracoscopy Versus Talc Slurry: A Phase III Study. (4/23/1996) | 155 |
| 1574-87 | Drabick, Joseph J., COL MC. CALGB 8763: Immunoglobulin and T Cell Receptor Gene Rearrangement in Adult Acute Lymphatic Leukemia. (10/27/1987) | 156 |
| 1577-80 | Drabick, Joseph J., COL MC. CALGB 8361 - Immunologic Diagnostic Studies in AML. (12/31/1981) | 157 |
| 1579-96 | Drabick, Joseph J., COL MC. CALGB 9254 - Anti-B4-Blocked-Ricin (NSC #639185) Adjuvant Post-Autologous Bone Marrow Transplant: A Phase III Study. (5/28/1996) | 158 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 1584-96 | Drabick, Joseph J., COL MC. CALGB 9665 - The CALGB Leukemia Tissue Bank. (6/25/1996) | 159 |
| 1590-89 | Drabick, Joseph J., COL MC. CALGB 8852: A Study of CHOPE in Diffuse Lymphomas. (1/31/1989) | 160 |
| 1591-97 | Drabick, Joseph J., COL MC. CALGB 9583: A Phase III Two-Arm Randomized Study Comparing Antiandrogen Withdrawal Versus Antiandrogen Withdrawal Combined with Ketoconazole and Hydrocortisone in Patients with Advanced Prostate Cancer. (1/28/1997) | 161 |
| 1592-97 | Drabick, Joseph J., COL MC. CALGB 9484: Linkage of Molecular and Epidemioligical Breast Cancer Investigations with Treatment Data: A Specialized Registry. (2/25/1997) | 162 |
| 1594-97 | Drabick, Joseph J., COL MC. CALGB 9760: Multidrug Resistance Studies in Acute Leukemia. (6/24/1997) | 163 |
| 1595-89 | Drabick, Joseph J., COL MC. CALGB 8961: RAS Mutations in Myelodysplasia. (4/25/1989) | 164 |
| 1596-97 | Drabick, Joseph J., COL MC. CALGB 9640: A Comparison of Intensive Sequential Chemotherapy Using Doxorubicin Plus Paclitaxel Plus Cyclophosphamide with High Dose Chemotherapy and Autologous Hematopoietic Progenitor Cell Support for Primary Breast Cancer in Women with 4-9 Involved. (7/29/1997) | 165 |
| 1597-97 | Drabick, Joseph J., COL MC. CALGB 9621: Phase I Study of MDR Modulation with PSC-833 with a Pilot Study of Cytogenetic Risk-Adapted Consolidation Followed by A Phase II Pilot Study of Immunotherapy with rIL-2 in Previously Untreated Patients with AML < 60 Years. (8/26/1997) | 166 |
| 1598-89 | Drabick, Joseph J., COL MC. CALGB 8952: Combination Chemotherapy for Advanced Hodgkin's Disease, Phase III. (8/29/1989) | 167 |
| 1599-98 | Drabick, Joseph J., COL MC. CALGB 9581: Phase III Randomized Study of Adjuvant Immunotherapy with Monoclonal Antibody 17-LA Versus No Adjuvant Therapy Following Resection for Stage II (Modified Astler-Coller B2) Adenocarcinoma of the Colon. (10/28/1997) | 168 |
| 1605 | Reid, Thomas J. III, LTC MC. Hemapheresis for Collection of Platelets for in vitro Study of Platelet Cryopreservation. (6/24/1997) | 169 |
| 1608 | Moores, Lisa K., LTC MC. Acute Hypoxemic Respiratory Failure in Bone Marrow Transplant Patients: An Imbalance of the Immunomodulating Cascade?. (10/28/1997) | 170 |
| 1614-98 | McLeod, David G., COL MC. A Uniformed Services Comprehensive Database and Tissue Repository for the Study of Epidemilogical, Detection, Natural History, and New Management Strategies for Prostate Cancer. (5/26/1998) | 171 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 1689 | Schenkman, Noah S., LTC MC. SWOG 9217: Chemoprevention of Prostate Cancer with Finasteride (Porscar) versus Placebo. (11/30/1993) | 172 |
| ***Infectious Disease Service*** | | |
| 00-1901 | Aronson, Naomi E., COL MC. Development of HIV Specific CD+ T Cells. (10/26/1999) | 185 |
| 01-19002 | Aronson, Naomi E., COL MC. Sodium Stibogluconate Treatment of Leishmaniasis. (3/27/2001) | 186 |
| 01-19003 | Sun, Wellington, COL MC. Phase 2b Evaluation of Tetravalent Live-Attenuated Dengue Vaccines. (7/31/2001) | 187 |
| 01-1901 | Wortmann, Glenn W., LTC MC. A Randomized, Open-Label, Phase III, International Study of Subcutaneous Recombinant IL-2 (Proleukin) in Patients with HIV-1 Infections and CD4+ Counts >300/mm3: Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT). (10/17/2000) | 189 |
| 02-19001E | Hawkes, Clifton A., LTC MC. Anthrax Exposure Clinic: Tolerability, Compliance and Follow-up of Antibiotic Prophylaxis Regimens. (1/23/2002) | Exempt |
| 02-19002E | Fukuda, Mark M., MAJ MC. Specificity of a Rapid Quantitative Real-Time PCR Diagnostic Assay plasmodium falciparum and vivax Malaria from Human Blood. (5/16/2002) | Exempt |
| 02-19004 | Tasker, Sybil A., CDR MC. In Vitro Immunogenicity Assessment of HIV Vaccine Candidates. (4/9/2002) | New |
| 02-19005 | Straight, Timothy M., CPT MC. Validation of a Diagnostic Algorithm for the Evaluation of Nosocomial Febrile Illness. (8/6/2002) | New |
| 1903-98 | Aronson, Naomi E., COL MC. Development of New Leishmania Diagnostic and Progostic Indicator. (5/26/1998) | 190 |
| 1905-98 | Aronson, Naomi E., COL MC. Evaluation of the Clinical Efficacy of Antiretroviral Resistance Testing (CERT). (7/7/1998) | 191 |
| 1906-98 | Wortmann, Glenn W., LTC MC. Preveon (adefovir dipivoxil) Expanded Access Program: Protocol GS-97-423. (7/7/1998) | 192 |
| 1909-99 | Nicholson, Diarmuid, Ph.D. DAC. Analytical Analysis of Recombinant Malaria Proteins. (5/18/1999) | 193 |
| 1976 | Aronson, Naomi E., COL MC. Cytokine Expression in Leishmaniasis Patients Treated with Sodium Stibogluconate (Pentostam) Therapy. (11/30/1993) | 194 |
| 1978 | Aronson, Naomi E., COL MC. Treatment of Leishmaniasis with Sodium Stibogluconate (Pentostam). (6/28/1994) | 195 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 1980 | Oster, Charles, COL MC. Pilot Investigation of Selected Desert Storm Veterans. (3/14/1995) | 196 |
| 1984 | Aronson, Naomi E., COL MC. The Long Term Efficacy of BCG Vaccine: a 56 Year Follow Up. (12/5/1995) | 197 |
| 1990 | Aronson, Naomi E., COL MC. Sodium Stibogluconate (Pentostam) Pharmacokinetics Protocol. (6/11/1996) | 198 |
| 1994 | Engel, Charles C., LTC MC. Electrocortical Underpinnings of Dissociation. (10/29/1996) | 199 |
| 1997 | Engel, Charles C., LTC MC. Testing for Mycoplasmal Infection: Criterion Validity and Replicbility of Nucleoprotein Gene Tracking and Forensic Polymerase Chain Reaction Tests. (10/28/1997) | 200 |
| 8836 | Aronson, Naomi E., COL MC. A Phase I Dose Escalation Study of Polyclonal CD4 T Cell EX Vivo Expansion for Immune System Restoration of HIV Infection. (9/30/1997) | 605 |
| 8837 | Aronson, Naomi E., COL MC. Molecular Epidemiology of HIV-1 in Military Populations. (9/30/1997) | 606 |
| 8838-98 | Hawkes, Clifton A., LTC MC. A Triservice Study of Human Immunodeficiency Virus Disease in United States Military Beneficiaries. (3/31/1998) | 607 |
| 8839-99 | Aronson, Naomi E., COL MC. A Phase I/II Study of the Safety, Survival, and Trafficking of Autologous CD4-zeta Gene-Modified T Cells With and Without Exogenous IL-2 in HIV Infected. (1/19/1999) | 608 |
| ***Nephrology Service*** | | |
| 00-1101 | Yuan, Christina M., LTC MC. The Effect of Enalapril and Mycophenolate Mofetil in PAN-Induced FSGS in the Rat. (11/2/1999) | 11 |
| 00-1102 | Yuan, Christina M., LTC MC. Tacrolimus and Distal Renal Tubular Acidosis in the Rat. (5/2/2000) | 12 |
| 00-1103 | Oliver, James D. III, LTC MC. Measurement of Electrolytes in Microdialysis Samples by Mass Spectometry. (8/1/2000) | 13 |
| 01-11002 | Yuan, Christina M., LTC MC. Electron Beam Computed Tomography as a Screening Tool in the Pre-Renal Transplant Assessment of Patients with End Stage Renal Disease. (1/16/2001) | 14 |
| 01-1101 | Welch, Paul G., LTC MC. Epidemiology of Military Beneficiaries Receiving End-Stage Renal Disease (ESRD) Therapy. (11/7/2000) | 15 |
| 02-11003 | Yuan, Christina M., LTC MC. Does the Combination of Pirfenidone, Enalapril, and Lovastatin Reduce Proteinuria and Glomerular/Interstitial Histologic Score in Rats with PAN-Induced FSGS and Existing Nephrotic Syndrome?. (11/13/2001) | New |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-11004 | Yuan, Christina M., LTC MC. The Effects of Ovarian Steroids on the Responsiveness of Mouse Renal Medullary Cells to Vasopressin. (11/13/2001) | New |
| 02-11005 | Yuan, Christina M., LTC MC. Is Delayed Gastric Motility Associated with Impaired Absorption of Tacrolimus in Diabetic Organ Transplant Recipients?. (1/29/2002) | New |
| 02-11013E | Trespalacios, Fernando, MAJ MC. Outcomes With Use of ACE Inhibitors in Dialysis Patients. (12/19/2001) | Exempt |
| 02-11014E | Maxwell, James, CPT MC. Post Kidney Transplant Humoral Rejection: A Retrospective Study of Presenting Features and Response to IVIG. (5/3/2002) | Exempt |
| 1186 | Abbott, Kevin C., LTC MC. The Clinical Efficacy of Transjugular Renal Biopsy--A Pilot Study. (5/6/1997) | 16 |
| 1194-98 | Oliver, James D. III, LTC MC. Improving Rates of Acute Renal Allograft Rejection with a Regimen of Cyclospsorin, Mycophenolate Mofetial and Prednisone. (5/29/1998) | 17 |
| 1196-99 | Stiles, Kevin, CPT MC. Is HSP47 Expression Upregulated in PAN-Induced FSGS in the Rat, and Does Pirfenidone Affect This Upregulation?. (10/13/1998) | 18 |
| 1197-99 | Yuan, Christina M., LTC MC. The Impact of Therapeutic Plasma Exchange on the Medications Used in Transplantion. (1/19/1999) | 19 |
| 1198-99 | Yuan, Christina M., LTC MC. Na+,K+-ATPase Inhibitor in the Mechanism of Hypertension in Diabetes Mellitus. (1/19/1999) | 20 |
| 1199-99 | Oliver, James D. III, LTC MC. Patterns of Protein Size-and Charge-Selectivity in Clinical Kidney Disease. (1/26/1999) | 21 |
| ***Pulmonary & Critical Care Medicine Service*** | | |
| 00-1701 | Kristo, David A., LTC MC. Does Use of a Temporary Silencer Adjustable Airway Dilator Predict Outcome Using Permanent Silencer Adjustable Airway Dilator in Treatment of Obstructive Sleep Apnea?. (3/28/2000) | 173 |
| 00-1702 | Kristo, David A., LTC MC. A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of 12 Weeks of 2 Oral Doses (200 mg and 400 mg Once Daily) of PROVIGIL (Modafinil) as Treatment for Adults with Excessive Day. (3/28/2000) | 175 |
| 01-17003 | Kristo, David A., LTC MC. Quality Management in Sleep Medicine via Telemedicine: Overseas Online Transfer of Polysomnograms via Internet File Transfer Protocol from Landstuhl Germany Army Medical Center to Walter Reed Army Medical Center. (5/15/2001) | 177 |
| 01-17004 | Taylor, Yvonne, DAC. A Comparison Between an Internet Communications Platform and Traditional Medical Care as a Health Care Management Model in Patients with Obstructive Sleep Apnea. (6/19/2001) | 178 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 01-17005 | Wink, Jennifer, CPT MC. Comparison of F-18 FDG Coincidence PET with Tc-99m Depreotide in the Evaluation of Pulmonary Lesions. (6/26/2001) | 179 |
| 01-17006 | Guerrero, Melaine L., CPT MC. Delivery of High Concentrations of Inspired Oxygen Using Humidified Oxygen by Nasal Cannula (Vapotherm). (7/31/2001) | 180 |
| 01-17007 | Moores, Lisa K., LTC MC. A Phase IV, Multicenter, Prospective, Open-Label, Observational Study to Evaluate Clinical Practice Patterns of Innohep (Tinzaparin odium Injection) in the Treatment of Acute Symptomatic Deep Venous Thrombosis. (8/31/2001) | 181 |
| 01-1701 | Hnatiuk, Oleh, LTC MC. Reference Values for Impulse Oscillometry in Normal Adults. (11/21/2000) | 182 |
| 02-17008 | Shorr, Andrew F., MAJ MC. Tc-99m Depreotide Scanning in Sarcoidosis. (10/23/2001) | New |
| 02-17009 | Helman, Donald, CPT MC. Patterns of Oropharyngeal Bacterial Colonization after Hospitalization. (4/23/2002) | New |
| 02-17010 | Kristo, David A., LTC MC. Comparison of Efficacy and Safety of Zolpidem-MR 12.5 mg and Placebo in Patients with Primary Insomnia. A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study. (4/23/2002) | New |
| 02-17011 | Parker, Joseph M., LTC MC. Vocal Cord Dysfunction and Hyperventilation: Do They Coexist?. (5/28/2002) | New |
| 02-17012 | Johnson, Scott J., MAJ MC. Perioperative Beta-Blockade in Patients with Chronic Obstructive Pulmonary Disease. (7/16/2002) | New |
| 02-17013 | Hnatiuk, Oleh, LTC MC. Reference Values for Impulse Oscillometry in Normal Adults. (7/16/2002) | New |
| 02-17014 | Greenberg, Bruce A., CPT MC. Pulmonary Aspiration of Enteral Feeding in Critically Ill Patients: Incidence, Clinical Significance, and Usefulness of Bedside Diagnostic Testing. (9/17/2002) | New |
| 02-17015E | Shorr, Andrew F., MAJ MC. Acute Respiratory Distress Syndrome (ARDS) Following Renal Transplantation: Incidence, Risk Factors,. (2/15/2002) | Exempt |
| 02-17016E | Moores, Lisa K., LTC MC. Retrospective Validation of Clinical Prediction Scores for Diagnosing Pulmonary Embolism. (3/5/2002) | Exempt |
| 02-17016EX | Parker, Joseph M., LTC MC. Clinical Characteristics of Patients with Vocal Chord Dysfunction at WRAMC and TAMC. (3/4/2002) | Exempt |
| 02-17017E | Humphreys, Christopher W., CPT MC. Inter-observer Variability in Scoring Systems for Pre-test Probability for Pulmonary Embolism. (3/20/2002) | Exempt |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-17018E | Lepler, Lawrence S., LTC MC. Computed Tomography vs. Plain Chest Radiography as a Screening Tool for Bronchogenic Carcinoma -- A Pilot Study to Assess Recruitment. (4/24/2002) | Exempt |
| 02-17019E | Eliasson, Arn, COL MC. Treatment of Air Hunger at End-of-Life. (4/24/2002) | Exempt |
| 02-17020E | Humphreys, Christopher W., CPT MC. Cost-Minimization Analysis of Two Algorithms for Diagnosing Acute Pulmonary Embolism. (9/16/2002) | Exempt |
| 02-17021E | Greenberg, Bruce A., CPT MC. Thalidomide Induced Acute Renal Failure: A Case Report and Review of the Literature. (9/25/2002) | Exempt |
| 1790 | Moores, Lisa K., LTC MC. Acute Hypoxemic Respiratory Failure in Bone Marrow Transplant Patients. A Retrospective Review. (4/25/1997) | 183 |
| ***Rheumatology Service*** | | |
| 00-3701 | Poitras, Jeanne M., CPT MC. Early Signaling Events in Lupus B Cells. (2/15/2000) | 396 |
| 00-3702 | Dennis, Gregory J., COL MC. Aberrant T Cell Receptors in Systemic Lupus Erythematosus. (3/7/2000) | 397 |
| 01-37001 | Roebuck, Jonathan, MAJ MC. Visconsupplementation in the Treatment of Chondromalacia Patellae. (2/20/2001) | 398 |
| 02-37002 | Mitchell, Jeanne P., MAJ MC. B Cell Signaling in Human Systemic Lupus Erythematosus (SLE). (6/11/2002) | New |
| 3724 | Dennis, Gregory J., COL MC. Immunogenetic Factors During the Clinical Evolution of Systemic Lupus Erythematosus. (7/30/1997) | 399 |
| 3726-98 | Mitchell, Jeanne P., MAJ MC. Prevalence and Impact of Cyclical Mastalgia in Rheumatology Clinic Patients. (3/10/1998) | 400 |
| 3727-98 | Tsokos, George C., COL MC. Lymphocyte Signaling Defects in Patients with Lupus. (7/21/1998) | 401 |
| 3729-99 | Downs, Walter, LCDR MC. The Clinical Efficacy and Tolerability of Moderate Dose Oral Compared to Subcutaneous Methotrexate in Rheumatoid Arthritis: A Prospective Crossover Trial. (2/16/1999) | 402 |
| ***Department of Neurology*** | | |
| 00-7102 | Warden, Deborah L., M.D. DAC. A Randomized Placebo-Controlled Trial of Setraline for Neurobehavioral Sequelae of Traumatic Brain Injury. (3/21/2000) | 531 |
| 00-7104 | Choi, John Y., MAJ MC. A Study of the Use of Telemedicine/Teleradiology in the Initial Management of Acute Stroke. (8/22/2000) | 533 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 00-7105 | Sartori, Roberto, MAJ MC. Effectiveness of Botulinum Toxin Type-A in the Treatment of Migraine Headache: A Randomized Controlled Trial. (9/26/2000) | 536 |
| 00-7106 | Sartori, Roberto, MAJ MC. Effectiveness of Botulinum Toxin Type-A in the Treatment of Tension-type Headache: A Randomized Controlled Trial. (9/26/2000) | 537 |
| 01-71001 | Russo, Michael B., LTC MC. Assessing States of Unconsciousness by Actigraphy. (3/20/2001) | 538 |
| 01-71002 | Cannard, Kevin, LTC MC. Investigation of the Administration of Baclofen Injection for the Management of Spasticity Associated with Stroke, Medtronic Protocol #D98-072. (3/27/2001) | 539 |
| 01-71003 | Jabbari, Bahman, COL MC. Genes for X-linked Torsion Dystonia-Parkinsonism in the U.S. Veterans of Panay Filipinos. (5/15/2001) | 540 |
| 02-71004 | Cannard, Kevin, LTC MC. Evaluation of the Analgesic Effects of Botulinum Toxin A in Post-Operative Pain and Recovery After Lumbar Spine Surgery. (11/20/2001) | New |
| 02-71004E | Choi, Jong-Ho R., MAJ MC. Feasibility Study of Wireless Teleradiology in Acute Brain and Cervical Spine Injury. (3/19/2002) | Exempt |
| 02-71005 | Cannard, Kevin, LTC MC. Assessment of the Efficacy of Botulinum Toxin A for Treatment of Chronic Neck and Back Pain Secondary to Trauma or Acute Strain. (11/29/2001) | New |
| 02-71006 | Ney, John P., CPT MC. Assessment of Long-Term Efficacy of Paravertebral Muscle Treatment with Botulinum Toxin A (BOTOX) for Chronic Low Back Pain. (2/12/2002) | New |
| 02-71007 | Choi, John Y., MAJ MC. A Pilot Study Using Actigraphy to Assess Functional Severity and Recovery of Motor Limbs in Acute Brain Injury. (4/9/2002) | New |
| 02-71008 | Campbell, William, LTC MC. Modafinil in the Treatment of Fatigue in Post-Polio Syndrome. (6/25/2002) | New |
| 02-71009 | Warden, Deborah L., M.D. DAC. A Randomized Placebo-Controlled Trial of Sertraline for Chronic Neurobehavioral Sequelae of Traumatic Brain Injury. (6/25/2002) | New |
| 02-71010 | Warden, Deborah L., M.D. DAC. Telemedicine Assessment of Neurobehavioral Consequences of Traumatic Brain Injury. (7/30/2002) | New |
| 02-71011 | Warden, Deborah L., M.D. DAC. Enhanced Head Protection for Paratrooppers: Efficacy of Countermeasures Against Traumatic Brain Injuries Sustained in Airborne Operations. (9/3/2002) | New |
| 02-71012 | Urban, Edward, M.D. DAC. A Study of the Use of Telemedicine/Teleradiology Consultation in Acute Stroke, Part II. (9/3/2002) | New |
| 7154 | Warden, Deborah L., M.D. DAC. Defense and Veterans Head Injury Program (DVHIP): WRAMC Core Evaluation Protocol. (8/31/1993) | 542 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 7161 | Jabbari, Bahman, COL MC. Proton Magnetic Resonance Spectroscopic Imaging in Patients with Movement Disorders. (4/25/1995) | 543 |
| 7162 | Labutta, Robert, COL MC. An Open Label Study of Interferon Beta-1a (Recombinant Human Interferon Beta) in Subjects with Multiple Sclerosis (Biogen Protocol Number, C94-801-P, Version 4). (4/25/1995) | 544 |
| 7174-98 | Warden, Deborah L., M.D. DAC. Markers of Possible Vulnerability to Symptoms Following Traumatic Brain Injury. (8/4/1998) | 546 |
| 7176-99 | Marini, Ann M., M.D. DoD. The Neuroprotective Effect of Non-NMDA Receptors in Cultured Rat Cerebellar Granule Cells from Sprague-Dawley Rat Pups. (11/17/1998) | 547 |
| ***Department of Nursing*** | | |
| 00-7502 | Combs, Elmer W., LTC AN. A Prospective Study of Stress in Army Reservists. (5/16/2000) | 560 |
| 00-7503 | Brosch, Laura R., LTC AN. Ethical Issues in Department of the Army Nursing Practice. (7/11/2000) | 561 |
| 01-75002 | Murdock, Peter H., CPT AN. Army Nurse Readiness. (1/2/2001) | 562 |
| 01-75003 | Spencer, Debra, MAJ AN. Improving Adherence in a Coronary Disease Reversal Program with Web-Based Technology. (2/20/2001) | 563 |
| 01-75004 | Patrician, Patricia A., LTC AN. Job Satisfaction Among Army Nurses. (7/10/2001) | 565 |
| 01-75005 | Patrician, Patricia A., LTC AN. Medication Error Reporting and the Work Environment in a Military Setting. (7/10/2001) | 567 |
| 01-75006 | Brosch, Laura R., LTC AN. Research Utilization of Registered Nurses in U.S. Army Hospitals. (7/20/2001) | 568 |
| 01-75007 | Patrician, Patricia A., LTC AN. Army Hospitals: Work Environment, Quality of Care and Intent to Leave. (7/10/2001) | 570 |
| 01-75008 | Patrician, Patricia A., LTC AN. Examining the Weight Management and Exercise Behaviors Among Active Duty Nursing Personnel in Maintaining Compliance with the Army's Weight Control Standards. (7/17/2001) | 571 |
| 01-75009 | Brosch, Laura R., LTC AN. Patient Handling Study. (8/7/2001) | 573 |
| 01-7501 | Saunders, Kenneth, CPT AN. A Comparison of Three Different Laryngeal Mask Airway Cuff Pressures on the Incidence and Severity of Post-Operative Sore Throat. (10/24/2000) | 574 |
| 01-75010 | Brown, Carlton G., CPT AN. Increasing Testicular Self-Examination in AD Soldiers: An Intervention Study. (9/14/2001) | 576 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-75011 | Mitzak, Anne, CPT AN. Intravenous Site Selection and Its' Role in Reducing Propofol Injection Pain. (1/15/2002) | New |
| 02-75012 | Brosch, Laura R., LTC AN. The Relationship of Job Stress to Job Satisfaction and the Intent of Army Nurse Corps Officers to Stay in Active Military Service. (2/5/2002) | New |
| 02-75013 | Patrician, Patricia A., LTC AN. Providers' Evaluation of Alternative Medications Use by Patients. (2/19/2002) | New |
| 02-75013E | Agazio, Janice, RN DoD. Military Nurses' Perceptions of Autonomy in Fixed versus Deployed Facilities: Implications for Readiness. (1/31/2002) | Exempt |
| 02-75014 | Nussbaum, George F., COL AN. Do Culturally Acquired Behavior Norms Impact Workplace Communication?. (3/5/2002) | New |
| 02-75014E | Brown, Carlton G., CPT AN. Implementation of A Stomatitis Assessment Tool for Blood and Marrow Stem Cell Transplantation Patients: A Research Utilization Project. (4/4/2002) | Exempt |
| 02-75015 | Patrician, Patricia A., LTC AN. A Study of the Safety and Feasibility of Telenursing for Remote Cardiac Rehabilitation. (5/14/2002) | New |
| 02-75015E | Agazio, Janice, RN DoD. Active Duty Women's Health Behaviors. (7/8/2002) | Exempt |
| 02-75016 | Agazio, Janice, RN DoD. Army Nursing Practice in Operations Other Than War. (7/9/2002) | New |
| 02-75016E | Agazio, Janice, RN DoD. Referral Patterns for Recurrent Acute Low Back Strain. (7/30/2002) | Exempt |
| 02-75017 | Combs, Elmer W., LTC AN. The Role of Mentoring in the Career Advancement of Hispanic Army Nurses. (8/20/2002) | New |
| 02-75017E | Usher, Staci E., CPT AN. The Effects of Pregnancy on the Army Physical Fitness Test. (9/16/2002) | Exempt |
| 02-75018 | Combs, Elmer W., LTC AN. Musculoskeletal Injury in AMEDD Soliders. (9/10/2002) | New |
| 02-75019 | Peverini, Anthony, CPT AN. Gender Differences in Propofol Dosage During Regional Anesthesia. (9/24/2002) | New |
| 7576-99 | Brosch, Laura R., LTC AN. E-mail as a Communication Tool in Army Nursing Management. (2/9/1999) | 578 |
| 7577-99 | Agnew, Jacqueline, COL AN. Development of a Reserve Specific Stress Inventory. (2/9/1999) | 580 |
| 7578-99 | Brosch, Laura R., LTC AN. Development and Evaluation of the Military Nursing Moral Distress Scale. (7/27/1999) | 582 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 7579-99 | Patrician, Patricia A., LTC AN. Nurses Influence on Patient Outcomes in US Army Hospitals. (7/27/1999) | 584 |

***Department of Obstetrics and Gynecology***

| | | |
|---|---|---|
| 00-4301 | Rose, G. Scott, LTC MC. GOG 178: Phase III Randomized Trial of 12 Months vs 3 Months of Paclitaxel in Patients with Advanced Ovarian, Fallopian Tube or Primary Peritoneal Cancer Who Attain a Clinically Defined Complete Response (CR) Following Platinum/Paclitaxel-Based Chemothe. (7/25/2000) | 403 |
| 00-4302 | Rose, G. Scott, LTC MC. GOG # 9901: Comparison of Quality of Life for Ovarian Germ Cell Cancer Survivors. (8/15/2000) | 404 |
| 00-4303 | Rose, G. Scott, LTC MC. GOG 175: A Randomized Phase III Trial of IV Carboplatin (AUC 6) and Paclitaxel 175 mg/m2 Q 21 Days x 3 Courses Plus Low Dose Paclitaxel 40 mg/m2/wk vs IV Carboplatin (AUC 6) and Paclitaxel 175 mg/m2 Q 21 Days X 3 Courses Plus Observation in Patients with Early Ovarian Carcinoma. (8/15/2000) | 405 |
| 00-4305 | Rose, G. Scott, LTC MC. GOG 171: Expression of the MN Protein in Atypical Glandular Cells of Undetermined Significance (AGUS or AGCUS) as a Protentional Diagnositic Biomarkers of Cervical Dysplasia/Neoplasia. (9/26/2000) | 406 |
| 00-4403 | Allard, Jay, LT MC. A Trial of Vitamin B Complex for the Treatment of Chemotherapy Induced Peripheral Neuropathy. (4/18/2000) | 407 |
| 00-4404 | Bush, Mark R., MAJ MC. The Creation of a Blood and Tissue Bank and the Collection of Clinical Data From Patients Undergoing In Vitro Fertilization. (6/27/2000) | 408 |
| 00-4405 | McKeeby, Jeff, CDR MC. A Prospective, Randomized, Double-Blind, Placebo Controlled Study of Oral Misoprostol Prior to Operative Hysteroscopy. (6/27/2000) | 409 |
| 00-4406 | McBroom, John W., MAJ MC. Characterization of Peritoneal Fluid in Differentiating Benign from Malignant Adnexal Masses. (7/5/2000) | 411 |
| 01-43002 | Rose, G. Scott, LTC MC. GOG 0179: A Randomized Phase III Study of Cisplatin vs. Cisplatin Plus Topotecan vs. MVAC in Stage IVB, Recurrent or Persistent Carcinoma of the Cervix. (4/17/2001) | 412 |
| 01-43003 | Maxwell, G. Larry, MAJ MC. GOG 0184: A Randomized Phase III Study of Tumor Volume Directed Pelvic Plus or Minus Para-Aortic Irradiation Followed by Cisplatin and Doxorubicin or Cisplatin, Doxorubicin and Paclitaxel for Advanced Endometrial Carcinoma. (4/24/2001) | 413 |
| 01-43004 | Rose, G. Scott, LTC MC. GOG 0182: A Phase III Randomized Trial of Paclitaxel and Carpoplatin Versus Triplet or Sequential Doublet Combinations in Patients with Epithelial Ovarian or Primary Peritoneal Carcinoma. (5/15/2001) | 414 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 01-43005 | Maxwell, G. Larry, MAJ MC. GOG 0189 - Randomized Phase III Crossover Trial of Chemotherapy (Doxorubicin/Cisplatin/Paclitaxel and G-CSF) VS Hormonal Therapy (Tamoxifen/Megestrol Acetate) in Patients with Stage III & IV or Recurrent Endometrial Cancer. (5/15/2001) | 415 |
| 01-4301 | Maxwell, G. Larry, MAJ MC. ACRIN 6651: Role of Radiology in the Pretreatment Evaluation of Invasive Cervical Cancer. (11/21/2000) | 416 |
| 01-44002 | Carlson, Nicole, LT MC. The Comparison of the Effectiveness of Burch Colposuspension Versus Suburethral Sling in the Management of Primary Genuine Stress Urinary Incontinence. (1/9/2001) | 417 |
| 01-44003 | Rose, G. Scott, LTC MC. Fragile Histidine Triad (FHIT) Expression in Advanced Cervical Carcinoma. (1/9/2001) | 418 |
| 01-44004 | Carlson, Nicole, LT MC. Creation of a Tissue Library for the Study of Molecular Alterations Characteristic of Uterine Leiomyomata. (2/20/2001) | 419 |
| 01-44005 | Parker, Mary F., LTC MC. An Observational Trial to Evaluate Tissue and Peripheral Immune Response to HPV 16-Induced Cervical Intraepithelial Neoplasia. (6/19/2001) | 420 |
| 01-4401 | Maxwell, G. Larry, MAJ MC. Creation of a Tissue Library for the Study of Molecular Carcinogenesis in Gynecologic Malignancies. (11/21/2000) | 421 |
| 02-43006 | Rose, G. Scott, LTC MC. GOG O174: A Randomized Phase III Trial of Weekly Parenteral Methotrexate Versus "Pulsed" Dactinomycin as Primary Management for Low Risk Gestational Trophoblastic Neoplasia. (10/23/2001) | New |
| 02-43007 | Rose, G. Scott, LTC MC. GOG 0194: A Phase III Study of Adjuvant Postoperative Irradiation With or Without Cisplatin/Taxol Chemotherapy Following TAH/BSO for Patients with Endometrial Cancer. (11/20/2001) | New |
| 02-43008 | Rose, G. Scott, LTC MC. GOG 176: A Phase II Trial of Pulse Actinomycin-D as Salvage Therapy for Failed Low Risk Gestational Trophoblastic Neoplasia. (1/29/2002) | New |
| 02-43009 | Rose, G. Scott, LTC MC. GOG #0185: A Phase III Randomized Study of Adjuvant Radiation Treatment Versus Radiation and Chemotherapy in Patients with Vulvar Cancer and Involved Nodes. (1/29/2002) | New |
| 02-43010 | Rose, G. Scott, LTC MC. GOG 9910: Vaccine Therapy with Tumor Specific p53 Peptides in Adult Patients with Low Burden Adenocarcinoma of the Ovary. (2/12/2002) | New |
| 02-43011 | Rose, G. Scott, LTC MC. GOG 0146M: A Phase II Evaluation of Tirapazamine (NSC #130181, IND, 45,525) in Combination with Cisplatin in the Treatment of Recurrent Platinum Sensitive Ovarian or Primary Peritoneal Cancer. (5/28/2002) | New |
| 02-43012 | Rose, G. Scott, LTC MC. GOG #0170-C: A Phase II Trial of ZD1839 (IRESSA TM) (NSC #715055, IND #61187) in the Treatment of Persistent or Recurrent Epithelial Ovarian or Primary Peritoneal Carcinoma. (7/30/2002) | New |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-44006 | Maxwell, G. Larry, MAJ MC. The Chemoprotective Effects of Progestin on the Endometrial Lining. (11/29/2001) | New |
| 02-44007 | Buller, Jerome L., MAJ MC. RF BIO - An Injectable Microstimulator for the Treatment of Refractory Urge Urinary Incontinence in Women. (1/29/2002) | New |
| 02-44008 | Maxwell, G. Larry, MAJ MC. Early Detection of Gynecologic Cancer Using the Protomics Based SELDI-TOF Method and a Heuristic Algorithm of Data Analysis. (5/28/2002) | New |
| 02-44019E | Lockrow, Ernest G., LTC MC. Laparoscopic Appendectomy Using the Laparoscopic Coagulating Shears. (2/15/2002) | Exempt |
| 02-44020E | Elkas, John Christopher, LCDR MC. The Use of Telemedicine in Gynecology Oncology. (6/3/2002) | Exempt |
| 02-44021E | Parker, Mary F., LTC MC. Impediments to Compliance with Scheduled Colposcopy Appointments. (6/3/2002) | Exempt |
| 02-44022E | Elkas, John Christopher, LCDR MC. Survival of Patients with Gynecologic Malignancies Treated Within the Military Health Care System. (6/4/2002) | Exempt |
| 02-44Ad-Ap | Sullivan, Anthony, CPT MC. Determining 24 Hour Gentamicin Dosage in Post Partum Patients with Endometritis. (2/6/2002) | Admin |
| 02-44Ad-Ap | Sullivan, Anthony, CPT MC. Absorption Kinetics of Rectally Administered Misoprostol in Post Partum Patients. (2/6/2002) | Admin |
| 4113 | Rose, G. Scott, LTC MC. GOG: Cooperative Gynecologic Oncology Group. (1/31/1974) | 422 |
| 4229 | Rose, G. Scott, LTC MC. GOG 86A: Master Protocol for Phase II Drug Studies in Treatment of Advanced or Recurrent Carcinoma of the Endometrium. (4/29/1986) | 423 |
| 4231 | Rose, G. Scott, LTC MC. GOG 87A: Master Protocol for Phase II Drug Studies in the Treatment of Recurrent or Advanced Uterine Sarcomas. (5/27/1986) | 424 |
| 4244 | Maxwell, G. Larry, MAJ MC. GOG 90: Evaluation of Cisplatin, Etoposide and Bleomycin (BEP) Induction Followed by Vincristine, Dactinomycin and Cyclophosphamide (VAC) Consolidation in Advanced Ovarian Germ Cell Tumors, Phase II. (3/31/1987) | 425 |
| 4247 | Maxwell, G. Larry, MAJ MC. GOG 95: Randomized Clinical Trial for the Treatment of Women with Selected Stage IC and II (A,B,C) and Selected Stage IAi and IBi and IAii and IBii Ovarian Cancer, Phase III. (5/26/1987) | 426 |
| 4254 | Maxwell, G. Larry, MAJ MC. GOG 93: Evaluation of Intraperitoneal Chromic Phosphate Suspension Therapy Following Negative Second-Look Laparotomy for Epithelial Ovarian Carcinoma, Stage III, Phase III. (7/28/1987) | 427 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 4255 | Maxwell, G. Larry, MAJ MC. GOG 78: Evaluation of Adjuvant Vinblastine, Bleomycin and Cisplatin Therapy in Totally Reducing Choriocarcinoma, Endodermal Sinus Tumor or Embryonal Carcinoma of the Ovary, Pure and Mixed with Other Elements, Phase II. (9/29/1987) | 428 |
| 4257 | Maxwell, G. Larry, MAJ MC. GOG 99: A Phase III Randomized Study of Adjunctive Radiation Therapy in Intermediate Risk Endometrial Adenocarcinoma. (10/27/1987) | 429 |
| 4266 | Rose, G. Scott, LTC MC. GOG 76A: Master Protocol for Phase II Drug Studies in the Treatment of Advanced or Recurrent Squamous Cell Carcinoma of the Cervix.. (7/26/1988) | 430 |
| 4274 | Rose, G. Scott, LTC MC. GOG 104: Intraperitoneal Cisplatinum/Intravenous Cyclophosphamide Vs. Intravenous Cisplatinum/Intravenous Cyclophosphamide in Patients with Nonmeasurable Disease Stage III Ovarian Cancer, Phase III. (1/31/1989) | 431 |
| 4277 | Rose, G. Scott, LTC MC. GOG 108: Ifosfamide and the Uroprotector, Mesna, with or without Cisplatin in Patients with Advanced or Recurrent Mixed Mesodermal Tumors of the Uterus, Phase III. (5/23/1989) | 432 |
| 4281 | Rose, G. Scott, LTC MC. GOG 8801 A Phase I Evaluation of Multiple Daily Fraction Radiation and Hydroxyurea in Patients with Stage IIB, III and IVA Carcinoma of the Cervix with Negative Para-aortic Nodes. (1/30/1990) | 433 |
| 4282 | Rose, G. Scott, LTC MC. GOG 8901 A Phase I Evaluation of Multiple Daily Fraction Radiation and 5FU Plus Cisplatin in Stage IIB, III and IVA Carcinoma of the Cervix with Negative Para-aortic Nodes. (1/30/1990) | 434 |
| 4309 | Maxwell, G. Larry, MAJ MC. GOG 120: A Randomized Comparison of Hydroxyurea vs. Hydroxyurea, 5-FU Infusion and Cisplatin vs. Weekly Cisplatin as Adjunct to Radiation Therapy in Patients with Stages II-B, III, or IV-A Carcinoma of the Cervix and Negative Para-Aortic Nodes. (6/30/1992) | 435 |
| 4310 | Rose, G. Scott, LTC MC. GOG: 136 Acquisition of Human Ovarian and Other Tissue Specimens and Serum to be Used in Studying the Causes, Diagnosis, Prevention and Treatment of Cancer. (8/25/1992) | 436 |
| 4311 | Maxwell, G. Larry, MAJ MC. GOG 134: A Phase III Trial of Taxol at Three Dose Levels and G-CSF at Two Dose Levels in Platinum-Resistant Ovarian Carcinoma. (9/29/1992) | 437 |
| 4312 | Rose, G. Scott, LTC MC. GOG 122 Whole Abdominal Radiotherapy versus Combination Doxorubicin-Cisplatin Chemotherapy in Advanced Endometrial Carcinoma. (10/27/1992) | 438 |
| 4319 | Maxwell, G. Larry, MAJ MC. GOG 118: Evaluation of the Predicted Value of Antineoplastic Drug Resistance Determined by In Vitro Assay. (11/30/1993) | 439 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 4320 | Maxwell, G. Larry, MAJ MC. GOG 140: An Assessment of Age and Other Factors Influencing Protocol Versus Alternative Treatments for Patients with Epithelial Ovarian Cancer Referred to Gynecologic Oncology Group Institutions. (11/30/1993) | 440 |
| 4323 | Maxwell, G. Larry, MAJ MC. GOG 26LL A Phase II Trial of Prolonged Oral Etoposide (VP-16) in Patients with Advanced Pelvic Malignancies. (12/21/1993) | 441 |
| 4324 | Maxwell, G. Larry, MAJ MC. GOG 109 A Randomized Comparison of 5-FU Infusion and Bolus Cisplatin As An Adjunct to Radiation Therapy Alone in Selected Patients with Stages 1-A2, 1-B and II-A Carcinoma of the Cervix Following Radical Hysterectomy and Node Dissection Phase III Inter. (12/21/1993) | 442 |
| 4325 | Maxwell, G. Larry, MAJ MC. GOG 123 A Randomized Comparison of Radiation Therapy and Adjuvant Hysterectomy Versus Radiation Therapy and Weekly Cisplatin and Adjuvant Hysterectomy in Patients with Bulky Stage 1B Carcinoma of the Cervix (Phase III). (12/21/1993) | 443 |
| 4329 | Maxwell, G. Larry, MAJ MC. GOG 149 A Randomized Study of Cisplatin Plus Ifosfamide and Mesna Versus Cisplatin, Bleomycin, Ifosfamide and Mesna in Stage IV-B, Recurrent or Persistent Squamous Cell Carcinoma of the Cervix. (1/25/1994) | 444 |
| 4333 | Rose, G. Scott, LTC MC. GOG 150: A Phase III Randomized Study of Accelerated Hyperfractionated Whole Abdominal Radiotherapy (AHWAR) Versus Combination Ifosfamide-Mesna with Cisplatin in Optimally Debulked Stage I, II, III or IV Carcinosarcoma (CS) of the Uterus. (1/25/1994) | 445 |
| 4339 | Maxwell, G. Larry, MAJ MC. GOG 152 A Phase II Randomized Study of Cisplatin (NSC #119875) and Taxol (Paclitaxel) (NSC #12973) with Interval Secondary Cytoreduction Versus Cisplatin and Paclitaxel in Patients with Suboptimal Stage III & IV Epithelial Ovarian Carcinoma. (5/31/1994) | 446 |
| 4365 | Maxwell, G. Larry, MAJ MC. GOG 157: A Randomized Phase III Trial Of Carboplatin (AUC 7.5) And Paclitaxel 175 mg/m2 q 21 Days X 3 Courses Versus The Same Regimen X 6 Courses, In Patients With Selected Stage IV and II (A,B,C) And Selected IA And IB Ovarian Cancer. (3/28/1995) | 447 |
| 4366 | Maxwell, G. Larry, MAJ MC. GOG 9404: p53 Mutation and c-erbB-2 Expression in Advanced Stage Epithelial Ovarian Carcinoma and Correlation with Prognostic Factors and Treatment Outcome. (4/18/1995) | 448 |
| 4370 | Maxwell, G. Larry, MAJ MC. GOG 158 A Phase III Randomized Study of Cisplatin and Paclitaxel (24-Hour Infusion) Versus Carboplatin and Paclitaxel (3-Hour Infusion) in Optimal Stage III Epithelial Ovarian Carcinoma. (8/29/1995) | 449 |
| 4372 | Maxwell, G. Larry, MAJ MC. GOG #LAPI - Orientation and Evaluation Study in Performing in GOG Standardized Procedure for Laparoscopic FIGO Staging in Adenocarcinoma of the Endometrium. (12/19/1995) | 450 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 4378 | Maxwell, G. Larry, MAJ MC. GOG #162 - A Phase III Randomized Trial of Cisplatin (NSC #119875) with Paclitaxel (NSC #125973) Administered by Either 24 Hour Infusion or 96 Hour Infusion in Patients with Selected Stage III and Stage IV Epithelial Ovarian Cancer. (5/28/1996) | 451 |
| 4380 | Rose, G. Scott, LTC MC. GOG #LAP2 - A Phase III Randomized Clinical Trial of Laparoscopic Pelvic and Para Aortic Node Sampling with Vaginal Hysterectomy and BSO Versus Open Laparotomy with Pelvic and Para-Aortic Node Sampling and Abdominal Hysterectomy and BSO in Endometrial Adenocarcinoma, Uterine Sarcoma, Clinical Stage I, IIA, Grade I, II, III. (7/30/1996) | 452 |
| 4382 | Maxwell, G. Larry, MAJ MC. GOG 9302 - Laparoscopic Staging in Patients with Incompletely Staged Cancer of the Ovary, Primary Fallopian Tube Carcinoma and Primary Peritoneal Carcinoma. (12/17/1996) | 453 |
| 4389 | Maxwell, G. Larry, MAJ MC. GOG 164 - A Randomized, Controlled Intergroup Trial of Salvage Therapy w/Paclitaxel & Carboplatin Vs. Salvage Therapy with Stem Cell Supported High-Dose Carboplatin, Mitoxantrone & Cyclophosphamide in Patients w/Persistent Low Volume Ovarian Cancer & .... (4/24/1997) | 454 |
| 4400 | Rose, G. Scott, LTC MC. GOG 137 - A Randomized Double-Blinded Trial of Estrogen Replacement Therapy Versus Placebo in Women with Stage I or II Endometrial Adenocarcinoma. (9/30/1997) | 455 |
| 4403-98 | Rose, G. Scott, LTC MC. GOG 141: Treatment of Patients with Suboptimal ("Bulky") Stage IB Carcinoma of the Cervix: A Randomized Comparison of Radical Hysterectomy and Pelvic and Para-Aortic Lymphadenectomy With or Without Neoadjuvant Vincristine and Cisplatin Chemotherapy. (2/5/1998) | 456 |
| 4404-98 | Maxwell, G. Larry, MAJ MC. GOG 165: A Randomized Comparison of Radiation Plus Weekly Cisplatin Vs. Radiation Plus PV1 (Protracted Venous Infusion) 5-FU in Patients with Stage II-B, III-B, and IV-A Carcinoma of the Cervix. (2/5/1998) | 457 |
| 4406-98 | Rose, G. Scott, LTC MC. GOG 161: A Phase III Trial of Ifosfamide (NSC #109724) Versus Ifosfamide Plus Paclitaxel (NSC #125973) in Patients with Advanced, Persistent or Recurrent Carcinosarcoma (Mixed Mesodermal Tumors) of the Uterus. (2/24/1998) | 458 |
| 4413-99 | Rose, G. Scott, LTC MC. The Effect of Environmental CO2 on Thermotolerance Associated Heat Shock Protein Synthesis. (3/2/1999) | 459 |
| 4417-99 | Scott, Lynnette, Ph.D. CIV. Evaluation of Metabolic Products of Embryo culture and their correlation with morphologic appearance and pregnancy outcome. (7/6/1999) | 460 |
| 4418-99 | Rose, G. Scott, LTC MC. GOG #9902: Quality of Life of Gynecologic Cancer Survivors (NCI 1 RO1 CA 79039-01). (9/21/1999) | 462 |
| 4419-99 | Rose, G. Scott, LTC MC. GOG 167: A Two Part Study of the Treatment of Atypical Endometrial Hyperplasia: Part A: A Prospective Study of Immediate Hysterectomy; Part B: A Randomized Phase II Study of Medoroxyprogesterone Acetate Versus Depoprovera. (9/21/1999) | 463 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 4420-99 | Parker, Mary F., LTC MC. Hyperspectral Diagnostic Imaging of the Cervix. (9/29/1999) | 464 |
| 44Ad-Ap1 | Leondires, Mark P., MAJ MC. The Safety and Effectiveness of Surgery With or Without Raloxifene (EvistaTM, Lilly) for the Treatment of Pelvic Pain Caused by Endometriosis. (9/15/2000) | Admin |

## *Department of Orthopaedics and Rehabilitation*

### *Orthopedics Surgery Service*

| | | |
|---|---|---|
| 00-2401 | Lehman, Ronald A., CPT MC. The Effect of Pedicle Screw Fit Using Image Guided Surgery Techniques. (10/5/1999) | 246 |
| 00-2402 | Polly, David W., COL MC. A Comparison of Standard Introperative Fluoroscopy vs. Fluoroscopy Using the FluoroNav Sterostatic System. (10/26/1999) | 247 |
| 00-2403 | Shawen, Scott B., CPT MC. The Relationship of Femoral Notching, Osteoporosis, and Supracondylar Fractures. (11/30/1999) | 248 |
| 00-2404 | Taylor, Kenneth F., MAJ MC. The Radioscaphoid Interval. A Sensitive Indicator of Early Perilunar Instability. (4/18/2000) | 249 |
| 00-2405 | Polly, David W., COL MC. MOSS-Miami and VertiGraft 2 Open Label Study # 199901. (8/22/2000) | 250 |
| 00-2406 | Xenos, John S., LTC MC. The Porous-Coated Anatomic Total Hip Prosthesis, Inserted Without Cement, Results after 15 Years in a Prospective Study. (9/12/2000) | 251 |
| 01-24003 | Andersen, Romney C., MAJ MC. Hip Arthroscopy in Young Active Adults Retrospective Case Series Report. (1/2/2001) | 252 |
| 01-24004 | Polly, David W., COL MC. An Observational Study to Record Process Measures and Analyze Cost Related to Iliac Crest Bone Graft Harvest for Spinal Fusion. (1/2/2001) | 253 |
| 01-24005 | Andersen, Romney C., MAJ MC. Prospective Cohort Analysis of Hip Arthroscopy in Young Active Adults with Two Years Follow-up. (2/6/2001) | 254 |
| 01-24006 | Polly, David W., COL MC. Adolescent Idiopathic Scoliosis Single Overhang Curve. (4/10/2001) | 255 |
| 01-24007 | Polly, David W., COL MC. A Multi-Center Study to Evaluate the Safety and Efficacy of DePuy AcroMed Titanium Surgical Mesh and MOSS-Miami Spinal System Pedicle Screws. (4/24/2001) | 256 |
| 01-24008 | Taylor, Kenneth F., MAJ MC. Functional and Clinical Outcome Following Arthroscopically Assisted Anterior and Posterior Cruciate Ligament Reconstruction in a High-Demand Patient Population. (6/26/2001) | 258 |
| 01-24009 | Lehman, Ronald A., CPT MC. Effects of Alendronate Sodium (FOSAMAX) on Spinal Fusion in the Rabbit Model. (8/14/2001) | 259 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 01-2401 | Wallace, Roxanne, CPT MC. Quantitative Analysis of the Neovascularization of Distraction Osteogenesis from the End of Distraction to Bone Maturity Correlated with Bone Histology, Mechanical Properties, and Radiography. (10/3/2000) | 261 |
| 01-24010 | Lehman, Ronald A., CPT MC. Biomechanics of Anatomic Versus Straight Forward Technique of Thoracic Pedicle Screw Placement: A Cadaveric Study. (9/14/2001) | 262 |
| 01-24011 | Kuklo, Timothy R., LTC MC. The Biomechanical Effects of Various Tapping Techniques with Insertion of Thoracic Pedicle Screws: A Cadaveric Study. (9/14/2001) | 264 |
| 01-2402 | Doukas, William C., LTC MC. Preoperative and Postoperative EMG Analysis of Rotator Cuff Tears: Clinical Outcome Correlation with MRI Findings, Size and Reparability. (11/30/2000) | 266 |
| 02-24012 | Doukas, William C., LTC MC. Global Advantage CTA Humeral Head Prosthesis for Treatment of Cuff Tear Arthropathy. (10/23/2001) | New |
| 02-24013 | Kirk, Kevin L., CPT MC. Initial Stability of Cementless Revision Femoral Stems after Extended Trochanteric Femoral Osteotomy: A Biomechanical Analysis of Distal Stem Design. (12/4/2001) | New |
| 02-24015 | Dhawan, Aman, CPT MC. The Effects of Tibial Malrotation on Tibiotalar Joint Biomechanics of the Medial and Lateral Gutters (facets).. (3/19/2002) | New |
| 02-24016 | McHale, Kathleen A., COL MC. Syndesmosis Fixation: The Biomechanical Effects of Three Versus Four Cortex Fixation. (4/18/2002) | New |
| 02-24017 | Farber, Gerald, LTC MC. Ulnar Nerve Entrapment: A Randomized Prospective Comparison of Subcutaneous Versus Submuscular Ulnar Nerve Transposition. (6/25/2002) | New |
| 02-24017E | Shawen, Scott B., CPT MC. Hemimetameric Segmental Shift: A Case Series and Review. (12/21/2001) | Exempt |
| 02-24018 | Murphy, Kevin P., LTC MC. Anterior Cruciate Liagment Reconstructino with Fracilis and Semitendinosus Tendons: Comparison Between Patients Over 40 Years of Age Versus Those Less Than 40. (7/16/2002) | New |
| 02-24018E | Belmont, Philip J., CPT MC. In Vivo Accuracy of Transpedicular Thoracic Screws in Patients With and Without Coronal-Plane Deformities. (1/4/2002) | Exempt |
| 02-24019 | Lenhart, Martha, LTC MC. Use of Telemedicine in Optimizing Care for Phalangeal Fractures. (8/20/2002) | New |
| 02-24019E | Dhawan, Aman, CPT MC. Thoracic Pedicle Screw Trajectory: Which Method Allows Greatest Margin of Error. (1/31/2002) | Exempt |
| 02-24020 | Polly, David W., COL MC. Effects of Fracture on 1,25 Dihydroxyvitamin D and Bone Density. (9/17/2002) | New |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-24020E | Lehman, Ronald A., CPT MC. Reliability and Validity of Sounding the Pedicle Prior to Insertion of Pedicle Screws in the Thoracic Spine.. (4/1/2002) | Exempt |
| 02-24021E | Lenhart, Martha, LTC MC. Use of Telemedicine in Optimizing Care for Phlangeal Fractures. (2/27/2002) | Exempt |
| 02-24022EX | Orchowski, Joseph, MD MAJ MC. Analysis for Salvage of Straight Forward Pedicle Screws With the Anatomic Trajectory in the Thoracic Spine. (3/20/2002) | Exempt |
| 02-24023E | Farber, Gerald, LTC MC. Revision of Ulnar Nerve Transpositions: A Retrospective Review. (9/25/2002) | Exempt |
| 2496 | Polly, David W., COL MC. PRO OSTEON Implant 500 Coralline Hydroxyapatite Bone Void Filler for Use in Filling the Iliac Crest Bone Donor Site. (10/29/1996) | 267 |
| ***Physical Medicine & Rehabilitation Service*** | | |
| 00-9601 | Pasquina, Paul F., MAJ MC. Skin-Contact Monochromatic Infrared Irradiation on Lateral Epicondylitis. (2/22/2000) | 632 |
| 00-9602 | Menetrez, Jennifer S., MAJ MC. Comprehensive Prospective Gait Evaluation of Patients with Spinal Cord Pathology. (4/18/2000) | 633 |
| 00-9603 | Gambel, Jeffrey, LTC MC. Comparison of Biochemical Markers Between Active Duty U.S. Servicemembers with Chronic Myofascial Pain Syndrome and Matched Controls. (6/6/2000) | 634 |
| 00-9604 | Marin, Raul, LTC MC. Determination of Low Back Muscle Usage by MRI Before and After Stepper machine Exercise. (9/19/2000) | 635 |
| 02-96005 | Babcock, Mary Sabado, CPT MC. Comparison of Botulinum Toxin Injection for Plantar Fasciitis Vs. Placebo: A Clinical Trial. (10/16/2001) | New |
| 02-96006 | Hannah, Mary C., CPT SP. New Plantar Fasciitis Orthotic (PFOs) Versus Traditional Conservative Treatment for Plantar Fasciitis: A Randomized Controlled Trial. (8/6/2002) | New |
| 02-96010E | Jensen, David, CPT MC. Epidemiological Analysis of Injuries from Army Ten Miler, A Three Year Retrospective Review. (6/3/2002) | Exempt |
| 02-96010EX | Amaker, Robinette J, LTC SP. Pain Perceptions and Adaptations Among Walter Reed Army Medical Center Beneficiaries. (6/3/2002) | Exempt |
| ***Department of Pathology and Area Laboratories*** | | |
| 01-48001 | Kaplan, Keith J., MAJ MC. Use of Robotic Telepathology as an Adjunct to Frozen Section Consultation. (3/13/2001) | 480 |
| 01-48002 | Myers, Cris P., COL MC. Oxidative and Nitrosative Stress in Carcinogenesis of CTCL (MF). (4/3/2001) | 481 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 01-48003 | Marrogi, Aizen J., LTC MC. Oxidative and Nitrosative Stress in Carcinogenesis of Colitis-Associated Malignancies. (5/8/2001) | 482 |
| 01-48004 | Turcan, William L., DoD. Extending the Expiration Date of Thawed Fresh Frozen Plasma and Plasma Frozen Within 24 Hours of Collection From 24 Hours to 48 Hours. (6/12/2001) | 483 |
| 02-48002E | Kaplan, Keith J., MAJ MC. Correlation of Reactive Cellular Changes on Cervicovaginal Cytology (Papanicolaou test) With Subsequent Cervical Biopsies and Pap Test Follow-Up. (9/4/2002) | Exempt |
| 02-48004 | Andriko, Jo-Ann, LTC MC. Ultrasound-Mediated Tissue Preservation. (5/14/2002) | New |
| 02-48005 | Marrogi, Aizen J., LTC MC. Oxidative and Nitrosative Stress in Carcinogenesis of CTCL in Archived Tissue Samples from Patients Diagnosed with Mycosis Fungoides (MF). (9/24/2002) | New |
| 4833-98 | Moul, Judd W., COL MC. Determination of Reference Values for Percent Free PSA in Patients for Prostatic Evaluation. (9/1/1998) | 485 |
| ***Department of Pediatrics*** | | |
| 00-6501 | Francis, Gary L., COL MC. The Role of Ki-67 Antigen in Differentiated Thyroid Cancers. (10/5/1999) | 486 |
| 00-6502 | Bauer, Andrew J., MAJ MC. Comparative Genomic Hybridization of Differentiated Thyroid Cancers. (10/12/1999) | 487 |
| 00-6503 | Bauer, Andrew J., MAJ MC. Role of Thyroid Transcription Factor-1 in Differentiated Thyroid Cancer. (11/2/1999) | 488 |
| 00-6504 | Fenton, Cydney L., MAJ MC. Role of Focal Matrix Metalloproteinases in Differentiated Thyroid Cancer. (11/30/1999) | 489 |
| 00-6601 | Edwards, E. Glenn, COL MC. POG 9900: ALinc 17 Classification Protocol - A Pediatric Oncology Group Non-Therapeutic Study. (8/15/2000) | 490 |
| 00-6602 | Edwards, E. Glenn, COL MC. POG 9907: ALinc 17 Cytogenetics Protocol: A Pediatric Oncology Group Non-Therapeutic Study. (8/15/2000) | 491 |
| 01-65001 | Francis, Gary L., COL MC. An Archival Fixed-Tissue Thyroid Tissue Bank. (4/3/2001) | 492 |
| 01-65001a | Powers, Patricia A., COL MC. The Role of Caveolin-1 in Thyroid Carcinoma. (4/10/2001) | 493 |
| 01-65001b | Bauer, Andrew J., MAJ MC. Preclinical Pilot Study to Determine if the Novel Tumor-Activated Fluoropyrimidine Carbamate Capecitabine (Xeloda, Hoffman-Laroche, Inc.) could be used to Treat Thyroid Carcinoma: Are cytidine deaminase, thymidine phosphorylase, dihydropyrimidine dehydroge.... (9/14/2001) | 495 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 01-65002 | Rick, James R., MAJ MC. In situ Expression of cagA in H. pylori Infected Children: A Case Series with Endoscopic and Histologic Correlation. (7/10/2001) | 496 |
| 01-65003 | Patterson, Harlan S., COL MC. Open Label Administriation of Human Botulism Immune Globulin. (7/24/2001) | 497 |
| 01-65Ad-Ap | Bauer, Andrew J., MAJ MC. Resistance and Hypersensitivity to Thyroid Hormone. (11/30/2000) | Admin |
| 01-66001 | Edwards, E. Glenn, COL MC. POG ALinC 17 - Induction Therapy for POG 9904, POG 9905 and POG 9906 (Consent Form) Only. (2/27/2001) | 498 |
| 01-66001a | Edwards, E. Glenn, COL MC. POG 9904: ALinC 17 Treatment for Patients with Low Risk Acute Lymphoblastic Leukemia: A Pediatric Oncology Group Phase III Study. (4/17/2001) | 499 |
| 01-66001b | Edwards, E. Glenn, COL MC. POG 9905: ALinC 17 Protocol for Patients with Standard Risk Acute Lymphoblastic Leukemia (ALL) - A Pediatric Oncology Group Phase III Study. (2/27/2001) | 500 |
| 01-66001c | Edwards, E. Glenn, COL MC. POG 9906: ALinC 17: Protocol for Patients with Newly Diagnosed High Risk Acute Lymphoblastic Leukemia (ALL) - Evaluation of the Augumented BFM Regimen: A Phase III Study. (4/17/2001) | 501 |
| 01-66002 | Edwards, E. Glenn, COL MC. ANBL00B1: Neuroblastoma Biology Studies. (4/24/2001) | 502 |
| 02-65000EX | Creamer, Kevin M., LTC MC. Pediatric Residents Training, Experience, and Comfort with End of Life Issues. (2/28/2002) | Exempt |
| 02-65001d | Eccles, Thomas G., CPT MC. The Role of Erythropoeitin and Erythropoeitin Receptor Expression in Thyroid Carcinoma. (2/19/2002) | New |
| 02-65001EX | Collura-Burke, Christina, LCDR MC. Asthma Education and Its Effect on Quality of Life. (6/3/2002) | Exempt |
| 02-65002E | Harmon, Abigail LT MC, LT MC. Provider's Skills in Evaluating the Middle Ear. (6/19/2002) | Exempt |
| 02-65003E | Lopreiato, Joseph O, CAPT MC. Parent/Patient Satisfaction After Ambulatory Visits Performed by Pediatric Residents. (7/3/2002) | Exempt |
| 02-65004E | Creamer, Kevin M., LTC MC. Retrospective Review of WRAMC's Pediatric Sedation Unit Database. (9/11/2002) | Exempt |
| 02-65005 | Bauer, Andrew J., MAJ MC. The Potential Role of Gastric Inhibitory Polypeptide in Obesity and in Cortisol Secretion. (12/11/2001) | New |
| 02-65006 | Modi, Juti, CPT MC. Characterization of Lymphocytic Infiltration in Childhood Thyroid Cancers (Note: Substudy 02-65001c). (1/22/2002) | New |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-65007 | Creamer, Kevin M., LTC MC. Correlation of BIS Number and University of Michigan Sedation Scale in Sedated Pediatric Patients. (8/6/2002) | New |
| 02-65008NR | Burklow, Thomas R., LTC MC. Clinical Use of the Amplatzer PFO Occluder. (9/3/2002) | New |
| 02-65Ad-Ap | O'Neill, Erin, LTC MC. Incidence and Neurodevelopmental Outcome of Preterm Infants Diagnosed with Periventricular Leukomalacia. (1/28/2002) | Admin |
| 02-66003 | Edwards, E. Glenn, COL MC. CCG A3961: Treatment for Infants and Children with Intermediated Risk Neuroblastoma, A Phase III Intergroup CCG/POG Study. (12/11/2001) | New |
| 02-66004 | Edwards, E. Glenn, COL MC. P9761: Phase II Trial of Irinotecan in Children with Refractory Solid Tumors: A COG Study. (8/27/2002) | New |
| 6121 | Edwards, E. Glenn, COL MC. POG 7799: Rare Tumor Registry. (1/22/1980) | 503 |
| 6188 | Edwards, E. Glenn, COL MC. POG 8650: National Wilm's Tumor Study - 4; A POG Phase III Study. (10/28/1986) | 504 |
| 6221 | Edwards, E. Glenn, COL MC. POG 8821: Intensive Multiagent Therapy Vs. Autologous Bone Marrow Transplant Early in First CR for Children with Acute Myelocytic Leukemia - A Phase III Study. (9/27/1988) | 505 |
| 6242 | Edwards, E. Glenn, COL MC. POG 8828 Late Effects of Treatment of Hodgkin's Disease: A POG Nontherapeutic Study. (5/23/1989) | 506 |
| 6261 | Edwards, E. Glenn, COL MC. POG 9047 Neuroblastoma Biology Protocol. (2/27/1990) | 507 |
| 6302 | Edwards, E. Glenn, COL MC. POG: 9151 Intergroup Rhabdomyosarcoma Study IV: Treatment for Stage 2 and 3 Diseases: A Phase III Trial. (11/26/1991) | 508 |
| 6314 | Edwards, E. Glenn, COL MC. POG 9284/85: Barriers to Enrollment on POG Frontline Therapeutic Clinical Trials and Development of Intervention Strategies: A POG Non-therapeutic Study. (3/31/1992) | 509 |
| 6323 | Edwards, E. Glenn, COL MC. POG 9233/34: A Phase III Randomized Trial of Standard vs. Dose-Intensified Chemotherapy <3 Years of Age with a CNS Malignancy Treated With or Without Radiation Therapy. (5/26/1992) | 510 |
| 6351 | Edwards, E. Glenn, COL MC. POG 9317: Chemotherapy for Children with Advanced-Stage (III/IV) Diffuse Undifferentiated Burkitt's Lymphoma and B-Cell ALL: A Phase IIII Study. (3/30/1993) | 511 |
| 6364 | Edwards, E. Glenn, COL MC. POG 9351/CCG 7921 Trial of Doxorubicin, Cisplatin and Methotrexate With and Without Ifosfamide, With and Without Muramyl Tripeptide Phosphatidyl Ethanolamine (MTP-PE) for Treatment of Osteogenic Sarcoma. (2/22/1994) | 512 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 6374 | Thompson, Mark, MAJ MC. The Role of Nitric Oxide in Cerebrovascular Autoregulation in the Newborn Piglet. (8/9/1994) | 513 |
| 6383 | Edwards, E. Glenn, COL MC. POG 9405 ALinC16: Protocol For Patients With Newly Diagnosed Standard Risk Acute Lymphoblastic Leukemia - A POG Phase III Study. (12/20/1994) | 514 |
| 6384 | Edwards, E. Glenn, COL MC. POG 9406 ALinC16: Protocol For Patients With Newly Dignosed High Risk Acute Lymphoblastic Leukemia - A POG Phase III Study. (12/20/1994) | 515 |
| 6386 | Edwards, E. Glenn, COL MC. POG 9362: A Phase II Study Of Alpha Interferon In HIV-Related Malignancies - A Pediatric Oncology Group-Wide Study. (3/28/1995) | 516 |
| 6387 | Edwards, E. Glenn, COL MC. POG 9421: Phase III Evaluation Of Standard vs. High Dose Ara-C Induction Followed By The Randomized Use Of Cyclosporin A As An MDR Reversal Agent, Compared To Allogeneic BMT, In Childhood AML. (3/28/1995) | 517 |
| 6388 | Edwards, E. Glenn, COL MC. POG 9201 ALINC #16 - Treatment for Patients with Lesser Risk Acute Lymphoblastic Leukemia - A Pediatric Phase III Study. (5/23/1995) | 518 |
| 6397 | Edwards, E. Glenn, COL MC. POG 9354/CCG 7932: Phase III Evaluation of Intensified Vincristine, Doxorubicin, Cyclophosphamide, Ifosfamide, and Etoposide in the Treatment of Newly-Diagnosed Ewing's Sarcoma or Primitive Neuroectodermal Tumor of Bone or Soft Tissue. (8/29/1995) | 519 |
| 6400 | Edwards, E. Glenn, COL MC. POG: An Overview of the Research Protocol Entitled POG 9440/CCG 4941: National Wilms' Tumor Study - 5: Therapeutic Trial and Biology Study. (9/26/1995) | 520 |
| 6401 | Edwards, E. Glenn, COL MC. POG: Support of Pediatric Oncology Group Activities, WRAMC. (1/30/1996) | 521 |
| 6405 | Rogers, Philip L., COL MC. A Multicenter Study to Determine the Prevalence and Clinical Characteristics of Barrett's Esophagus in Childhood. (5/28/1996) | 522 |
| 6408 | Edwards, E. Glenn, COL MC. POG 9605 - ALinC 16: Protocol for Patients with Newly Diagnosed Standard Risk Acute Lymphoblastic Leukemia (ALL). (6/25/1996) | 523 |
| 6410 | Edwards, E. Glenn, COL MC. POG 9404 - T-Cell #4 Protocol: Intensive Treatment for T-Cell Acute Lymphoblastic Leukemia and Advanced Stage Lymphoblastic Non-Hodgkin's Lymphoma. (8/27/1996) | 524 |
| 6414 | Dinauer, Catherine A., MAJ MC. Oncogene Expression in Thyroid Neoplasia in Children. (10/1/1996) | 525 |
| 6416 | Levin, Sondra W., M.D. DAC. Analysis of Parental Time Allocation in Families where Children with Special Needs Live with their Unaffected Siblings. (11/19/1996) | 526 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 6423 | Francis, Gary L., COL MC. Sphingomyelinase and Ceramide Regulate Steroid Synthesis. (2/3/1998) | 527 |
| 6425-98 | Burklow, Thomas R., LTC MC. Power Spectrum Analysis as a Marker of Diabetic Autonomic Neuropathy in Children and Adolescents with Diabetes Mellitus. (5/26/1998) | 528 |
| 6429-99 | Dinauer, Catherine A., MAJ MC. Bone Mineral Density in Survivors of Childhood Thyroid Cancer. (4/27/1999) | 529 |
| 6430-99 | Dinauer, Catherine A., MAJ MC. Acute Pediatric Care in a Pediatric Clinic Versus A General Emergency Department: A Performance Improvement Project Comparing Outcomes and Patient Satisfaction. (8/10/1999) | 530 |
| 7166 | Mosijczuk, Askold D., COL MC. An Open-Label Uncontrolled Trial of Long-Term Treatment with Poly-ICLC in Patients with Malignant Gliomas and Multiple Sclerosis. (4/23/1996) | 545 |
| ***Department of Pharmacy*** | | |
| 01-36001 | Rutledge, Matthew R., MAJ MS. Perceptions of Pain Control: Oncology Patients and Their Physicians. (5/29/2001) | 395 |
| ***Department of Preventive Medicine*** | | |
| 02-35001E | Wolfgang, Edward, DAC. The Lack of Disease Reporting at One Military Treatment Facility. (5/22/2002) | Exempt |
| ***Department of Psychiatry*** | | |
| 00-7201 | Grieger, Thomas, LCDR MC. Naturalistic Study of Pharmacotherapy in Patients with Schizoaffective Disorder, Bipolar Disorder, and Schizophrenia. (3/14/2000) | 548 |
| 01-7201 | Black, Nancy, MAJ MC. Development of a Child and Adoleslcent Psychiatry Database. (10/17/2000) | 549 |
| 02-72002 | Chun, Ryo Sook, COL MC. Evaluation of the Effect of a WEB-BASED Automated Mental Health Intake System on Parent/Guardian Satisfaction and Discussion Providers' Response. (2/19/2002) | New |
| 02-72003 | Wain, Harold J., Ph.D. DoD. A Demonstration Project: Description of Well-Being and Satisfaction in Subjects Assigned to Follow-up Psychiatric Treatment in the Traditional Approach Vs. a Telemedicine Approach. (2/26/2002) | New |
| 02-72004 | Morris, James, MAJ MC. A Multi-Center Prospective Study on Pediatrics Seasonal Affective Disorder (SAD) Incidence. (6/25/2002) | New |
| 02-72007E | Levandowski, Dale, MAJ MC. Predicting Psychiatric Readmissions, A Retrospective. (10/11/2001) | Exempt |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-72008E | Lange, Christopher, CPT MC. Perceived Efficacy by a Consulter About Their Child and Adolescent Psychiatric Consultation. (11/26/2001) | Exempt |
| 02-72009E | Levandowski, Dale, MAJ MC. Prescribing Trends of Psychotropic Medications in Children and Adolescents in a Military Health Care Facility. (4/4/2002) | Exempt |
| 7279-98 | Malone, Ricky D., LTC MC. The Frequency and Nature of Forensic Issues in an Inpatient Adult General Psychiatric Population. (3/25/1998) | 550 |
| 7280-98 | Ritchie, Cameron E., LTC MC. Suicidal Behavior in Active Duty Patients. (4/10/1998) | 551 |
| 7284-99 | Black, Nancy, MAJ MC. Comparison of Parental Therapeutic Alliances Before and After Initial Psychiatric Interviews: Telepsychiatry Versus In-Person Appointments. (11/17/1998) | 552 |
| 7285-99 | Ritchie, Cameron E., LTC MC. Assessing Pre-Military Psychiatric Illness, Risk Factors Leading to Early Onset of Psychiatric Illness, and Inter-Rater Reliability of Psychiatric Diagnosis. (2/2/1999) | 553 |
| ***Department of Psychology*** | | |
| 00-7301 | Kelly, Mark, Ph.D. DAC. Computerized Neuropsychological Assessment of Army Aviators (CNAAA): Development of a Digitized Database and Preliminary Investigator of the Relationship of ANAM, CogScreen and MicroCog to Aviator Trainee Checkflight Performances. (8/1/2000) | 554 |
| 01-73002 | James, Larry C., LTC MS. CD-ROM Technology to Increase Appropriate Self-Care and Preventive Behaviors Among Enlisted Women. (6/5/2001) | 556 |
| 01-7301 | Baggett, Mark R., MAJ MS. Computer Automated Neuropsychological Assessment of U.S. Army Aviators. (11/30/2000) | 557 |
| 02-73003E | James, Larry C., LTC MS. A Retrospective Analysis of the WRAMC LEAN project. (12/21/2001) | Exempt |
| 02-73003EX | Jones, Alvin, Ph.D. DAC. An Examination of the Validity of Three Sets of MMPI/MMPI-2 Personality Disorder Scales. (5/30/2002) | Exempt |
| 02-73004 | Dunivin, Debra, MAJ MS. The Impact of Group Psychosocial Interventions on Quality of Life for Breast Cancer Patients and Their Partners: A Pilot Study. (6/25/2002) | New |
| 02-73005E | Cooper, Marc A, CPT MC. Mental Health Diagnoses and Health Care Utilization in the US Military: Detailed Analysis of Defense Medical Surveillance Data. (6/26/2002) | Exempt |
| 7302 | Jones, Alvin, Ph.D. DAC. Analysis of Component Neurocognitive Processes for the Trial Making Test: An Examination of Age Related Changes. (7/8/1997) | 559 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| ***Department of Radiology*** | | |
| ***Diagnostic Radiology Service*** | | |
| 01-47002 | Feuerstein, Irwin M., M.D. DAC. Postmenopausal Coronary Artery Disease and Osteoporosis: A Pilot Study. (4/17/2001) | 474 |
| 01-47003 | Brazaitis, Michael P., COL MC. Field Trial of Mobile Digital Telemammography - Phase I (Installation and Testing). (5/22/2001) | 475 |
| 01-4701 | Feuerstein, Irwin M., M.D. DAC. A Prospective Study of Outcomes of Patients Examined with Electron Beam Computed Tomography of the Coronary Arteries. (11/21/2000) | 476 |
| 02-47004 | Choi, Jong-Ho R., MAJ MC. Multi-Center Trial of Detection of Colorectal Neoplasma by CT Virtual Colonoscopy in a Screening Population. (1/29/2002) | New |
| 02-47005 | Dinauer, Philip A., MAJ MC. Detection of Glenoid Labral Tears and Rotator Cuff Tears: Comparison of Intravenous Contrast-Enhanced and High-Resolution Noncontrast MR Imaging of the Shoulder. (5/14/2002) | New |
| 02-47006E | Choi, Jong-Ho R., MAJ MC. Correlation of Magnetic Resonance Imaging Characteristics of the Prostate with Pathologic Findings and Clinical Outcome: The Clinical Value of Preoperative Magnetic Resonance Imaging in Prostrate Cancer. (12/13/2001) | Exempt |
| 02-47007E | Shapeero, Lorraine G., M.D.. Imaging Abnormalities of the Proximal Tibiofibular Joint: Diagnosis and Prevalence. (2/27/2002) | Exempt |
| 02-47008E | Statler, John D., MAJ MC. A Novel Tool for Teaching Ultrasound Guided Biopsy: Trainee Satisfaction Survey. (8/7/2002) | Exempt |
| 4705 | Jabbari, Bahman, COL MC. Proton Magnetic Resonance Spectroscopic Imaging in Patients with Partial Epilepsy. (4/25/1995) | 477 |
| 4710-99 | Feuerstein, Irwin M., M.D. DAC. Comparison of Electron Beam Computed Tomographic Virtual Colonoscopy (EBCT-VC) with Visual Colonoscopy, Using Each Patients as Their Own Control. (3/23/1999) | 478 |
| ***Nuclear Medicine Service*** | | |
| 00-4501 | Stack, Aaron L., MAJ MC. Feasibility, Accuracy and Efficiency of an Internet Based Tele-Nuclear Consultation System for the Military. Phase I: Phantom Studies. (10/12/1999) | 465 |
| 01-45002 | Montilla-Soler, Jaime, CPT MC. Preoperative Evaluation of Breast Carcinoma Utilizing Tc99m-Depreotide. (5/15/2001) | 466 |
| 01-45003 | Bridwell, Robert S., MAJ MC. An Open-Label, Multicenter, Phase 3 Trial Evaluating Ventricular Function as Assessed by Left Ventricular Ejection Fraction and Wall Motion using echnetium-99m Tetrofosfmin Gated SPECT Imaging. (6/19/2001) | 468 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 01-4501 | Bridwell, Robert S., MAJ MC. Intraoperative Staging of Lung Cancer Using the Gamma Probe and Tc-99m Depreotide. (12/12/2000) | 469 |
| 02-45004 | Bridwell, Robert S., MAJ MC. IM-D-CEA-C14 Pharmacokinetic and Biodistribution of Multiple Administration of CEA-Scan (Arcitumomab) Following Complete Resection of Primary Colorectal Carcinoma. (1/15/2002) | New |
| 02-45005 | Bridwell, Robert S., MAJ MC. What is the Sensitivity of Tc-99m Apcitide to Detect Acute Pulmonary Emboli?. (4/9/2002) | New |
| 02-45006 | Bridwell, Robert S., MAJ MC. IM-D-MN3-22: Phase II Study of LeukoScan Imaging in Patients with Acute Anthrax Infections. (5/14/2002) | New |
| 02-45007 | Bridwell, Robert S., MAJ MC. An Open-Label, Multicenter Clinical Study to Evaluate the Diagnostic Utility of Leutech Scintigraphy for the Detection of Inhalational Anthrax in Patients Who Have Symptoms Suggestive of or Consistent with A Diagnosis of Inhalational Anthrax. (7/16/2002) | New |
| 02-45008 | Bridwell, Robert S., MAJ MC. A Pilot Open-Label Clinical Study to Evaluate Pulmonary Imaging with LeuTech. (7/16/2002) | New |
| 4546 | Allen, Thomas, LTC MC. Intravenous Administration of 131I-6-B Iodomethylnorcholesterol (NP-59) for Adrenal Evaluation and Imaging. (4/24/1997) | 470 |
| ***Radiation Therapy*** | | |
| 01-46001 | Warlick, William B., MAJ MC. Evaluation of Intra-Prostatic Radio-opaque Markers for Prostate Localization and Refinement of External Beam Treatment Techniques. (1/16/2001) | 471 |
| 4601 | Roberts, Scott, M.D.. RTOG 94-08: A Phase III Trial of the Study of Endocrine-Therapy Used as a Cytoreductive and Cytostatic Agent Prior to Radiation Therapy in Good Prognosis Locally Confined Adenocarcinoma of the Prostate. (5/23/1995) | 472 |
| 4602 | Roberts, Scott, M.D.. RTOG 94-13 - A Phase III Trial Comparing Whole Pelvic Irradiation Followed by a Conedown Boost to Boost Irradiation Only and Comparing Neoadjuvant to Adjuvant Total Androgen Suppression (TAS). (2/27/1996) | 473 |
| ***Department of Surgery*** | | |
| ***Anesthesia-Operative Service*** | | |
| 00-2001A | Buckenmaier, Chester C., LTC MC. Pressor Effects of Hemoglobin Based Oxygen Carrying Solutions on Human Blood Vessels. (3/7/2000) | 201 |
| 00-2002A | Mongan, Paul, LTC MC. Developing a Control Population for Alternative Phenotyping for Malignant Hyperthermia Using Peripheral B Lymphocytes. (3/14/2000) | 202 |
| 01-20002A | Cohen, Steven P., LTC MC. Comparison of One-Needle Versus Multiple-Needle Technique for Lumbar Medial Branch Block. (9/18/2001) | 204 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 01-2001A | Mongan, Paul, LTC MC. Comparison of Two Plasminogen Activators in Reducing Bleomycin Induced Pulmonary Fibrosis in the Rat. (10/3/2000) | 205 |
| 02-20003A | Buckenmaier, Chester C., LTC MC. Double-Blinded, Placebo Controlled Prospective Randomized Trial Evaluating the Efficacy of Continuous Paravertebral Catheter with Paravertebral Block in Breast Cancer Surgery. (8/13/2002) | New |
| 02-31003E | Cohen, Steven P., LTC MC. Intradiscal Electrothermoplasty: Risk Factors for Complications and Failures. (3/1/2002) | Exempt |
| 02-31004E | Cohen, Steven P., LTC MC. The Ability of Intravenous Ketamine to Predict Response to Dextromethorphan. (8/26/2002) | Exempt |
| 2078A | Bettencourt, Joseph A., LTC MC. In Vitro Diagnosis of Malignant Hyperthermia With 4-Chloro-M-Cresol and Ryanodine. (5/25/1999) | 206 |
| ***Army Audiology & Speech Center*** | | |
| 00-2501 | Grant, Kenneth W., Ph.D. DAC. Spectro-Temporal Properties of Auditory-Visual Integration for Understanding Spoken Language. (11/30/1999) | 268 |
| 00-2503 | Grant, Kenneth W., Ph.D. DAC. Auditory-Visual Integration for Improved Human/Machine Interaction. (2/22/2000) | 270 |
| 00-2507 | Grant, Kenneth W., Ph.D. DAC. Auditory Supplements of Speechreading. (8/1/2000) | 273 |
| 01-25003 | Lentz, Jennifer S, Ph.D. DAC. Complex Sound Segregation by Hearing-Impaired Listeners. (7/10/2001) | 275 |
| 01-2501 | Cord, Mary T., M.A. DAC. Performance of Directional Microphone Hearing Aids in Everyday Listening Situations. (10/3/2000) | 276 |
| 01-2502 | Walden, Brian E., Ph.D. DAC. Performance of Custom-Fit Versus Fixed Format Hearing Aids for Precipitously-Sloping High-Frequency Hearing Loss. (11/14/2000) | 277 |
| 01-2565a | Summers, Walter Van, Ph.D. DAC. Dead Regions in the Cochlea and Their Influence on Speech Processing. (11/7/2000) | 279 |
| 01-2570a | Leek, Marjorie R., Ph.D. DAC. Spread of Masking by Harmonic Complexes in Normal-Hearing and Hearing-Impaired Listeners. (6/12/2001) | 280 |
| 02-25004 | Walden, Brian E., Ph.D. DAC. Prediction Hearing Aid Microphone Preference in Everyday Listening. (2/5/2002) | New |
| 02-25005 | Cord, Mary T., M.A. DAC. Relationship Between Laboratory Measures of Directional Advantage and Everyday Success with Directional Microphone Hearing Aids - A Pilot Study. (3/19/2002) | New |
| 02-25006 | Chandler, David W., COL MC. Reliability and Validity of Otoacoustic-Emission (OAE) Paradigms. (6/4/2002) | New |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-25007 | Solomon, Nancy P., Ph.D. DAC. Assessment and Validation of Tongue Fatigue for Speech. (8/6/2002) | New |
| 02-25008 | Grant, Kenneth W., Ph.D. DAC. Discrimination of Temporal Asynchrony Within and Across Sensory Modalities. (9/10/2002) | New |
| 02-2565b | Summers, Walter Van, Ph.D. DAC. Effects of Presentation Level on Recognition of Low and High-Frequency Speech. (4/16/2002) | New |
| 2550 | McClean, Michael D., Ph.D. DAC. Neuromotor Control of Speech Rate During Syllable Repetition. (1/30/1996) | 281 |
| 2565 | Summers, Walter Van, Ph.D. DAC. Auditory Processing and Sensorineural Hearing Loss. (3/14/1997) | 282 |
| 2570 | Leek, Marjorie R., Ph.D. DAC. Hearing Loss and the Perception of Complex Sounds. (8/26/1997) | 283 |
| 2577-98 | Summers, Walter Van, Ph.D. DAC. Influences of Masker Phase on Detection of Brief Signals. (5/5/1998) | 285 |
| 2585-99 | McClean, Michael D., Ph.D. DAC. Neuromotor Basis of Stuttering (NIH Application, DC03659 R01). (10/27/1998) | 287 |
| 2587-99 | Lentz, Jennifer S, Ph.D. DAC. Spectral Shape Discrimination by Normal-Hearing and Hearing Impaired Listeners. (1/12/1999) | 289 |
| 2588-99 | McClean, Michael D., Ph.D. DAC. Variations in Orofacial Reflexes with Stuttering Severity. (6/29/1999) | 290 |
| 2591-99 | Lentz, Jennifer S, Ph.D. DAC. Complex Sound Analysis by Persons with Impaired Hearing (Application for NIH NRSA Post Doctoral Fellowship). (9/14/1999) | 291 |
| ***Critical Care Medicine Service*** | | |
| 00-3002 | Popa, Christian, MAJ MC. Noninvasive Screening for Coronary Artery Disease Using A Digital Electronic Stethoscope. (8/1/2000) | 376 |
| 01-30001 | Popa, Christian, MAJ MC. Remote Consultation on the Critically Ill Patient Via Telecommunication. (6/14/2001) | 377 |
| 02-30000E | Jackson, William L, CPT MC. Characteristics of Patients Undergoing Lumbar Puncture in the Medical Intensive Care Unit. (1/18/2002) | Exempt |
| 02-30001E | Jackson, William L, CPT MC. Vasopressin Adversely Affects Cardian Performance in Septic Shock. (1/18/2002) | Exempt |
| 02-30003 | Ramage, Anthony S., MAJ MC. Oropharyngeal Decontamination for the Prevention of Ventilator Associated Pneumonia with Chlorhexidine Oral Rinse. (10/23/2001) | New |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 3000 | Blanchard, Jeremy, CPT MC. Characterization of the Cytokines Mediating Different Phases of Inflammation Following Controlled Abdominal Trauma. (7/29/1997) | 378 |
| 3002-99 | Popa, Christian, MAJ MC. Characterization of the Cytokines Mediating Different Phases of Inflammation Following Controlled Head Trauma. (10/27/1998) | 380 |
| ***General Surgery Service*** | | |
| 00-2001 | Peoples, George E., LTC MC. Cytotoxic T Lymphocyte Recognition of Epithelial Cancers. (4/4/2000) | 207 |
| 00-2002 | Peoples, George E., LTC MC. Sentinel Lympho Node (SLN) Evaluation in Colorectal Cancer (CRC). (4/18/2000) | 208 |
| 00-2003 | Rehrig, Scott, CPT MC. Evaluation of Neutrophil Activation in Diabetes After Carotid Endarterectomy. (4/18/2000) | 209 |
| 00-2004 | Peoples, George E., LTC MC. Phase Ib Trial of HER2/neu Peptide (E75) Vaccine in Patients at High Risk for Recurrence after Surgical Extirpation of Prostate Cancer. (5/23/2000) | 210 |
| 00-2005 | Peoples, George E., LTC MC. Phase Ib Trial of HER2/neu Peptide (E75) Vaccine in Breast Cancer Patients at High Risk for Recurrence after Surgical and Medical Therapies. (5/23/2000) | 211 |
| 00-2006 | Peoples, George E., LTC MC. Creation of a Retrospective and Prospective Database of Patients Evaluated and Treated for Breast Cancer. (7/25/2000) | 212 |
| 01-20003 | Peoples, George E., LTC MC. A Prospective Randomized Phase III Study Comparing Radiofrequency Ablation Versus Cryosurgical Ablation for the Treatment of Malignant Liver Tumors. (1/23/2001) | 213 |
| 01-20004 | Peoples, George E., LTC MC. A Randomized, Double Blind, Multi-Center, Comparative Phase III Study of Intravenous BMS-284756 Follow-up..Intravenous Piperacillin/Tazobactam With or Without Oral moxicillin/Clavulanate Follow-up in the Treatment of Complicated Skin and Skin Structure I. (1/23/2001) | 214 |
| 01-20005 | Anderson, Jimie, CPT MC. Comparison of Doppler Flow Characteristics of the Superior Mesenteric Artery to Invasive Pulmonary Artery Catheterization in Critically Ill Patients. (5/22/2001) | 215 |
| 01-20006 | Shriver, Craig D., LTC MC. Tissue and Blood Library Establishment for Molecular, Biochemical and Histologic Study of Breast Disease. (5/22/2001) | 217 |
| 01-20007 | Shriver, Craig D., LTC MC. Creation of a Blood Library for the Analysis of Blood for Molecular Changes Associated with Breast Disease and Breast Cancer Development. (5/22/2001) | 220 |
| 01-2001 | Shriver, Craig D., LTC MC. Creation of a Database of Patients at a High Risk for Breast Cancer. (11/30/2000) | 223 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 01-2002 | Peoples, George E., LTC MC. A Prospective, Randomized, Double Blind, Multicenter Trial Assessing the Safety and Efficacy of Sequential (Intravenous/Oral) BAY 12-88093 (Moxifloxacin) 400mg Every 24 Hours Compared to Intravenous Piperacillin/Tazobactam 3.375 grams Every 6 Hours Follo. (12/12/2000) | 224 |
| 02-20005E | Nelson, Jeffrey M, MAJ MC. Anal High Grade Intraepithelial Lesions Associated with HIV Seropositivity. (6/17/2002) | Exempt |
| 02-20008 | Stojadinovic, Alexander, MAJ MC. Electrical Impedence Scanning of Thyroid Nodules Prior to Thyroid Surgery: A Prospective Study. (6/11/2002) | New |
| 02-20009 | Stojadinovic, Alexander, MAJ MC. Electrical Impedence Imaging for Early Detection of Breast Cancer in Young Women. (6/11/2002) | New |
| 02-27000E | Mulligan, Charles Ray Jr., MAJ MC. Current Trends and Surgical Management of Mediastinal Tumors. (11/15/2001) | Exempt |
| 02-31002E | Winslow, Catherine P., MAJ MC. Questionnaire: Selecting a Plastic Surgeon. (11/5/2001) | Exempt |
| 2076 | Quang, Eiping, Ph.D.. Gamma Probe Assisted Detection of Micrometastasis in Well-Differentiated Thyroid Cancer. (11/25/1997) | 225 |
| 2078-99 | Ward, David T., MAJ MC. Characterization of the Perioperative Serum Cytokine Elaboration in Patients Undergoing Hepatic Resection/Cryoablation. (10/20/1998) | 226 |
| 2079-99 | Shriver, Craig D., LTC MC. Intraductal Carcinoma of the Breast Treated by Conservative Surgery: Insights Based on Histopathologic Evaluation using Computer Graphic Three Dimensional Reconstruction. (12/15/1998) | 227 |
| 2080-99 | Anderson, Jimie, CPT MC. Alteration in Colonic Motility Secondary to Inflammatory Bowel Disease. (4/20/1999) | 228 |
| ***Neurosurgery Service*** | | |
| 02-22001 | Moquin, Ross, CDR MC. Pre and Post-Surgical Evaluation of Gait in Patient with L4/5 or L5/S1 Spondylolysis or Spondylolisthesis. (12/11/2001) | New |
| ***Ophthalmology Service*** | | |
| 00-2301 | Chun, Dal W., CPT MC. Evaluation of Digital Fundus Imaes as a Diagnostic Method for Surveillance of Diabetic Retinopathy. (12/14/1999) | 237 |
| 00-2302 | Subramanian, Prem S., MAJ MC. Expression of Markers of Vascular Proliferation in Human Choroidal Neovascular Membranes. (4/4/2000) | 238 |
| 01-23001 | Weichel, Eric D., CPT MC. Telemedical Examination of Eyelid Lesions: Correlation of Remote Diagnosis with in Person Clinical Exam and Pathologic Analysis. (4/3/2001) | 239 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 01-2335-99a | Bower, Kraig, S., LTC MC. Night Vision Goggle and Night Firing Range Performance After Myopic Excimer Laser Keratorefractive Surgery in U.S. Army Personnel. (11/21/2000) | 240 |
| 01-2335-99b | Bower, Kraig, S., LTC MC. Prospective Evaluation of Keratorefractive Surgery in Army Aviator Trainee. (9/25/2001) | 241 |
| 01-2335-99c | Bower, Kraig, S., LTC MC. Operational Assessment of Refractive Surgery for Rated Army Aviators: A Prospective Evaluation. (9/25/2001) | 242 |
| 2328 | Ward, Thomas P., MAJ MC. The Effect of Differing Enucleation Techniques on Cure Rate and Survival Time of Patients with Uveal Malignant Melanoma: A Comparison of Standard Enucleation, "No-Touch" Enucleation, and Enucleation with Stabilization of Intraocular Pressure. (3/5/1996) | 243 |
| 2334-99 | Eiseman, Andrew S., MAJ MC. 5 Fluorouracil Induced Dacryostenosis and Lid Malposition. (11/24/1998) | 244 |
| 2335-99 | Bower, Kraig, S., LTC MC. Initial Evalaution of Excimer Laser Keratorefractive Surgery in U.S. Army Personnel. (4/20/1999) | 245 |
| ***Organ Transplant Service*** | | |
| 2635-99 | Kirk, Allan D., CDR MC. Monitoring for Donor-Specific Hyporesponsiveness Following Renal and Pancreatic Allotransplantation. (6/22/1999) | 292 |
| 2636-99 | Kirk, Allan D., CDR MC. Live Donor Renal Donation for Allotransplantation. (6/22/1999) | 294 |
| 26Ad-Ap2 | Kirk, Allan D., CDR MC. Tolerance Induction Following Human Renal Transplantation Using Treatment with a Humanized Monoclonal Antibody Against CD52 (Campth-1H). (11/19/1999) | Admin |
| 26Ad-Ap3 | Swanson, John S. III, LTC MC. Sirolimus Monotherapy to Optimized Activation Induced Cell Death (AICD) In Renal Transplants Following Depletion Induction with Thymoglobulin. (9/5/2000) | Admin |
| 26Ad-Ap5 | Swanson, John S. III, LTC MC. Screening Protocol for Patients Needing a Kidney, Kidney-Pancreas, or Islet Cell Transplant. (7/24/2001) | Admin |
| ***Otolaryngology-Head & Neck Surgery Service*** | | |
| 00-2502 | Cote, Christopher, CPT MC. Efficacy of Endobronchial Adhesives in Experimental Lung Volume Reduction. (12/7/1999) | 269 |
| 00-2504 | Cable, Benjamin B., CPT MC. Radiofrequency Ablation of Oral Lymphangiomas, A Pilot Study. (4/18/2000) | 271 |
| 00-2505 | Brietzke, Scott E., CPT MC. Investigation of Alternative Sclerotherapy Agents for Injection Snoreplasty Palatal Stiffening Using the Beagle Canine Model: Pilot Study. (6/6/2000) | 272 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 00-2509 | Casler, John D., LTC MC. The Determination of a Suitable Animal Model for Teaching Endoscopic Surgery of the Paraanasal Sinuses Based on CT Imagining, Endoscopic Examination and Anatomical Skull Analysis. (9/5/2000) | 274 |
| 01-32003 | Brietzke, Scott E., CPT MC. Palatal Sclerotherapy with Sotradecol as a Treatment for Obstructive Sleep Apnea Syndrome. (2/27/2001) | 381 |
| 01-32004 | Brietzke, Scott E., CPT MC. Treatment of Snoring with Palatal Stiffening Injection Sclerotherapy Using Ethanol. (2/27/2001) | 383 |
| 01-32005 | Casler, John D., LTC MC. A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Cevimeline in the Treatment of Xerostomia to Radiation Therapy for Cancer in the Head and Neck Region (Protocol 2011A-PRTO003). (7/24/2001) | 385 |
| 01-3201 | McClellan, James S. Jr., CPT MC. Endoscopic Transection of the Corrugator and Procerus Muscles Through an Open Rhinoplasty Approach. (11/14/2000) | 386 |
| 01-3202 | Battiata, Andrew, CPT MC. Does Oral Steroid Therapy After Tonsillectomy Decrease Postoperative Pain and Morbidity? A Prospective, Double Blinded, Placebo Controlled Analysis. (11/30/2000) | 387 |
| 02-25002E | Sanchez, Jose E, LCDR MC. Endoscopic Skull Base Surgery: An Integrated Approach. (6/3/2002) | Exempt |
| 02-25003E | Gillespie, Christina, CPT MC. Is the Genetic Mutation Associated with Familial Mondini Malformation Actually a Previously Identified Dominant Mutation. (6/26/2002) | Exempt |
| 02-32006 | Bentley, Anthony A., LTC MC. Surgical Correction of the Incompetent Nasal Valve - A Rhinometric Analysis. (10/9/2001) | New |
| 02-32007 | Doolittle, Andrew, CPT MC. Mighty Mitomycin: Novel Use of Topical Mitomycin to Prevent Middle Ear Adhesiions in an Animal Model. (1/8/2002) | New |
| 02-32008 | Pazos, George A., LCDR MC. Investigation of Nasal Obstruction on the Outcome of Home-Based and Hospital-Based Evaluations of Obstructive Sleep Apnea and Snoring. (1/15/2002) | New |
| 02-32009 | McLeod, Ian K., CPT MC. The Use of Intraoperative Rapid Parathyroid Hormone Assay in Predicting Postoperative Hypocalcemia Following Total/Near-Total Thyroidectomy. (1/29/2002) | New |
| 02-32010 | Winslow, Catherine P., MAJ MC. An Innovative Approach to Management of the Aging Brow: Radiofrequency Avlation of Procerus and Corrugator Muscles. (6/18/2002) | New |
| 02-32011 | Winslow, Catherine P., MAJ MC. The Transconjunctival Approach with Orbital Septal Cauterization: An Anatomical Study. (6/18/2002) | New |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 2572 | Cote, Christopher, CPT MC. Determining the Prevalence of Occult Carotid Disease in Patients with Head and Neck Squamous Cell Carcinoma Using Color Flow Duplex Imaging. (10/28/1997) | 284 |
| 2584-99 | Criswell, Mark A., CPT MC. A New Treatment for Xerostomia in Postirradiated Head & Neck Cancer Patients. (10/27/1998) | 286 |
| ***Peripheral Vascular Surgery Service*** | | |
| 00-2101 | Goff, James M., LTC MC. Intraoperative Carotid Duplex: A Prospective Study of the Clinical Significance of Residual Defects Following Carotid Endarterectomy. (1/18/2000) | 229 |
| 00-2102 | Gillespie, David L., LTC MC. Clinical and Pathophysiologic Efficacy of SEPS the Endoscopic Treatment of Incompetent Perforating Veins of the Lower Extremity in Patients with Chronic Venous Insufficiency (CEAP Classes 4-6). (7/25/2000) | 231 |
| 01-2101 | O'Donnell, Sean D., LTC MC. Percutaneous Arterial Closure After Diagnostic and Interventional Endovascular Procedures: A Prospective Randomized Evaluation of the Perclose Device in Patients with Peripheral Vascular Disease. (10/24/2000) | 233 |
| 02-21000E | O'Donnell, Sean D., LTC MC. Popliteal Entrapment -- An Anatomical Review. (2/15/2002) | Exempt |
| 02-21001E | Wakefield, Matthew C, CPT MC. Re-evaluation of Carotid Duplex for Visual Complaints: Who Really Needs to be Studied. (3/19/2002) | Exempt |
| 02-21002 | Parker, Mary V., MAJ MC. Three-Dimensional Computed Tomography Versus Arteriography for Endovascular Aortic Graft Sizing. (11/20/2001) | New |
| 2125 | Villavicencio, Leonel J., M.D. DAC. Post-Sclerotherapy Pigmentation. Can it be Prevented by Early Microthrombectomy? A Controlled Trial in Varicose Vein Patients. (2/25/1997) | 234 |
| 2130-99 | Gillespie, David L., LTC MC. Dose Protease Gene Expression Vary by Location in the Lower Extremity in Patients with Primary Varicose Veins or Chronic Venous Insufficiency as Compared to Controls?. (2/2/1999) | 235 |
| 2131-99 | Gillespie, David L., LTC MC. Is the Bacterium Chlamydia Pneumoniae a Possible Inciting Agent for the Development of Atherosclerosis of the Carotid or Coronary Arteries?. (4/6/1999) | 236 |
| ***Plastic Surgery Service*** | | |
| 02-29001 | Jorgenson, Daniel S., COL MC. Breast Reduction in Physically Active Women: Descriptive Report of Active Duty Army Soliders. (3/19/2002) | New |
| 02-29002 | Jorgenson, Daniel S., COL MC. Mentor Adjunctive Study for Silicone Gel-Filled Mammary Prostheses. (7/16/2002) | New |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| *Urology Service* | | |
| 00-2801 | McLeod, David G., COL MC. Mentor Saline Filled Testicular Prosthesis Adjunct Study. (1/18/2000) | 295 |
| 01-28001 | Dean, Robert C., LTC MC. SWOG: S0000 -Selenium and Vitamin E Cancer Prevention Trial (SELECT), Phase III Study. (2/20/2001) | 296 |
| 01-28002 | McLeod, David G., COL MC. A Pilot Study to Evaluate the Safety and Feasibility of Thermal Ablation with ThermoRodsTM for Residual Prostate Cancer Following External Beam Radiation Therapy. (3/20/2001) | 297 |
| 01-28003 | McLeod, David G., COL MC. AMS002.2: Evaluation of the Safety and Tolerability of Transurethral Dehydrated Alcohol Injection for the Treatment of Benign Prostatic Hyperplasia. (5/15/2001) | 298 |
| 01-28004 | Paquette, Edmond, MAJ MC. An Exploratory Comparison Between Lemonade and Potassium Citrate: The Impact on Urine pH and 24 Hour Urine Parameters. (6/26/2001) | 300 |
| 01-28005 | McLeod, David G., COL MC. An Open-Label, Multi-Center, Ascending, Single Dose Study Investigating the Pharmacokinetics, Pharmacodynamics and Safety of FE200486 in Prostate Cancer Patients. (8/21/2001) | 301 |
| 01-28006 | McLeod, David G., COL MC. An Open-Label, Multi-Center, Extension, Single Dose Study Investigating the Long-Term Safety and Tolerability of Repeat Doses of FE200486 in Prostate Cancer Patients. (8/21/2001) | 302 |
| 01-2857-98a | Moul, Judd W., COL MC. Outcome Comparison of Radical Prostaectomy Pathologic Specimens. (5/1/2001) | 303 |
| 01-2857-98b | Moul, Judd W., COL MC. Study of CPDR Multicenter Database to Develop Nomograms on % of Positive Biopsy Cores, Gleason Sum, and Pre-Biopsy PSA to Predict Pathologic Stage in Radical Prostatectomy Patients. (6/5/2001) | 304 |
| 01-2857-98c | Moul, Judd W., COL MC. Development of Internet-Accessible Prediction Models for Prostate Cancer Diagnosis, Treatment and Follow-up. (8/7/2001) | 306 |
| 01-2871-98a | McLeod, David G., COL MC. Characterization of Novel Prostate Specific Gene, PCGEM1. (2/20/2001) | 307 |
| 01-2871-98b | McLeod, David G., COL MC. The Use of Transformed Prostate Cell Lines CPDR7, CPDR8 and CPDR9 to Evaluate the Capacity of T Lymphocytes to Recognized Prostate-derived Antigens. (4/10/2001) | 309 |
| 01-2871-98c | McLeod, David G., COL MC. Characterization of a Prostate Specific G-Protein Coupled Receptor (PSGR) in Prostate Cancer. (8/7/2001) | 311 |
| 02-01-28001 | Moul, Judd W., COL MC. S000A: Prevention of Alzheimer's Disease With Vitamin E and Selenium (PREADVASE), Phase III Ancillary to S0000 - SELECT. (7/30/2002) | New |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-28007 | Schenkman, Noah S., LTC MC. Mutiservice Laparoscopic Surgical Training in Pigs (Sus scrofa domestica) Using the DaVinci Surgical System. (11/13/2001) | New |
| 02-28008 | McLeod, David G., COL MC. A Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial Evaluating DCVaxTM Prostate Autologous Dendritic Cells Loaded with Recombinant Prostate Specific Membrane Antigen (rPSMA) for the Treatment of Metastatic Hormone Refractory Prostate Cancer (Trial DC3-HRPC). (2/12/2002) | New |
| 02-28009 | McLeod, David G., COL MC. An Open-Label, Multi-Center, Ascending, Single Dose Study Investigating the Pharmacokinetics, Pharmacodynamics and Safety of FE200486 in Prostate Cancer Patients - Protocol FE200486 CS06. (7/30/2002) | New |
| 02-28010 | McLeod, David G., COL MC. An Open-Label, Multi-Center, Extension Study Investigating the long-Term Safety and Tolerability of Repeat Doses of FE200486 in Prostate Cancer Patients - Protocol FE200486 CS06A. (7/30/2002) | New |
| 02-28011 | McLeod, David G., COL MC. An Open-Label Trial on the Effect of I.V. Zometa 4 mg on Bone Mineral Density in Hormone Sensitive Prostate Cancer Patients with Bone Metastasis. (8/13/2002) | New |
| 02-2801a | McLeod, David G., COL MC. The Utility of Using Gene-Specific DNA Hypermethylation Detectable in Serum as an Early Detection Molecular Marker of Prostate Cancer. (4/18/2002) | New |
| 02-2801b | Moul, Judd W., COL MC. Clinical Study Protocol: FastPackTM FREE PSA Immunoassay. (7/23/2002) | New |
| 02-2801c | Moul, Judd W., COL MC. Clinical Study Protocol: FastPackTM PSA Immunoassay. (7/23/2002) | New |
| 02-2857-98d | Moul, Judd W., COL MC. Assessing the Predictive Accuracy of Prostate Cancer Prognostic Factors Using Traditional Statistical Methods and Artificial Neural Networks. (10/2/2001) | 313 |
| 02-2857-98e | Moul, Judd W., COL MC. Statistical Modeling Using Pre-Operative Prognostic Variables in Predicting Extracapsular Extension, Positive Margins and Outcome After Radical Prostatectomy for Prostatic: Retrospective Study using the CPRDR Prostate Cancer Database. (10/9/2001) | 314 |
| 02-2857-98f | Moul, Judd W., COL MC. A Deterministic Computer Model of Prostate Cancer Progression Following Radical Prostatecomy. (1/8/2002) | 315 |
| 02-2857-98g | Moul, Judd W., COL MC. The Utility of Gene-Specific DNA Hypermethylation Within Diagnostic Sextant Biopsies as an Early Detection Molecular Marker of Prostate Cancer. (4/18/2002) | New |
| 02-2857-98h | Moul, Judd W., COL MC. Evaluation of Gene-Specific DNA Hypermethylation as a Molecular Marker to Predict Risk of Biochemical Recurrence Among Men with Clinically Localized Prostate Cancer Who Undergo Radical Prostatectomy. (5/7/2002) | New |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-2857-98i | Taylor, John A., LCDR MC. Clinical Significance of Post Therapy PSA Detected by Ultra Sensitive Assays in the Follow-up of Prostate Cancer (CaP). (6/4/2002) | New |
| 02-2857-98j | Moul, Judd W., COL MC. Prostate Cancer Lifestyle Trial and CPDR Database Comparison. (6/4/2002) | New |
| 02-2857-98k | Moul, Judd W., COL MC. Assessment of Hormonal Therapy on Survival Benefit of Prostate Cancer and Development of an Optimal Management System for Hormonal Therapy. (9/24/2002) | New |
| 02-2871-98d | Moul, Judd W., COL MC. Characterization of Novel Immortalized Primary Prostate Cancer Cell Lines. (7/23/2002) | New |
| 02-2871-98e | Moul, Judd W., COL MC. Serum Protein Patterns as Potential Diagnostic and Prognostic Biomarkers for Prostate Cancer. (5/7/2002) | New |
| 02-2871-98f | Moul, Judd W., COL MC. Functional Characterization of Hespin, A Transmembrane Serine Protease in Prostate Cancer. (7/23/2002) | New |
| 02-2871-98g | Moul, Judd W., COL MC. Probing Mechanisms of p53 Regulation of Maspin Expression in Prostate Cancer Cells. (8/20/2002) | New |
| 02-2871-98h | Moul, Judd W., COL MC. PMEPA1, A Prostate Abundant-Androgen Regulated Gene: Evaluation of Expression and Function in Prostate Cancer. (9/10/2002) | New |
| 2801 | McLeod, David G., COL MC. Establishment of a Serum Bank for the Future Detection of New Prostate Cancer Markers in Serum of Patients with Prostate Cancer, Benign Prostate Conditions, and no Prostate Disease. (12/6/1994) | 316 |
| 2802 | Moul, Judd W., COL MC. Center for Prostate Disease Research Prostate Cancer Radical Prostatectomy Follow-up Questionnaire. (12/13/1994) | 317 |
| 2804 | Schenkman, Noah S., LTC MC. Medical Therapy in Benign Prostatic Hyperplasia: Full-Scale Trial. (1/31/1995) | 318 |
| 2809 | McLeod, David G., COL MC. Multi-Center Prospective Cohort Study to Evaluate the Safety and Effectiveness of the American Medical Systems (AMS) Ambicor TM Inflatable Penile Prostheses. (8/29/1995) | 319 |
| 2812 | McLeod, David G., COL MC. A Randomized Double-Blind Comparative Trial of Bicalutamide (Casodex TM) Versus Placebo in Patients with Early Prostate Cancer. (11/28/1995) | 320 |
| 2813 | Moul, Judd W., COL MC. A Phase II Study to Determine the Effects of Finasteride and Flutamide on Patients with Rising PSA's who Have had Radical Prostatectomy, Radiation, or Cryoablation Treatment for Localized, Primary Prostate Cancer. (2/27/1996) | 321 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 2827 | Moul, Judd W., COL MC. A Phase II Study to Determine the Effect of Flutamide on Patients with Rising PSA's Who Have Had Radical Prostatectomy, Radiation or Cryoablation Treatment for Localized Primary Prostate Cancer. (1/28/1997) | 322 |
| 2832 | Moul, Judd W., COL MC. Retrospective Study of CPDR Multicenter Database to Develop Nomograms Based on Sextant Positive Biopsy Cores, Gleason Sum, and Pre-Biopsy PSA to Predict Pathologic Stage in Radical Prostatectomy Patients. (11/19/1997) | 323 |
| 2834 | Moul, Judd W., COL MC. Retrospective Review of Three-Dimensional (3D) Computerized Tumor Volume Determination in Radical Prostatectomy Specimens from Black and White Patients. (11/24/1997) | 324 |
| 2836 | Moul, Judd W., COL MC. Three-Dimensional, Ultrasonic Visualization Prostate Cancer. (11/25/1997) | 325 |
| 2837 | McLeod, David G., COL MC. NPCP 2200 A Comparison of Leuprolide with Leuprolide and Flutamide in Previously Untreated Patients with Clinical Stage D2 Cancer of the Prostate. (2/26/1985) | 326 |
| 2840-98 | McLeod, David G., COL MC. Agent Orange Exposure in Vietnam Veterans and the Risks of Prostate Cancer. (2/10/1998) | 327 |
| 2841-98 | Dean, Robert C., LTC MC. Association of 6q Allelic Losses in a Subset a Primary Human Prostate Cancer. (2/10/1998) | 328 |
| 2843 | McLeod, David G., COL MC. ECOG EST 1887 A Phase III Trial of Cystectomy Alone Vs. Neoadjuvant M-VAC + Cystectomy in Patients with Locally Advanced Bladder Cancer. (10/25/1988) | 329 |
| 2843-98 | Moul, Judd W., COL MC. Statistical Modeling Using Pre-Operative Prognostic Variables in Predicting Extracapsular Extension, Positive Margins and Outcome After Radical Prostatectomy for Prostate Cancer: Retrospective Study Using the CPDR Prostate Cancer Database. (2/2/1998) | 330 |
| 2846-98 | Moul, Judd W., COL MC. Assessing the Predictive Accuracy of Prostate Cancer Prognositic Factors Using Traditional Statistical Methods and Artificial Neural Networks. (3/12/1998) | 331 |
| 2852-98 | Petroski, Rayford, MAJ MC. Comparison of Disease Progression in pT3 Prostate Cancer Receiving Adjuvant or Salvage Radiotherapy Following Radical Prostatectomy. (5/5/1998) | 332 |
| 2854-98 | McLeod, David G., COL MC. ECOG EST 3886 Randomized Phase III Evaluation of Hormonal Therapy Vs. Observation in Patients with Stage D1 Adenocarcinoma of the Prostate Following Pelvic Lymphadenectomy and Radical Prostatectomy. (2/5/1998) | 333 |
| 2857-98 | Moul, Judd W., COL MC. Multicenter Prostate Cancer Database for the Center for Prostate Disease Research (CPDR) with Patterns of Care, Outcomes, and Prognostic Analysis. (5/26/1998) | 334 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 2858-98 | McLeod, David G., COL MC. An Ultrasound Based System for Examination and Diagnosis of Prostate and Urinary Conditions - A Phase I Clinical Study. (5/26/1998) | 346 |
| 2859-98 | McLeod, David G., COL MC. SWOG 8894 A Comparison of Bilateral Orchiectomy with or without Flutamide for the Treatment of Patients with Histologically Confirmed Stage D2 Prostate Cancer. (2/5/1998) | 348 |
| 2861-98 | McLeod, David G., COL MC. ECOG P-Z887 A Phase I Study of Intravesical Tumor Necrosis Factor in the Treatment of Superficial Bladder Cancer. (2/5/1998) | 349 |
| 2864-98 | Moul, Judd W., COL MC. ECOG EST 9887 A Phase III Trial of Treatment of Pathologic Stage C Carcinoma of the Prostate with Adjuvant Radiotherapy. (2/5/1998) | 350 |
| 2867-98 | McLeod, David G., COL MC. Advanced Computer Algorithms for Assessing Prognostic and Treatment Variables in Prostate Cancer. (6/22/1998) | 351 |
| 2871-98 | McLeod, David G., COL MC. Creation of a Tissue Library for the Molecular Biologic Study of Patients with Prostate Cancer. (7/21/1998) | 352 |
| 2873-98 | Dean, Robert C., LTC MC. Macroscopic and Microscopic Anatomy of the Arterial Supply to the Human Vas Deferens. (8/11/1998) | 361 |
| 2877-98 | McLeod, David G., COL MC. Study of the Safety and Effectiveness of the Mentor Saline-Filled Testicular Prosthesis. (9/1/1998) | 362 |
| 2879-99 | McLeod, David G., COL MC. A Randomized Double-Blind Comparative Trial of Bicalutamide (CASODEXTM) 150mg Montherapy Versus Placebo in Patients with a Rising PSA after Radical Prostatectomy for Prostate Cancer. (10/20/1998) | 363 |
| 2881-99 | Moul, Judd W., COL MC. Retrospective Study of the CPDR Prostate Cancer Database to Perform Statistical Modeling Using Pre-Treatment Prognostic Variables in Predicting Disease Progress After Radiotherapy for Clinically Localized Prostate Cancer. (10/29/1998) | 364 |
| 2883-99 | Siegel, Timothy, MAJ MC. Cyclosporine Treatment and the Effect on Post Vasovasostomy Semen Parameters in the Lewis Rat. (11/3/1998) | 365 |
| 2887-99 | Dean, Robert C., LTC MC. ALZA Overactive Bladder Registry Design Document. (6/8/1999) | 366 |
| 2888-99 | McLeod, David G., COL MC. An Open-Label, Randomized, Parallel Group Study Comparing the Perioperative Administration of Procrit (Epoetin Alfa) Plus Iron Versus Iron Alone in Patients Undergoing Radical Retropubic Prostatectomy for the Treatment of Prostate Cancer. (6/22/1999) | 367 |
| 2889-99 | Moul, Judd W., COL MC. Radical Prostatectomy of Prostate Cancer Patient and Circulating Cancer Cell Test (CCCT). (7/27/1999) | 368 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 2890-99 | Dean, Robert C., LTC MC. Creation of A Prospective and Retrospective Database of Patients Evaluated and Treated for Urinary Incontinence. (8/24/1999) | 369 |
| 2891-99 | Schenkman, Noah S., LTC MC. Ureteral Stenting after Distal Ureteroscopy and Stone Retrieval: A Prospective Randomized Study. (8/24/1999) | 370 |
| 2892-99 | Moul, Judd W., COL MC. #VCL 1102-202: Phase II Study Evaluating the Safety and Efficacy of Neoadjuvant Leuvectin Immunotherapy for the Treatment of Prostate Cancer (and Amendment 1). (8/31/1999) | 371 |
| 2893-99 | Moul, Judd W., COL MC. #VCL 1102-203: Phase II Study Evaluating the Safety and Efficacy of Leuvectin Immunotherapy for the Treatment of Locally Recurrent Prostate Cancer Following Radiation Therapy (and Amendment 1). (8/31/1999) | 373 |
| 2894-99 | Schenkman, Noah S., LTC MC. Database of Urinary Stone Patients. (9/7/1999) | 375 |
| ***Deployment Health Clinical Center*** | | |
| 02-89003 | Engel, Charles C., LTC MC. A Randomized Clinical Trial of Cognitive-Behavioral Treatment for PTSD in Women. (10/16/2001) | New |
| 02-89004 | Liu, Xian, Ph.D. DoD. Veterans Status and Health and Mortality in Older Americans. (1/22/2002) | New |
| 02-89005 | Engel, Charles C., LTC MC. Use of Focus Groups to Develop Background Information in Support of Health-e VOICE: A Web-Based Clinical Risk Communication Distance-Learning Tool. (2/12/2002) | New |
| 02-89006 | Engel, Charles C., LTC MC. Brief Cognitive-Behavioral Treatment for Victims of Mass Violence. (6/25/2002) | New |
| 8900-99 | Engel, Charles C., LTC MC. Antibiotic Treatment of Gulf War Veterans' Illnessess. (3/23/1999) | 610 |
| 8901-99 | Engel, Charles C., LTC MC. A Randomized, Multi-Center, Controlled Trial of Multi-Modal Therapy in Veterans with Gulf War Illnesses. (3/23/1999) | 611 |
| ***Dewitt Army Community Hospital*** | | |
| 02-83002E | Saguil, Aaron, CPT MC. The Role of Research in Influencing the Discussion of Spiritual Beliefs and Practices with Family Practice Patients. (4/15/2002) | Exempt |
| 02-83003E | Saguil, Aaron, CPT MC. Travel Requirements of Physicians in Sports Medicine Fellowship Programs. (6/10/2002) | Exempt |
| ***Fort Belvoir, VA*** | | |
| 01-83001 | Bell, Michael, MAJ MC. Factors Related to Infant Feeding Choices. (2/13/2001) | 590 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| ***Fort Knox, KY*** | | |
| 00-8101 | Dunn, Sheryl L., MAJ MS. A Prospective Study to Evaluate the Testing of Individual Donor Units from Voluntary Blood Donations for the Presence of HIV-1/HCV RNA. (6/20/2000) | 589 |
| 02-81002 | Raney, Lance, MAJ MC. Evaluation of Problem-Knowledge Couplers in the Military Health System. (3/26/2002) | New |
| ***Fort Monmouth, NJ*** | | |
| 8500-99 | Spain, John, MAJ MS. An Analysis and Comparison of Pharmacy Service Provider Selection Among Military Beneficiaries for Maintenance Medication. (1/5/1999) | 591 |
| ***Landstuhl Regional Medical Center*** | | |
| 00-8501 | Morris, Francis, COL MC. Prevalence of Helicobacter pylori Seropositivity in Allergic Rhinitis and Asthma. (1/11/2000) | 592 |
| 00-8502 | Schneider, Brett J., CPT MC. Tele-Psychiatry in the Division: A Study of Diagnostic Reliability and Cost Benefits using Desktop VTC. (7/18/2000) | 593 |
| 00-8503 | Schissel, Daniel, MAJ MC. Genetic Investigations of Psueofolliculitis Barbae, PFB, in United States Armed Forces. (8/15/2000) | 595 |
| 00-8504 | Hess, Todd D., LTC MC. Racial Differences in Central Corneal Thickness Between Caucasian and African-American Subjects. (9/19/2000) | 597 |
| 02-85005 | Driscoll, Dennis M., LTC AN. Nursing's Retention of Trauma Resuscitation Skills. (11/13/2001) | New |
| 02-85006 | Ramirez, Haby I., CPT MS. Remote Armed Forces Tele-ocular Health: A Pilot Study. (5/28/2002) | New |
| 8502-99 | Etzenback, John, MAJ MC. Highly Toxic Clone of Actinobacillus actinomycetemcomitans and Polymorphism in Interleukin-1 and Tumor Necrosis Factor-a Gene. (12/15/1998) | 598 |
| ***PENTAGON*** | | |
| 02-90001NR | Erickson, Ralph Loren, LTC MC. Pentagon Post-Disaster Health Assessment (PPDHA). (10/4/2001) | New |
| ***Telemedicine Directorate*** | | |
| 01-87001 | Jacobs, Mark, MA DoD. The Comparison of Digital Camera Running Gait Analysis to the Telemedicine Consult System: A Pilot Study. (5/29/2001) | 602 |


* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

| PROTOCOL NUMBER | PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE | PAGE* VOL II |
|---|---|---|
| 02-87001E | Abbott, Kevin C., LTC MC. Walter Reed Army Medical Center's Web-based Electronic Health Portal. (9/23/2002) | Exempt |
| 02-87002 | Poropatich, Ronald, COL MC. User Needs Assessment and Usability Studies of Personal Digital Assistants (PDAs) in Clinical Practice. (2/19/2002) | New |
| 02-87003 | Poropatich, Ronald, COL MC. Benchmark Usability Study of Personal Digital Assistants (PDAs) in Clinical Practice, Participatory Design and Visioning. (4/16/2002) | New |
| 02-87004 | Marin, Raul, LTC MC. Neuromuscular Rehabilitation Via Telebiofeedback as a Portal for Home Care. (4/30/2002) | New |
| 8700 | Schenkman, Noah S., LTC MC. Evaluation of Telesurgical/Robotic Presence. (11/25/1997) | 603 |
| 8701-98 | Bower, Kraig, S., LTC MC. Clinical Evaluation of a High Resolution Digitized Stereo Video Slit Lamp for Use in Teleophthalmology. (7/14/1998) | 604 |

* Page # for protocol summary in vol II. New is an FY2002 protocol which doesn't yet require an annual summary.

FY 2002 PUBLICATIONS BY DEPARTMENT/SERVICE AND AUTHOR

| CITATION | TYPE |
|---|---|
| ***DENTAL ACTIVITY (WRAMC)*** | |
| Demsar WJ : Palatal mucosal calcified nodule: Case report and review of the literature. 56th Annual Meeting of the American Academy of Oral and Maxillofacial Pathology, New Orleans LA, April 2002. | Presentation |
| Demsar WJ, SB Williams : Palatal mucosal calcified nodule: Case report and review of the literature. Oral Surgery Oral Medicine Oral Pathology, 94:211, 2002. | Abstract |
| Haddad JI : Osteochondroma of the mandible condyle presenting as temporomadibular joint dysfunction: A case report. General Dentistry, 50(2):200, March-April 2002. | Abstract |
| Shroff DV, A McWhorter, S Seale : Evaluation of aggressive pulp therapy in a population of vitamin d-resistant rickets patients. Pediatric Dentistry, 24(4):347-350, July-August 2002. | Abstract |
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| Agnello V : NK, LAK cells: Origin, receptors, function. National Institutes of Health, Bethesda MD, May 2002. | Presentation |
| Agnello VA, MR Nelson : Portal hypertension associated with noncaseating granulomatous disease in a patient with common variable immunodeficiency. J Allergy Clin Immunology, 109(1):S193 abstract # 571, 2002. | Abstract |
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| Ales N : Adhesion glycoproteins, cell trafficking. National Institutes of Health, Bethesda MD, April 2002. | Presentation |
| Brown L, H Patterson, R Katial : A case of cyclical asthma exacerbations and associated left upper lobe collapse. Ann of Allergy, Asthma, and Immunology, 88(1):18, January 2002. | Publication |
| Brown LL, WF Kelly, OW Hnatiuk, RK Katial : A case of common variable immunodeficiency with asymptomatic BOOP. J Allergy Clin Immunology, 109(1):S195 abstract # 579, January 2002. | Abstract |
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| Chowdhury BA : FDA perspective on the use of objectives methods in evaluation of rhinitis drugs. Annual American Academy of Allergy, Asthma, & Immunology, New York NY, March 2002. | Presentation |
| Engler R : Asthma in military. MG Timboe, NARMC, Washington DC, August 2002. | Presentation |
| Engler R : Bioterrorism. National Institutes of Health, Bethesda MD, May 2002. | Presentation |

# FY 2002 PUBLICATIONS BY DEPARTMENT/SERVICE AND AUTHOR

| CITATION | TYPE |
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DEPARTMENT OF CLINICAL INVESTIGATION (DCI)

# ANNUAL RESEARCH PROGRESS REPORT

# FY 2002 VOLUME II

WALTER REED ARMY MEDICAL CENTER, WASHINGTON, DC

Report Date: 15 December 2001 Work Unit # 00-1001

# DETAIL SUMMARY SHEET

TITLE: The Stability of Physical Symptoms and Psychiatric Illness Among Primary Care Patients

KEYWORDS:

PRINCIPAL INVESTIGATOR: Jeffrey L. Jackson, LTC MC
ASSOCIATES: Mark Passamonti

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: C
INITIAL APPROVAL DATE: 01 February 2000

## STUDY OBJECTIVE

1. To assess the natural history of mental disorders among primary care patients at 1 and 5 years follow-up.
2. To assess the outcome of the physical symptom for which patient initially sought medical care, 1 and 5 years later.

## TECHNICAL APPROACH

Surveys conducted one and five years after initial enrollment in two WRAMC studies (WU 1039, WU 1057-98).

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been no new recent literature findings. The number of subjects enrolled to the study since last APR at WRAMC is 475 and the total enrolled to date at WRAMC is 475. Enrollment is complete. There have been no adverse events during this study and no patients withdrew from the study.

## CONCLUSIONS

We were unable to get follow-up information on 392 of the 500 patients enrolled in study work unit # 1039. Data analysis is ongoing. We were only able to enroll 50% of the subjects in work unit # 1057-98, due to the constrained time limits due to delay in protocol approval. The focus of data analysis will be on the 5-year follow-up cohort defined by subjects in work unit # 1039, rather than the 1-year follow-up among subjects in work unit # 1057-98.

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Report Date: 26 November 2001 Work Unit # 00-1002

# DETAIL SUMMARY SHEET

TITLE: Myositis–Specific Antibodies in Subjects with Idiopathic Interstitial Lung Disease

KEYWORDS: myositis-specific antibody, anti-Jo-l antibody, interstitial lung disease, idiopathic pulmonary fibrosis

PRINCIPAL INVESTIGATOR: CPT Donald Helman, MC
ASSOCIATES: LTC Gregory Argyros MC; CPT Jesse Bolton MC

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: C
INITIAL APPROVAL DATE: 08 February 2000

## STUDY OBJECTIVE

- Determine the prevalence of myositis specific antibodies (MSA) in subjects with idiopathic interstitial lung disease.
- Compare clinical characteristics of those vs. those without MSA.

## TECHNICAL APPROACH

- Subjects identified through pulmonary service
- Interested subjects sign consent form, undergo directed history and physical examination, have existing radiology and laboratory data reviewed, and undergo one time blood draw.
- Sera are screened for baseline chemistries, for indicators of muscle inflammation, and for the anti-Jo-l antibody.

## PRIOR AND CURRENT PROGRESS

No pertinent published literature specifically regarding our study question.
No amendments or modifications since last review.
Since last review, we have enrolled three more patients at WRAMC. Zero subjects enrolled at BAMC. The number of subjects enrolled to the study since last APR at WRAMC is three, and the total enrolled to date at WRAMC is 23. The total number enrolled study-wide is 35, if multi-site study.

## CONCLUSIONS

The prevalence of anti-Jo-l antibodies in subjects with idiopathic interstitial lung disease is very low (95% CI 0-9%).

Report Date: 1 January 2002 Work Unit # 00-1003

# DETAIL SUMMARY SHEET

TITLE: Can Ambulatory Teaching Seminars Improve Amount and Quality of Feedback to Medical Students in the Outpatient Setting?

KEYWORDS: Feedback, Ambulatory Teaching, Medical Students

PRINCIPAL INVESTIGATOR: Stephen M. Salerno MAJ MC
ASSOCIATES: Jeffrey L. Jackson LTC MC

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: C
INITIAL APPROVAL DATE: 22 February 2000

## STUDY OBJECTIVE

To determine if attending physicians in the ambulatory setting can improve the amount and quality of written and verbal feedback given to medical students after three 90-minute seminars on evaluation and feedback.

## TECHNICAL APPROACH

Nine faculty members were consented and participated in a pre-post study of a faculty development program consisting of three 90-minute interactive seminars teaching evaluation, feedback, and One-Minute Preceptor micro skills. Survey and audiotapes were collected of ambulatory teachings encounters with 3rd year medical students before and after the intervention. The audiotapes were transcribed and coded by individuals blind to the identity of the teachers and learners. Transcripts were coded using the Teacher Learner Interactive Assessment System; a qualitative tool designed to comprehensively code all utterances into mutually exclusive categories. Ten percent of audiotapes were double coded to assess inter-rater agreement. Surveys assessed learner and teacher satisfaction, perception of amount and quality of several aspects of the encounter including feedback. Finally, both learners and teachers recorded a grade for the encounter using the RIME taxonomy. All data was acquired in accordance with study protocol.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Review of Recent Literature:

There has continued to be scant literature on the delivery of feedback to medical students in the ambulatory setting. The faculty development model we used based on the "One Minute Preceptor" trial was described in a September 2001 study on resident physicians in the inpatient setting. (Furney SL, Orsini AN, Orsetti KE, Stern DT, Gruppen LD, Irby DM. Teaching the One-Minute Preceptor: A Randomized Controlled Trial. *J Gen Intern Med* 2001; 16:620-624.) This study measured by student and intern satisfaction with resident teaching and resident self-evaluation. The residents undergoing training in Five Microskills techniques felt better able to evaluate and provide feedback to their learners, which was similar to our results. Learners had significantly greater perception that they had a larger part in clinical decision making, more feedback, and greater stimulus to self-directed learning when "One-Minute Preceptor" techniques were used. This differs from our results where no significantly different perception in learners was demonstrated. We feel that the teachers and learners in the inpatient setting may have had greater length and continuity of interaction allowing more subtle changes to be detected.

Prior and Current Progress:

The data from this study was collected between February and July of 2000 and no data has been collected since this period of time. The study protocol should be considered closed for administrative purposes, though the data obtained from the study may result in additional abstracts or publications for several years.

Nine teachers and 64 third year medical students participated; providing 45 audiotaped encounters before and 48 encounters after the seminars. 17,859 utterances were coded. Coders achieved a high degree

of agreement (Spearman's rho >0.8). In the baseline encounters, 17% of teacher utterances were some form of feedback, predominantly (92%) minimally positive statements such as "right" or "I agree". Only 8% of feedback utterances were specific and none were interactive. Most (91%) of the feedback was positive. After the faculty development workshops, the amount and quality of feedback increased; teachers were more likely to provide verbal feedback (OR 1.21; 95% CI 1.07-1.36) and that feedback was nearly twice as likely (OR 2.08; 95% CI 1.45-2.99) to be specific. Both learner (p=0.82) and teacher (p=0.08) satisfaction with the amount of feedback did not change before and after the seminars. Learner perception the feedback was linked to specific behaviors did not change (p=0.80) as a result of the seminars. However, teacher satisfaction that the feedback provided was specific did significantly improve after the seminars. (p=0.007). The total time spent teaching during the ambulatory encounters was 14.2 $\pm$ 5.3 minutes before and 15.6 $\pm$ 6.7 minutes after the seminars, a non-significant difference (p=0.28).

275 post-encounter written feedback statements were also analyzed; 48 written statements before and 49 after the seminars. After the workshops, the average number of feedback statements per card increased slightly, with 2.6 $\pm$ 1.3 statements before and 3.1 $\pm$ 2.0 statements after the seminars (p=0.2). Most (58%) of the feedback was formative, with the remainder summative. The most common (30%) type of feedback was formative feedback dealing with student knowledge base. After the seminars the amount of specific feedback increased from 21% to 32% (p=0.02) and the proportion of feedback dealing with student skills increased from 15 to 29% (p=0.01). Preceptors were nearly twice as likely (OR 1.93; 95% CI 1.05 – 3.59) to give corrective written feedback after the seminars.

We also examined teacher-student agreement on grades. Preceptors graded 7% of students as reporters 7% of students as reporters, 46% as interpreters 45% as managers 45%, and 2% as educators. There was poor agreement among students and teachers (weighted kappa =0.0374) on grades after each encounter. Of the 71% encounters where teachers and students disagreed, the students assigned themselves a higher grade 76% of the time. In all cases of disagreement, teachers and students differed only by one RIME grade. Learning climate, student perception of the amount of feedback, and overall student satisfaction with the encounter were not associated with student-preceptor agreement on post-encounter grades (p>0.05 for all). The number of feedback statements and whether the statements were specific or corrective were also not related to student-preceptor agreement on post-encounter grades.(p>0.05 for all).

## CONCLUSIONS

Faculty development seminars can modestly improve the quality of written and verbal feedback in the outpatient setting. Students and teachers frequently disagree over the exact nature of student performance, and student-teacher agreement with student performance does not seem related to the amount or quality of feedback delivered.

Report Date: 02 October 2002 Work Unit # 1044

# DETAIL SUMMARY SHEET

TITLE: Improving Teaching in the Ambulatory Setting: A Study Using Observed Teaching Sessions and Participant Evaluations

KEYWORDS: Teaching, Ambulatory, Behaviors

PRINCIPAL INVESTIGATOR: O'Malley, Patrick MAJ MC
ASSOCIATES: Jeffrey L. Jackson, LTC MC; Steven Salerno, MAJ MC

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: C
INITIAL APPROVAL DATE: 2 August 1996

## STUDY OBJECTIVE

To study the types, frequency, and effectiveness of teaching behaviors in ambulatory teaching

## TECHNICAL APPROACH

Prospective study of 103 audiotaped ambulatory encounters involving medical students and interns in the General Internal Medicine clinic at WRAMC. Patients, learners, and teachers filled out surveys before and after the encounters detailing their satisfaction with their encounters. Prospective, qualitative, collective case-study of consecutive audiotaped teaching sessions involving consenting faculty, students, interns, and 103 out of 120 eligible adult patients with acute medical problems presenting to a non-continuity walk-in clinic. Audiotapes were transcribed and qualitatively analyzed by 3 coders using a grounded theory approach, facilitated by NUDIST qualitative software.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Data collection completed in November 1996. Previously reported on the impact of learner involved care on patient satisfaction, and the qualitative assessment of what learners value most in ambulatory learning encounters (see list of publications). A coding scheme to categorize teaching behaviors, derived from the transcribed audiotapes, has been developed and inter-rater reliability assessed. We have a publication in press (Teaching and Learning in Medicine) describing the tool and the prevalence of teaching behaviors. Our plan is to do further analysis to correlate this with learner, patient, and teacher assessment of the satisfaction with and quality of the learning encounter.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 103. The total number enrolled study-wide is NA, if multi-site study.

## CONCLUSIONS

A teacher and learner interactive analysis system (TELIAS) has been developed and a report of this tool is in press.

Report Date: 2 March 2002 Work Unit #1051

# DETAIL SUMMARY SHEET

TITLE: The Yield of Endobronchial Biopsy in the Diagnosis of Sarcoidosis

KEYWORDS: sarcoidosis, biopsy

PRINCIPAL INVESTIGATOR: Shorr, Andrew F. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: General Medicine INITIAL APPROVAL DATE: 24 April 1997

STUDY OBJECTIVE
To determine the yield of Endobronchial Biopsy in the diagnosis of sarcoidosis and to determine the relationship between endobronchial disease and other aspects of sarcoidosis (i.e. airway hyper reactivity, ACE level, and Dimmer status).

TECHNICAL APPROACH
Patients have a series of breathing tests and blood tests and the results of these are correlated with the results from endobronchial biopsy done during bronchoscopy for the diagnosis of suspected sarcoidosis. No modifications have been made to the protocol since it is completed.

PRIOR AND CURRENT PROGRESS
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 46. There have been no adverse events and our data show Endobronchial Biopsy safely increases the yield of Fibrooptic Biopsy.

CONCLUSIONS
Endobronchial Biopsy increases the yield of Fibrooptic Biopsy.
Endobronchial involvement is a risk factor for airway hyperactivity.

Report Date: 2 October 2001

Work Unit # 1053

# DETAIL SUMMARY SHEET

TITLE: Adrenal Suppression Following Short-Term Use of Corticosteroids: Results of a Prospective Study

KEYWORDS: Corticosteroids, adrenal suppression, low-dose ACTH stimulation test

PRINCIPAL INVESTIGATOR: O'Malley, Patrick MAJ MC
ASSOCIATES: Torrens, Javier MAJ MC; Sachar, David CPT MC

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: O
INTIAL APPROVAL DATE: 05 November 1997

## STUDY OBJECTIVE

To determine the presence and duration of measurable adrenal suppression following short-term, high dose prednisone therapy.

## TECHNICAL APPROACH

Prospective study of a convenience sample of patients being treated with short-term, high dose corticosteroid therapy. Participants will be tested for adrenal suppression using a low-dose ACTH stimulation test, at 1 week, and 4 weeks after completion of therapy.

## PRIOR AND CURRENT PROGRESS

As of February 2001, we have completed a prospective assessment of the hypothalamic-pituitary-adrenal axis in a convenience sample of 25 outpatients from Walter Reed Army Medical Center prescribed prednisone (≥20 mg/day) for 5-21 days. A super-sensitive, low dose (1μg) ACTH stimulation test was performed at 1 and 4 weeks post treatment. Serum cortisol levels were measured at 0 and 30 minutes after 1μg ACTH stimulation, at 1 and 4 weeks. At present, a completed manuscript is being prepared for publication.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 25. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

The mean age of the patients was 56.3 years (range 21-85 yrs): 76% were female, and 56% were prescribed oral steroids for respiratory disease. One week after completion of steroid therapy 92%of participants had competent adrenal responses, while 96% were adrenally competent at four weeks. Our data suggests that in medical outpatient receiving short courses of high-dose prednisone, there appears to be a finite period beyond which detectable adrenal suppression is unlikely to occur. Adrenal suppression after short course pulse steroids is probably short-lived and clinically insignificant beyond a few weeks, though further study in larger samples and in patients with significant co-morbidity is needed. The current practice of routine supplementation for stress responses in this group of patients requires further review.

Report Date: 1 April 2002 Work Unit # 1054-98

# DETAIL SUMMARY SHEET

TITLE: Retrospective Analysis of CCEP Phase II Results from the Walter Reed Gulf War Health Center, 1994-96

KEYWORDS: Gulf War, symptoms, somatization, depression

PRINCIPAL INVESTIGATOR: Roy, Michael LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: C
INITIAL APPROVAL DATE: 6 May 1998

## STUDY OBJECTIVE

The objective of this protocol is to perform descriptive analysis of Gulf War veterans evaluated in the Comprehensive Clinical Evaluation Program, and compare them with patients seen at other sites within the CCEP, as well as with all Gulf War veterans' in particular, to examine ill-defined conditions and psychological diagnoses.

## TECHNICAL APPROACH

Comparisons between groups performed primarily by descriptive analysis due to large sample sizes. Data has been extracted from mental health reports by two independent chart abstractors after ensuring that abstraction was reliable by determination of kappa scores for inter-observer variability. The abstracted data is in the process of being analyzed by multivariate linear regression to attempt to identify predictors of psychological conditions.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 660. The total number enrolled study-wide is n/a, if multi-site study. The PI has been too busy with other projects to finish this study and submit it for publication, which has now been the case for several years, so it appears prudent to consider the study completed at this time.

## CONCLUSIONS

Studied Gulf War veterans demonstrated high mean symptom counts, high self-reported disability, and a high prevalence of mental disorders. More detailed evaluation of Gulf War veterans, such as that performed at the WRAMC Gulf War Health Center, points away from a mystery illness, and toward known diagnoses such as depressive and anxiety disorders in many symptomatic Gulf War veterans. Identified predictors of mental disorders include: symptom count, symptom severity, and serious illness worry. Careful consideration of depressive and anxiety disorders is warranted in veterans with multiple symptoms that are not readily explained upon initial medical evaluation.

Report Date: 15 May 2002

Work Unit # 1056-98

# DETAIL SUMMARY SHEET

TITLE: Characterization of the Esophageal Striated Muscle in Patients with Achalasia: A Prospective Study

KEYWORDS: achalasia-striated muscle, manometry

PRINCIPAL INVESTIGATOR: Dunaway, Peter CPT MC
ASSOCIATES: Maydonivitch, Corinne; Wong, Roy COL MC

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: C
INITIAL APPROVAL DATE: 16 June 1998

STUDY OBJECTIVE:
To prospectively compare the esophageal striated muscle manometric characteristics between achalasia patients and age matched controls.

TECHNICAL APPROACH:
Use standard esophageal manometer to measure individual striated muscle contractions. No modifications from the original protocol have been made.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
There are no significant findings with this study or in the literature. No adverse events have occurred.

The number of subjects enrolled to the study since last APR at WRAMC is zero, and the total enrolled to date at WRAMC is five.

CONCLUSIONS:
Due to lack of enrollment, we are closing this study.

Report Date: 28 November 2001 Work Unit # 1060-99

# DETAIL SUMMARY SHEET

TITLE: Diagnostic Accuracy of Pleural Fluid Cholesterol and Lactate Dehydrogenase in Identifying Exudates vs. Transudates

KEYWORDS: pleural effusions, pleural cholesterol, pleural lactate dehydrogenase, exudates, transudates

PRINCIPAL INVESTIGATOR: CPT Jasmine T. Daniels MC
ASSOCIATES: Colin Daniels MD, William Kelly MD, Audrey Chang PhD, David Van Echo MD, Lisa Moores MD

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: O
INITIAL APPROVAL DATE: 12 January 1999

## STUDY OBJECTIVE

1. To validate the results of Costa et al and evaluate the accuracy of Light's criteria in our population of patients.

2. To determine if measurement of pleural fluid cholesterol in combination (paired or triple) with other pleural fluid measurement (LDH and protein) will provide similar or better sensitivity and/or specificity than Light's criteria (which uses serum and pleural fluid measurements) in differentiating exudative and transudative pleural effusions.

## TECHNICAL APPROACH

Have recruited another associate investigator, David Van Echo MD, to assist in gathering the clinical data. We are currently undergoing the process of determining the inter-rater variability and will not have Dr. Van Echo begin data collection independently until this variability has been determined to be $\geq$ 90% (as per the original protocol outline).

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 44 and the total enrolled to date at WRAMC is 151. The last data analysis was performed after 100 patients were enrolled, and there is one pending at this time. There have been no adverse events related to this protocol.

## CONCLUSIONS

The initial data analysis suggests that the diagnostic accuracy of pleural fluid measures of LDH and cholesterol alone are approaching that of Light's criteria, and may ultimately be used in differentiating exudates and transudates. However, ongoing data collection continues.

Report Date: 5 October 2001

Work Unit # 00-1101

# DETAIL SUMMARY SHEET

TITLE: The Effect of Enalapril and Myccophenolate Mofetil in PAN-Induced FSGS in the Rat

KEYWORDS: enalapril, focal and segmental sclerosis, kidney, mycophenolate mofetil

PRINCIPAL INVESTIGATOR: Christina M. Yuan, LTC MC
ASSOCIATES: Dr. Sharda Sabnis, Mrs. Luana Kiandoli

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: C
INITIAL APPROVAL DATE: 2 November 1999

STUDY OBJECTIVE:
In a rat model of focal and segmental sclerosis (FSGS), does treatment with mycophenolate mofetil (MMF) po in addition to the po ACEI, enalapril, given at 3 and 12 weeks after initiation of the disease, result in amelioration of the histologic changes seen in untreated rats.

TECHNICAL APPROACH:
66 male Sprague Dawley rats were divided into 6 groups. Negative controls (normal); positive controls (with PAN induced FSGS); and animals with PAN induced FSGS treated with a) enalapril beginning 3 weeks after initiating FSGS with PAN; b) enalapril and MMF beginning at 3 weeks; c) enalapril beginning at 12 weeks after initiating FSGS; and d) enalapril and MMF beginning at 12 weeks. The 3 week time point was chosen because the earliest renal histologic change is seen at that time point. The 12 week time point was chosen because the animals are nephrotic at that time (and the disease is thus "clinically evident"). At 3, 12, and 18 weeks animals were placed in metabolic cages, and 24-hour urine collected for protein and creatinine. At 18 weeks, after metabolic cage work was completed, all animals were euthanized under anesthesia (ketamine/telazol), and blood and kidneys removed for determination of serum creatinine and renal histology. Euthanasia was accomplished by exsangination, followed opening the chest and ventricular cavity.

PRIOR AND CURRENT PROGRESS:
All rats have been entered into the protocol and were euthanized in May through June 2000 (reported in last APR). Histopathologic evaluation and measurements of proteinuria, and creatinine clearance at 18 weeks are complete. We suspect the six sudden deaths reported in the last APR were secondary to hyperkalemia due to enalapril in the setting of renal insufficiency. Two rats (in each of the MMF groups) developed diarrhea, a recognized complication of MMF.

CONCLUSIONS:
Treatment of PAN-induced FSGS with enalapril/MMF after onset of histopathologic changes and proteinuria appears to somewhat ameliorate interstitial disease at 18 weeks, but has no effect on glomerular disease. Proteinuria at 18 weeks vs. 12 weeks was reduced in all treated groups, with no reduction seen in + PAN controls, suggesting that enalapril, but not MMF, has an effect in reducing proteinuria. MMF has no effect beyond enalapril alone. A paper is in preparation.

Report Date: 11 March 2002

Work Unit # 00-1102

# DETAIL SUMMARY SHEET

TITLE: Tacrolimus and Distal Renal Tubular Acidosis in the Rat.

KEYWORDS: tacrolimus, renal tubular acidosis, rats

PRINCIPAL INVESTIGATOR: CM Yuan, LTC MC
ASSOCIATES: Luana Kiandoli

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 2 May 2000

STUDY OBJECTIVE:
To develop a rat model of renal tubular (non-anion gap) acidosis due to tacrolimus administration. This syndrome is frequently observed in humans receiving the drug in immunosuppressive doses, but has not been described in rats.

TECHNICAL APPROACH:
Forty-one rats (12 controls, 20 receiving 1 mg/kg/day tacrolimus (low dose), and 9 receiving 3 mg/kg/day tacrolimus (high dose) will be randomly entered. They will receive daily either tacrolimus PO in cherry syrup on a whole wheat biscuit, or cherry syrup alone (controls) for up to 8 weeks. Tail blood will be drawn at 4, 6, and 8 weeks to determine presence of acidosis (defined as serum bicarbonate >3 meq/liter lower than control animals), and tacrolimus level. Upon development of acidosis or at 8 weeks of treatment, animals will be placed in metabolic cages, and urine collected to determine urine anion gap and creatinine clearance. Animals will be anesthetized, aortic blood collected for blood gas determination, electrolytes, and BUN/creatinine. They will then be euthanized, and kidneys harvested for histopathologic evaluation. Up to two rats from each group will also undergo bicarbonate loading (per protocol) while anesthetized, to demonstrate the tubular site of acidosis.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
Forty-one rats were treated with oral tacrolimus as per protocol, and all were euthanized in May through June. There were no unexpected deaths; and all animals completed the experiment. Kidneys, serum, and plasma were collected as per protocol. Renal histopathology and serum chemistry is complete. Tacrolimus levels remain to be assayed.

The animals did not develop a significant metabolic acidosis at any time point. There was no significant histopathologic change -- evidence that there was no permanent/irreversible renal damage due to the drug (which can occur at high doses). However, the rats did develop hypomagnesemia and excessive urinary magnesium excretion, which is seen in human patients treated with tacrolimus.

There have been no significant new findings in the literature that would impact on this study. No further animal work will be done. Close-out progress reports have been sent to AFIP IACUC.

CONCLUSIONS:
See above.

Report Date: 03 July 2002

Work Unit # 00-1103

# DETAIL SUMMARY SHEET

TITLE: Measurement of Electrolytes in Microdialysis Samples by Mass Spectrometry

KEYWORDS: electrolytes, microdialysis, inductively-coupled plasma mass spectrometry

PRINCIPAL INVESTIGATOR: Yuan, Christina LTC MC
ASSOCIATES: Oliver, III James D. MAJ MC; Atkins, James L. COL MC; Abdel-Rahim, Maged M. MS; Morris, Elena R.; Pamnani, Motilal B. MBBS, PhD

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 01 August 2000

## STUDY OBJECTIVE

To measure potassium, calcium, and magnesium concentrations in microliter-volume samples obtained by the insertion of microdialysis probes in rat tissues (obtained under active animal use protocol USUHS #G176HX; administered and performed at USUHS).

## TECHNICAL APPROACH

This is an experimental laboratory protocol using existing samples obtained during the performance of an established USUHS animal use protocol (USUHS #G176HX). Twenty animals were approved for use in USUHS #G176HX. Interstitial electrolytes are measured using 15 µl samples using inductively coupled plasma-mass spectrometry (ICP-MS) with internal standards as follows: Rb for K; $^{44}$Ca for Ca, and $^{26}$Mg for Mg.

## PRIOR AND CURRENT PROGRESS

Previously we validated the method for potassium/rubidium. We have established the calibration method for use of the internal standards and demonstrated the viability of the approach on in vitro samples of Ca and Mg, as well. We have begun analysis on the in vivo samples for potassium, calcium, and magnesium.

## CONCLUSIONS

Interstitial potassium concentrations during hemorrhagic shock are elevated earlier, and to a greater degree, than intravascular concentrations. At this point, no clear trend has been seen in the calcium and magnesium concentrations.

Report Date: 2 November 2001 Work Unit # 01-11002

# DETAIL SUMMARY SHEET

TITLE: Electron Beam Computed Tomography (EBCT) as a Screening Tool in the Pre-Renal Transplant Assessment of Patients with End Stage Renal Disease

KEYWORDS:

PRINCIPAL INVESTIGATOR: Yuan, Christina M LTC MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Nephrology INITIAL APPROVAL DATE: 16 January 2001

STUDY OBJECTIVE: To describe the association of EBCT coronary artery calcium score with risk for cardiac events defined by clinical cardiovascular risk assessment (Eagle Score), and cardiac stress test (Dobutamine stress ECHO) in ESRD patients who are candidates for renal transplant, or who are on the transplant list. Secondary objectives are to describe the association of EBCT coronary calcium score with 1) coronary angiographic findings in patients who subsequently receive cardiac catheterization for clinical indications; 2) demographic features (age, sex, race, time on dialysis, hypertension, diabetes) and laboratory values (PTH, homocysteine, CRP, calcium and phosphorus); and 3) occurrence of "hard" coronary events at 1,2,and 3 years post initial evaluation.

TECHNICAL APPROACH: 150 patients with ESRD (CrCl < 20 cc min), who are potential candidates for kidney or kidney pancreas transplantation, and meet the inclusion and exclusion criteria will be entered. This is a prospective, observational study with cross sectional entry. After baseline collection of laboratory, EKG, and demographic data, all participants will undergo a clinical cardiovascular assessment with Eagle score, and referred for Dobutamine Echocardiogram and EBCT (cardiologist, transplant clinician, and patient are blinded to EBCT). Patient will be assessed, and referred for further work-up by cardiology, as clinically indicated (based on EKG, clinical assessment, and Dobutamine Echocardiogram). Yearly, a history of cardiac events will be elicited by telephone, mail, or in person. Analysis of primary outcome: Association between EBCT and Eagle score/Dobutamine stress ECHO will be examined using analysis of variance and discriminate analysis.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE The study received final approval on 1 March 2001. Accrual began in late May 2001. An addendum was submitted for Persantine Thallium testing to be done in place of Dobutamine stress ECHO testing in patients who had a body habitus that did not allow for adequate Echocardiography. This was approved on 31 July 2001. No new literature has been generated on this subject—most recent check was the review of the abstracts submitted to the ASN in October 2001. EBCT was being studied in dialysis patients—but not specifically in patients being evaluated for transplant or on the waiting list. Eight subjects have been entered into the study. Three patients are on dialysis; five are pre-dialysis. No patient had a greater than intermediate Eagle score. Dobutamine stress ECHOs have been performed on three of the eight participants. All three have been "cleared" for transplant surgery. The other Dobutamine stress ECHOs are to be scheduled. No patient has required a Persantine Thallium because of body habitus. There have been no adverse events. There have been no withdrawals. The number of subjects enrolled to the study since last APR at WRAMC is 8 and the total enrolled to date at WRAMC is 8. The total number enrolled study-wide is NA, if multi-site study.

CONCLUSIONS: None available at present.

Report Date: 26 September, 2001 Work Unit # 01-1101

# DETAIL SUMMARY SHEET

TITLE: Epidemiology of Military Beneficiaries Receiving End-Stage Renal Disease (ESRD) Therapy

KEYWORDS:

PRINCIPAL INVESTIGATOR: Welch, Paul COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Nephrology INITIAL APPROVAL DATE: 07 November 2000

STUDY OBJECTIVE: We sought to characterize the military beneficiary population receiving ESRD therapy. Goals included identifying and describing all prevalent military ESRD patients for 1998, and comparing the military ESRD population with the entire US ESRD population.

TECHNICAL APPROACH: The 1998 Defense Manpower Data Center (DMDC) database was compared with the United States Renal Data System (USRDS) database to identify military ESRD patients contained within the USRDS cohort registry. Analysis of all military beneficiaries and the military ESRD population was done using SPSS 9.0 for windows. Racial distribution for the entire military population was estimated from the 27% of military beneficiaries whose race was known.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE: This is the first APR since the study was approved. The following are preliminary results of our analysis. 8,177,611 military beneficiaries are listed in the DMDC database for 1998. Compared with the US population, the military beneficiary population is older (mean 38.4 + 23.2 years vs. mean 36.2 for US), predominantly male (53.4% vs. 48.9% for US), has lower proportion whites (77.3% vs. 82.5% for US), and higher proportion blacks (18.2% vs. 12.7% for US). 17,470 military beneficiaries receiving treatment for ESRD were identified in the USRDS. According to the USRDS, 1,687 (9.7%) of the military ESRD patients died prior to 1998, 1,090 died during 1998, 2,546 started ESRD therapy during 1998, and 4,812 began ESRD therapy after 1998. Point prevalent count (as of 12/31/98) was 9,881 and period prevalence count was 10,971. Unadjusted military ESRD incidence (311 per million vs. 320 per million for US) and prevalence (1,208 per million vs. 1,177 per million for US) were similar to the US population. Unadjusted incidence and prevalence by ESRD etiology were also similar. ESRD incidence ratios (black vs. white) were 1.58 in military vs. 3.10 for US, and prevalence ratios were 2.16 in military vs. 3.58 for US. Reduced racial disparity appeared to be due to lower incidence and prevalence of ESRD in black military beneficiaries. Based on period prevalence and average US costs for ESRD care, $476,657,030 was spent caring for military ESRD patients in 1998. We plan to calculate adjusted incidence and prevalence prior to submitting this work for publication. No individual patients will be interviewed, charts reviewed, or specimens collected. All work has and will be done with previously established databases.

CONCLUSIONS: The military beneficiary population appears to be older, and have a higher proportion of males and racial minorities compared with the US population. ESRD in military beneficiaries by overall unadjusted incidence and prevalence, and by ESRD etiology, appears similar to the US population. ESRD racial disparity between blacks and whites appears to be less in the military. After accounting for deaths and confirming assumptions for military population racial distribution, adjusted ESRD incidence and prevalence should be calculated for the military and compared with the US population. ESRD epidemiology in the military can be used to identify needs, design health promotion programs, measure effects of outcomes management programs, and track progress toward meeting kidney goals of *Healthy People 2010* in the MHS.

Report Date: 1 April 2002 Work Unit # 1186

# DETAIL SUMMARY SHEET

TITLE: The Clinical Efficacy of Transjugular Renal Biopsy: A Pilot Study

KEYWORDS: kidney biopsy, transjugular approach, fluoroscopy

PRINCIPAL INVESTIGATOR: Abbott, Kevin LTC MC
ASSOCIATES: Yuan, Christina LTC MC

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: C
INITIAL APPROVAL DATE: 6 May 1997

## STUDY OBJECTIVE

The main purpose of the study is to describe the diagnostic utility and morbidity associated with transjugular renal biopsy performed at Walter Reed Army Medical Center.

## TECHNICAL APPROACH

The study is a descriptive analysis of the tissue adequacy and diagnosis obtained by the transjugular route. Potential subjects are those adults for whom percutaneous renal biopsy would be contraindicated, in the opinion of their nephrologist, and have been referred for transjugular kidney biopsy. Study was designed to describe retrospectively the outcomes of patients who had the procedure before the study was initiated (exempt), and prospectively (with informed consent) in patients who had already been referred/set up for the procedure. Information to be obtained included indications, adequacy of the tissue obtained, the ability of the pathologist to render a histologic diagnosis, and immediate post-procedure complications. The clinical data collected was at the time of the procedure, and within 24 hours of the procedure.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A recent series of patients who received concurrent kidney and liver biopsy by the transjugular route in patients being evaluated for liver transplant (Sam et al, AJKD;37: 1141 (2001)) has been reported from a group in the United States. This is the largest group of patients reported on thus far in the United States. The investigators used a technique and needle similar to that in use at WRAMC. The tissue adequacy and number of complications was acceptable, especially in patients with such a high bleeding risk due largely to their liver disease. We decided to close our study, both because of this recent series and because we are doing fewer transjugular renal biopsies at WRAMC due to the availability of real-time ultrasound, and laparoscopic kidney biopsy. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 10 (one subject had 2 biopsies and is thus counted twice). The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS:

Adequate tissue for diagnosis was obtained in 9/10 biopsies and in 9/9 patients. 9/9 patients could be accurately diagnosed. The most frequent indication was bleeding diathesis. One patient required two biopsies to obtain adequate tissue. Adequacy of biopsy appeared to correlate with capsular perforation retrograde. A paper is in review.

Report Date: 05 April 2002 Work Unit # 1194-98

# DETAIL SUMMARY SHEET

TITLE: Improving Rates of Acute Renal Allograft Rejection with a Regimen of Cyclosporin, Mycophenolate Mofetial and Prednisone

KEYWORDS: kidney transplantation, allograft rejection, allograft failure, cyclosporin, mycophenolate mofetil

PRINCIPAL INVESTIGATOR: Oliver, James LTC MC
ASSOCIATES: Abbott, Kevin LTC MC; Yuan, Christina LTC, MC; Welch, Paul COL, MC; Swanson, S. John LTC, MC; Reinmuth, Bruce

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 29 May 1998

## STUDY OBJECTIVE

To describe the rates of rejection, graft and patient survival achieved in the WRAMC Renal Organ Transplant program as compared to national averages.

## TECHNICAL APPROACH

A retrospective review of transplant data from the WRAMC Organ Transplant database, from inpatient and outpatient charts being conducted in parallel with querying of the United States Renal Database System (USRDS). Rejection rates as a function of patient characteristics and of immunosuppressive regimen are being compared.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 132. The total number enrolled study-wide is N/A, if multi-site study. The data has been mined and analyzed and five abstracts have been presented to the American Society of Nephrology and the National Medical Association annual meetings in 1999 and 2000. We now intend to submit a modification request to include WRAMC transplants from 1997 to 2001 into the study.

## CONCLUSIONS

Transplant outcomes at WRAMC from 1992-1997 were improved from national data over the same time period. Racial differences between outcomes seen nationally were not seen at WRAMC. Introduction of mycophenolate mofetil and tacrolimus nationally appears to be resulting in some initial trends in improving outcomes.

Report Date: 19 September 2001 Work Unit # 1196-99

# DETAIL SUMMARY SHEET

TITLE: Is HSP47 Expression Upregulated in PAN-Induced FSGS in the Rat, and Dose Pirfenidone Affect This Upregulation?

KEYWORDS: Heat shock proteins, pirfenidone, focal and segmental glomerulosclerosis (FSGS)

PRINCIPAL INVESTIGATOR: C.M. Yuan, LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: C
INITIAL APPROVAL DATE: 13 October 1998

## STUDY OBJECTIVE

PAN-induced FSGS in the rat is a model for FSGS in the human, and will be used in this study to investigate the effects of Pirfenidone, an antifibrotic agent, with and without an ACE inhibitor and an HMG-CoA reductase inhibitor on renal histology and renal function over time. The role of Hsp47 (a collagen chaperone, and a marker of fibrosis) will also be investigated.

## TECHNICAL APPROACH

Sprague Dawley rats will have FSGS induced with serial subcutaneous injections of PAN, and treated with either vehicle, oral enalapril and sq lovastatin; oral pirfendione; or pirfenidone/enalapril/lovastatin. A group of normal control animals receiving vehicle alone will also be studied. Animals will be euthanized at 3, 12, and 18 weeks post PAN-induction, and the light microscopic histopathology of the kidneys assessed. Immunostaining of renal tissue for Hsp47 will also be performed at these time points, as will ELISAs for Hsp47 and TGF-beta in rat serum. 24-hour urine studies, and terminal serum studies for renal function will also be performed.

## PRIOR AND CURRENT PROGRESS

We have completed the animal studies (150 animals), and have shown that at 18 weeks the Pirfenidone/enalapril/lovastatin treated animals are indistinguishable from normal controls with regard to renal function, proteinuria, and renal histology. The enalapril/lovastatin treated animals have intermediate histology, and pirfenidone-treated animals alone are not distinguishable from FSGS control animals. TGF-Beta plasma assays were completed, but proved not to be associated with histologic outcome.

## CONCLUSIONS

The combination of Pirfenidone/enalapril/lovastatin in PAN-induced FSGS appears to inhibit renal function loss as well as chronic histologic change. A paper is in review in Kidney International. All animals (150) approved for the study have been entered, and have been euthanized. One died unexpectedly in an accident, after leaping from a table during an injection.

Report Date: 21 November 2001 Work Unit # 1197-99

# DETAIL SUMMARY SHEET

TITLE: The Impact of Therapeutic Plasma Exchange on the Medications Used in Transplantation

KEYWORDS: Plasmapheresis; Immunosuppression; Pharmacokinetics

PRINCIPAL INVESTIGATOR: Yuan, Christina M LTC MC
ASSOCIATES: Viola, Rebecca MPh

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 19 January 1999

STUDY OBJECTIVE:
Prospective, descriptive study to document the clearance of various immunosuppressive drugs used in renal transplantation by plasmapheresis (TPE). Clearance of one of the following drugs will be assessed using pheresed plasma levels and plasma volume and patient plasma levels: daclizumab; mycophenolate mofetil; ganciclovir; cyclophosphamide; OKT3, and cytomegalovirus hyperimmune globulin.

TECHNICAL APPROACH
Patients ≥ 18 years old undergoing plasmapheresis for various medical indications, and receiving any of the above medications will be asked to participate. Drug levels will be drawn peripherally prior to TPE, immediately post TPE, and at 2 and 4 hours post TPE. Levels will also be determined in the plasma effluent, and the volume of the effluent will be used to determine total clearance of drug. Levels will be determined at various laboratories. All data regarding clearance will be provided to the patient's physician, so that drug dosing and re-dosing may be done in accordance with the clearance data. 5 patients will be entered, as opportunity presents itself. The diseases for which TPE is performed are rare, and the use of these drugs concurrently is also rare.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
No patients have been entered into the study in the past year. None have presented that met the inclusion criteria. The requirement for post-transplant plasmapheresis is a very rare occurrence in our small program -- due to low incidence of post-transplant FSGS. We would like to keep the study open for five years pending the next case.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is NA, if multi-site study.

CONCLUSIONS
None at present.

Report Date: 21 November 2001 Work Unit # 1198-99

# DETAIL SUMMARY SHEET

TITLE: Na+, K+-ATPase Inhibitor in the Mechanism of Hypertension in Diabetes Mellitus

KEYWORDS: diabetes; sodium pump inhibitor, ouabain

PRINCIPAL INVESTIGATOR: Yuan, Christina LTC MC
ASSOCIATES: Victor Bernet, MAJ, MC; Kevin Abbott, LTC, MC

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 19 January 1999

STUDY OBJECTIVE:
To determine whether the presence of elevated levels of ouabain-like factor (OLF) is associated with diabetic nephropathy in Type I and Type II diabetics vs. diabetic patients without nephropathy.

TECHNICAL APPROACH
Patients seen in the endocrine and nephrology clinics with type I or type II diabetes with or without nephropathy (as defined by presence of fixed proteinuria/albuminuria and hypertension) will be invited to participate in the study. A one time 10 cc sample of plasma and RBCs will be collected from a peripheral vein for determination of OLF levels. Levels will be measured in a blinded fashion. BP, weight, urine protein, serum creatinine, and glycosylated hemoglobin will also be determined. Patients must be $\geq$ 18 years or $\leq$ 75 years of age, not pregnant, not s/p kidney transplant, and with a serum creatinine of 1.5 mg% or less to be in the study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been no pertinent developments in the recent literature. At present, 26 patients have been entered into the protocol. Two additional patients have refused entry. Three quality control samples have been sent. 23 participants have NIDDM; 3 have IDDM. There have been no withdrawals. An addendum to extend recruitment to March 2003 was approved by DCI in May 2001. The protocol was randomly audited in June 2001, with no significant issues identified at the time of audit.

The number of subjects enrolled to the study since last APR at WRAMC is 10 and the total enrolled to date at WRAMC is 26. The total number enrolled study-wide is NA, if multi-site study.

CONCLUSIONS:
None yet available.

Report Date: 19 November 2001

Work Unit # 1199-99

# DETAIL SUMMARY SHEET

TITLE: Patterns of Protein Size- and Charge-Selectivity in Clinical Kidney Disease

KEYWORDS: glomerulonephritis, proteinuria, permselectivity

PRINCIPAL INVESTIGATOR: James D. Oliver MAJ MC
ASSOCIATES: Christina Yuan LTC MC; Paul Welch LTC MC; Sharda Sabnis MD; Maged Abdel-Rahim MS

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 26 January 1999

STUDY OBJECTIVE:
To determine the fractional excretion of specific proteins in renal disease and controls, and to examine whether the patterns of proteinuria correlate with histological characteristics demonstrated on renal biopsy.

TECHNICAL APPROACH
Patients seen in the nephrology clinic with kidney disease who are being referred for renal biopsy will have blood and urine samples drawn to measure the fractional excretions of various proteins: β-2 microglobulin, retinal binding protein, transferring, pancreatic and total amylase, IgG and IgG4, and albumin polymers. These will be compared to values obtained from a matched set of health control volunteers. From the biopsy specimens, the essential diagnostic category and grading of the severity of disease will be determined in a blinded fashion. The fractional excretions will be correlated to the histological changes. Patients must be over 18 years of age and not s/p kidney transplant to be eligible.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
To date, we have obtained assays for retinol binding protein, $\beta_2$ microglobulin, and IgG. These assays have been calibrated and their sensitivities verified. We have identified commercial assays available for albumin, transferrin, and pancreatic amylase and will be obtaining them and performing the necessary calibration experiments on them in the upcoming months. As no assay is commercially available for salivary amylase, we plan to develop our own ELISA. We anticipate enrollment beginning around February 2002.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

CONCLUSIONS
None drawn to date.

Report Date: 31 August 2001 Work Unit # 00-1201

# DETAIL SUMMARY SHEET

TITLE: A Randomized Trial Comparing the Effects of Atorvastatin and Pravastatin on Carotid Intima-Media Thickness

KEYWORDS: Randomized Trial, atherosclerosis, HMG-CoA reductase inhibitor

PRINCIPAL INVESTIGATOR: Allen J. Taylor LTC MC
ASSOCIATES: Louis Coyle DO, Patrick Flaherty Do, Thor Markwood MD, Steve Kent MD, Patrick G. O'Malley MD, MPH

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: O
INITIAL APPROVAL DATE: 26 October 1999

## STUDY OBJECTIVE

To evaluate the relative effects of two different HMG-CoA reductase inhibitors on carotid atherosclerosis regression.

## TECHNICAL APPROACH

This study is a randomized study comparing the efficacy of atorvastatin and pravastatin on carotid atherosclerosis (carotid intima-media thickness). Patients beginning cholesterol lowering therapy who have a baseline serum cholesterol of 160mg/dL or greater and who are not currently on cholesterol lowering medication are randomized to one of the open-label treatment arms: pravastatin 40mg qd, or atorvastatin 80 mg qd. The primary endpoint is the change in carotid intima-media thickness over 12 months. Lab monitoring is performed at baseline, 3 and 12 months. The sample size for statistical significance is 132 patients. The protocol is approved for a maximum of 200 patients.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Recent literature supports that all statins appear to improve inflammatory variables (a secondary outcome of this study). Limited data comparing the effects of different statins on inflammation suggest that they appear to be fairly equivalent. No data are yet available to invalidate the principle hypotheses of this protocol. Thus, the risk of this protocol (expressed in terms of the relative efficacy of the two drugs being studied) appears to be the same or lower than when the study was originally approved. The number of subjects enrolled to the study since last APR at WRAMC is 50, and the total enrolled to date at WRAMC is 161. Enrollment to new patients was closed in February 2001, and the patients are now completing the one-year follow-up period. There have been twenty study withdrawals, due to either patient request or drug intolerance. Thus 141 patients (with a required sample size of 132) remain in the study.

## CONCLUSIONS

The study has closed to enrollment and is nearing completion in approximately February 2002.

Report Date: 3 December 2001 Work Unit # 00-1202

# DETAIL SUMMARY SHEET

TITLE: SWITCH: Statins at WRAMC: Interventions for the Treatment of Cholesterol-An Observed Study of the Formulary Switch to HMG-coA Reductase Inhibitors Mandated by the Department of the Defense Pharmacoeconomic Center

KEYWORDS: HMG-CoA reductase inhibitors, therapeutic interchange

PRINCIPAL INVESTIGATOR: Allen J. Taylor MD LTC MC
ASSOCIATES: David L. Jones MD MPH; Karen Grace Pharm D; Jennifer Swiecki Pharm D; Richard Hyatt M.S.; Rebecca Viola R.Ph.

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: C
INITIAL APPROVAL DATE: 30 November 1999

STUDY OBJECTIVE: To monitor the safety and efficacy of HMG-coA reductase ("statin") therapy in outpatients being switched to agents mandated by the Department of Defense (DOD) Pharmacoeconomic Center (PEC).

TECHNICAL APPROACH:
Prospective, observational study using FDA-recommended monitoring of statin therapy.

Methodology: This is an 18-week observational study evaluating the safety and efficacy of the algorithm-based conversion to cerivastatin or simvastatin. Patients presenting to the WRAMC pharmacy to obtain refills of their currently prescribed statin medication between January and April 2000 were referred to the lipid clinic where they received their new medication with drug information counseling and drug interaction screening by a pharmacist. The specific agent (i.e. cerivastatin or simvastatin) was determined according to an algorithm based on a statin equivalency chart. After this, they were offered enrollment in the SWITCH protocol.

This study closed to enrollment on 30 April 2000. At the time of the last APR, data analysis was ongoing, thus the study remained open at that time.

PRIOR AND CURRENT PROGRESS
Between 3 January and 30 April 2000, 1359 eligible patients presented for conversion of their statin. Of these, 980 (72.1%) consented to participate in the study. Renal insufficiency (serum creatinine > 2.0 mg/dL) was subsequently detected in 38 patients, leaving 942 subjects in the study cohort, as reported in the last APR.

The number of subjects enrolled to the study since last APR at WRAMC is 980 and the total enrolled to date at WRAMC is 980.

CONCLUSIONS
This study is complete.

Report Date: 02 November 2001 Work Unit # 01-12001

# DETAIL SUMMARY SHEET

TITLE: Acetylcysteine for the Prevention of Contrast Associated Nephropathy in Diabetic Patients Undergoing Coronary Angiography

PRINCIPAL INVESTIGATOR: Gorman, Patrick COL MC
ASSOCIATES: Hudak, Craig LTC MC

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: O
INITIAL APPROVAL DATE: 23 January 2001

STUDY OBJECTIVE The primary objective is to determine if acetylcysteine plus hydration is superior to hydration alone for the prevention of contrast-associated renal dysfunction in diabetic patients undergoing coronary angiography. The null hypothesis of this trial is that acetylcysteine will not be superior to standard therapy (hydration) for the prevention of contrast-associated deterioration in renal function.

TECHNICAL APPROACH Patients have been recruited during pre-cardiac catheterization counseling from the WRAMC Cardiology Clinic and National Navy Medical upon referral for elective cardiac catheterization and selective coronary angiography. Up to 200 patients will be enrolled. This study is a randomized, prospective, open-label study comparing the effects of acetylcysteine plus oral hydration versus oral hydration alone in diabetic patients undergoing coronary angiography. Patients undergo separate randomization at the two study sites, NNMC and WRAMC. Patients are randomly assigned in a 1:1 ratio to one of two arms, standard hydration with the study drug, acetylcysteine, and standard hydration only. All patients receive standard hydration therapy in the following manner: combined oral pre-hydration (1 liter of clear liquids in the ten hours before arrival in the cardiac catheterization laboratory) and intravenous post-hydration (0.45N saline at 300 cc/hr for a total of six hours). Oral fluids will be encouraged after the procedure. Hydration status for patients is followed as indicated on the data collection form monitoring total oral and IV fluids pre and post cardiac catheterization. Patients allocated to the acetylcysteine arm receive standard hydration therapy and 600 mg of acetylcysteine, prescribed by an investigator, orally twice daily beginning on the day prior to contrast exposure and ending on the day of exposure for a total of four doses. Kidney function has been tested by measuring serum creatinine and related variables contained in a standard "Chem 7 or profile 1" noted on the data collection form. These tests measure pre and post angiography. The investigators follow patients within the study period. After the study period the standard follow-up for patients post cardiac catheterization occurs, i.e. the primary angiographer is responsible for follow-up of patients.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This study is ongoing with continued enrollment at both WRAMC and NNMC. National Naval Medical Center was added as an additional test site. There have been a total of sixty patients enrolled to date at WRAMC test site, and fifteen patients enrolled at NNMC test site. There has been one report of an adverse event filed from the WRAMC test site, and no reports of adverse events filed from the NNMC test site. The study size at present does not allow for statistically significant analyses.

The number of subjects enrolled to the study since last APR at WRAMC is sixty, and the total enrolled to date at WRAMC is sixty. The total number enrolled study-wide is seventy-five.

CONCLUSIONS
This study is ongoing successfully at both NNMC and WRAMC, with hopes of enrolling 70 patients per treatment arm to allow for a significantly powered study. Requested study size continues to be 200 patients to allow for dropouts at both study sites. Request approval for another year with hopes of completing enrollment prior to that time.

Report Date: 25 July 2002

Work Unit # 01-12002

# DETAIL SUMMARY SHEET

TITLE: Remote Echocardiographic Consults – Diagnostic Concordance – Intra and Inter Consults

KEYWORDS:

PRINCIPAL INVESTIGATOR: Malik, Anwar K., LTC, MC
ASSOCIATES: COL Marina N. Vernalis, MC; Daniel B. Rayburn PhD

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: O
INITIAL APPROVAL DATE: 5 June 2001

## STUDY OBJECTIVE

To compare diagnostic findings of echocardiograph studies read from VHS tape versus Digital formats.

## TECHNICAL APPROACH

115 ECHO studies have been acquired both digitally and on VHS format at Dewitt Army Community Hospital from July 2000 to June 2001. VHS formats have been read and digital formats have been transferred to WRAMC and are available for interpretation and comparison. We plan to use these studies retrospectively subject to same inclusion/exclusion criteria and methodology as presented in the original protocol.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

All the 75 studies have already been read off the VHS tape and reports have already been processed. However, due to multiple taskings, staffing difficulties, and technical difficulties the digitally transmitted versions of the same studies have not been read so far.

The number of subjects enrolled to the study since last APR at WRAMC is 75 and the total enrolled to date at WRAMC is 75.

## CONCLUSIONS

Request extension for another year in order to complete the protocol.

Report Date: 30 May 2002 Work Unit # 01-12003

# DETAIL SUMMARY SHEET

TITLE: ARBITER II: **AR**terial **BI**ology for the Investigation of the **T**reatment **E**ffects of **R**educing Cholesterol - A Randomized, Placebo-Controlled, Double-Blind Trial Evaluating the Effect of Long-Acting Niacin on Carotid Intima-Media Thickness

KEYWORDS:

PRINCIPAL INVESTIGATOR: Taylor, Allen LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: O
INITIAL APPROVAL DATE: 31 July 2001

STUDY OBJECTIVE
The purpose of this study is to evaluate the effect of niacin when added to an HMG-CoA reductase inhibitor on carotid atherosclerosis progression.

TECHNICAL APPROACH
This is a double-blind, placebo controlled trial of niacin in the regression of atherosclerosis in patients with known coronary heart disease already treated with a statin. Patients are treated for one year, to the primary endpoint of carotid atherosclerosis assessment utilizing ultrasound measurement of intima-media thickness.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The study began enrollment in December 2001. To date, 73 patients have been enrolled. An amendment was submitted in January 2001 and approved in February 2001 detailing the involvement of the pharmacy service, approval of a recruitment letter, and additional study measurements at the six-month visit (requiring re-consent). An amendment is currently pending to identify eligible participants utilizing the Integrated Clinical Database to whom a recruitment invitation will be mailed. A single patient developed a skin rash several days after beginning study medication. This patient remains blinded to therapy, is continuing her original statin therapy, and followed in an intent-to-treat manner.

The number of subjects enrolled to the study since last APR at WRAMC is 73 and the total enrolled to date at WRAMC is 73.

CONCLUSIONS
Enrollment is ongoing towards our approved target enrollment of 200. The combination therapy appears to be well tolerated to date.

Report Date: 3 December 2001

Work Unit # 1215

# DETAIL SUMMARY SHEET

TITLE: The Utility of Electron Beam Computed Tomography (EBCT) as a Screening Test for Coronary Artery Disease and as an Intervention for Risk Factor Modification Among Over 40 Active Duty Personnel

KEYWORDS: Coronary artery disease, risk factors, prognosis, computed tomography

PRINCIPAL INVESTIGATOR: Taylor, Allen LTC MC
ASSOCIATES: O'Malley, Patrick MAJ MC; Jones David LTC MC; Vernalis, Marina COL MC; Feuerstein, I; Brazaitis, M COL MC

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: O
INITIAL APPROVAL DATE: 25 November 1997

## STUDY OBJECTIVE

To evaluate the prevalence, relationship to coronary risk factors, management impact and prognosis of coronary calcium detected using electron beam computed tomography in active duty Army personnel.

## TECHNICAL APPROACH

A. 2000 consecutive, over age 40 active duty Army personnel from the National Capital Area will be screened for conventional coronary risk factors and electron beam computed tomography. This cohort will be followed annually for the occurrence of cardiovascular events.
B. 450 of the participants will be enrolled in a randomized controlled trial (2x2 factorial design) comparing immediate vs. deferred EBCT results and standard care vs. case management risk factor modification.

## PRIOR AND CURRENT PROGRESS

As of 2 November 2001, 1563 patients have been enrolled in the cohort study; 450 of these patients have also consented to participate in the randomized controlled trial portion of PACC. The phase I results (Aim 1) are completed, comprising reporting on the risk factors and prevalence of coronary calcium in the first 630 enrollees. The contract to SAR Inc. (employees handle data collection and management for the study) was renewed through MRMC as of August 2001 for the coming year. Funding is currently through a CDMRP grant and a parallel MRMC human subject review process is proceeding.

The following amendments to the protocol have been completed in the past year:
February 2001:
This addendum resulted in the following protocol modifications:

1. Mailed questionnaire: We have modified our telephone interview questionnaire to create a version that is self-reporting. This will be mailed (hard copy or electronically, as desired) to any participant who requests a mailed follow-up survey. To enable us to obtain source documents on events, subjects sign a standard release form when they joined the study.
2. Withdrawal from annual follow-up. Although the study has adequate power for losses to follow-up, minimizing these enhances the validity of the study. We request permission to send these volunteers a one-time note that provides our contact information and invites them to re-contact us through either returning a reply card or the self-reporting survey. Subjects who withdraw from our annual follow up procedure will continue to be tracked through administrative databases (e.g., the Social Security Death Index) to assess for interim events, but will not be telephonically contacted.

CONCLUSIONS: The initial aim of PACC (to define the prevalence of coronary artery calcification in the Army over-40 physical population) is complete. Enrollment in the cohort study is over approximately 80% complete, and enrollment in the randomized trial is complete. The randomized trial will be completed in March 2001. Continued subgroup analyses on questions of interest within the approved dataset are continuing.

Report Date: 3 December 2001 Work Unit # 1217

# DETAIL SUMMARY SHEET

TITLE: Use of Electron Beam Computed Tomography in the Preoperative Evaluation of Noncardiac Vascular Surgery Patients

KEYWORDS: Electron beam computed tomography; preoperative cardiac evaluation

PRINCIPAL INVESTIGATOR: Allen J. Taylor MD LTC MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Cardiology INITIAL APPROVAL DATE: 16 December 1997

STUDY OBJECTIVE
To determine the utility of preoperative EBCT in predicting immediate and short-term outcomes among arterial surgical patients operated at WRAMC.

TECHNICAL APPROACH:
Subjects are recruited from the Vascular Surgery Clinic during their preoperative evaluation. EBCT is obtained prior to, or shortly after, admission. Follow-up blood tests and ECGs are obtained for up to 72 hours postoperatively. Follow-up telephone contacts are made over the ensuing twelve months.

PRIOR AND CURRENT PROGRESS
As of July 2000, 77 patients had been enrolled, and 46 patients completed the study procedures. Enrollment has been slower than anticipated for a number of reasons: lower than expected surgical volume, exclusion criteria, and inconsistent availability of staff to recruit patients. Because of this, a decision was made to stop enrollment in July 2000 and to analyze the data collected to date. These data have been analyzed, and have been synthesized as a manuscript.

CONCLUSIONS
The investigators have terminated enrollment in this study. The data are analyzed, and a manuscript is submitted for clearance.

Report Date: 1 May 2002

Work Unit # 1218-98

# DETAIL SUMMARY SHEET

TITLE: Assessment of Clinical Outcome Using Prothrombin Time Patient Self Testing (PST) to Monitor Long Term Anticoagulation Therapy

PRINCIPAL INVESTIGATOR: Calagan, Jennifer L. LTC MC
ASSOCIATES: John, Cheryl RN; Vernalis, Marina COL MC

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: O
INITIAL APPROVAL DATE: 16 June 1998

## STUDY OBJECTIVE

To assess the use of Patient Self-Testing (PST) to monitor the effect of Coumadin® therapy for effectiveness, safety and convenience/compliance. To assess the use of HealthBuddy® telephone/internet communication device to monitor further complications, status and Coumadin® use in WRAMC Coumadin® Clinic patients. Additionally, to compare the use of PST and HealthBuddy® to standard/traditional in-hospital monitoring of effects of Coumadin® therapy.

## TECHNICAL APPROACH

PST has been conducted using the ProTime® Microcoagulation System (ITC, Edison, NJ). An initial group of patients was advised of the protocol, trained in the use of the system, and then randomized to either standard monitoring or the PST arm. The member of the second group was further trained on the use of the system, given supplies and tracking forms, and issued a home unit. Patients in the first/control group will remain under the standard clinic protocol for monitoring of PT/INR, but will be also trained in and given report and tracking forms. The outcomes studied will be percentage of time within therapeutic range, precision in dose adjustment, patient compliance, complications and patient satisfaction. After this study was started, funding and the technology to monitor patient health status, Coumadin® use, potential complications and other relevant changes to medical regimen became available in the form of the HealthBuddy®, a device which allows two-way non-simultaneous exchange of information between Coumadin® Clinic and the patient at home. The device plugs into an existing phone line and is programmed to communicate via the Internet with a server that can post the responses to a secure, pass-worded web site. This should allow patients and Coumadin® Clinic to exchanges questions and information without a patient visit on-site or a series of phone calls. This device has been used with other medical conditions (e.g. diabetes) but never tested for use in a high volume clinic with military population on fairly high-risk therapy. The need for prompt detection of aberrancies in INR, patient's medical condition, or new or deleted medications suggest that such a device might improve efficacy of therapy while reducing potential for complications or earlier detection of complications. The protocol was amended to now include four arms: the original two (control and PST), a HealthBuddy® arm, and an arm with both devices. It will also include subgroups of "new" patients.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 156 and the total enrolled to date at WRAMC is 156. The total number enrolled study-wide is N/A, if multi-site study.
Amendments/Modifications: None
Adverse Events in study patients:
Major: (not felt to be related to study, expected in this population, not counseled in Consent form)
- Death (2)
- Myocardial Infarction (2)
- Pacemaker needed (1)
- Admission for MRSA infection (1)
- Admission for renal failure (1)

Admission elective blepharoplasty (1)
Admission for Total Hip Replacement (1)
Admissions (2) for pleurocentesis (patient had been receiving before enrolled) (1)
Admission for respiratory distress (CHF) (1)
Admission for right carotid endarterectomy (1)
Admissions (2) for complication of anemia (same pt as above RCEA)

Major: (related to Coumadin® use)
Admissions (2) for supratheraputic Coumadin® (patient had admissions which occurred prior to enrollment also) (1)
Admission for hemarthrosis and supratheraputic Coumadin® (1)
Right groin hematoma in cardiac catheterization patient (unclear relation to Coumadin®) (1)

Unanticipated (expected in these patients, not counseled as AE of protocol):
ER visit-Neurologic symptoms, negative CT scan (1)

Patients withdrawn from study:
None terminated by the project
24 withdrew at own request
48 declined to continue in assigned arm or could not qualify in assigned arm

CONCLUSIONS

Study has stopped new enrollment based on time needed to complete follow-up and budget remaining. Target enrollment was not met. Study closed 28 February 2002 for enrollment. Data has not yet been analyzed. Patient acceptance of the two technologies is now being assessed with preliminary data. Full analysis will await completion of data collection. Preliminary data indicates that inability to use ProTime® device to standard and dissatisfaction with either the ProTime® or the Health Buddy® caused withdrawals or change of arm to control group treatment. Dissatisfaction with not being assigned to a ProTime® group also caused withdrawals. Some withdrawals were due to discontinuation of Coumadin® therapy by PCP or specialist.

Adverse events occurred in different study groups and do not appear to be related to the study. These did occur predominantly in study groups that utilized ProTime® Patient Self-Testing device. Adverse outcomes in most study patients were consistent with those expected in a similar population based on natural history data.

Report Date: 11 September 2001

Work Unit # 1223-99

# DETAIL SUMMARY SHEET

TITLE: Multinational, Multi-center Double-Blind Randomized Active Controlled Parallel Group Study Comparing the Efficacy and Safety of Long-Term Treatment with Valsartan, Captopril, and Their Combination in High Risk Patients after Myocardial Infarction

KEYWORDS: Myocardial infarction, Angiotensin, Congestive heart failure

PRINCIPAL INVESTIGATOR: Allen J. Taylor LTC MC
ASSOCIATES: Thomas Ostronic LTC MC

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: C
INITIAL APPROVAL DATE: 25 May 1998

## STUDY OBJECTIVE

The primary objective of this study is to compare captopril, valsartan, or their combination in patients with reduced ejection fraction on the prevention of mortality after myocardial infarction.

## TECHNICAL APPROACH

After informed consent is obtained, patients are randomized in a double blind, allocation concealed fashion to one of the three experimental arms. Scheduled dose titration ensues, and patients are tracked for recurrent cardiovascular events.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The principal aim of this study is to compare the effects of captopril, valsartan or their combination on post myocardial infarction mortality. The results of VAL-HEFT were reported in November 2000 at the Annual Scientific Sessions of the American Heart Association. This study failed to find any mortality benefit of adding valsartan to an ACE-inhibitor for patients with class 2 and 3 heart failure. Subsequently, concerns have arisen over the observation that patients on beta-blockers in this trial were at increased risk of adverse outcomes. Because of this possible adverse interaction of captopril and valsartan with beta-blocker medication, the principal investigator at his site has elected to terminate this study at WRAMC.

We began active recruitment 3 April 2000. Two WRAMC patients have been enrolled to date (overall study enrollment worldwide is complete at 14,000). As previously reported, one of these patients died of out-of-hospital sudden cardiac death. The second subject was withdrawn from study medication on 8 August 2001, and is now treated with standard of care open-label ACE inhibitor therapy.

## CONCLUSIONS

This study is terminated at WRAMC. No patients at WRAMC are continuing on the study protocol or study medication.

Report Date: 1 August 2002 Work Unit # 1224-99

# DETAIL SUMMARY SHEET

TITLE: Non-Invasive Coronary Artery Disease Reversal

KEYWORDS: Heart Disease Reversal; Lifestyle Modification; Coronary Artery Disease

PRINCIPAL INVESTIGATOR: Vernalis, Marina COL MC
ASSOCIATES: Ocuin, Esther LTC MC

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: O
INITIAL APPROVAL DATE: 21 September 1999

STUDY OBJECTIVE

The overall purpose of this study is to determine if comprehensive lifestyle changes (low-fat vegan diet supplemented with soy and antioxidants, moderate aerobic exercise, stress management, and group support) can slow, stop or reverse the progress of coronary artery disease. Specific objectives are as follows:

1. To investigate the efficacy of intensive lifestyle modification in improving the clinical status of patients with moderate to severe coronary artery disease (CAD) measured by a 50% reduction in angina frequency. Secondary endpoints to this objective will measure New York Heart Association (NYHA) class and exercise time.
2. To investigate the effect of intensive lifestyle modification on levels of CAD associated "markers" (such as lipids, homocysteine, C-reactive protein and fibrinogen) via development and analysis of study data banks.
3. To investigate the effect of intensive lifestyle modification on measurements of established CAD (such as exercise tolerance, NYHA functional class, angina, blood pressure and weight).
4. To determine if a disciplined military active duty and retired patient population can achieve and adhere to the goals of this lifestyle change program in a non-residential, outpatient setting. This will be determined using patient questionnaires addressing degrees of observance of the program's components.
5. To determine the potential effects of the program on DoD healthcare expenditures for CAD treatment.
6. To establish a sera bank for possible future research of markers as yet unidentified.

TECHNICAL APPROACH

A. Study Design - This ongoing study is designed as a prospective, non-randomized, single-arm (treatment), observational trial, in which each individual serves as his/her own control, comparing outcomes to baseline data. The Non-Invasive Coronary Artery Disease Reversal protocol received final approval by the WRAMC DCI on 21 September 1999. Required revisions were received on 28 January 2000.

B. Study Addenda - The WRAMC Human Use Committee has approved two addenda since the last review. Addendum 4 modifies the Personal Adherence Log (PAL) that participants complete to record their daily program activities. It specifically allows for better data reporting and analysis of both aerobic and non-aerobic exercise. This addendum was approved on 6 November 2001. Addendum 5 required a consent form change to incorporate language requested by MRMC further clarifying that stress testing using isotope imaging and performed in nuclear medicine will not be used in this study. Additional language was added to the consent form as a result of a WRAMC HUC recommendation: "possible risk of salt overload as a result of no salt restriction specified in the dietary guidelines and risk of musculoskeletal injury, coronary event, angina and/or possible heart attack as a result of exercising". This addendum also clarified the use of the exercise treadmill data from the 6 non-clinically indicated thallium tests in the final data analysis. However, no perfusion data will be used. It further clarified that thallium studies conducted other than by the CADRe program can be utilized in the data analysis. This addendum was approved 13 April 2002.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 51 and the total enrolled to date at WRAMC is 136. These subjects have been recruited through health care provider referrals, self-referrals from approved advertisements and previous/current participant referrals. All branches of the federal services are represented. Fifty-four have completed the one-year program and 59 are actively participating in the maintenance program. Twenty-one participants (15.4% dropout rate) have either voluntarily withdrawn or have been medically withdrawn from this study. One was withdrawn as a result of death, thirteen relayed a lack of commitment to continue with the program, two could not begin the program as a result of their active duty spouses' unexpected reassignment, one disenrolled to seek other treatment options, and three disenrolled after exacerbation of chronic illness and one disenrolled for cardiac instability as a result of the screening process. Two patients are in a hold status and are anticipated to start the program in October 2002.

Participants span the age spectrum of 31 to 80 years old with a mean age of 60.23 years (SD=10.112), 32% are female, and 19% are from minority groups. Sixty-six percent have documented coronary artery disease (CAD). Of those with CAD, 57% have had at least one revascularization procedure (bypass surgery or angioplasty). Additionally, 65% of the participants suffer from hypertension, 18% with diabetes and 71% are taking cholesterol-lowering medications. Of the enrolled participants, 23 are active duty, 79 are from the retired ranks, 33 are eligible family members and one is a Secretary of Defense designee.

Adverse events related to subjects

There has been one serious adverse event in the course of this study. Participant died as a result of a massive right hemisphere hemorrhagic CVA. Death (1), Cardiac related hospitalizations (may include an ER visit) (18), Cardiac related ER Visits (6), Cardiac Catheterizations with or without interventions (25), Ambulatory Surgery (non-cardiac) (5), Non-cardiac related hospitalization (17), Non-cardiac related ER visits (30), Other (musculoskeletal injury-1 & possible TIA-1) (2). All adverse events (Death, ER visits, hospitalizations, etc) have been submitted to WRAMC Department of Clinical Investigations (DCI) for review.

CONCLUSIONS

At enrollment, one third of those with known CAD had significant functional limitations upon enrollment. After 3 months, over 75% of those same patients significantly improved their functional ability. This means they were able to bathe, walk, shop, and do other ordinary day-to-day activities without difficulty.

Both aerobic (exercise in target heart rate) and non-aerobic exercise has been measured. Participants exercise for an average of 3.6 hours per week. Treadmill exercise testing data is available on 79 participants who have completed 3 months of program participation. Preliminary results on those who have completed 12 months of program participation shows that 55% of the total exercise time is attributable to non-aerobic exercise because of limiting musculoskeletal conditions or symptoms due to panvascular disease. Despite the latter, preliminary results show a significant improvement in treadmill exercise time since enrollment and suggests the duration and not necessarily the type of activity plays a role in the sustainment of the improved function. This is coupled with a significant overall improvement in cardiovascular fitness as defined by METS (metabolic equivalent). After three months, patients increased their fitness level by 1.72 METS. This equates to an increase in walking from 1.8 miles per hour (mph) to 3.4 mph on a flat surface. Twelve-month preliminary data shows sustainment of both exercise time and workload at a significant level. This is very encouraging since there is evidence-based data that an increase of 1-MET in functional capacity may convey a 12% increase in survival.

Functional health improvement has also been validated in this population through the use of the Health Status Survey (SF-36), which is a widely used tool for measuring health status and outcomes. As seen in the above table, improvements have been seen in both the physical and mental components of this tool.

The overall mean compliance with the plant-based vegetarian dietary guidelines after 12 months of participation is 92 %. Participants have done remarkably well in integrating this ultra-low fat diet into their daily routine. Although Dr. Ornish did not design this program for weight loss, reduction in weight and body fat is a natural by-product. The average weight loss at 12 weeks is 11 pounds with almost 4% reduction in body fat and seems to hold steady at one year.

After 3 months, there is a mean reduction in total cholesterol for the 98 participants of 21 points and the LDL by 19 points. This is seen in patients on statin therapy as well. High-density lipoprotein (HDL) levels decrease by 8 points and triglycerides increase by 11 points. The decrease in HDL and increase in triglycerides are similar to the findings of Dr. Dean Ornish in both his initial Lifestyle Heart Trial as well as the Multicenter Lifestyle Demonstration Project. Although the Lifestyle Heart Trial showed plaque regression, there appears to be competing effects of the program on the HDL and triglycerides. The importance of the latter is not clear and needs further clarification possibly through lipoprotein kinetics.

The Ornish Program model recommends 60 minutes of stress management every day. Overall stress management adherence is highest during the first 12 weeks (69% or 41 minutes/day) and decreases to 37 minutes/day at 12 months. This has been a difficult component for this population to integrate into their lives. Regardless, reduction in stress as measured by the Perceived Stress Scale (PSS) is significant at both 3 month and 12 month time periods. However, when the data is compared by gender, the benefit is only seen in men at both 3-months and 12-months. Group support is the other psychosocial interventional component of the program. The Center for Epidemiological Studies Depression Scale (CESD) and the Modified Cook Medley Hostility Scale (CMHS) are reliable tools that we use to measure the value of group support. Both these instruments have shown a decrease of depression and hostility. Again, when groups are compared by gender, only males seem to benefit. Until recently the existing data suggests that psychosocial interventions are an additive component to coronary artery disease outcomes. However, a recent abstract presented at the American Heart Association meeting in November 2001 suggests that the use of group intervention positively impacts white men but doesn't hold true with minorities or women (ENRICH study).

The short-term data we have achieved in our program is impressive by way of physiologic and emotional measures. These changes argue well for being able to demonstrate long-term success with respect to more definitive outcomes such as adverse clinical CV events including hospitalization for an acute coronary syndrome or the need for future coronary revascularization procedures. In addition, the effects of the core components on carotid intima media thickness (CIMT), a validated measure of atherosclerosis burden, will shed important information on the regression or stabilization of plaque. Results of the CIMTs from these subjects are not yet available.

The program has the potential to operationalize bench research and to identify what is clinically applicable not only to the military population but the general population. Future goals include a randomized, prospective study to tease out the relevance of the core components especially as it relates to psychosocial interventions. It will also be important to identify the additive effects of lifestyle modification to pharmacoprevention of atherosclerotic cardiovascular disease.

Report Date: 21 August 2001

Work Unit # 00-1301

# DETAIL SUMMARY SHEET

TITLE: The Effect of Retinols, Tamoxifen and Octreotide on Cellular Proliferation and Control of Thyroglobulin, TSH Receptor and Sodium-Iodide Synporter mRNA Expression in Thyroid Cancer Tumor Cell Lines

KEYWORDS: Retinols, Tamoxifen, Octreotide, Cellular Proliferation, Thyroglobulin, TSH Receptor, Sodium-Iodide Symporter, Thyroid Cancer, Tumor Cell Lines

PRINCIPAL INVESTIGATOR: Burch HB
ASSOCIATES: Rhooms PK

DEPARTMENT: Medicine
SERVICE: Endocrine-Metabolic

STATUS: C
INITIAL APPROVAL DATE: 5 October 1999

STUDY OBJECTIVE

To assess the effect of retinols, tamoxifen, and octreotide on cellular proliferation and control of thyroglobulin, TSH receptor and sodium synporter mRNA expression in thyroid cancer tumor cell lines.

TECHNICAL APPROACH

To apply quantitative PCR to the measurement of changes in the above mRNA levels in response to the above effectors. In addition, a cellular proliferation assay will assess the effects of these mediators on cellular proliferation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This protocol is being resubmitted at Eisenhower AMC where the former PI, Dr Joseph Woods will continue this work. While a fellow at WRAMC, Dr. Woods obtained and initiated culture of thyroid cell lines from an outside laboratory. These cell lines have been frozen and will be shipped to Dr. Wood upon approval of his protocol at EAMC.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study.

CONCLUSIONS

None.

Report Date: 28 November 2001 Work Unit # 00-1302

# DETAIL SUMMARY SHEET

TITLE: The Effect of Omeprazole Therapy on Serum Calcitonin (CT)

PRINCIPAL INVESTIGATOR: CPT Jeannie Baquero MC
ASSOCIATES: MAJ Victor Bernet MC, Barbara Solomon, DNSc, CPT Mark Cummings MC, COL Roy K.H Wong, MC

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: C
INITIAL APPROVAL DATE: 1 February 2000

## STUDY OBJECTIVE

Determine the effect of omeprazole therapy on serum calcitonin levels.

## TECHNICAL APPROACH

The study is an observational descriptive study. Patients currently taking omeprazole will be recruited from the GI Clinic to have a single blood draw for this study. Patients eligible for the study will have a brief history and thyroid examination performed by one of the endocrinology investigators. Samples will be drawn and labeled in such a fashion that all assays are performed in a blinded manner. Blood will be batch analyzed for serum gastrin and calcitonin by Quest Diagnostics, 33608 Ortega Highway, San Juan Capistrano, CA 92690-6130. All samples will be collected and stored in the Endocrinology Clinic. The samples will be sent by the Endocrine clinic to Quest and assayed as a batch to minimize inter-assay variation. Any excess of the samples will be discarded after the results are completed. Subjects will not be informed of the experimental lab results unless calcitonin levels are elevated greater than 100pg/ml. If this occurs the subject will be referred to the Endocrinology Service for additional evaluation.

Data collected will include the omeprazole dose, duration of dose, age, gender, thyroid history, and thyroid examination of participants. Serum gastrin and calcitonin will be measured at <1 month, 1-6 month, >6-12 months, >12 months after starting therapy. The data will be collected using a data collection form. Each patient will be given a unique identifier that will be used on a master list kept in the endocrinology clinic. This identifier will be used on the master data sheet to maintain patient confidentiality. The subjects will be further categorized based on dose of omeprazole: 20mg Qd or >/= 40mg Qd. This is an addendum to the original protocol which separated the groups into </= 40mg Qd and >40mg Qd. A total of 86 subjects where collected for evaluation, which is lower than the desired amount of subjects but sufficient end points for the analysis.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 12 and the total enrolled to date at WRAMC is 86. The total number enrolled study-wide is 86, if multi-site study. There have been no new amendments since last review. A total of 86 subjects where obtained at completion of this study. There have been no adverse reactions from the study, and no patients where withdrawn from the study. Our study shows that there is no correlation between serum calcitonin levels and omeprazole duration or dose. Univariate analysis showed that there was a significant difference in serum calcitonin and gastrin levels between women and men. Gender differences in serum calcitonin can be explained by the recognized normal gender variation. However, gastrin gender variation has not previously been shown and will need to be further explored.

## CONCLUSIONS

1) Our study showed no correlation between serum calcitonin levels and omeprazole duration or dose.
2) These findings would suggest that patients taking omeprazole should be able to undergo calcitonin screening if desired. Although, we did not specifically investigate the response of benign nodular thyroid tissue to omeprazole, but existing evidence would indicate the response to omeprazole to be similar.
3) Gastrin levels appear to be higher in women than in men omeprazole. A gender difference in gastrin levels has never been reported, and further studies are needed to explain this possible correlation.

Report Date: 8 January 2002

Work Unit # 00-1303

# DETAIL SUMMARY SHEET

TITLE: Galectin-3 Levels as a Marker of Thyroid Cancer in Fine-Needle Aspiration (FNA) Samples

KEYWORDS: Thyroid Cancer, FNA

PRINCIPAL INVESTIGATOR: LTC Victor Bernet, MC
ASSOCIATES: J. Anderson, Y. Vaishnav, B. Solomon, K. Burman, M. Ringel, M. Saji, C. Adair

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: O
INITIAL APPROVAL DATE: 8 February 2000

## STUDY OBJECTIVE

- Confirm and expand the previously reported immunohistochemical findings that Galectin-3 staining us found predominantly in papillary and follicular thyroid cancer tissue in contradistinction to benign nodules and normal thyroid tissue.
- Develop a quantitative RT-PCR assay to measure levels of Galectin-3 in thyroid tissue.
- Assess the level of Galectin-3 mRNA expression in various types of benign and malignant thyroid histo-pathology samples.

## TECHNICAL APPROACH

Patients undergoing thyroidectomy for standard clinical indications consented to have their removed tissues be "snap frozen" in liquid nitrogen and stored at -70° C. In total, 38 such histopathologically diagnosed frozen tissue frozen tissue specimens consisted of 7 normal (NL), 9 benign (BN), 7 papillary thyroid cancer (PTC), 9 follicular thyroid cancer (FTC) and 6 follicular adenoma (FA) were included in this study. Genomic RNA from these frozen specimens was recovered using a standard Trizol method (Tri Reagent ®, Molecular Research, Inc.) A quantitative RT-PCR was developed for Gal-3 using a sequence specific ogligonucleotide probe and forward and reverse primers. A 103 bp long Gal-3 c-DNA segment, spanning thee junction of exon 4 and 5 (GeneBank ACC# NM_002306) was amplified using the forward primer: ACGGTGAAGCCCAATGCA and reverse primer TGACTCTCTCCTGTTGTTCTCATTGAA; and antisense probe AATGATGTTGCCTTCCACTTTAAC CCAGG labeled with 5'-reporter dye (FAM) and 3'-quencher dye (TAMRA). To help validate the kinetic quantitative RT-PCR method, human thyroid m-RNA (Clontech) was utilized for the construction of standard curves and GADPH (glyceraldehydes-3-phospate dehydrogenase) m-RNA was used as an endogenous reference for Gal-3. The m-RNA templates were excluded from the negative standards. For each sample, the amount of target (Gal-3) and the endogenous reference were determined from the calibration curves. The target amount was then divided by the reference amount to obtain normalized values. Two techniques, agarose gel electrophoresis and cycle sequencing were utilized to confirm the identity of the PCR amplified 103 bp-c-DNA segment (Gal-3).

## PRIOR AND CURRENT PROGRESS

Presently, we have been working on the use of Galectin-3 in FNA samples instead of frozen tissue. While proceeding with the studies approved in our last addendum from June 2000, testing thirty slides done on prior FNAs, it was found that RNA could indeed be isolated from diff-quik stained slides. Although we were forced to make adjustments in the housekeeping product, which we were using to normalize Galectin-3 levels, secondary to a base pair size issue. Then we proceeded to prospectively collecting FNA samples. As planned, both washings from the FNA needle hubs with Trizol and one diff-quik slide was collected from each of twenty patients in order to gauge success rates between the two methods for RNA isolation (hub washings vs. RNA recovery from diff-quik stained slide). Preliminarily, it appears that the two techniques yield similar amounts of RNA, with the use of diff-quik slides being somewhat superior, as they can be reviewed for follicular and lymphocyte content, unlike the FNA washings. Of note, either technique

appeared to yield minimal Galectin-3 expression in these specific samples, but the results are very much hampered by the fact that there was a paucity of thyroid cancer or even follicular adenomas in these prospectively collected samples. It is imperative that we test diff-quik stained slides containing papillary and follicular neoplasia prior to proceeding to the larger portion of the prospective study.

In light of the above assessment, an addendum was submitted in July 2001, and permission was received to collect up to thirty more FNA specimens from the pathology archives in order to test slides containing: 1) papillary thyroid cancer, 2) follicular adenoma, and 3) follicular thyroid cancer. We are presently working on this part of the study. These results will enable us to determine if our techniques are sound and that we can anticipate to be able to distinguish benign from malignant samples when we proceed to final phase consisting of prospective collection of a total of up to 180 more samples as specified by the initial protocol.

To date, we have studied 37 frozen specimens out of an approved number of 40, and 30/30 diff-quik FNA slides from pathology archives. We have prospectively collected 20 samples of an approved 200. We are presently evaluating the 30 specimens from pathology archives approved in the addendum from July 2001.

CONCLUSIONS:

- Results indicate that Gal-3 can indeed be amplified and quantitatively measured by RT-PCR from mRNA isolated from thyroid histology samples.
- Galectin-3 mRNA can be isolated from FNA samples either using diff-quik prepared slides or by washing the FNA needle hub at the time of the procedure. Use of diff-quik slides has the advantage of allowing the investigation to assess the cellularity present on the slide.
- B-Actin or PBGD can be used as housekeeping products for assessment of Galectin-3 in FNA samples.
- Galectin-3 mRNA appears to be expressed in only low levels in benign lesions. Further study is being done on samples containing adenoma or cancerous cells.

Report Date: 3 May 2002

Work Unit # 00-1304

# DETAIL SUMMARY SHEET

TITLE: Investigations of Activation of BAG-1 and p73 Genes in Thyroid Cancer in Tissue

KEYWORDS: Thyroid cancer, molecular markers, protein, immunohistochemical analysis, mRNA, RT-PCR, BAG-1, p73

PRINCIPAL INVESTIGATOR: Yashesh Vaishnav
ASSOCIATES: Victor Bernet; Henry Burch; Carol Adair; Jeffery Anderson; Brian Reinhardt

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: C
INITIAL APPROVAL DATE: 13 June 2000

STUDY OBJECTIVE: 1) To identify activation of the potential cancer genes BAG-1 and/or p73 in thyroid cancer tissue. 2) To explore if we can quantitatively amplify expression levels of BAG-1 and/or p73 mRNA isolated from cancerous thyroid tissue. 3) To determine whether levels of BAG-1 and/or p73 isolated from cancerous thyroid tissues can be used as markers of different subclasses of thyroid cancers.

TECHNICAL APPROACH: *Qualitative Assessment of BAG-1 and p-73 gene by Immunohistochemical Analysis:* For qualitative assessment of BAG-1 and p73 in normal (5 BN) and cancerous (5 PTC, 5 FTC) tissues, paraffin-embedded thyroid tissues were obtained from WRAMC Pathology paraffin-embedded tissue archives. The immunohistochemical analysis for BAG-1 and p73 were performed. Briefly, paraffin-embedded tissues were sectioned (4-5 $\mu$M thick) and mounted on a silicon-coated glass slides in triplicates. The slides were deparaffinized in xylene and rehydrated through a series of decreasing content of ethanol solution, and finally in distilled water. Endogenous peroxide activity was quenched using 6% hydrogen peroxide in methanol for 15 minutes. Slides were then placed in a humid chamber and incubated at room temperature for 30 minutes with 10% normal goat serum (D30025, Dimension Laboratories) in phosphate buffer saline containing 0.1% Triton X-100 (Sigma Chemical Co., St. Louis, MO) to block nonspecific staining. Sections were routinely incubated overnight at 4° C with either polyclonal antibody with either BAG-1 or p73. Sections were next incubated for 30 minutes with 200x dilution of biotinylated goat antirabbit IgA (BA-1000, Vector Laboratories, Inc., Burlingam, CA). Slides were washed extensively with phosphate buffered saline between each of the above steps. Sections were then exposed to diaminobenzadine (D-5637, Sigma) peroxidase substrate solution for 5 minutes, and then washed with distilled water to stop the diaminobenzadine reaction. The sections were then rehydrated through a graded ethanol series and xylene, then coverslipped using Permount (SP153-100, Fisher Scientific Co.) For the positive control, sections known to stain positively were included in each batch; and, for the negative control, sections were prepared by replacing primary antibody with mouse or goat ascites fluid (Sigma Chemical Co.). All slides were examined by 3 investigators. The investigators were blinded to clinical and pathological information of the specimens.
*Quantitative Assessment of BAG-1 from the Paraffin-embedded Tissues, and Frozen Thyroid Tissues by Quantitative RT-PCR:* Total RNA from sections (6 $\mu$M thick) from 15 Paraffin-embedded tissue samples (5 BN, 5 FTC and 5 PTC) and were extracted from deparafinization with xylene and ethanol treatments and from these specimens total RNA was extracted in Trizol (Sigma). Total RNA from frozen thyroid tissues (3 BN, 6 PTC and 4 FTC) was also extracted in Trizol. The details of the RNA recovery procedures were included in the original Protocol (WU-001304) in the technical Appendix IA and IB. These techniques have been previously used at WRAMC with very good results. The RNA recovered served as substrate for quantitative reverse transcriptase polymerase chain reaction (RT-PCR) amplification. The extracted total RNA isolated from the tissue specimens was subjected to RT-PCR in a duplicate manner using GGAGGAAATGGCGGCAG as the forward primer and GGTCGTGCTTCTCATTGCTG as the reverse primer (PCR product size = 62 b.p.). To quantitatively amplify BAG-1 using ABI PRISM 700 Sequence Detection System with a fluorescent-labeled BAG-1 specific oligonucleotide probe CCTTCAACACCCCAGCCATGTACGTT (Taqman Probe) was utilized. To help validate the kinetic quantitative RT-PCR method, calibration curves were constructed using human

thyroid mRNA (Clontech). The human thyroid mRNA was serially diluted to produced a standard curve that ranged from 8 pG - 2000 pG using 5 different concentrations. No mRNA template was used for the negative controls. β-Actin gene was used as endogenous reference BAG-1. For β-actin, GCGAGAAGATGACCCAGATCAT (forward primer) and (GGTACGGCCAGAGGCGT (reverse primer) were used; and β-actin specific probe for quantification purposes of β-actin TaqMan Probe CCTTCAACACCCCAGCCATGTACGTT. The amount of the target gene and endogenous reference for each sample was determined from the calibration curves. The target amount was divided by the reference amount to obtain the normalized target values.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE: Prior Progress: There is much interest in discovering a reliable molecular marker or set of markers for aiding clinicians in discriminating benign from cancerous thyroid nodules. Our group set out to determine if BAG-1, a multifunctional antiapoptotic protein and p-73 an apoptotic protein previously identified also in breast cancer, are expressed in thyroid tissue. Additionally, if found to be expressed in thyroid tissue, might BAG-1and/or p73 be a suitable marker for the thyroid cancer. Slides prepared from 15 paraffin block specimens were examined utilizing immunohistochemical staining techniques with BAG-1and p73 specific IgG antibody. These samples included papillary thyroid cancer (PTC, n=5); follicular thyroid cancer (FTC, n=5); and normal thyroid tissue (NL or BN, n=5). The slides were interpreted for either presence of BAG-1 or p73 staining by three separate reviewers who were blinded to the histological diagnosis. There was not observed any noticeable intensity pattern of staining in the case of p73 proteins and, therefore, p73 study was not carried out further. In the case of BAG-1, all the three reviewers consistently noted BAG-1 staining in the cytoplasm of all 15 specimens. The intensity of cytoplasmic staining was judged to be variable from weekly to strongly positive, but no consistent pattern of staining was found which would permit differentiation between the varying types of thyroid whether cancerous or normal tissue. In an attempt to determine if quantitative RT-PCR assessment of BAG-1 expression would allow differentiation of PTC, and FTC from NL, RNA was isolated from 15 paraffin block tissue specimens (PTC, n=5; FTC, n=5; and NL, n=5). Levels of BAG-1 mRNA were determined by real-time quantitative RT-PCR using BAG-1 specific primers with an internal fluorescent probe, with values normalized to simultaneously measured β-actin mRNA. The following levels of BAG-1 [ng BAG-1/pg β-actin mRNA expressions were determined: NL, 1250 +/-837; PTC, 1136 +/- 951; and FTC, 2510 +/- 1901. Statistical analysis did not reveal any significant difference between the groups, despite the trend for BAG-1 to be somewhat higher in the FTC lesions.

Current Progress: In order to compare the expression levels of BAG-1 mRNA in paraffin-embedded thyroid tissues with that in frozen thyroid tissues, we examined the levels of BAG-1 in 13 additional frozen thyroid cancerous and normal (benign) tissue specimens (NL, n=3; PTC, n=6; and FTC, n=4) utilizing quantitative RT-PCR technology essentially as described previously. The following mean levels of BAG-1 mRNA [ng BAG-1/pg β-actin] were determined: NL, 1950.19 (n=3); PTC, 1909. 8 (n=6); and FTC, 4681.99 9 (n=4). Again the statistical analysis did not reveal any significant difference between the groups, despite the trend for BAG-1to be somewhat higher in the FTC lesions. The number of enrolled subjects is N/A.

Notes:

- Only thyroid tissue specimens, either paraffin-embedded thyroid tissue blocks obtained from the WRAMC Pathology archives and/or frozen thyroid tissues from Endocrine Frozen Tissue Bank (WRAMC) were utilized for these studies. Use of 170 such specimens has been approved by the DCI for this Work Unit.
- There were no amendment or modifications to the research since the last review.
- There were no adverse events since the last review.

CONCLUSIONS Our preliminary results from both paraffin-embedded and frozen thyroid tissues do not indicate that BAG-1 and p73 expression will be useful markers to detect presence of thyroid cancer. However, it is likely that the limited number of specimens in the study may have restricted the ability to establish a clear difference by RT-PCR in BAG-1 expression between the groups, and consideration could be given to test a larger number of specimens.

Report Date: 19 September 2001 Work Unit # 00-1305

# DETAIL SUMMARY SHEET

TITLE: A 20 Week Multicenter, Double-Blind, Randomized Parallel-Group Fixed Dose Study to Prospectively Evaluate the Efficacy, Safety, and Tolerability of Oral Natelglinide (120 mg) Compared to Oral Rosiglitazone Monotherapy (8 mg) in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise Alone

KEYWORDS: Nateglinide; Rosiglitazone; Diabetes Mellitus

PRINCIPAL INVESTIGATOR: Robert A. Vigersky, COL MC
ASSOCIATES: Barbara Solomon, DNSc.

DEPARTMENT: Medicine
SERVICE: Endocrinology

STATUS: C
INITIAL APPROVAL DATE: 18 July 2000

## STUDY OBJECTIVE

Primary:

Evaluate the effect of nateglinide monotherapy compared to rosiglitazone monotherapy on glycosylated hemoglobin ($HbA_{1C}$) after 20 weeks of double-blind treatment in patients with Type 2 diabetes mellitus inadequately controlled by diet and exercise alone.

Evaluate the safety and tolerability of nateglinide monotherapy and rosiglitazone monotherapy.

Secondary:

Evaluate the effect on prandial glucose, insulin, C-peptide, fasting lipid parameters (total cholesterol, triglycerides, LDL-C, HDL-C), fasting plasma glucose (FPG) and body weight after 20 weeks of double-blind treatment of nateglinide monotherapy compared to rosiglitazone monotherapy in patients with Type 2 diabetes mellitus inadequately controlled by diet and exercise alone.

## TECHNICAL APPROACH

Investigational therapy and reference therapy Nateglinide tablets will contain either 120 mg (FCN 3742038.00.009C; .010C) or matching placebo (FCN 3741865.00.013H; .018H). Rosiglitazone 4 mg capsules will be purchased commercially and will be blinded to match the corresponding placebo capsules.

All labels will be in the local language and will comply with local regulations. Labels will bear a letter A (nateglinide medication tablets) or B (rosiglitazone medication capsules), the period of the study for which the contents should be used, the randomization number (where appropriate), and details about correct storage.

Period I: Single - Blind Period Dosing Instructions

The first dose of Period I medication will be administered as the first main meal dose after the completion of all procedures at the week -4 visit. The last dose of Period I medication will be the dose taken with the meal challenge at the week 0 visit.

The patient will be instructed to take one tablet from Bottle A (nateglinide matching placebo) with a glass of water up to 30 minutes prior to three main meals and two capsules from Bottle B (rosiglitazone matching placebo) with breakfast only.

In order to maintain the study blinding, subjects should not be informed that they are on placebo medication during the first 4 weeks of treatment.

Period II: Double - Blind Period Dosing Instructions

The first dose of nateglinide Period II medication will be the first main meal dose after the completion of all procedures at the week 0 visit. The last dose of period II medication will be the dose taken with the meal challenge at the week 20 visit.

The patient will be instructed to take one tablet from Bottle A (nateglinide or matching placebo) with a glass of water up to 30 minutes prior to three main meals and to take two capsules from Bottle B (rosiglitazone or matching placebo) with breakfast only.

General Dosing Instructions

Subjects must be instructed on the following points related to study medication dosing:
Take one tablet from Bottle A, 1-30 minutes before breakfast, lunch and dinner.
Take two capsules from Bottle B with breakfast. If breakfast is missed, take two capsules from Bottle B with the next meal.
Plan regularly scheduled meals (breakfast, lunch, dinner), so as not to deviate from the dosing regimen.
If a meal is missed, do not take the study medication from Bottle A.
Do not take the morning dose of study medication (Bottle A or Bottle B) or eat breakfast on the day of a scheduled study visit.
After each study visit, the first dose of study medication (Bottle A and Bottle B) should be taken before their next main meal.
Bring medication bottle(s) back to the study center with each visit.
Refer toTable 1 for the study dosing scheme.

Treatment assignment

After satisfying the Week -4 inclusion/exclusion criteria, each patient will receive a unique subject identification number. The subject identification number is composed of two parts. The first part is the center number, assigned to the center by the sponsor, and the last part is the subject number, which is sequentially assigned by the center to patients as they enter the study. For example, the third patient enrolled in Center 35 would be identified as 035-0003. Once assigned, subject numbers must not be reused. Patients may not be rescreened.
After meeting the Week 0 inclusion/exclusion criteria, each patient will be randomized to one of the treatment groups. This occurs when a patient is assigned the next available patient pack, which is identified by a randomization number. The randomization number is printed on the two-part labels on each bottle of medication, and must be recorded in the CRF. At the end of the study, this will allow the sponsor to determine which patient received which medication.

Blinding

The double dummy blinding of the study will be maintained by the use of identical placebo and active tablets/capsules for each study drug.
Randomization will be performed by Novartis Drug Supply Management using a validated system that automates the random assignment of treatment groups to randomization numbers. The randomization scheme will be reviewed by the Quality Management Biostatistics Group in Novartis Medical Information Processing and Statistics Department and locked by them after approval.
Randomization data are kept strictly confidential; accessible only to authorized persons, until the time of unblinding. At the conclusion of the trial, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis. Only when the study has been completed, the data file verified, and the protocol violations determined will the drug codes be broken and made available for data analysis.

Concomitant therapy

The use of the following medications may interfere with the study evaluations and interpretation of study results and therefore is not permitted.
Any antidiabetic agent other than those permitted by the protocol. This includes all sulfonylureas within 5 months prior to week -4, and all other oral antidiabetic agents (biguanides, repaglinide, α-glucosidase inhibitors and thiazolidinediones) within 4 weeks prior to Week -4 and during the full course of the study. For those patients taken off oral anti-diabetic medication with the intent to enter the patient in the study, written informed consent will be obtained at the time of discontinuation of medication. It is the physician's responsibility to monitor the patient during this period.
Corticosteroids except those taken by inhalation or by topical application.
Change in dosage of thyroid supplement within 3 months prior to Week –4 or during the study.
All other prior non-study medication(s) will be allowed, provided the need for such medication(s) is a continuation of a need that existed prior to entry into the study and the manner with which these medication(s) will be used remains essentially unchanged. Sugar-containing (syrups) and sympathomimetic (e.g., Sudafed®) preparations should be avoided.

If any medication other than those being taken at Week-4 is required during the study, the reason will be reported on the Past History or Adverse Event CRF as appropriate and the medication will be reported on the Concomitant Medications or Significant Non-Drug Therapies CRF.

Treatment compliance

Patients will be instructed to return medication bottles to the study site at each visit. Treatment compliance will be assessed by a count of the remaining study medication returned by the patient at each visit. Records of the amount of study medication dispensed and returned at each visit, and intervals between visits will be kept in the patient's source documentation. Drug accountability will be reviewed by the field monitor during site visits and at the completion of the trial.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been three amendments to the protocol:
Amendment 1 changes the sulfonylurea treatment period from with 5 months of week –4 to within 2 months of week –4.
Amendment 2 changes the inclusion criteria for Period I from a medical history of Type 2 diabetes mellitus of ≥ 3 months and ≤ 5 years to only ≥ 3 months. In addition, the exclusion criteria for Period I is raised from 200 mg% to 240 mg%.
Amendment 3 reduces the inclusion criteria of HbA1c in Period II from 7.5% to 7.0%.

Enrollment for this multicentered study through May 2001 is 138 patients out of 345 screened. Enrollment has been extended a third time to 30 June 2001. One each of the following adverse events have been reported -- none of which were judged to be related to the drug: Ischemic entercolitis, aplastic anemia, hepatic encephalopathy, sudden death, hypoglycemic coma, elevated CRP, hypotension, asthma, hyperglycemia with sudden death, acute elevation in liver function tests, and interstitial pneumonia. All these cases occurred in Japanese centers. Two rashes have been reported – one in the US and one in Japan. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 138, if multi-site study.

CONCLUSIONS:

Due to the strict criteria for enrollment (despite the loosening of the inclusion criteria), no patients were enrolled in this study during the enrollment period. As a result the study is closed.

Report Date: 23 November 2001 Work Unit # 01-13001

# DETAIL SUMMARY SHEET

TITLE: A Comparison of the Effects of Rosiglitazone and Metformin on Markers of Inflammation and Carotid Plaque Burden in Patients with Type 2 Diabetes Mellitus. Cardiovascular Effects of Hypoglycemic Medication in Diabetes – CHD Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Stocker, Derek CPT MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Endocrine INITIAL APPROVAL DATE: 23 January 2001

STUDY OBJECTIVE
Primary objective: Does rosiglitazone have an anti-inflammatory effect compared to metformin, measured as a decrease in certain markers of inflammation, particularly C-reactive protein?
Secondary objective: Does rosiglitazone have an anti-atherosclerotic effect compared to metformin, measured as a decrease in carotid plaque burden?

TECHNICAL APPROACH
We are enrolling poorly controlled type 2 diabetics in a study of two FDA-approved medications, rosiglitazone and metformin. Patients are randomly assigned to one of these medications in an open-label study and followed for six months. Over this period, serial carotid intimal thicknesses (CITs) are obtained to assess for changes in atherosclerosis and serial labs are drawn to check for the anti-inflammatory effects of each of these medications.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
No significant study findings to date. No amendments or modifications to original approved protocol. No adverse reactions. No patients withdrawn. No pertinent published studies on these effects in either medication are listed in Medline following those listed in the original protocol.

The number of subjects enrolled to the study since last APR at WRAMC is 9 and the total enrolled to date at WRAMC is 9. The total number enrolled study-wide is 9 if multi-site study.

CONCLUSIONS
No significant findings at this point. Our results could help determine future medication choices in poorly controlled diabetics in whom a new medication is indicated.

Report Date: 12 March 2002

Work Unit # 01-13002

# DETAIL SUMMARY SHEET

TITLE: Using Telemedicine and Wireless Technology to Improve Diabetic Outcomes in Poorly Controlled Patients

KEYWORDS: Diabetes Mellitus, Telemedicine

PRINCIPAL INVESTIGATOR: Vigersky, Robert A. COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: O
INITIAL APPROVAL DATE: 20 March 2001

STUDY OBJECTIVE: Determine whether or not patients who are given one of three different technologies to communicate their home blood sugar results to their provider have better glycemic control than those who get "routine" Diabetes Instititute care.

TECHNICAL APPROACH
STANDARD CARE: Group 1.
All patients will receive standard Diabetes Institute care. During the patient's initial visit, a comprehensive medical history will be taken to confirm the diagnosis, review and reassess the previous treatment, evaluate past and present degrees of glycemic control, determine the presence or absence of chronic complications of diabetes, assist in formulating a management plan, and provide a basis for continuing care. A physical examination will be performed during the initial evaluation. Each patient will undergo any routine laboratory tests as deemed appropriate by the health care provider. A diabetes management plan will be formulated as an individualized therapeutic alliance among the patient and family, the provider, and other members of the health care team skilled in diabetes management.

RESEARCH: Group 2,3, and 4.
After obtaining baseline laboratory data, eligible patients will be randomized to one of three intervention groups using a computerized random number generator program. Patients assigned to Group 2 (the first intervention group) will transmit their glucose measures through a modern compatible to their glucometer to a specially designed secure website. Group 3, the second intervention group, will consist of patients who will transmit their glucose measures via WebTV to the same specially designed website. Group 4, the third intervention group, will consist of patients who will transmit their glucose measurements via their Internet accessible computer to the same specially designed website. Patients who transmit their glucose measures through a modem will not be able to view graphical or tabular representations of their data. Patient who transmits their glucose measures using a WebTV device or personal computer will be able to view graphical or tabular representations of their data. Patients in Group 2,3 and 4 will transmit their glucose data using 128-bit encryption technology to their health care provider weekly. Nurse practitioners will review these data weekly and intervene personally with the patient whenever it is clinically appropriate. All research groups will also receive standard Diabetes Institute care as outlined above for Group 1.

Patients in an intervention group (Group 2,3 or 4) will receive training to support the technology assigned to their group. The project officer to each participant at the medical treatment facility will administer training where he/she usually receives diabetes care (Walter Reed Army Medical Center, DeWitt Family Health Center, Fairfax Family Health Center, or Kimbrough Ambulatory Care Center). The patient training modules will include specially developed educational materials manuals and videotaped instruction (not to exceed thirty minutes). Patients will schedule appointments for training with the project officer.

Identifying patients only will protect patient confidentiality be a unique serial number on their glucometer, regardless of the technology used. Only the treating nurse practitioners and Principal and Associate Investigators will know this number and the patient's identifying information. Patients who transmit data to the secured WRAMC website via modem will utilize a TCP/IP connection. Patients who transmit using a WebTV device will access the

secure WRAMC website via an HTTP connection. Displayed responses will be limited to historical data and the patient's first name. Patients who transmit data using a personal computer will also access the secure WRAMC website using an HTTP connection.

Displayed responses will be limited to historical data and the patient's first name. Risks to patients are only that of potential breach of confidentiality. In no case will patient identifiers will be included in an electronic transmission. The Principal Investigator will keep the complete list in a secure file at WRAMC.

The WRAMC diabetes database will serve as the central repository for all data from this study. Data collected by Health Sentry will be available to the Principal and Associate Investigators in real time via secure encryption technology. The data remains on the Health Sentry server to allow for historical trends to be clinically evaluated. Patients will have access to their own data on the Health Sentry server.

TECHNOLOGY: The software development and maintenance and the establishment of a secure website will be performed under contract by Health Sentry, who will modify a previously developed proprietary product for the investigators. This unique software allows the patient to use any brand of glucose meter to download their data into a secure website. Patients will not be required to execute any paperwork for the technology contractor, which might reveal their identity beyond the glucometer serial number. The patients will enter the website through the WRAMC website. The data will be automatically analyzed and displayed in both numeric graphic formats. All Principal and Associate Investigators will have continued free and open access to the secured patient data. Health Sentry will also produce a patient training module that will include manuals, user's guides, and videotapes. These specially developed educational materials will be owned by WRAMC and maintained on the facility. Participating patients will not be permitted to retain the technology instrument (modem, WebTV device, or computer cable) provided them by Health Sentry after completion of this study. Health Sentry will maintain an 800 number hotline for support. The only patient data resident in the Health Sentry database will be the patient's glucometer serial number and blood glucose levels.

Group 2: Health Sentry, will provide the following support for the glucometer:
Fifty patients will receive a modem, and then be assigned a unique participant identifier (their glucometer serial number). The study participants will communicate their glucose measures using a standard telephone line to the Diabetes Institute health care provider weekly. The modem will be pre-customized by Health Sentry to dial a toll free phone number to the contractor's server. Software to migrate this information into the common database using a secure website.

Group 3: Health Sentry, will provide the following to support WebTV use:
Fifty patients will receive a WebTV control device and WebTV keyboard to upload their glucometer measurements. The WebTV controller devices will interface with the patient's glucometer and deliver these readings using an infrared beam to the WebTV appliance. These data will be transmitted directly to the Health Sentry server. No Health Sentry employee or affiliate, nor will any individual, institution or organization outside of the WRAMC Diabetes Institute have access to any patient demographic data. The contractor will not analyze or otherwise dispose of patient data. The contractor will store anonymized patient data distribution to investigators. Patients will be identified by meter serial number only. Software to migrate this information into the common database using secure website that appears to study participants to be integrated into the WRAMC website.

Group 4: Health Sentry, will provide the following to support PC use:
Fifty compatible computer cable links to allow patients to upload their glucometer measures using their own Internet capable PC's. These data will be transmitted directly to the Health Sentry server. The contractor will not analyze or otherwise dispose of patient data. The contractor will store anonymized patient data for distribution to instigators. Software to migrate this information into the common database using a secure website that appears to study participants to be integrated into the WRAMC website.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE: One of the major milestones of this project was getting the protocol approved. This was the culmination of a long, rigorous, and duplicative process. The time-line for this approval is as follows:
Submission to P8 Program – 13 Sep 2000
Approval Letter from USAMRMC – 1 Dec 2000
Acceptance of Funding – 4 Dec 2000
Protocol Writing initiated 5 Dec 2000
MIPR Received – 30 Jan 2001
Protocol Submitted to DCI – 8 Feb 2001
Protocol Reviewed by CIC and HUC – 6 Mar 2001
Revisions Requested by CIC and HUC – 3 Apr 2001
Revisions Submitted to CIC and HUC – 23 May 2001, 12 June 2001, 2 Jul 2001 and 5 Jul 2001
Submitted to CIRO – 9 Jul 2001
Submitted to USAMRMC – 9 Jul 2001
Review and Revisions requested by USAMRMC contractor – 19 Sep 2001
Revisions Submitted – 26 Sep 2001
Further Revisions requested by USAMRMC contractor – 19 Sep 2001
Further Revisions Submitted – 25 Oct 2001
Acceptance by USAMRMC – 4 Nov 2001
Final DCI acceptance – 14 Nov 2001

Contract and Receipt of Deliverable from Health Sentry: The contract for the hardware/software services was put up for bid in FEB 01 and Health Sentry Technology was selected as the vendor in Mar 2001. The contract was signed in Apr 2001. Over the subsequent eight months, we have worked closely with them in directing the provision of the contract deliverables. They have provided the following deliverable included in the contract:
Patient Training Manuals
Provider Training Manuals
Hardware – Roche Modems, Computer Cables, WebTV Equipment, and customized remote glucose
Software – Modification of HeathSentry.net Diabetes monitoring service website for WRAMC use, Diabetes Management software development

A review of recent literature shows no studies addressing this problem. The number of subjects enrolled to the study since last APR at WRAMC is 34 and the total enrolled to date at WRAMC is 34. The total number enrolled study-wide is n/a, if multi-site study. There have been no adverse events.

CONCLUSIONS: Despite considerable delays in initiating this study, with the hiring of new project officer in December 2001 good progress has been made. The following time line goals were established:
31 May 2002 – cessation of patient recruitment
30 Nov 2002 – completion of all 6-month trials of technology
30 Dec 2002 –0 data analysis
31 Jan 2003 – preparation and submission of abstracts to the Endocrine Society and/or American Diabetes Association annual meeting (June 2003)
31 Jan 2003 – preparation an submission of a manuscript

Report Date: 30 January 2002 Work Unit # 01-13003

# DETAIL SUMMARY SHEET

TITLE: The Avandia Worldwide Awareness Registry (AWARe): Comparison of Avandia and Actos in "Real World" Medical Practice

KEYWORDS: Diabetes Mellitus. Avandia, Actos, Rosiglitizone, Pioglitizone

PRINCIPAL INVESTIGATOR: Vigersky, Robert A. COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: O
INITIAL APPROVAL DATE: 27 March 2001

STUDY OBJECTIVE

The objective of this study is to determine:

a. Whether thiazolidinedione (TSD) class of antidiabetic pharmaceutical agents has beneficial effects on cardiovascular risk factors (e.g. lipids, blood pressure, and proteinuria)
b. The safety and compliance with antidiabetic drug therapy in a population of patients with Diabetes Mellitus Type 2
c. In a "real world" treatment setting whether rosiglitizone or pioglitizone provide sustainable glycemic control in the long term (6 months-1 year)
d. The impact of antidiabetic drug therapy on patient's health-related quality of life and satisfaction with treatment
e. Whether differences exist between the two currently available drugs in the thiazolidinedione class, Avandia and Actos, in Objectives a-d

TECHNICAL APPROACH

This is a combination of an observational and a randomized control trial. The observational and randomized control trial. The observational aspect is standard of care for the Diabetes Institute. It involves the monitoring of patients' data who are treated with a sulfonylurea and/or a TZD and/or metformin and who are not placed on a TZD during the duration of the study. The interventional aspect is the randomization of patients who require a TZD to either rosiglitizone or pioglitizone.

As a part of the research, demographic and clinical data on enrolled patients will be entered into the Avandia Worldwide Awareness Registry (AWARe).

PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 87 and the total enrolled to date at WRAMC is 87. The total number enrolled study-wide is unknown, if multi-site study.

There have been no adverse events.

CONCLUSIONS

Data collection is progressing as planned and the rate of enrollment is increasing. Outstanding technical issues remain, however, relating to the 1CHCS conversion on 1 September 2001 that prevents the transmission of SIG on each prescription to be captured by ICDB.

Report Date: 12 March 2002 Work Unit # 01-13004

# DETAIL SUMMARY SHEET

TITLE: Pilot Study: Recombinant TSH Stimulation of Radioactive Iodine Uptake in Hyperthyroidism

KEYWORDS: Thyroid, Thyrotoxicosis, Thyrogen

PRINCIPAL INVESTIGATOR: Bernet, Victor LTC MC
ASSOCIATES: Dr. Aaron Stack, Dr. Thomas Allen, and Dr. Henry Burch

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: O
INITIAL APPROVAL DATE: 15 May 2001

## STUDY OBJECTIVE

1. Determine the effect of rhTSH on RAIU in patients with hyperthyroidism, specifically those cases with only minimally abnormal RAIU levels.
2. Assess the response of patient symptoms as well as Free T4 and Free T3 levels in hyperthyroid patients receiving rhTSH in combination with RAIU or with $^{131}I$ treatment.
3. Evaluate the number of patients achieving euthyroidism or hypothyroidism within six months' status $^{131}I$ treatment in conjunction with rhTSH/.

## TECHNICAL APPROACH

We propose a two-phase study consisting of a total of ten patients with hyperthyroidism with radioactive iodine uptakes (RAIUs) of 15% to 30%. Entry into the study would be limited to those patients who have undergone evaluation by an endocrinologist and have been found to have primary hyperthyroidism as evidenced by history, physical examination, thyroid blood tests (TSH, free T4 and/or free T3) plus standard CBC and Chem 20 panel. The TSH level would need to be suppressed to $\leq$ 0.3 mIU/L, where as the Free T4 and Free T3 would range between the upper normal to mildly elevated beyond the normal range (but no higher than a Free T4 > 40 pmol/L, Free T3 > 8.5 pmol/L), consistent with autonomous thyroid function. A 99m-technetium thyroid scan and 24-hour RAIU are to have been completed within thirty days prior to entrance into study, and must confirm the presence of autonomous (overactive) thyroid tissue. Participation will require the finding of a 24-hour RAIU between 15% and 30%. Patients will be offered the standard range of therapies to include: antithyroidal medication (propylthoiuracil or methimazole), surgery, or $^{131}I$ as appropriate for their form of hyperthyroidism.

In summary, those patients meeting inclusion and exclusion criteria, who have chosen $^{131}I$ therapy, after careful discussion of therapeutic options with their endocrinologist, will be offered entry into the study.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Final approval for proceeding with this study was not received from DCI until 10 December 2001. Presently, we have yet to be able to recruit our first patient. No new scientific literature has been published which would indicate that either the study would be unsafe or that a change in methods is required.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

## CONCLUSIONS

None. Continue with attempts to enroll patients as planned.

Report Date: 22 April 2002 Work Unit # 01-13005

# DETAIL SUMMARY SHEET

TITLE: Determination of Thyroid Nodule Malignancy with 18F-FDG Coincidence Imaging and Tc-99m Depreotide Scintigraphy

KEYWORDS:

PRINCIPAL INVESTIGATOR: Langley, Roy W. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Endocrine INITIAL APPROVAL DATE: 19 June 2001

## STUDY OBJECTIVE

The objective of this study is to determine if non-invasive imaging using 18F-FDG and Tc-99m Depreotide can determine thyroid nodule malignancy and how this compares to FNA.

## TECHNICAL APPROACH

Subjects with thyroid nodules awaiting thyroidectomy are imaged using 18F-FDG Coincidence Imaging and Tc-99m Depreotide Scintigraphy. The results are compared with the cytology from FNA and the histology from thyroidectomy.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Eleven subjects have been enrolled to date. Not all have yet had thyroidectomy. Two subjects have had histologically confirmed thyroid carcinoma. Formal imaging results and ROI calculations are underway in this initial group of subjects. Preliminarily, depreotide imaging has been positive in both subjects with thyroid carcinoma and in one subject with a follicular adenoma. There have been no adverse events and no subjects have withdrawn from the study. There is no benefit to subjects from this study. The number of subjects enrolled to the study since last APR at WRAMC is 11 and the total enrolled to date at WRAMC is 11.

## CONCLUSIONS

The sample size to date is too small for meaningful results. Subjects continue to be actively recruited.

Report Date: 8 August 2001

Work Unit # 1392-98

# DETAIL SUMMARY SHEET

TITLE: Circulating Micro-Metastasis in Patients with Thyroid Neoplasia

KEYWORDS:

PRINCIPAL INVESTIGATOR: Gary L Francis, COL MC
ASSOCIATES: Yvonne Lukes DCI

DEPARTMENT: Pediatrics
SERVICE: Pediatric Endocrinology

STATUS: C
INITIAL APPROVAL DATE: 28 October 1999

## STUDY OBJECTIVE

1) Do patients with thyroid cancer have detectable thyroid cells in the peripheral circulation as determined by RT-PCR for Tg-mRNA? 2) Does the presence of Tg-mRNA correlate with clinical staging of thyroid cancer and clinical outcome; 3) Does the presence of Tg-mRNA correlate with expression HGF/cMET or P53; 4) Does the level of Tg-mRNA vary in normal individuals after thyroid palpitation; 5) Can the level of Tg-mRNA be used in conjunction with FNA in the detection of thyroid cancer.

## TECHNICAL APPROACH

1) Evaluation of Tg-mRNA levels in normal subjects before and after thyroid palpitation.
2) Evaluation of serum VEGF levels by ELISA patients with benign and malignant thyroid disease.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 38. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

Thyroglobulin mRNA can be detected in peripheral blood of patients with thyroid cancer and other thyroid diseases. Within the group of cancer patients, Tg mRNA levels correlate with Tg protein and 131-iodine uptake.

Report Date: 15 March 2002 Work Unit # 1395-98

# DETAIL SUMMARY SHEET

TITLE: Establishment of a Thyroid Patient Serum Bank

KEYWORDS:

PRINCIPAL INVESTIGATOR: Burch, Henry LTC MC.
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Endocrine INITIAL APPROVAL DATE: 21 April 1998

STUDY OBJECTIVE
To collect serum from a variety of patients with endocrine disorders to facilitate future research requiring serum.

TECHNICAL APPROACH
Obtain informed consent. Perform standard phlebotomy, centrifuge, and store specimens at -70° C.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
No new serum samples have been obtained since last APR.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 158. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
None.

Report Date: 21 February 2003

Work Unit # 1396-98

# DETAIL SUMMARY SHEET

TITLE: Establishment of a Thyroid Tissue Bank

KEYWORDS:

PRINCIPAL INVESTIGATOR: Burch, Henry LTC MC.
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: O
INITIAL APPROVAL DATE: 21 April 1998

STUDY OBJECTIVE
To create and maintain a tissue and fine needle aspiration bank from patients with a variety of thyroid disorders, in order to facilitate future research projects requiring thyroid tissue.

TECHNICAL APPROACH
After obtaining informed consent, a small piece of tissue being removed for clinical indications is snap frozen in liquid nitrogen and stored in a -70 C freezer.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Surgical thyroid tissue continues to be collected for the thyroid tissue bank. There have been no adverse events associated with participation in this protocol.

The number of subjects enrolled to the study since last APR at WRAMC is 37 and the total enrolled to date at WRAMC is 115. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
None.

Report Date: 20 December 2001 Work Unit # 1399-99

# DETAIL SUMMARY SHEET

TITLE: The Effect of Retinoic Acid on Sodium-Iodide Symporter mRNA Expression in Thyrocytes Circulating in the Blood Stream – A Pilot Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Bernet, Victor J. LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: C
INITIAL APPROVAL DATE: 16 February 1999

## STUDY OBJECTIVE

To determine the effects of 13-cis-retinoic acid on the quantity of sodium-iodide symporter (NIS) messenger RNA in peripheral blood.

## TECHNICAL APPROACH

To begin to evaluate the function of the circulating cells, we sought to determine whether oral 13-cis-retinoic acid administrations would be associated with an increase in NIS mRNA expression in peripheral blood of subjects with no known thyroid disease. Total RNA was extracted from whole blood (Ultraspec RNA isolation system) obtained from 9 subjects (mean age +/- SD: 24 +/- 11 years, 44% female) taking oral 13-cis-retinoic acid for acne (Accutane, mean dose +/- SD 71 mg +/-20, duration of therapy mean +/- SD 11 +/- 8 wks) and from 5 normal subjects. All participants had normal thyroid physical examinations. In addition to serum Tg immunoassay, NIS and Tg mRNA expression was determined by quantitative RT-PCR (ABI PRISM 7700 sequence detection system).

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No further progress has been made on this study. PI is requesting that it be closed at this point in time.

## CONCLUSIONS

A combination of loss of personnel with prior patient recruitment problems and results which preliminarily revealed no significant difference in NIS expression between controls and patients (albeit on a cross section review) lead to no progress being made on proceeding to the prospective portion of this study. At this time, it would seem most prudent to close this study.

Report Date: 14 October 2001 Work Unit # 00-1401

# DETAIL SUMMARY SHEET

TITLE: Exploration Of Genome-Wide Expression Profiles In Subtypes Of Colorectal Neoplasia – A Pilot Study

KEYWORDS: Colon Cancer, genetics

PRINCIPAL INVESTIGATOR: James Walter Kikendall COL MC
ASSOCIATES: Eugenia Rued-Pedraza COL MC

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: C
INTIAL APPROVAL DATE: 14 December 1999

STUDY OBJECTIVE:
To explore the differential patterns of gene expression in normal, adenomatous polyp and cancer tissues in the colon using micro-array technology.

TECHNICAL APPROACH:
In the feasibility study we will enroll up to 40 subjects scheduled for colonoscopy because of specific criteria. Participants will complete a data form. Tissue will be collected during the clinically indicated colonoscopy if the patient has a neoplastic lesion of appropriate size. Data forms and tissue will be anonymized prior to transfer to NCI for genetic analysis by micro-array.

PRIOR AND CURRENT PROGRESS:
We have made no progress in the last year due to lack of personnel. The number of subjects enrolled to the study since last APR at WRAMC is 0, and the total enrolled to date at WRAMC is 2.

CONCLUSIONS:
Completion of this study would require a nearly full-time recruiter to interview all subjects scheduled for colonoscopy, determine eligibility, administer informed consent, collect tissue, and process tissue. Therefore, the study is closed.

Report Date: 12 January 2002 Work Unit # 00-1403

# DETAIL SUMMARY SHEET

TITLE: The Effect of *Helicobacter pylori* eradication on the severity of Gastro-esophageal Acid Reflux as Determined by 24-hr pH Measurement

KEYWORDS: *H. pylori*, Gastroesophageal Reflux

PRINCIPAL INVESTIGATOR: Brian P. Mulhall, CPT MC
ASSOCIATES: Roy Wong COL MC, Corinne Maydonovitch, Allan Andrews CPT MC, Roger Fincher MAJ MC

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 18 January 2000

STUDY OBJECTIVE: To assess the effect of *H. pylori* eradication on gastro-esophageal reflux and whether the pattern of the gastritis from *H. pylori* infection plays any role in potential changes in gastric acidity and associated gastro-esophageal reflux.

TECHNICAL APPROACH:
We plan to enroll 250 patients in order to satisfy our goal of 80 patients completing the study (after several exclusionary steps). All adult patients presenting with gastro-esophageal reflux disease (GERD) symptoms will be offered participation. Serology for *H. pylori* IgG antibody will be performed to screen for *H. pylori* infection. Seropositive patients will undergo $^{13}$C-urea breath testing (UBT), to document active *H. pylori* infection and 24-hr esophageal pH testing and manometry to establish the presence and severity of GERD. A symptom questionnaire will also be completed. Patients with active *H. pylori* infection will undergo upper endoscopy and gastric biopsies. Histology will be used to determine the presence and pattern of gastritis and *H. pylori*. Four biopsies will be frozen for subsequent PCR analysis of the H. pylori genome to assess for virulence factors. Cag-A serology will be attained to assess its prevalence and relation to GERD severity. Patients will receive antibiotic therapy to eradicate *H. pylori* infection, and UBT will be repeated 10 weeks later to confirm eradication. Patients then will have repeat 24-hr esophageal pH testing and symptom questionnaire to determine post-eradication GERD severity compared to pre-eradication status. The presence of antibodies to Cag-A will be compared to histological gastritis, GERD severity, and to post-eradication symptom changes. This study will provide a better understanding of the role of *H. pylori* and its eradication in GERD, and may have important implications in the management of GERD and *H. pylori* infections.

Previous protocol addendum added Urea breathing testing to the initial evaluation in order to appropriately document active *H. pylori* infection prior to endoscopy. This served to reduce up-front risk to study patients who might eventually not be offered enrollment (due to H. pylori negativity). This has served to decrease institutional burden, as well.

PRIOR AND CURRENT PROGRESS:
The number of subjects enrolled to the study since last APR at WRAMC is 4 and the total enrolled to date at WRAMC is 21 of 69 consented. (The total number consented study-wide is 69, with 21 that were H. pylori positive and 15 who have completed the study.) Study enrollment was not actively pursued for the six months after the departure of Dr. Roger Fincher as efforts were being made (by Dr. Fincher) to concomitantly enroll patients at his new duty center. His protocol is undergoing review by EAMC DCI presently. The four patients enrolled prior to Dr. Fincher's departure successfully completed their pH and endoscopy studies this summer and fall and all data have been collected and recorded. With the high likelihood that EAMC DCI will approve Dr. Fincher's parallel protocol, forty-eight new subjects at WRAMC have been contacted by the undersigned PI (since 01 January 2002) and will be interviewed over the next several weeks for consideration and informed consent for enrollment.

Several conclusions can be made from our preliminary data. Of the eight subjects that had completed the protocol in April 2001, 7/8 had successful eradication of their Helicobacter pylori with standard antibiotic therapy. Despite eradication of this organism, patient's overall Johnson/Demeester score (a measure of the degree of acid reflux) did not change substantially (from 27.0% to 26.9%). Symptom scores were likewise unchanged. This runs contrary to previous data arguing that eradication of H. pylori may actually increase GERD and GERD symptoms. Further, of the 17 patients enrolled in April, all patients were demonstrated to have carditis (inflammation of the cardia of the stomach). Interestingly, the presence or severity of carditis did not correlate with the presence and severity of esophagitis 5 cm above the lower esophageal sphincter—though the severity of carditis did strongly correlate with the degree of antritis (antral inflammation). As such, this may argue that carditis is related more so to H. pylori infection than it is to GERD.

Findings (regarding a specific type of cardia inflammation specifically correlated with Helicobacter pylori) conflict with several recent studies, but replicate findings of el-Zimaity, Morini, and Voutilainen. The latter study described carditis in patients without associated gastritis but correlated these findings with GERD-related esophagitis. Similarly, Bowrey also found carditis in distinct populations of patients with GERD or H. pylori and determined that the histological findings could only be distinguished with special stains. They propose that the carditis develops due to a similar immunological mechanism in both processes. Several studies have attempted to further delineate the relationship between H. pylori infection and GERD, but have been flawed because of retrospective design or small numbers of enrolled patients. Oberg completed a retrospective analysis on 229 patients with GERD or dyspepsia and found no relationship between complaints of GERD and H. pylori infection. They did not study organism eradication and its effects on GERD symptomatology.

There is a great deal of on-going interest in the relationship between H. pylori and GERD and the concomitant relationship that H. pylori and carditis. The studies cited and various expert opinion/reviews have not been yet produced resolutions on either issue.

CONCLUSIONS: Preliminary data has been promising and the respective abstracts were met with interest at our professional meeting. Given the ongoing controversy, further investigation is warranted, and this study may be an important contribution to this continued quandary. Though enrollment was briefly halted, enrollment will be accelerated at WRAMC through the winter and spring of 2002 with a goal of completing enrollment in the fall to winter of 2002.

Report Date: 1 February 2002 Work Unit # 00-1404

# DETAIL SUMMARY SHEET

TITLE: A Comparison of Pediatric and Adult Colonoscopes in Adult Patients Presenting for Routine Colonoscopy

KEYWORDS:

PRINCIPAL INVESTIGATOR: Cumings, Mark D. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Gastroenterology INITIAL APPROVAL DATE: 21 March 2000

STUDY OBJECTIVE
To evaluate use of a pediatric colonoscope with an adult colonoscope by comparing a) total procedure time, b) time to reach cecum, and c) rate at which the endoscopist reaches the cecum.

TECHNICAL APPROACH
Adult patients presenting to our clinic for colonoscopy will be assessed for entry in the study by the primary investigator prior to the date of the colonoscopy. Patients will be recruited by the primary investigator, gastroenterology fellows, and staff at the time of initial patient interview with the physician. Prior to the initiation of the study, a randomization schedule will be used to assign subjects to either the pediatric or adult colonoscope study groups. The primary investigator will contact patients prior to their scheduled colonoscopy to inquire about study participation. Those patients wishing to participate will then be evaluated for exclusion criteria. On the day of the procedure the patient will be consented by either the endoscopist or primary investigator. The GI staff will be aware of the assigned scope, but the patient will not know which scope is assigned. A gastroenterology staff physician will perform all endoscopies. Patients will undergo standard bowel preparation using Go-Lytely. All patients will receive the standard pre-procedure care: brief history by the nurse, insertion of a peripheral IV, recording of demographic data, and recording of initial vital signs. Pre-menopausal women will be required to undergo pregnancy testing with a qualitative urine pregnancy test prior to colonoscopy. During the procedure vital signs will be monitored every 5 minutes and recorded every 15 minutes. Patients will be provided sedation (opioids and benzodiazepines) prior to and during the procedure as deemed necessary by the endoscopist. The amount of time for each procedure will be recorded. Procedure start time will be the time the colonoscope is inserted into the anal canal. Procedure end time will be when the scope is removed from the patient. Time will be recorded in minutes and seconds. Both the total time it takes to reach the cecum (TTC) and total time for procedure (TTP) will be recorded. TTC is the length of time from insertion to visualization of cecal landmarks, to include ileocecal valve. TTP is the length of time from insertion to removal of scope from the patient. Prior to the start of the study, baseline times will be established for each staff by taking the average times of 10 procedures each using the pediatric scope and adult scope. Following the procedure the patient will be recovered for approximately one hour in the GI recovery area. Once recovered and prior to departing the clinic, the Endoscopic nurse will obtain pain and satisfaction scores from the patient using a visual analogue scale. The pain and satisfaction assessment will be repeated approximately 24 hours after the procedure.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
No patients have been recruited for this study. Thus, since protocol approval, there has not been any progress. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

CONCLUSIONS Not applicable.

Report Date: 5 February 2002 Work Unit # 00-1405

# DETAIL SUMMARY SHEET

TITLE: Phase II Study of Long Term PEG Intron for Patients Who Have Failed to Respond to Rebetron/Interferon with Advanced Fibrosis and Cirrhosis Secondary to Hepatitis C

KEYWORDS: Hepatitis C, Cirrhosis, Interferon

PRINCIPAL INVESTIGATOR: Holtzmuller, Kent COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Gastroenterology INITIAL APPROVAL DATE: 21 March 2001

## STUDY OBJECTIVE

The specific aims of this proposal are to evaluate the role of long term PEG-Intron therapy on the natural history of patients with advanced chronic HCV infection with a primary focus on prevention of hepatic decompensation, progression of fibrosis and hepatoma development. Viral clearance is not an endpoint, although viral levels will be obtained annually.

## TECHNICAL APPROACH

Randomized trial of PEG-Intron 0.5mcg per kgweekly clochine 0.6 mg bid in prior non-responders to interferon/REBETRON with advanced fibrosis/cirrhosis (Ishak stage 4-6). The length of therapy is four years. After the first six months of therapy, the study subjects will be seen quarterly for clinical evaluation for decompensation of liver function, clinical screening for development of hepatocellular cancer and liver biopsies for determination of progression of liver fibrosis every two years.

## PRIOR AND CURRENT PROGRESS

WRAMC did not enter any subjects into this trial and has withdrawn from study participation.

## CONCLUSIONS

None.

Report Date: 1 February 2002 Work Unit # 00-1406

# DETAIL SUMMARY SHEET

TITLE: Screening for Barrett's in Patients With and Without Heartburn. A Multi-Center Trial

KEYWORDS:

PRINCIPAL INVESTIGATOR: Cumings, Mark D. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: C
INITIAL APPROVAL DATE: 21 March 2000

## STUDY OBJECTIVE

To determine the relative prevalence of Barrett's esophagus in persons with and without symptoms of gastro esophageal reflux disease. To determine the relative prevalence of Barrett's esophagus in males vs. females, and Caucasians vs. African-Americans.

## TECHNICAL APPROACH

Patients who are age 40 or older, have had no previous EGD, and are planning to receive sedation for their colonoscopy will be assessed for entry in the study. The primary investigator will contact patients prior to their scheduled colonoscopy to inquire about study participation. Those patients wishing to participate will then be evaluated for exclusion criteria. On the day of the procedure the patient will be consented by either the endoscopist or primary investigator. The primary investigator, or designee, will have the patient complete two questionnaires prior to the procedure. Gastroenterology fellows and gastroenterology staff physicians will perform colonoscopies and upper endoscopies. Patients will undergo standard bowel preparation using either Go-Lytely or oral fleet phospho-soda. All patients will receive the standard pre-procedure care: brief history by the nurse, insertion of a peripheral IV, recording of demographic data, and recording of initial vital signs. Premenopausal women will be required to undergo pregnancy testing with a qualitative urine pregnancy test prior to the procedure. During the procedure vital signs will be monitored every 5 minutes and recorded every 15 minutes. Patients will be provided sedation (opioids and benzodiazepines) prior to and during the procedure as deemed necessary by the endoscopist. After receiving sedation the patient will undergo upper endoscopy first, followed by colonoscopy. The patients who refuse will be excluded but their refusal will be recorded. Following the procedure the patient will be recovered for approximately one hour in the GI recovery area. Indiana University Hospital will supply biopsy forceps (Microvasive). Pyloritek (Serum Industries) containers will be supplied Indiana University. Containers will be sent to WRAMC from Indiana University for shipping of formalin fixed tissue to their pathology lab. Tissue samples will be taken, shipped, and stored for the duration of the trial (approximately three years). Once the study is over the tissue will be destroyed. No genetic research will be conducted. All patient identification information will be maintained at WRAMC by the primary investigator; we will code the samples and data sheets and maintain code at WRAMC.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Multicenter study completed. Primary center is at Indiana University. Data analysis is ongoing. Final report not yet available. The number of subjects enrolled to the study since last APR at WRAMC is 40 and the total enrolled to date at WRAMC is 100. The total number enrolled study-wide is >1000, if multi-site study.

## CONCLUSIONS

Final results from study not yet available.

Report Date: 14 March 2002

Work Unit # 00-1407

# DETAIL SUMMARY SHEET

TITLE: Tele-Hepatitis Phase I Validation of Desktop Video Teleconferencing (VTC) System at 384 kb ISDN for Evaluation of Patients with Hepatitis.

KEYWORDS: Telemedicine, VTC, hepatitis, ISDN

PRINCIPAL INVESTIGATOR: Inku Hwang
ASSOCIATES: Kent C. Holtzmuller, Michael A. Dunn, Maria H. Sjogren, Roy H. Wong, Ronald K. Poropatich

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 16 May 2000

## STUDY OBJECTIVE

1. Determine the diagnostic concordance of visual physical exam findings in patients with chronic hepatitis using in person vs. desktop VTC at 128kb connection.
2. Determine the patient satisfaction of using VTC consultation system.
3. Determine physician satisfaction of using VTC consultation system.
4. Estimate cost savings of using VTC consultation system in place of traditional face-to-face consultation for follow-ups.

## TECHNICAL APPROACH

We hope to validate the use of inexpensive desktop VTC system connected at 384 kb connectivity to visually diagnose patients with findings from chronic hepatitis. Diagnostic concordance between in person evaluation vs. those performed using the VTC will be compared. Also, both patients and physicians will be surveyed for both level of experience with VTC and computer systems and satisfaction of such a system. Finally, for those patients on TDY from distant sites, we will collect monetary and time cost data for their visit to Walter Reed. There have been no modifications in methodology from the initial approved protocol.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been no updates in the literature on the use of telemedicine in hepatitis. We have the equipment installed and connectivity completed among three VTC systems. We have enrolled and completed examinations of two patients thus far. We have had no adverse events, and no patients have withdrawn from our study.

## CONCLUSIONS

No conclusions can be drawn from our study thus far given small number of subjects.

Report Date: 2 June 2002 Work Unit # 00-1408

# DETAIL SUMMARY SHEET

TITLE: A Randomized Multicenter Trial Comparing Induction PEG Intron-A Plus Ribavirin Versus PEG-Intron A in Patients Who Have Previously Not Responded or Have Relapsed Following Intron-A Based Therapy for Chronic Hepatitis C, With Maintenance Therapy for Patients Who Continue to Remain Non-Responsive

KEYWORDS: Hepatitis C, Interferon, Ribavirin

PRINCIPAL INVESTIGATOR: Holtzmuller, Kent COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Gastroenterology INITIAL APPROVAL DATE: 18 July 2000

STUDY OBJECTIVE:
The primary objective of this study is to evaluate the efficacy of pegylated interferon alfa- 2b and ribavirin in patients with hepatitis C who have previously failed an interferon based protocol.

TECHNICAL APPROACH:
There have been no modifications to the protocol design. The number of patients that WRAMC is allowed to enter the study has been increased by 20 patients to a total of 40. This is an open label trial where HCV patients who have previously been treated with interferon based anti-viral therapy are treated with pegylated interferon alfa-2b and ribavirin for 48 weeks. The patients are randomized to pegylated interferon alfa-2b 1.5 mcg/kg/week + ribavirin 1000-1200 mg/day for 12 weeks followed by pegylated interferon alfa-2b 1.0 mcg/kg + ribavirin 800 mg/day for 36 weeks or pegylated interferon alfa-2b 1.0 mcg/kg + ribavirin 800 mg/day for 48 weeks.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
No serious adverse events in the last year. Twenty-one of the patients at WRAMC have completed the study. Two patients are still receiving medication. There will be no more patients enrolled in this protocol.

The number of subjects enrolled to the study since last APR at WRAMC is 3 and the total enrolled to date at WRAMC is 23. The total number enrolled study-wide is 550, if multi-site study.

CONCLUSIONS:
The study is ongoing and there are no conclusions to date.

Report Date: 14 January 2002 Work Unit # 01-14001

# DETAIL SUMMARY SHEET

TITLE: Association of Helicobacter pylori Infection with Coronary Heart Disease Detected by Electron Beam CT

KEYWORDS:

PRINCIPAL INVESTIGATOR: Polish, Roger CPT MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Gastroenterology INITIAL APPROVAL DATE: 9 January 2001

STUDY OBJECTIVE
To determine if an association between Helicobacter pylori infection and Coronary Heart Disease exists.

TECHNICAL APPROACH
The associate investigator (AI) from the Department of Radiology will provide two lists of patients who have presented to the WRAMC EBCT for routine examinations and are potential participants in the study. One will be of patients with zero calcium score (controls), the other of patients with a high calcium score >300 (cases).

1. Letters will be mailed to all patients inviting them to participate in our study. (See appendix 2). One month after the first letter a second letter will be mailed to those patients that did not respond to the first letter. One month after the second letter was mailed a third letter will be sent. A maximum of three letters will be mailed. One month after the third letter we will prospectively enroll patients until our goal of 214 patients in each group is reached.
2. Enrolled patients will answer a questionnaire (appendix 1). This will include questions of demographic data such as age, race, rank and education (as a measure of socioeconomic status).
3. Phlebotomy of 21 cc's will be performed on all enrolled patients.
4. Serum of 14 cc's will be used to test for H. pylori IgG, CRP, Lipid profile, Fibrinogen and Chlamydia pneumonia.
5. Serum of 7cc of blood will be frozen and stored at the GI lab in USUHS until completion of the study (1 year). Patients that test positive for H. pylori IgG will have CAG-A tested on these frozen samples. CAG-A testing will be performed using an ELISA at the laboratory of Dr Andre Dubois. The identity of the patients will not be on the samples, these will only have a coded number. Patients may ask that their serum be withdrawn at any time. Patients that test positive will be notified of this result.
6. Frozen serum will be destroyed at the completion of the study. There will be no human genetic studies performed on the sera. There have been no modifications to the methodology.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of 76 patients have been enrolled to date. There are 62 patients in the high calcium group and 14 in the zero calcium group. There have been no adverse events related to the study. There is currently no review of recent literature or publication from this research study.

CONCLUSIONS
Patient enrollment is in progress. No conclusion can be drawn at this time.

Report Date: 5 March 2002 Work Unit # 01-14002

# DETAIL SUMMARY SHEET

TITLE: An Efficacy and Safety Study of Intravenous Pantoprazole in the Prevention of Recurrent Peptic Ulcer Bleeding After Successful Hemostasis (Sponsored Study by Wyeth-Ayerst Research.)

KEYWORDS:

PRINCIPAL INVESTIGATOR: Dunaway, Peter CPT MC
ASSOCIATES: Wong, Roy COL MC

DEPARTMENT: Medicine STATUS: O
SERVICE: Gastroenterology INITIAL APPROVAL DATE: 17 April 2001

## STUDY OBJECTIVE

To evaluate the efficacy and safety of intravenous pantoprazole in the prevention of re-bleeding in patients with bleeding peptic ulcer disease after successful endoscopic hemostatic therapy. This study will compare the mortality rate, units of blood transfused after endoscopy, length of hospital stay, length of intensive care unit (ICU) stay, and the need for urgent intervention between treatment groups.

## TECHNICAL APPROACH

Patients presenting to the WRAMC ER with an upper GI bleed will be screened as potential candidate for this study. The on-call GI fellow will contact the PI when a patient presents with signs and/or symptoms consistent with a GI bleed. All GI staff and fellows will be familiarized with this study for screening and baseline evaluation. When all inclusion and exclusion criteria have been considered and the patient demonstrates bleeding source from a peptic ulcer and the patient is eligible to continue in the study, random administration of intravenous test article (IV Protonix or IV Zantac) will start within 2 hours of endoscopy and successful hemostasis. The PI will perform the baseline ophthalmology exam. The day 4 post-infusion eye exam will be performed by a staff from the Department of Ophthalmology. The patient will remain in the ICU or when medically stable, be transferred to the medical ward during the 72-hour infusion.

The study coordinator or principal investigator will contact the patients at days 14 and 30 for post treatment follow-up interviews.

## PRIOR AND CURRENT PROGRESS

FDA approved Protonix IV for Zollinger-Ellison Syndrome. There are currently 59 centers throughout the United States that are identifying potential patients. As of December 2001, 62 patients have been randomized at these sites. The total number of subjects enrolled to date at WRAMC is 1 that was a screen failure. The total number randomized study-wide is 62.

There have not been any adverse events expected and/or serious reported at this time.

## CONCLUSIONS

Patient enrollment is in progress. No conclusion can be drawn at this time.

Report Date: 1 March 2002

Work Unit # 01-14003

# DETAIL SUMMARY SHEET

TITLE: Effect of Complete Intraesophageal Acid Ablation Upon Cellular Markers of Proliferation, Differentiation, and Apoptosis in Long-Segment Barrett's Esophagus

PRINCIPAL INVESTIGATOR: Dunaway, Peter CPT MC
ASSOCIATES: Wong, Roy KH COL MC, Maydonovitch, Corinne

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 24 April 2001

STUDY OBJECTIVE To determine the effect of intraesophageal acid ablation upon cellular markers of proliferation and differentiation in specialized intestinal metaplasia.

TECHNICAL APPROACH Subjects with diagnosis of LSBE will be invited to participate in the study. These subjects will be on some form of anti-secretory therapy as routine therapy for BE. To determine the degree of acid reflux, subjects will first have an esophageal manometry performed followed by a 24 hr pH study. The following day, the subjects will undergo an esoophagogastroduodenoscopy examination (EGD) where 4 jumbo biopsy samples will be taken from each of the six sites specified as per the protocol. Two sets of biopsies will be shipped to Dr. Jeffrey Lee, who will perform the COX-2 and PCNA staining. Another set of biopsies will be kept in 10% formalin, for DNA flow cytometry at a future date. The final set will be stored in a -70° C freezer for quantitative COX-2 mRNA DNA flow cytometry at a future date. The final set will be stored in a -70° C freezer for quantitative COX-2 mRNA analysis at a future date. The final set will be stored in a -70° C freezer for quantitative COX-2 mRNA analysis at a future date. These stored samples will be analyzed within 5 years or will be discarded. Subjects will then have their anti-secretory discontinued for 2 weeks, but will be allowed to take over the counter antacids. They will then undergo a repeat 24 hr pH study to quantify the degree of acid reflux into the esophagus. A second EGD with a similar distribution of jumbo biopsies will be performed and the same histologic and immunohistochemical analyses will be performed. The biopsies will be distributed, shipped, and analyzed in a similar manner. Subjects will then be put on high dose acid suppression with Rabeprazole (40 mg BID/TID) plus ranitidine (150 mg QHS), for two weeks and subjects will then undergo a final 24 hr pH study for adequacy of ablation, and final EGD with biopsies exactly like that mentioned above. The biopsies will be distributed, shipped, and analyzed in a similar manner. Changes in histology and immunohistochemistry will then be compared within and between the three treatment regiment groups (clinical PPI therapy, off therapy, and total acid ablation). A two-page symptom related questionnaire will be given to the patient prior to each 24-hr pH study. This will be returned the following day when the patient presents for the EGD.

PRIOR AND CURRENT PROGRESS
The requested change to increase the dose is based on the fact that our first 3 patients did not achieve complete gastric acid suppression on the 40 mg/20 mg + Zantac dosing regimen. Unfortunately, none of these patients achieved complete gastric acid suppression on the 40 mg bid + Zantac regimen either. However, complete esophageal acid suppression was achieved in 2 of the 3 patients. Based on this data, we plan to increase the Aciphex dose to 40 mg po tid if complete gastric acid suppression is not achieved after the 2nd pH study.) Based on the current low acceptance rate (16%), we anticipate difficulty in achieving the estimated sample size of 20 patients. In order to increase our enrollment rate, we are offering monetary compensation for 3 pH studies and 3 EGDs completed.

The number of subjects enrolled to date at WRAMC is 8. There have not been any adverse events (AEs) expected and/or serious adverse events (SAEs) at WRAMC site. One patient has withdrawn from the study because he could not symptomatically tolerate being off his anti-secretory therapy for two weeks.

CONCLUSIONS
No conclusion can be drawn at this time.

Report Date: 5 April 2002 Work Unit # 01-14004

# DETAIL SUMMARY SHEET

TITLE: The Timing of Liver Enzyme Elevation and Hepatitis C Seroconversion in a Cohort of United States Military Gulf War Veterans

KEYWORDS:

PRINCIPAL INVESTIGATOR: COL Kent C. Holtzmuller MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Gastroenterology INITIAL APPROVAL DATE: 1 May 2001

STUDY OBJECTIVE
To determine the rate of HCV and presence of abnormal liver enzymes in serum samples banked in the DOD Serum repository prior to the Persian Gulf War (PGW) in subjects found to have hepatitis C or elevated serum enzymes following the PGW.

TECHNICAL APPROACH
CCEP and AFIP databases were utilized to identify subjects who were hepatitis C positive or who had elevated liver enzymes following the PGW. These subjects were cross-referenced with serum samples banked prior to the PGW at the DOD serum repository. The HCV samples obtained are being assessed for hepatitis C. The ALT is being assessed on the samples obtained from the abnormal ALT patients.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been no articles published on this subject in Gulf War Veterans.

The number of subjects enrolled to the study since last APR at WRAMC is 53 hepatitis C and 197 abnormal ALT samples at the DOD Serum repository. The total enrolled to date at WRAMC is the same number. The total number enrolled study-wide is n/a, if multi-site study.

CONCLUSIONS
The serum samples are currently being tested at WRAMC DPALS. Data are not yet available. The study should be completed within the next six months.

Report Date: 05 April 2002

Work Unit # 01-14005

# DETAIL SUMMARY SHEET

TITLE: Tele-Hepatitis Phase I: Validation of Desktop Video Teleconferencing for Evaluation of Patients with Hepatitis C

KEYWORDS:

PRINCIPAL INVESTIGATOR: COL Kent C. Holtzmuller MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 29 May 2001

STUDY OBJECTIVE
To determine the concordance of visual physical exam findings between exams performed via desktop Video Teleconferencing (VTC) and in person, face-to-face exams.

TECHNICAL APPROACH
There have been no changes to the protocol. Direct face-to-face exams will be performed by a physician and then compared to a different physician's exam performed via VTC.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The equipment and infrastructure to perform the VTC exams was installed in the GI clinic in March 2002. Patient solicitation to participate in the study will begin next week.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is n/a, if multi-site study. A literature search was performed, and no new relevant articles were found.

CONCLUSIONS
None to date.

Report Date: 31 May 2002 Work Unit # 01-14006

# DETAIL SUMMARY SHEET

TITLE: B-Catenin Mutations and Nuclear Accumulation are Early Events in Hepatic Carcinogenesis: Role as a Marker to Determine Risk for Hepatocellular Carcinoma in Hepatitis B Patients

KEYWORDS:

PRINCIPAL INVESTIGATOR: Holtzmuller, Kent, COL, MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 12 June 2001

## STUDY OBJECTIVE

1. To establish the prevalence of β-catenin nuclear localization and mutation in subjects with hepatocellular carcinoma and in subjects with chronic viral hepatitis.

2. To observe if the presence of such β-catenin mutations may be used as a biomarker for future HCC development in subjects with cirrhosis due to chronic viral infection.

## TECHNICAL APPROACH

The liver biopsy procedure log books in the Gastroenterology Clinic, WRAMC, are being reviewed to identify patients who have undergone liver biopsy for the diagnoses of hepatitis C, hepatitis B, and hepatocellular carcinoma beginning in May 1991. The pathology report and liver tissue block will be identified. Four 4 um and two 50 um tissue sections will be obtained from the tissue block. The tissue slides will be coded by a unique identifier. Subjects will not be identified by name or SSN. The coded tissue will be sent to Dr. Marrogi at the NIH for the β-catenin studies. There has been no change to the protocol.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The liver biopsy procedure logbook is currently being reviewed to find patients who meet the diagnostic criteria for entry into the study. Patients and their tissue blocks have not been selected to date. It is expected that it will take another two months to completely review the procedure log. Patients will be selected at that time. The tissue blocks will then be reviewed to determine if adequate liver tissue is available to be included in the study.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

## CONCLUSIONS

No conclusions can be yet determined from this study.

Report Date: 14 November 2001 Work Unit # 1432

# DETAIL SUMMARY SHEET

TITLE: Short Segment Barrett's Esophagus: Prevalence, Clinical Characteristics, and Responses to Long-Term Antisecretory Therapy

KEYWORDS: short segment, Barrett's Esophagus, Prilosec

PRINCIPAL INVESTIGATOR: Cumings, Mark MAJ MC

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 29 November 1994

## STUDY OBJECTIVE

To determine: 1) the prevalence of Short-Segment Barrett's Esophagus (SSBE) in patients undergoing upper endoscopy in WRAMC's Gastroenterology Clinic; and 2) the response of SSBE to maximal antireflux therapy with Prilosec; and 3) the incidence of specialized intestinal metaplasia of the esophagus in a cohort of patients originally identified in part I; and 4) the 24hr pH and esophageal manometry characteristics of patients with specialized intestinal metaplasia of the gastroesophageal junction (EGJSIM).

## TECHNICAL APPROACH

This has been two-part study with several addenda to allow further study. In Part I, patients complete a questionnaire prior to endoscopy (EGD). During the patient's routine EGD, photographs and four biopsies of the distal esophagus will be obtained to evaluate the presence of SSBE. In Part II, patients found to have SSBE undergo repeat EGD with biopsy, manometry, and 24-hour pH prior to treatment with Prilosec and are then followed at 3-month intervals for 2 years. In the follow-up phase to Part I, 151 patients found to have specialized intestinal metaplasia (SIM) of the esophagus (at the EGJ, SSBE and LSBE) in part I are asked to return for repeat surveillance biopsies to assess the incidence of SIM in this cohort. In a recently approved addendum, we have been given permission to perform 24hr pH analysis and esophageal motility/manometry on our cohort of 45 patients that have been demonstrated to have EGJSIM.

## PRIOR AND CURRENT PROGRESS

The aim of this study is to determine the extent of reflux in patients with EGJ-SIM, and compare this data to patients with SSBE and LSBE. Methods: 13 patients (9 male, 4 female, mean age 68.3) with EGJ-SIM determined by two biopsies immediately below the SCJ underwent EM and 24-h dual pH monitoring at 0 and 5cm above the LES. We compared the results to 21 patients, (14 male, 7 female, mean age 61.5) with SSBE, 18 patients (17 male, 1 female, mean age 53.7) with LSBE, and 15 controls (9 male, 4 female, mean age 35.9) who had normal 24-h pH studies. Results: EGJ-SIM patients were older than patients with LSBE ($p=0.018$) and controls ($p=0.001$). Degree of reflux by 24-h pH score, percent total, percent upright, and percent supine was lower in EGJ-SIM patients compared to SSBE patients, and significantly decreased compared to LSBE patients. This trend remained consistent when measured 0 cm above LES. Fewer EGJ patients (62%) had abnormal pH scores compared to SSBE patients (72%) and LSBE patients (100%) ($p<0.0076$).

| EM and 24-h pH data (mean) at 5 cm above LES | *p<0.05 vs. EGJ-SIM alone | | | | |
|---|---|---|---|---|---|
| | Control | EGJ-SIM | SSBE | LSBE | *p* Value |
| LES Pressure | 16.87 | 16.54 | 12.27 | 5.08* | 0.000 |
| Esoph amplitude | 94.53 | 101.58 | 77.55* | 54.83* | 0.013 |
| 24-h pH score | 8.55* | 25.72 | 40.47 | 112.27* | 0.000 |
| % total reflux | 1.86* | 5.43 | 8.63 | 24.35* | 0.000 |
| % upright reflux | 2.82 | 7.57 | 10.68 | 25.60* | 0.000 |
| % supine reflux | 0.09 | 1.12 | 5.11 | 20.01* | 0.000 |

## CONCLUSIONS

Patients with EGJ-SIM tend to have higher sphincter pressures, lower Johnson/DeMeester scores, and higher amplitude of esophageal contractions when compared to patients with Barrett's epithelium. EGJ-SIM patients have milder degrees of esophageal acid exposure compared to patients with SSBE and LSBE.

Report Date: 9 August 2001

Work Unit # 1439

# DETAIL SUMMARY SHEET

TITLE: A Questionnaire for Gastroesophageal Reflux: Development of a Diagnostic and Research Tool Applicable to the General Population

KEYWORDS: gastroesophageal reflux disease

PRINCIPAL INVESTIGATOR: Osgard, Eric CPT MC
ASSOCIATES: Maydonovitch, Corinne

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: C
INITIAL APPROVAL DATE: 29 October 1996

## STUDY OBJECTIVE

To develop a short-form questionnaire to be used as a screening tool to accurately identify patients in the general populations who have gastroesophageal reflux disease (GERD). This questionnaire will be developed from two previously published GERD questionnaires that are available in the literature, each with inherent properties that make their use for screening in the general population less than optimal.

## TECHNICAL APPROACH

Phase I: 400 patients, scheduled for endoscopy and manometry with pH testing will be identified. Each will complete the two existing questionnaires. Results will be correlated to the objective findings of the above procedures. The existing questionnaires will then be reduced into a short-form version.
Phase II: The short-form questionnaire will be tested as a screening tool in the population of military health care beneficiaries. Using a mailer, 200 respondents willing to participate will be identified. Each will complete the new questionnaire and undergo endoscopy and manometry with pH testing. The accuracy if the questionnaire will be assessed according to the results of these objective tests.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 64. There have been no adverse events. The PI was transferred to Tripler AMC in Hawaii after completing his fellowship training. Because of this and lack of enrollment over the past two years, this study is being closed.

## CONCLUSIONS

Data collection is incomplete. Evaluation of available data collection for Phase I of the study showed a poor correlation between the patient questionnaire answers and the pH monitor data.

Report Date: 25 January 2002 Work Unit # 1443

# DETAIL SUMMARY SHEET

TITLE: The Effects of Lamivudine on Renal Function in Patients with Chronic Active Hepatitis B and Proteinuria

KEYWORDS:

PRINCIPAL INVESTIGATOR: Dunaway, Peter CPT MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: C
INITIAL APPROVAL DATE: 27 January 1998

STUDY OBJECTIVE:
To determine how the immunosuppressant medicine, Lamivudine, affects renal function in patients with proteinuria and/or renal insufficiency secondary to chronic active hepatitis B.

TECHNICAL APPROACH:
Screen for patients in the Liver Clinic at Walter Reed Army Medical Center who have chronic, active hepatitis B, need therapy, and have renal insufficiency and/or proteinuria secondary to hepatitis B. There have been no changes in the initial plan stated in the original protocol.

PRIOR AND CURRENT PROGRESS
No patients have been eligible for enrollment in this study since approval.

CONCLUSIONS
None.

Report Date: 1 March 2002 Work Unit # 1446-98

# DETAIL SUMMARY SHEET

TITLE: Hypnosis for the Treatment of Upright Gastro-Esophageal Reflux

KEYWORDS: Upright Reflux

PRINCIPAL INVESTIGATOR: Cumings, Mark MAJ MC
ASSOCIATES: Roy Wong COL MC, Dr. Harold Wain, Corrinne Maydonovitch

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 28 April 1998

## STUDY OBJECTIVE

A) To study the efficacy of hypnosis versus omeprazole in the treatment of upright reflux
B) To determine the prevalence and types of psychiatric abnormalities in patients with upright reflux
C) To characterize the pathophysiology of successful treatment in patients undergoing hypnosis

## TECHNICAL APPROACH

Addendum: The prospective arms of the trial were terminated due to poor enrollment in that phase with an appropriate adjustment of the title. A psychiatric questionnaire (PRIME-MD) was added to streamline psychiatric assessment. Patients are now offered self-hypnosis, with a psychiatric evaluation to determine hypnosis capacity, as a "pilot-study"-like format with repeat pH measurement and gastric emptying at 8 weeks after starting the self-hypnosis.

Current Approach: Those patients identified to have upright reflux by symptom pattern would undergo 24-hr pH testing to confirm upright reflux. Those found to have upright reflux on clinically ordered pH tests would also be offered enrollment in the study. A validated psychiatric questionnaire, Prime-MD-II, will be completed and a gastric emptying study will be completed. All subjects will be offered self-hypnosis training in conjunction with the routine medical therapy they were receiving prior to study enrollment. After 8 weeks, the subjects doing self-hypnosis will be asked to return for a repeat 24-hr pH test off medications, but while using self-hypnosis. They would be asked to get another gastric emptying study using self-hypnosis to quantify any potential differences in gastric emptying using self-hypnosis versus the previously attained baseline gastric emptying study. The use of a "partial study", with those patients unwilling to try self-hypnosis still having the validated psychiatric questionnaire and gastric emptying study, would be continued. Patients who completed the study prior to the recent addendum are being contacted, re-consented and are completing the psychiatric questionnaire to complete our database.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Regarding a recent review of the literature, there is no new data in the literature concerning the mechanism and treatment of upright reflux. There have been no amendments or modifications to the study since the last APR. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 23. There have been no adverse events and no subject withdrawals.

## CONCLUSIONS

Preliminary data suggests that there is no specific gastric emptying pattern in upright refluxers, as some patients had delayed while others had rapid gastric emptying. Furthermore gastric emptying pattern does not play a role in severity of reflux.

Report Date: 26 July 2002

Work Unit # 1451-98

# DETAIL SUMMARY SHEET

TITLE: The Use of Garlic as an Antimicrobial in *Helicobacter pylori* Eradication

KEYWORDS: *Helicobacter pylori*

PRINCIPAL INVESTIGATOR: Brian P. Mulhall MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: C
INITIAL APPROVAL DATE: 22 September 1998

## STUDY OBJECTIVE

The objective of this study was to evaluate the possible effectiveness of using a common nutritional supplement (garlic) to eradicate/treat *H. pylori* infections.

## TECHNICAL APPROACH

Patients are screened for possible active infection by serological tests, and if positive, receive an EGD and breath testing (addendum) to confirm active infection, take cultures, and endoscopic grading of gastritis. If active infection is confirmed, they are randomized to nutritional supplement vs. placebo for four weeks of treatment with omeprazole (assuming all exclusion criteria are avoided). Dietary and symptom questionnaires are distributed several times during the trial to each patient. Eight weeks after beginning therapy a second EGD is performed and *H. pylori* status is again tested. If the patient remains positive they are offered treatment with standard antibiotic therapy. There have been no changes in methodology since the last Annual Progress Report.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 52. The total number enrolled study-wide is 64, with 26 total patients completing the entire protocol. The study has been closed for enrollment and final mRNA studies are being completed presently.

## CONCLUSIONS

One patient (from a total of 26 patients) demonstrated successful eradication of *H. pylori* during the study (3.4%, CI 0.10-19.6). This one patient with successful *H. pylori* had been stratified in the low-dietary garlic intake group taking the garlic supplements. This represents a 14.3% eradication rate for garlic therapy compared to placebo (CI 0.2-36). There was no significant change in mRNA or cytokine levels between the two groups. There have been no Adverse Events at WRAMC or MAMC.

High-dose garlic intake has an unacceptably low eradication rate for *H. pylori.* High-dose garlic intake appears to have no significant impact (in *H. pylori* infected patients) on cytokine activity or mRNA expression during therapy. So, contrary to other earlier (mostly *in vitro*) studies, we have found no compelling evidence for a significant antimicrobial effect of garlic in supradietary dosages. Our data compares with other more recent studies, suggesting no evidence of clinical outcomes (organism eradication or decrease in the incidence of gastric cancer). Our study goes further than other studies in demonstrating the absence of cytokine or mRNA effects in *H. pylori* infection or virulence during garlic therapy.

Report Date: 10 October 2001

Work Unit # 1454-99

# DETAIL SUMMARY SHEET

TITLE: Efficacy of Infergen (15meg) for Chronic Hepatitis C in Patients Who Are Non-Responders and Relapsers to Combination Therapy with Intron-A + Ribavirin. A Multicenter Trial

PRINCIPAL INVESTIGATOR: Sjogren, Maria H. COL MC
ASSOCIATES: Holtzmuller, Kent LTC MC

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: C
INITIAL APPROVAL DATE: 24 November 1998

STUDY OBJECTIVE The primary objective of this clinical trial is to determine the efficacy of Infergen 15 mcg 3 times per week or Infergen 9 mcg daily for 40 weeks after an induction dose of 15 mcg daily for 8 weeks in patients who did not respond or relapsed after combination therapy with Intron A + Ribavirin.

TECHNICAL APPROACH Patients with biopsy proven chronic hepatitis C, who are non responders or relapsed after receiving Intron A + Ribavirin will be treated with Infergen 15ug subcutaneously daily for 8 weeks as induction therapy followed by 15 ug 3 times per week or Infergen 9 mcg daily for 40 weeks. Patients with undetectable HCV-RNA at week 24 will be withdrawn from the study. The total enrollment for this multicenter trial was to be approximately 400 patients. Last APR showed an enrollment of 510 because other sites interpreted protocol language as allowing them to enroll as many as possible. This was reported, discussed and solved with HUC last year.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 7. The total number enrolled study-wide is 510, if multi-site study. No new subjects were enrolled during this APR period. All subjects have finished treatment and observation period. The antiviral response intent to treat (ITT) analysis and per-protocol (took meds for 48 weeks) for the four groups is as follows:

| | **Prior Relapsers** | | **Prior non-responders** | | **Prior Relapsers** | | **Prior non-responders** | |
|---|---|---|---|---|---|---|---|---|
| ITT | Week 24 15 TIW | Week 24 9 QD | Week 24 15 TIW | Week 24 9 QD | Week 48 15 TIW | Week 48 9 QD | Week 48 15 TIW | Week 48 9 QD |
| | 29/60 | 31/62 | 32/205 | 43/183 | 17/60 | 17/62 | 11/205 | 22/183 |
| Per Protocol | Week 24 15 TIW | Week 24 9 QD | Week 24 15 TIW | Week 24 9 QD | Week 48 15 TIW | Week 48 9 QD | Week 48 15 TIW | Week 48 9 QD |
| | 29/45 | 31/44 | 32/147 | 43/146 | 17/22 | 17/25 | 11/23 | 22/39 |

Data at week 72 has not been received in a complete fashion yet. Available data shows the following:

Relapsers
15mcg TIW: 3/8 had sustained antiviral response
9 mcg/daily: 3/8 had sustained antiviral response

Non-responders
15mcg TIW: 1/9 had sustained antiviral response
9 mcg/daily: 4/10 had sustained antiviral response

Discontinuation and adverse event data: As per design of the study 220 subjects discontinued therapy at week 24 because of detectable HCV RNA. 64 discontinued because of expected side effects. 54 withdrew consent. 12 were discontinued because of lack of compliance. 18 were discontinued because of investigator's discretion. No deaths occurred.

CONCLUSIONS Both doses appear to have a similar response in relapsers, but the 9mcg/day dose appears to be superior to the 15mcg TIW. When data from week 72 is all in, we will be able to make a final assessment. The medication was well tolerated, no major side effects were observed.

Report Date: 20 February 2002 Work Unit # 1456-99

# DETAIL SUMMARY SHEET

TITLE: Long-Term Prevention of Recurrent Peptic Ulcer Hemorrhage in Patients Infected with *Helicobacter Pylori*: A Multi-Center, NIH-Funded, Prospective, Randomized Double-Blind Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Gastroenterology INITIAL APPROVAL DATE: 23 March 1999

## STUDY OBJECTIVE

The objectives of this study are:

1) To determine the efficacy and safety of H.pylori eradication alone versus H.pylori eradication combined with daily full dose H2RA in preventing recurrences of duodenal ulcer and gastric ulcer hemorrhage
2) To document whether recurrences of ulcer hemorrhage are associated with NSAIDS-ASA and/or H.pylori recurrence of *H. pylori* infection

## TECHNICAL APPROACH

Patients diagnosed within six months with DU or GU hemorrhage with *H.pylori* infection may enter the study at either phase I or phase II. *H.pylori* infection will be documented using CLO, ELISA, histopathology and/or C13 breath test. In phase I, study patients will receive ten days of antimicrobial therapy for *H.pylori* eradication. Eradication will be documented by C13 urea breath test at least six weeks after completion of antimicrobial therapy. Those in whom eradication is successfully achieved will be randomized to the H2RA vs. placebo in a double-blind fashion. Patients whose *H.pylori* was not eradicated by two courses of antimicrobial therapy or diagnosed with greater than/equal to five gastric and/or duodenal erosions after *H.pylori* eradication will receive full-dose H2RA and will also be followed up long term as a comparator group. All patients in Phase II will be followed-up long-term for a median of 36 months. The follow-up entails an interview of their symptoms associated with GU and/or other health, changes in health status and direct and indirect costs associated to health reasons. Enrollment is closed for this study.

## PRIOR AND CURRENT PROGRESS

There are a total of 351 patients actively enrolled in phase II or comparator group of the study from 27 study sites. Seventeen patients are from WRAMC, with one new patient this reporting period. 126 patients withdrew from the study; three patients are from WRAMC. There are a total of 297 adverse events reported; of those reported, eleven are from WRAMC and they were non-serious and unrelated to the study. There have been no major complications or drug related adverse events. There is currently no review of recent literature or publication from this research study. .

## CONCLUSIONS

No conclusion can be drawn at this time.

Report Date: 6 June 2002 Work Unit # 1457-99

# DETAIL SUMMARY SHEET

TITLE: Colorectal Neoplasia Screening with Colonoscopy in Asymptomatic Women at Regional Navy/Army Medical Centers: The CONCeRN Trial

KEYWORDS: colorectal care, cancer screening, colonoscopy

PRINCIPAL INVESTIGATOR: John Eastone LCDR MC USN
ASSOCIATES: James Walter Kikendall COL MC USA

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: C
INITIAL APPROVAL DATE: 18 May 1999

## STUDY OBJECTIVE

Primary: To determine the incidence of advanced colonic neoplastic lesions (i.e. adenomas with high grade dysplasia, villous adenomas, colorectal cancers, and/or adenomatous polyps $\geq$ 1 cm in diameter) in a cohort of asymptomatic women referred for colorectal cancer screening
To determine if selected factors (i.e. age, race, obesity, tobacco use, aspirin/NSAID use, alcohol use, use of hormonal replacement therapy, family history of colon cancer, and presence of diminutive adenomatous polyp (adenomatous polyp < 1 cm) in the distal 60 cm of the colon) predict the presence of advanced neoplastic lesions, using both univariate and multiple logistic regression analysis.

Secondary: To estimate the sensitivity and specificity of flexible sigmoidoscopy for advanced neoplastic lesions in the proximal colon.

Tertiary: To gather data for cost-effectiveness analysis of colonoscopy among asymptomatic women referred for colorectal cancer screening To gather a cohort of women with normal screening colonoscopy who can be randomized to have repeat coloscopy in 7 or 10 years in order to ascertain the appropriate interval between screening colonoscopies.

## TECHNICAL APPROACH

Request for change of PI submitted June 2001 and approved.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

126 subjects recruited from WRAMC to date. 1328 patients enrolled in the study to date (all sites included)
No complications or adverse reactions to date. No patients withdrawn from study to date.
Review of recent literature shows no studies pertaining to the use of screening colonoscopy in average risk women. A Veterans Administration study (VA – Coop 380) published in the New England Journal of Medicine in which 96% of participants were male showed that colonoscopy detected 25% more advanced neoplastic lesions than one-time flexible sigmoidoscopy and fecal occult blood testing. This study supports the contention that colonoscopy is a useful tool for screening average risk individuals.

## CONCLUSIONS

At the time of the last data analysis (n-1328), 20.5% of subjects had tubular adenomas found and removed during colonoscopy. Four point eight percent (64/1328) had advanced adenomas. Sixty-nine percent of all subjects with tubular adenomas had normal flexible sigmoidoscopy, and 69% of subjects with advanced adenomas had normal flexible sigmoidoscopy examinations. Analysis of risk factors indicated age $\geq$ 65 years as the only risk factor independently associated with the development of adenomatous polyps.

Report Date: 18 October 2001

Work Unit # 00-1501

# DETAIL SUMMARY SHEET

TITLE: CALGB 89804 Randomized Phase III Trial of Combinations of Oxaliplatin (OXAL), 5-Fluorouracil (5-FU), and Irinotecan (CPT-11), as Initial Treatment of Patients With Advanced Adenocarcinoma of the Colon and Rectum

KEYWORDS:

PRINCIPAL INVESTIGATOR: Willis, Carl MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 19 October 1999

STUDY OBJECTIVE

The primary objective of this trial is to compare the time to progression in patients with locally advanced or metastatic colorectal cancer who receive ARM F which is Oxaliplatin plus 5FU plus Leucovorin or ARM G which is Irinotecan plus Oxaliplatin (the two experimental regimens) to those receiving ARM A which is Irinotecan plus 5FU plus leucovorin (the control regimen). The secondary objective is to compare the time to progression of patients receiving the two experimental regimens. The primary secondary outcome measure in this trial is overall survival. Other secondary objectives include evaluation of toxicity, response rate, and time to treatment failure. Also, to compare quality-of-life parameters in-patients on these regimens.

TECHNICAL APPROACH

All eligible patients will be randomized to one of the three treatment regimens. They will be monitored with laboratory values, appropriate scans/studies for tumor measurements, and physical exams to determine response to therapies. ARM A treatment is given weekly for four weeks with a two-week rest period; each cycle is 6 weeks. ARM F treatment is given on days 1 and 2 every two weeks; each cycle is 2 weeks. ARM G treatment is given on day 1 every three weeks; each cycle is 3 weeks. Patients continue on therapy until disease progression, in the absence of unacceptable toxicity. If they achieve a complete response on two consecutive cycles' therapy may be discontinued.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No patients from WRAMC have been entered on this study to date. This study was originally designed as a 6-regimen/arm study. New data presented in March 2000, from two randomized trials, indicated that the addition of Irinotecan to a standard 5FU plus leucovorin regimen resulted in improved patient outcome. The new standard therapy increased response rate, time to progression, and survival. It appeared that the likelihood of a statistical significant difference between regimens of the same drug combination was remote. Because of this, the trial was collapsed from 6 to 3 regimens/arms per update #8, dated 5/15/2000. The changes and a new consent were approved by HUC on 7/18/00. There were two other updates (update #9, approved 9 February 2000) that were consent form changes and to change an added risk. There was a temporary suspension (memo dated 11 May 2001 submitted to DCI on 11 May). National accrual to this study is 993 patients. Projected accrual remains at 1125 patients.

The study is now permanently closed at WRAMC since no patients were enrolled. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 993, if multi-site study.

CONCLUSIONS

No conclusions have been reached.

Report Date: 20 November 2001 Work Unit # 00-1502

# DETAIL SUMMARY SHEET

TITLE: CALGB 49906: A Phase III Study of Doxorubicin-Cyclophosphamide Therapy Followed by Paclitaxel or Docetaxel Given Weekly or Every 3 Weeks in Patients With Axillary Node-Positive Breast Cancer

KEYWORDS: Node Positive, Breast Cancer, Paclitaxel vs. Docetaxel

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 27 January 2000

STUDY OBJECTIVE
To determine whether docetaxel improves disease-free survival and overall survival when compared to paclitaxel following four cycles of doxorubicin-cyclophosphamide therapy for women with node-positive breast cancer. To determine whether weekly administration of taxanes (paclitaxel or docetaxel) for 12 weeks improves disease-free survival and overall survival when compared with conventional (every three weeks) schedule for four cycles following four cycles of doxorubicin-cyclophosphamide therapy. To compare the toxicity of both drugs, docetaxel and paclitaxel, given in the weekly or every three week cycles.

TECHNICAL APPROACH
All eligible patients will be randomized to one of four possible treatment arms (A,B,C, or D). All patients will initially receive four cycles of doxorubicin-cyclophosphamide. Subsequent treatment will be according to randomization. Treatment A: Paclitaxel will be given over three hours every three weeks x four cycles. Treatment B: Paclitaxel will be given over one hour every three weeks x 12 weeks. Treatment C: Docetaxel will be given over one hour every three weeks x four cycles. Treatment D: Docetaxel will be given over one hour every week x 12 weeks. Following chemotherapy, all patients with positive estrogen receptors will be given oral Tamoxifen for five years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Three WRAMC patients have been entered on this protocol since it was opened in March 2000, two during this reporting period. Two adverse events were reported to the IRB during this reporting period. No WRAMC patients have withdrawn from the study. National accrual to the study thus far is 2605. Minor changes were made to the study during this reporting period.

The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is 2605, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 05 April 2002 Work Unit # 00-1503

# DETAIL SUMMARY SHEET

TITLE: CALGB 159806: ERBB-2 and P53 in response and Outcome After Paclitaxel Chemotherapy for Metastatic Breast Cancer

KEYWORDS: Erb-B-2, p53, paclitaxel, metastatic breast cancer

PRINCIPAL INVESTIGATOR: Joseph P. Drabick COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 09 May 2000

STUDY OBJECTIVE
To correlate the growth factor receptor ErbB-2 and p53 with response rate, time to progression, and overall survival of patients with metastatic breast cancer treated with paclitaxel on CALGB 9342. To determine if amplification and over-expression of ErbB-2 must be present in order to predict response to paclitaxel.

TECHNICAL APPROACH
Primary tissue from patients enrolled on CALGB 9342 will be used for histopathological evaluation, immunohistochemical evaluation, FISH, sequence analysis, p53 analysis and genomic sequencing will be done. The methods for assessing ErbB-2 and p53 will be correlated.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This is a minimal risk study in that only existing pathological material will be studied. No adverse events have been reported. We are still attempting to receive 2 paraffin blocks. No changes to the original protocol design, objectives or technical approach have occurred.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is 116, if multi-site study.

CONCLUSIONS
The study is ongoing. No conclusions have been reached.

Report Date: 31 May 2002

Work Unit # 00-1504

# DETAIL SUMMARY SHEET

TITLE: CALGB 89803 A Phase III Intergroup Trial of Irenotecan (CPT-11) (NSC #6163480 Plus Flourouracil/Leukovorin (5-FU/LV) Versus Flourouracil/Leukovorin Alone After Curative Resection for Patients with Stage III Colon Cancer.

KEYWORDS: Colon Cancer; Stage III; Irinotecan (CPT-11); Fluorouracil/Leukovorin (5FU/LV)

PRINCIPAL INVESTIGATOR: Joseph Drabick, COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 July 2000

STUDY OBJECTIVES:
To determine if the addition of CPT-11 to the standard 5FU/LV treatment improves overall and disease free survival in Stage III colon cancer patients after curative resection.

TECHNICAL APPROACH
Eligible patients will be randomized to one of two treatment regimens.
Treatment A is the standard adjuvant treatment with 5FU and Leukovorin (LV) which is given weekly for 6 weeks followed by 2 rest weeks repeated times 4 cycles. Treatment B is the addition of CPT-11 to 5FU/LV, which is given weekly for 4 weeks followed by 2 rest weeks repeated times 5 cycles. A CBC and Chemistries will be done every treatment week. After therapy is completed the patient will be observed for recurrence. Follow-up will include physical exams, lab-work and chest x-rays. Other follow-up exams, such as CT scans, will be PRN.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This protocol has been closed to any further accrual. It has met accrual. However, before this closure, effective 15 May 2001, the CALGB identified an unacceptable toxicity profile in the number of thrombotic events. A Broadcast Message was sent to all CALGB members regarding this unexpected number of events on 13 March 2001. The study was temporarily suspended 27 April 2001. The CALGB made adjustments to dose modifications for patients experiencing diarrhea and a change was made to the protocol in the 15 May 2001 Monthly Posting for the CALGB. This update of 15 May 2001 was submitted to the IRB under separate cover. The dose modification applies to patients who are presently being treated on the study. After further independent review of the study's adverse events by the CALGBs and the North Central Cancer Treatment Group's Data and Safety Monitoring Board, the analysis revealed an "imbalance in the number of deaths occurring within 60 days after the initiation of treatment". A letter to the Editor was submitted to the NEJM recommending extreme caution with the regimen used in Treatment B. This letter was sent to the CALGB investigators 17 May 2001.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is 1264, if multi-site study.

CONCLUSIONS
The study objectives have not yet been answered. The study has met accrual and has been closed to further enrollment. An unexpected number of thrombotic events and deaths were identified and reported to members of the CALGB, to the NCI and FDA. No patients from WRAMC experienced unexpected severe toxicity. No patients from WRAMC were randomized to ARM B, which added CPT-11 to the standard treatment of 5FU/LV, which was the treatment arm associated with more unexpected severe events. However, all patients on this study will be monitored closely for signs and symptoms of thrombotic events and treated accordingly. No conclusions have been reached.

Report Date: 31 May 2002 Work Unit # 00-1505

# DETAIL SUMMARY SHEET

TITLE: CALGB 19901 Phase II Study of Fludarabine Induction Followed by Campath-1 H Consolidation in Untreated Patients with Chronic Lymphocytic Leukemia

KEYWORDS: Phase II; Fludarabine; Campath-1H; Chronic Lymphocytic Leukemia

PRINCIPAL INVESTIGATOR: Joseph Drabick, COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 25 July 2000

STUDY OBJECTIVE:
To determine the overall complete response rate, the infectious toxicities, the progression-free and overall survival and the immunologic effects of sequential treatment with fludarabine and Campath-1H in previously untreated patients with active chronic lymphocytic leukemia.

TECHNICAL APPROACH
INDUCTION with Fludarabine is to be given 5 days per week during weeks 1,5,9 and 13 (a total of four 28 day cycles). Two months later, CONSOLIDATION with Campath-1H is to be given three times per week for 6 weeks. Restaging bone marrows will be done after INDUCTION, before CONSOLIDATION, at the end of CONSOLIDATION and two months after CONSOLIDATION.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
In February 2001, this study was temporarily suspended after having met its accrual goal while an amendment to the study was being considered. In April 2001, a Broadcast Message was sent notifying all investigators of a higher than expected frequency of primary and secondary cytomegalovirus (CMV) infections in patients treated with Campath-1H on this study. This Broadcast Message was submitted to WRAMC's IRB on 4/20/01 in the form of an Adverse Event report. Effective 5/15/01 the CALGB reactivated this study. Also, on 5/15/01 amendments to the study, per updates #5 and #6, addressed a change in the route of administration of Campath-1H from intravenous dosing to subcutaneous injection, CMV monitoring was defined in detail, and the addition of 18 more patients to the study who will receive Campath-1H via subcutaneous route. No response data has been reported to date. There is one patient from WRAMC on the study. She has finished both fludarabine and Campath-1H. She experienced grade 3 insomnia/unusual nightmares felt to be related to fludarabine. An adverse event report was submitted to WRAMC IRB 16 January 2001. She has been tested and evaluated for CMV infection and remains negative. The total number of subjects enrolled in the study since it was approved at WRAMC is one. The total number enrolled study-wide is 66.

CONCLUSIONS:
No conclusions have been reached at this time.

Report Date: 25 July 2002

Work Unit # 00-1506

# DETAIL SUMMARY SHEET

TITLE: CALGB 99808 Docetaxel and Estramustine Versus Mitoxantrone and Prednisone for Advanced, Hormone Refractory Prostate Cancer, Phase III

KEYWORDS: Advanced Hormone Refractory Prostate Cancer; Docetaxel; Estramustine; Mitoxantrone; Prednisone; Phase III

PRINCIPAL INVESTIGATOR: Drabick, Joseph J. COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 18 September 2000

## STUDY OBJECTIVE

To compare overall survival and progression-free survival in patients with hormone refractory metastatic prostate cancer, Stage D1 or D2, who are randomized either to treatment on Arm 1, estramustine + docetaxel, or Arm 2, mitoxantrone and prednisone. To compare the toxicities between the two study arms. To evaluate Quality of Life. To record PSA values for future correlations with response and survival. To compare responses between the two treatment groups.

## TECHNICAL APPROACH

Eligible patients will be randomized to ARM 1 or ARM 2. Patients in ARM 1 will receive estramustine orally, three times per day on days 1 and 2, will receive docetaxel IV on day 2, and 3 doses of dexamethasone prior to receiving docetaxel. ARM 1 will be given every 21 days. All patients will take low dose enteric-coated aspirin, 325 mg, orally, daily for anticoagulation therapy. A maximum of 12 cycles will be given. If no toxicity occurs during cycle 1 the dose of docetaxel will be escalated. If significant toxicity occurs, the dose of docetaxel will be reduced. Additionally, all patients will require additional prophylaxis against arterial events. One of the following 3 anticoagulants are to be used -- coumadin, levenox, or fragmin in addition to the aspirin. Patients on ARM 2 will receive mitoxantrone, IV, on day 1 and prednisone orally twice a day on days 1 to 21. ARM 2 will be given every 21 days. A maximum of 12 cycles will be given. If no toxicity occurs during cycle 1, the mitoxantrone dose will be escalated. If, after a dose, escalation of significant toxicities occurs, the dose of mitoxantrone will be reduced.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature. The objectives of this investigation have not been fulfilled by prior studies.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 515, if multi-site study. Grade 4 toxicities include 8 cardiovascular, 3 gastrointestinal, 33 hematologic, 2 hemorrhage, 2 infection, 3 lung, 1 neurologic and 1 pain. Grade 5 toxicities include 4 ADR, 1 cardiovascular infection, 1 liver, 1 lung, and 1 renal/bladder.

Ref: CALGB Statistical Report June 2002

## CONCLUSIONS

Too early.

Report Date: 25 July 2002

Work Unit # 00-1507

# DETAIL SUMMARY SHEET

TITLE: CALGB 9764 Genetic Changes in Diffuse Aggressive Non-Hodgkin's Lymphoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 19 September 2000

STUDY OBJECTIVE:
To estimate the proportions of patients with rearrangements affecting the MYC, BCL2, and BCL6 genes determined by FISH, overtly amplified chromosomal regions and non-random copy number changes of chromosomal regions determined by CGH. To investigate the prognostic importance of these genetic markers by studying their relationships with the clinical outcomes: response to therapy, failure-free survival (FFS), and overall survival (OS) (response to therapy). To investigate the interrelationships among these genetic and biological markers and their relationships with clinical features of the disease, such as disease site (nodal vs. extranodal) and stage of disease.

TECHNICAL APPROACH:
There is a retrospective and prospective component. The retrospective component is for patients who were enrolled on CALGB 8852 and CALGB 9351. They are eligible if tissue blocks obtained at diagnosis and at time of refractory/relapsed NHL are available for submission to the CALGB Pathology Coordinating Office (PCO), at the Ohio State University, B054 Graves Hall, 333 West 10th Avenue, Columbus, Ohio 43210-1239 and to Memorial Sloan-Kettering Cancer Center, Department of Human Genetics, 1275 York Avenue, NYC 10021. Only blocks from subjects who are still living will be collected. No consent form is required for the retrospective component.
The prospective component requires that consent be obtained from patients who are being treated for NHL on a CALGB treatment study. Participation in this study is not mandatory for participation in a CALGB treatment study. A Research Coordinator/Nurse will obtain tissue blocks from the Pathology Departments. When the above institutions receive the tissue blocks, a Unique Patient Number (UPN) will be assigned to each patient's blocks to protect the patient's identity. There has not been any change to the original methodology.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been no publications reporting data on this study or other studies with similar design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 867, if multi-site study. No grade 4 toxicities reported.

Ref: CALGB Statistical Report Jun 2002

CONCLUSIONS
Too early.

Report Date: 18 October 2001 Work Unit # 00-1601

# DETAIL SUMMARY SHEET

TITLE: A Feasibility Study of Campath-1H and GM-CSF Combination in Patients with Chronic Lymphocytic Leukemia and Small Cell Lymphocytic Lymphoma

KEYWORDS: chronic lymphocytic leukemia, antibody, campath

PRINCIPAL INVESTIGATOR: Drabick, Joseph LTC MC
ASSOCIATES: Joseph Flynn CPT MC, Margaret Lucas PA-C, Kathy Park RN

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 26 October 1999

STUDY OBJECTIVE: To determine the safety profile if administering Campath-1H with GM-CSF. To determine if GM-CSF increases the intensity of CD20 expression on CLL cells and the degree and time sequence of change in CD55 and CD59 expression following treatment with Campath-1H.

TECHNICAL APPROACH: Patients received Campath-1H 30mg three times weekly (with usual dose titration in first week) for up to 12 weeks, depending on response to treatment. Patients were randomized to one of two schedules of GM-CSF: arm A to be given GM-CSF at 250mcg SQ every day starting 4 weeks after the first dose of Campath-1H and continuing throughout treatment and arm B that began daily doses of GM-CSF one week prior to starting Campath-1H therapy and continues GM-CSF throughout therapy.

PRIOR AND CURRENT PROGRESS: This study was done in conjunction with John Hopkins University. A total of five patients have been enrolled at WRAMC on this study. Enrollment completed on March 2000 at WRAMC. Sixteen patients have been enrolled at JHU, for a total of 21 patients receiving treatment on this protocol. Nine of these patients completed 8-12 weeks of Campath-1H therapy. Of the patients treated at WRAMC, one patient had a PR, one died on study, and three had PD (two of whom have since died). There were a total of four SAEs here at WRAMC (including the death on the study), and three of these were possibly R/T study drug. (Neutropenia/fever, Hickman catheter infection and pneumonia, and cardiac arrest.) Study-wide, the most frequent adverse event was fever and chills, and the most frequent serious event was gr 4 thrombocytopenia. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is 21, if multi-site study. Campath-1H was recently approved by the FDA for the treatment of CLL.

The following adverse events have been recorded and reported to the FDA (from both sites):

1. Grade III bilirubin elevation not likely r/t study drug but to choledocholithiasis
2. Death on study – cardiac arrest, possibly r/t study drug
3. Neutropenia and fever x2
4. spinal cord infarct, probably unrelated
5. Hickman catheter infection, pneumonia, possibly related (occur off tx, patient with PD)
6. Reaction during transfusion, neutropenic and admitted
7. Hemolytic anemia (same patient hospitalized x2 with this)
8. IV antibiotics, gram pos culture
9. RLE DVT
10. hypotension
11. fever
12. sepsis, fungal lung
13. GI bleed, hemoptysis

CONCLUSIONS:
Manuscripts on patients' response and toxicity are being prepared as are those related to biologic correlates. In general, infusion related toxicity with or without GM-CSF appears similar in the first several weeks of therapy, with significant increases in inflammatory cytokines in both groups.

Report Date: 02 August 2001

Work Unit # 00-1603

# DETAIL SUMMARY SHEET

TITLE: A Multi-center Phase 2 Study of Oral N-Acetyl Dinaline (CI-994) in the Treatment of Patients with Chronic Lymphocytic Leukemia (protocol 994-05)

KEYWORDS: immunology, oncology, chronic lymphocytic leukemia

PRINCIPAL INVESTIGATOR: Drabick, Joseph LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 14 December 1999

STUDY OBJECTIVE:
To determine the anti-tumor activity of N-acetyl Dinaline (CI-994) in patients with chronic lymphocytic leukemia. To determine the safety profile of CI-994 when administered using a chronic daily oral dosing regimen.

TECHNICAL APPROACH:
Patients will receive oral daily doses of CI-994. They will be monitored hematologically every week for the first month, and every 2 weeks by PE. Patients that do not have PD may continue to receive treatment until maximal response, or progressive disease occurs. During this stage they will be followed with labs every 2 weeks, and with a PE every 4 weeks. Dose adjustments may be made for toxicities.

PRIOR AND CURRENT PROGRESS:
A total of seven patients have been enrolled in this study at WRAMC, and nineteen study wide. The best response seen in the patients treated here at WRAMC was one PR. This was also the best response seen study wide. There were two SAEs seen at this site, (both cases of pneumonia), and only two other SAEs study-wide. (GR 3 hemoptysis and GR 3 MI, both unlikely related).

CONCLUSIONS:
This study is being closed by Park-Davis, as the response rate seen does not justify continuing the study.

Report Date: 29 January 2002 Work Unit # 00-1605

# DETAIL SUMMARY SHEET

TITLE: Prospective Evaluation of Fatigue in Patients with Chronic B-Cell Chronic Lymphocytic Leukemia

KEYWORDS: Fatigue, Chronic Leukemia

PRINCIPAL INVESTIGATOR: CPT Amanda M. Weeks, MD
ASSOCIATES: CPT Joseph Flynn, DO; MAJ John Byrd, MD; Maragret Lucas, PA-C; Kathy Park, RN

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 18 January 2000

## STUDY OBJECTIVE

I) To evaluate fatigue experienced by Chronic Lymphocytic Leukemia (CLL) patients as compared to that experienced by matched members of the general medical population.
II) To evaluate the relationship between fatigue and disease stage of CLL.
III) To evaluate the progression of fatigue over time in patients with untreated CLL.
IV) To evaluate the relationship of response to therapy and fatigue in CLL patients.
V) To determine if there is a correlation with cytokines and fatigue experienced by CLL patients.
VI) To evaluate the overall quality of life experienced by CLL patients as compared to that experienced by the general medical population.

## TECHNICAL APPROACH

Patients with CLL will be enrolled into one of three study groups. Cohort 1 is a prospective, case controlled study of fatigue in CLL. Cohort 2 is a cross sectional study when compared with cohort 1 to detect changes in fatigue related to treatment status. Treatment status includes standard treatment, alkylator therapy, fludarabine, and fludarabine refractory. Cohort 3 is a longitudinal assessment of fatigue over time in patients receiving treatment. After enrollment, all cohorts will fill out a questionnaire with age, sex, date of CLL diagnosis, current disease stage, current medications, treatment received for CLL, and current medical conditions other than CLL. A CBC and B2 microglobin level will be drawn. All patients will fill out the FACT-An/F scale with assistance from the investigator. Cohort 1 will do this at the beginning, at six months and at study completion in one year. Cohort 2 will do this at the beginning. Cohort 3 will do this at treatment initiation, mid-cycle in their treatment, and at one month after treatment. The control group will be recruited from the resident panels in the General Internal Medicine clinic after the CLL patients are registered in order to match underlying medical problems. They will fill out the same data in the questionnaire with the exception of the CLL questions. A CBC will be drawn at the beginning and end of the study, and patients will fill out the FACT-An/F scale at the beginning, middle, and end of the study.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 11. The total number enrolled study-wide is 11, if multi-site study.

## CONCLUSIONS

Ongoing.

Report Date: 18 December 2001 Work Unit # 00-1606

# DETAIL SUMMARY SHEET

TITLE: A Phase II Evaluation of Rubitecan, A Novel Oral Topisomerase I Inhibitor, in Newly Diagnosed, Recurrent, and Refractory Multiple Myeloma

KEYWORDS: myeloma, rubitecan

PRINCIPAL INVESTIGATOR: Joseph J. Drabick COL MC
ASSOCIATES: John C. Byrd MAJ MC, Carl Willis MAJ MC

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 8 February 2000

## STUDY OBJECTIVE

The purpose of this phase II study is to determine if rubitecan, an oral topisomerase I inhibitor, has clinical activity in patients with recurrent, refractory, or newly diagnosed multiple myeloma.

## TECHNICAL APPROACH

The structure of the protocol has not been changed to date. Patients found to be eligible are treated with oral rubitecan according to prior treatment status. Patients will receive rubitecan as a single oral dose in the morning, Monday-Friday, with a rest on Saturday and Sunday. Patients are evaluated at 2-week intervals for toxicity and at monthly intervals for activity. Dose may be modified according to toxicity or lack thereof. Patients will continue on treatment until there is evidence of progression of myeloma or toxicity.

## PRIOR AND CURRENT PROGRESS

Three patients have been enrolled in this study at WRAMC. Two SAEs have been submitted. One of these was for a patient who experienced ARF, with the rubitecan possibly contributing to this problem. He was also found to have pyelonephritis, BPH, and urosepsis. The other SAE reported was for mental status changes probably not related to study drug. This drug is not yet approved by the FDA for any clinical indication. It is being studied in some hematological malignancies and many solid tumors.

The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 3.

## CONCLUSIONS

Patients are still being enrolled to this study and no conclusions have been drawn to date.

Report Date: 18 December 2001 Work Unit # 01-15005

# DETAIL SUMMARY SHEET

TITLE: CALGB 79804: Issues of Survivorship Among Breast Cancer Survivors

KEYWORDS:

PRINCIPAL INVESTIGATOR: Joseph J. Drabick COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 27 February 2001

STUDY OBJECTIVE

1. To determine the prevalence of physical, economic, psychosocial and spiritual consequences of survivorship, including issues related to reproduction, menopause, osteoporosis, post-mastectomy/lumpectomy pain, and lymphedema among a cohort of disease-free long-term breast cancer survivors.
2. To determine how these problems affect overall health related quality of life (HRQL).

TECHNICAL APPROACH

Potentially eligible patients were identified by research personnel at Wake Forest University School of Medicine (WFUSM) and by research personnel at WRAMC. An introductory letter was sent to potential patients. About one week after the letters were sent, the patients were contacted by phone by research personnel from WRAMC to further explain the study, answer questions, assess interest in participation in the study, and arrange for a follow-up appointment at WRAMC to complete the consent process. After registration to the study a professional research interviewer from WFUSM will send a questionnaire to the patient. After the questionnaire is returned to WFUSM, the data will be transcribed to data form for analysis.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of 13 patients from WRAMC were registered to this study. No adverse events occurred. No patients withdrew from the study. The study closed to accrual 15 November 2001 after a sufficient number of participants were enrolled to answer the study objectives.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 13. The total number enrolled study-wide is 235 if multi-site study.

CONCLUSIONS

No conclusions have been reached. Analysis is ongoing.

Report Date: 1 February 2002

Work Unit # 01-15006

# DETAIL SUMMARY SHEET

TITLE: CALGB 89904: A Randomized Phase II Study of Gemcitabine/Cisplatin, Gemcitabine/Docetaxel, Gemcitabine/Irinotecan, or Fixed Dose Rate Infusion Gemcitabine in Patients with Metastic Pancreatic Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 20 March 2001

## STUDY OBJECTIVE

The primary objective of this study is to assess survival rate of patients with metastatic pancreatic cancer treated with one of four novel gemcitabine-based combination chemotherapy regimens.

Secondary objectives are to estimate the time to disease progression with metastatic pancreatic cancer treated with one of four chemotherapy regimens, to estimate the biomarker CA19-9 response to each regimen and to correlated the CA19-9 response with radiologic response and survival, and to assess the toxicity of each chemotherapy regimen in this patient population.

## TECHNICAL APPROACH

Patients will be randomized to one of the four chemotherapy arms. Gemcitabine alone or in combination with one of the following chemotherapy agents that have been approved by the FDA for other cancers—Cisplatin, Docetaxel, or Irinotecan. Depending on the chemotherapy regimen assigned, the patient will be treated weekly times three weeks with one week of rest, or weekly times two weeks with one week of rest. Patients will be treated until disease progression, if unacceptable toxicities develop, or the patient withdraws consent.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study was approved by the WRAMC HUC on 20 March 2001. To date, two patients from WRAMC have been enrolled. One patient continues on treatment without the development of treatment limiting side effects or progressive disease. One patient has died while on study treatment. This event (death) has been reported to the HUC via a 'report of adverse event' and to the CALGB and NCI via Adeers. The patient's death was not believed to be related to study treatment. Total national accrual to this study is 26.

The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 26.

## CONCLUSIONS

No conclusions have been reached. The study is ongoing.

Report Date: 21 February 2002 Work Unit # 01-15007

# DETAIL SUMMARY SHEET

TITLE: CALGB 99903: A Phase II Study of Arsenic Trioxide (NSC #706362, IND #57974) in Urothelial Cancer

KEYWORDS: Phase II; Arsenic Trioxide; Urothelial Cancer; IND (Investigational New Drug)

PRINCIPAL INVESTIGATOR: Flynn, Joseph CPT MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 17 April 2001

STUDY OBJECTIVE

1. To determine the efficacy of arsenic trioxide in patients with measurable urothelial carcinoma of the bladder, urethra, or renal pelvis.
2. To determine the toxicity of arsenic trioxide administered to patients with urothelial cancer.

TECHNICAL APPROACH

Adult healthcare beneficiaries with a diagnosis of transitional cell carcinoma of the bladder, urethra, ureter or renal pelvis, seen in the Hematology/Oncology Clinic at WRAMC will be evaluated for study eligibility. All females must have a negative pregnancy prior to study entry. Prior to each cycle, female subjects of childbearing potential must have a negative pregnancy test and be using an adequate method of contraception. Arsenic trioxide 0.3mg/kg/day will be infused over one hour daily for five consecutive days every four weeks. (one week of treatment, three weeks rest). Every two cycle the patients will be restages for response. Lab work (CBC and chemistries) will be done prior to every cycle. An EKG will be done prior to every cycle. Patients will have a physical exam and toxicity assessment prior to every cycle. Continuation of therapy will be based on severity of toxicities and disease response. After the first twelve patients (group-wide) are enrolled the study will be suspended to accrual to evaluate the response rate. If one or fewer responses are observed, the trial will be terminated. If two or more patients respond an additional 23 patients will be enrolled. If six or more responses are observed at the end of the second stage, the study will be considered for a Phase III setting.

PRIOR AND CURRENT PROGRESS

No patients from WRAMC have been enrolled in this study over the past year. The study has been temporarily suspended, effective November 2001, for planned analysis of data per protocol. This change has been reported to the IRB with approval. No grade 4 toxicities have been reported; two grade 3 toxicities of one neutropenia and one dehydration. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 12, if multi-site study.

CONCLUSIONS

No conclusions have been reached. The study is ongoing. We await the results of the planned interim analysis.

Report Date: 09 July 2002

Work Unit # 01-15008

# DETAIL SUMMARY SHEET

TITLE: CALGB 80001: Feasibility Study of Sentinel Lymph Node Staging for Colon Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Drabick, Joseph J. COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: W
INITIAL APPROVAL DATE: 26 June 2001

STUDY OBJECTIVE
Study withdrawn before receiving final approval letter.

TECHNICAL APPROACH
Study withdrawn before receiving final approval letter.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Study withdrawn before receiving final approval letter.

CONCLUSIONS
Study withdrawn before receiving final approval letter.

Report Date: 31 May 2002 Work Unit # 01-15009

# DETAIL SUMMARY SHEET

TITLE: CALGB 49805: A Phase III Randomized Double Blind Study of Letrozole Versus Placebo in Women with Primary Breast Cancer Completing Five or More Years of Adjuvant Taxmoxifen

KEYWORDS: Randomized; Double Blinded; Letrozole; Placebo; Breast Cancer; Tamoxifen

PRINCIPAL INVESTIGATOR: Joseph Drabick, COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 24 July 2001

STUDY OBJECTIVE
Primary: To determine the disease-free survival and overall survival (all cause mortality) for women who have previously received ≥ five years of adjuvant tamoxifen, randomized to receive either letrozole 2.5 mg daily or placebo daily for five years. Secondary: To evaluate the incidence of contralateral breast cancer. To evaluate the long term clinical and laboratory safety of letrozole with special attention on: lipid profile as assessed by blood sampling (in a limited number of centers); cardiovascular morbidity and mortality (i.e., significant coronary heart disease, which includes myocardial infarctions and angina requiring percutaneous transluminal coronary angioplasty of coronary artery bypass graft, fatal and nonfatal strokes and all vascular deaths) as assessed by reported toxicity; the incidence of all bone fractures (with particular emphasis on hip and wrist fractures as indicators of osteoporosis) as assessed by reported toxicity; changes in bone density (in a limited number of centers); common toxicities as assessed by reported toxicity. To evaluate overall quality of life.

TECHNICAL APPROACH
Patients having completed five years of Tamoxifen ending <2 months from study entry will be randomized to Letrozole or placebo. This is a double blinded study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Seven WRAMC patients have been entered on this protocol. No adverse reactions have been reported from the CALGB. National accrual to this study is 569. Projected accrual to this study is 4800.

The number of subjects enrolled to the study since last APR at WRAMC is 7 and the total enrolled to date at WRAMC is 7. The total number enrolled study-wide is 2354, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 18 September 2001

Work Unit # 01-1501

# DETAIL SUMMARY SHEET

TITLE: CALGB 99901: A Phase II Study of 9-Nitrocamptothecin (9-NC, IND #60, 162) For Hormone Refractory Prostate Cancer

KEYWORDS: prostate cancer, hormone-refractory

PRINCIPAL INVESTIGATOR: Flynn, Joseph CPT MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 21 November 2002

## STUDY OBJECTIVE

To evaluate the therapeutic efficacy of 9 nitrocamptothecin (objective response and serological parameters) in patients with metastatic, hormone refractory prostate cancer. To evaluate the safety, tolerance, and toxicity of 9-NC as single agent chemotherapy in this group of patients. To determine time-to-disease progression and duration of response (objective and PSA) with single agent 9-NC in this group of patients.

## TECHNICAL APPROACH

9-NC will be administered orally at the dose of 1.5 mg/m$^2$ for five consecutive days each week for three consecutive weeks followed by a break of one week. 9-NC is to be given once daily in the morning on an empty stomach with acidic juice. Patients should maintain oral fluid intake of at least three liters per day.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of zero patients have been enrolled at this site, 28 study wide (as of 10 April 2001). The study was suspended in June of 2001 to allow for a planned analysis of data. Sufficient patients have been accrued to answer study questions and the study is permanently closed to accrual as of 17 September 2001. There was one patient experiencing a Grade 3 toxicity in each of the following categories: neutrophils/granulocytes, transfusion (PRBCs), diarrhea, hematuria.

## CONCLUSIONS

Conclusions for this study have not yet been broadcast.

Report Date: 17 June 2002 Work Unit # 01-15010

# DETAIL SUMMARY SHEET

TITLE: CALGB 49801: Phase III Trial of Tamoxifen Alone vs. Tamoxifen Plus Radiation for Good Risk Ducts Carcinoma In-Situ (DCIS) of the Female Breast

KEYWORDS:

PRINCIPAL INVESTIGATOR: Ketchum, Lloyd CPT MC
ASSOCIATES:

DEPARTMENTS: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 31 August 2001

STUDY OBJECTIVE
In the defined good-risk group, assess the role of whole breast radiation plus tamoxifen compared to tamoxifen alone in decreasing or delaying the appearance of local failure, both invasive and *in s*itu, and preventing the need for mastectomy. Assess distant disease-free survival to affirm the hypothesis that the proportion of patients in either arm who fail with progression to invasive local disease can be successfully salvaged with further definitive local therapy and adjuvant systemic therapy as appropriate to the individual case.

TECHNICAL APPROACH
These patients have been diagnosed in the early stage of breast cancer. The anti-estrogen hormone tamoxifen may be appropriate to use after the surgeon has removed the cancer. In this study, treatment with tamoxifen will be compared to treatment with tamoxifen plus radiation therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This will be the first APR for this study, which has reported no publications at this time.
The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 156, if multi-site study. No Grade 4 toxicities reported.

Ref: CALGB Statistical Report

CONCLUSIONS
Too early.

Report Date: 17 June 2002

Work Unit # 01-15011

# DETAIL SUMMARY SHEET

TITLE: CALGB 159902: Molecular Markers of Pleural Involvement In Resected Non-small Cell Lung Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENTS: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 31 August 2001

## STUDY OBJECTIVE

To confirm the relationship between the presence of malignant cells in pleural lavage liquids and disease-free survival. To determine the incidence of expression of K-ras codon 12 mutation, mRNA encoding surfactant protein-A, or telomerase activity, in cells found in pleural lavage of patients undergoing thoracotomy for surgical resection of NSCLC. To examine the relationship between the presences of K-ras mutations, mRNA encoding surfactant protein-A, and telomerase activity in cells obtained by pleural lavage and the time to recurrence of disease, patterns of failure, and survival. To determine whether the presence of cells determined malignant by cytologic analysis in pleural lavage is associated with expression of K-ras mutations, mRNA encoding surfactant protein-A, or telomerase activity. To correlate the identification of K-ras mutations in pleural lavage cells with the presence of K-ras mutations in the primary tumor specimens.

## TECHNICAL APPROACH

Immediately after the chest is entered during thoracotomy it will be examined by the operating surgeon for gross evidence of metastases. If appropriate disease type and stage are found, the surgeon will lavage the pleura with 300ml of normal saline. The lavage liquid will be collected by suction, heparin added and placed on ice.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This is the first APR for this study. There have been no publications reporting data from this study or studies with similar study design in literature.

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is 153, if multi-site study. No Grade 4 toxicities reported.

Ref: CALGB Statistical Report

## CONCLUSIONS

Too early.

Report Date: 25 July 2002 Work Unit # 01-15012

# DETAIL SUMMARY SHEET

TITLE: CALGB 509901: Phase II Study of Melanoma Vaccine (NSC#683472/675756, IND 6123) and Low-Dose, Subcutaneous Interkeukin-2 in Advanced Melanoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Gorak, Edward J. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 14 September 2001

STUDY OBJECTIVE
Estimate clinical response rate to gp 100:209-217(210M) melanoma vaccine and low-dose, subcutaneous interleukin-2. Observe induction of gp 100:209-217(210M) reactive T cells in peripheral blood mononuclear cells (PBMC) by ELISPOT assay for interferon gamma. Observe response duration and progression free intervals. Observe CALGB accrual rate for this phase II study in metastatic melanoma. Establish feasibility of HLA subtyping and ELISPOT monitoring.

TECHNICAL APPROACH
Study treatment will consist of two vaccinations of the investigational drug known as melanoma vaccine, followed by five days of IL-2 given by a subcutaneous injection, and then one week later, another five days of IL-2 given by a subcutaneous injection.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been no publications reporting data from studies with similar design in the literature. This is the first APR for this study.

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 9, if multi-site study. No grade 4 toxicities reported.

Ref: CALGB Statistical Report Jun 02

CONCLUSIONS
Too early.

Report Date: 5 October 2001 Work Unit # 01-1502

# DETAIL SUMMARY SHEET

TITLE: CALGB 59906: A Phase II Study of Sequential Doxorubicin and Topotecan in Relapsed or Refractory Intermediated or High-Grade Non-Hodgkin's Lymphoma

KEYWORDS: Hodgkin's disease, chemotherapy, cycles, relapsed

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 21 November 2000

STUDY OBJECTIVE:
To evaluate the response rate and time-to-progression or failure in patients with relapsed or refractory intermediate- or high-grade NHL to the combination of sequential doxorubicin/topotecan. To evaluate the toxicity of sequential doxorubicin/topotecan in patients with relapsed or refractory intermediate-grade NHL or high-grade NHL.

TECHNICAL APPROACH
Patients will be treated for a maximum of six cycles. Each cycle will consist of 21 days. Patients will receive doxorubicin IVP on day 1 and topetecan IV on days 3, 4, 5. Treatment will be for a minimum of two cycles in the absence of intolerable toxicity or clear progression of disease.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This study was approved WRAMC on November 21, 2000. The CALGB activated this study on 15 July 2000. This is the first APR. As of April 2001, four patients had been entered on this protocol study wide, zero enrolled here at WRAMC. There have been no SAEs reported.

This study remains open to accrual. No conclusions drawn to date.

Report Date: 4 October 2001 Work Unit # 01-1503

# DETAIL SUMMARY SHEET

TITLE: CALGB 59804: A Phase I/II Study of Gemcitabine/Vinorelbine/Liposomal Doxorubicin in Relapsed/Refractory Hodgkin's Disease

KEYWORDS: Hodgkin's disease, chemotherapy, relapse

PRINCIPAL INVESTIGATOR: Drabick, Joseph LTC MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 30 November 2000

STUDY OBJECTIVE:
To evaluate the toxicity of four dose levels of gemcitabine, Navelbine, and Doxil (GND) in patients with relapsed Hodgkin's disease. To determine the complete and partial response rates of relapsed Hodgkin's disease to the combination of GND.

TECHNICAL APPROACH
Patients will be registered to one of four gemcitabine/Navelbine/Doxil (GND) dose levels. There will be no intrapatient dose escalations. Patients will receive a maximum of 6 cycles, each cycle consisting of 21 days. The chemotherapy will be given on days 1 and 8 of each cycle, intravenously. Restaging will occur every two cycles. Non-responding patients will be removed from therapy after two cycles.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Three WRAMC patients have been entered on this study. None of these patients have experienced an SAE and no patient has withdrawn from the study. National accrual to the study is nine. Projected accrual to the study is 70.

This is the first APR required.

CONCLUSIONS
This study remains open to accrual. No conclusions have been reached.

Report Date: 7 November 2001

Work Unit # 01-1504

# DETAIL SUMMARY SHEET

TITLE: CALGB 59901: A Phase II Study of 506U78 in Patients with Previously Systemically Untreated Cutaneous T-Cell Lymphoma or With Refractory or Relapsed Non-Cutaneous Peripheral T-Cell Lymphoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Joseph Drabick COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 12 December 2000

## STUDY OBJECTIVE

This study has two objectives. 1. To determine the complete and partial remission rates, as well as the remission duration, in patients with previously systemically untreated cutaneous T-cell lymphoma (CTCL) or with refractory or relapsed non-cutaneous peripheral T-cell lymphoma (PTCL) receiving 506U78 (1.5 gm/m²/day) on an alternate day schedule (days 1, 3, 5). 2. To determine the safety and toxicity associated with 506U78 administered on this schedule to these patients.

## TECHNICAL APPROACH

Eligible patients will receive study drug, 506U78, as a 2-hour IV infusion at a dose of 1.5g per m2 on Monday, Wednesday and Friday (days 1,3,5) every 21 days until disease progression, complete response, or development of unacceptable toxicity. Renal function will be closely monitored and treatment will be modified if necessary. A physical exam, lab-work, and toxicity assessment will be done before each cycle. A weekly CBC will be done, with dose modification if necessary. Restaging studies will be done after every two cycles to assess for response to treatment. Careful assessment for neurological toxicity will be continuous and treatment will be stopped it this toxicity occurs.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study remains open to accrual. There have been no patients from WRAMC registered. No serious unexpected adverse events have been reported by CALGB. Projected target accrual is 50. There have been 4 patients accrued to this study group wide. There was one update (1/15/01) after initial WRAMC/IRB approval which addressed a consent form change adding memory loss and slurred speech as potential side effects. The amendment was submitted 5/01 to DCI and approved by WRAMC /IRB 6/01.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 4, if multi-site study.

## CONCLUSIONS

The study is ongoing. No conclusions have been reached

Report Date: 25 January 2002 Work Unit # 01-16002

# DETAIL SUMMARY SHEET

TITLE: Microarray Analysis of Breast Cancer: A Pilot Feasibility Study

KEYWORDS: breast cancer, microarray, gene expression profiles

PRINCIPAL INVESTIGATOR: McGrail, Lisa MAJ MC
ASSOCIATES: Shriver, Craig COL MC

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 9 January 2001

STUDY OBJECTIVE Determine the feasibility of developing tissue procurement and processing procedures for future microarray projects. Analyze gene expression profiles between specimens of matched normal to cancerous breast tissue via microarray technology.

TECHNICAL APPROACH
There have been no modifications to the methodology. In summary, tissue specimens were obtained after definitive surgical resection of a breast tumor. The surgeon and pathologist determined together if there was excess tissue to be used in this study. Fifty percent of the tumor tissue and fifty percent of the normal tissue were immediately prepared and processed for microarray analysis by the PI. The other fifty percent of the tumor was stored and then transported to Windber Research Institute (WRI) for microarray analysis. All tissue was devoid of patient identifiers. All tissue was coded with an identifier.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been eleven patients enrolled to date and we have stopped all accrual. There have been no patients withdrawn from the study, and no adverse reactions. One of the patients enrolled is a man who did not have residual tumor at time of mastectomy. Another patient enrolled underwent bilateral mastectomy. There have been no amendments or modifications made to the study. There has been no benefit to patients as this was not the intent of this study. The results from WRI are summarized in the table below: (Two tissue samples have not yet been processed.)

| Sample Code | Type | Date Sample Obtained | Status | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Tissue in Freezer as Received | Wt (g) | Protein Extracted from Tissue/Used | RNA Extracted from Tissue/Used | DNA Extracted from Tissue/Used | Amount of Tissue and/or Product Left |
| P1NW | Biopsy | 02/12/01 | No | 0.63 | Yes/Yes | Yes/No | No | 20% |
| P1CW | Biopsy | 02/12/01 | No | 0.62 | Yes/Yes | Yes/Yes | No | 20% |
| P2NW1 | Biopsy | 02/23/01 | Yes | 3.70 | No/No | No/No | No | 100% |
| P2NW2 | Biopsy | 02/23/01 | Yes | 1.51 | No/No | No/No | No | 100% |
| P2NWNode | Biopsy | 02/23/01 | Yes | .097 | No | No | No | 100% |
| P3NW | Biopsy | 03/08/01 | No | 0.73 | Yes/Yes | Yes/No | No | 60% |
| P3CW | Biopsy | 03/08/01 | No | 0.52 | Yes/Yes | Yes/No | No | 60% |
| P4CW | Biopsy | 03/08/01 | No | 0.25 | Yes/No | Yes/No | No | 95% |
| P5NW | Biopsy | 03/26/01 | No | 0.16 | No | Yes/Yes | No | 5% |
| P5CW | Biopsy | 03/26/01 | No | 0.17 | No | Yes/Yes | No | 5% |
| P6NW1 | Biopsy | 04/17/01 | Yes | 2.45 | No | No | No | 100% |
| P6NW2 | Biopsy | 04/17/01 | Yes | 0.16 | No | No | No | 100% |
| P7N-L | Biopsy | 04/17/01 | Yes | 15.06 | No | No | No | 100% |
| P7N-R | Biopsy | 04/20/01 | Yes | 27.84 | No | Yes/No | No | 100% |
| P8NW | Biopsy | 05/01/01 | No | 1.06 | Yes/Yes | Yes/Yes | No | 0% |
| P8CW | Biopsy | 05/01/01 | No | 0.80 | Yes/Yes | Yes/Yes | No | 0% |
| P9NW | Biopsy | 05/22/01 | No | 0.35 | No | Yes/Yes | No | 20% |
| P9CW | Biopsy | 05/22/01 | No | 0.39 | No | Yes/Yes | No | 20% |

The results from the laboratory at Georgetown University are summarized below:

| Sample | Tumor Wt. (mg) | RNA Amount | Tissue Discarded | Tissue Consumed | Amt. Tissue Left |
|---|---|---|---|---|---|
| P1CG | 200 | 72ug | No | Yes | Protein Extracted from Tissue/Used |
| P1NG | Not processed | Not processed | Yes | No | 0% |
| P2CG | 690 | 108ug | No/given to WRI | No | 0% |
| P2CG-Node | 280 | 80ug | No | Yes | 0% |
| P2NG | Not processed | Not processed | Yes | No | 0% |
| P3CG | 350 | 70ug | No | Yes | 0% |
| P3NG | 1570 | 76ug | No | Yes | 0% |
| P4CG | 20 | 12ug | No | Yes | 0% |
| P4NG | Not processed | Not processed | Yes | Not processed | 0% |
| P5CG | 60 | 20ug | No | Yes | 0% |
| P5NG | Not processed | Not processed | Yes | No | 0% |
| P6NG* | 700 | 16ug | Yes | Yes | 0% |

Samples of P7-11NG and P7-11CG were not processed due to loss of financial funding and instead the samples were sent as a whole to WRI. The normal tissue samples did not yield adequate amounts of mRNA to perform microarray analysis; therefore the small amounts of RNA generated were either lost in processing or discarded along with any unprocessed tissue. A small amount of RNA from sample P2CG was forwarded to WPI. There is no tissue remaining at the Georgetown University site.

Due to the fact that the normal breast RNA was insufficient in amount for analysis, normal mRNA was purchased as a control. We then used the mouse metastatic breast cancer cell line MCF10-A as a bridge to normal breast tissue. Microarray analysis was then performed on samples: normal breast tissue to MCF10-A, MCF10-A to P1CG, MCF10-A to P2CG, and MCF10-A to P2CG-Node. A list of down-regulated and up-regulated genes was then generated and the results are summarized in the tables below:

Down Regulated Genes

| Clone ID | NorBre/MCF | P1/MCF | P2/MCF | P2No/MCF | Gene Title |
|---|---|---|---|---|---|
| 310519 | 8.125 | 0.139 | 3.006 | 4.943 | Coagulation factor X |
| 325070 | 8.125 | 0.139 | 3.006 | 4.943 | EST |
| 283398 | 8.125 | 0.139 | 3.006 | 4.943 | Homo sapiens mRNA; cDNA DKFZp761J17121 |
| 121543 | 8.125 | 0.139 | 3.006 | 4.943 | ESTs |
| 138345 | .356 | 0.405 | | 3.164 | Transmembrane trafficking protein |
| 214980 | .356 | 0.405 | | 3.164 | Hypothetical protein, clone Telethon (Italy_B41) Strait02 |
| 685185 | 3.56 | 0.405 | | 3.164 | ESTs, weakly similar to S22423 phosphoprotein phosph |
| 239877 | 8.125 | 0.139 | 3.006 | 4.943 | Histone deacetylase 3 |
| 129585 | 8.125 | 0.139 | 3.006 | 4.943 | Ribosomal protein S27a |
| 209624 | 8.125 | 0.139 | 3.006 | 4.943 | Homo sapiens clone CDABP0113 m RNA sequence |
| 127766 | 8.125 | 0.139 | 3.006 | 4.943 | EST |
| 198871 | 3.56 | 0.405 | | 3.164 | Homo sapiens m RNA; cDNA DKFZp434H092 |
| 29404 | 3.56 | 0.405 | | 3.164 | Hypothetical protein FLJ10743 |
| 826074 | 3.56 | 0.405 | | 3.164 | ESTs |

Up Regulated Genes

| Clone ID | NorBre/MCF | P1/MCF | P2/MCF | P2No/MCF | Gene Title |
|---|---|---|---|---|---|
| 812050 | 0.417 | 2.092 | 0.257 | 0.315 | Patched related protein translocated in renal cancer |
| 971367 | 0.417 | 2.092 | 0.257 | 0.315 | Ribosomal protein |
| 397360 | 0.417 | 2.092 | 0.257 | 0.315 | ESTs |
| 325014 | 0.417 | 2.092 | 0.257 | 0.315 | Pre-B-cell leukemia transcription factor 3 |
| 148296 | 0.299 | 2.161 | 4.226 | 3.945 | ESTs, Moderately similar to ALU1 |
| 114101 | 0.299 | 2.161 | 4.226 | 3.945 | ESTs |
| 746347 | 0.299 | 2.161 | 4.226 | 3.945 | ESTs, highly similar to homolog of the Aspergillus nidulans sudD gene |
| 767495 | 0.417 | 2.092 | 0.257 | 0.315 | GLI-Kruppel family member GL13 (Greig cephalopolysyndactyly syndrome) |
| 165828 | 0.417 | 2.092 | 0.257 | 0.315 | FH1/FH2 domain-containing protein |
| 279810 | 0.417 | 2.092 | 0.257 | 0.315 | Homo sapiens cDNA DKFZp564O1016 |
| 436051 | 0.417 | 2.092 | 0.257 | 0.315 | ESTs, weakly similar to putative p150 (h. sapiens) |
| 220376 | 0.299 | 2.161 | 4.226 | 3.945 | ESTs, weakly similar to 1207289A reverse transcriptase related protein |
| 30476 | 0.299 | 2.161 | 4.226 | 3.945 | ESTs |
| 827171 | 0.299 | 2.161 | 4.226 | 3.945 | Leucine-rich repeat-containing 2 |

Microarray technology provides a versatile platform to understand the mechanism of breast cancer development. It can be applied to monitoring chromosome changes, tumor classification, drug discovery, as well as mechanisms of tumor development and metastasis. In the past year there has been a sentinel article published by Hedenfalk et al. (N Engl J Med 2001 Feb 22;344(8):539-48) which used microarray technology to examine the gene expression profiles of BRCA1 and BRCA2 hereditary breast cancers. They concluded that there are different groups of genes expressed between these cancers suggesting an inheritable influence on gene expression profiling.

Several other studies have been published which each aim to evaluate a specific gene or signal that is believed to play a role in tumorgenesis by using microarray technology. For example, Li et al. (Free Radic Biol Med 2001 Feb 1:30(3):260-7) studied the mitochondrial antioxidant enzyme manganese-containing superoxide dismutase (MnSOD) which functions as a tumor suppressor gene in the human breast cancer cell line MCF-7. They found that reconstitution of MnSOD in tumor cells modulates down-stream effecter genes. Kauramiemi et al. (Cancer Res 2000 Oct 1;60(19):5323-8) used microarrays to examine the role of MYB oncogene amplification in hereditary BRCA1 breast cancer. They found this amplification was uncommon in sporadic breast cancers but common in cancers from BRCA1 mutation carriers, suggesting it plays a role in cell cycle regulation. While microarray technology remains in its infancy, its potential for understanding the mechanisms which govern tumor cell development and progression is vast.

The number of subjects enrolled to the study since last APR at WRAMC is 11 and the total enrolled to date at WRAMC is 11.

CONCLUSIONS

We are now continuing to process and analyze the data generated, although we are no longer accruing patients. We expect this research will continue over the course of the next year. We have shown that tissue procurement and processing for microarray analysis is highly feasible. This pilot study laid the groundwork for the currently on-going Tissue Banking initiative of the Clinical Breast Care Project which will have far reaching implications for understanding the development and mechanisms of breast cancer. The hope is that one day drugs can be developed from research such as ours, aimed at specific cell targets that will arrest cancer development or possibly prevent it altogether.

Report Date: 21 March 2002

Work Unit # 01-16004

# DETAIL SUMMARY SHEET

TITLE: Expression of Human Papilloma Virus in Second Primary Malignancies Associated with Chronic Lymphocytic Leukemia

KEYWORDS:

PRINCIPAL INVESTIGATOR: Flynn, Joseph M. CPT MC

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 13 March 2001

STUDY OBJECTIVE:
The objectives of this protocol are to ascertain whether human papilloma virus may be identified in conjunction with second primary tumors associated with patients with Chronic Lymphocytic Leukemia.

TECHNICAL APPROACH
Tumors identified in patients with CLL and matched controls are being analyzed by PCR for determination of presence of human papilloma virus. We seek the ability to increase the number of cases studied as more of the original 43 patients from #1606 have been retrieved. This will add to the power of this study. The initial number requested was based on a request by the DCI for a number of tissue blocks that we were able to retrieve at that time.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
As of this request, tissue samples of 23 tumors have been identified and have been processed per protocol. The matched control population has been identified though have not been studied as yet. There remains no available research that has demonstrated what we are trying to discern in this population.

The number of subjects enrolled to the study since last APR at WRAMC is 21 and the total enrolled to date at WRAMC is 21. The total number enrolled study-wide is 21, if multi-site study.

CONCLUSIONS
We continue to work toward completing this trial. Once the controls have been fully identified and provided to our group, we will complete the PCR processing and subsequent analysis of results. This will likely take another several months.

Report Date: 1 September 2002 Work Unit # 01-16005

# DETAIL SUMMARY SHEET

TITLE: A Phase II, Open-Label, Randomized, Multicenter Trial to Evaluate the Preliminary Efficacy and Safety of Hu1D10 in Patients with Relapsed or Refractory Grades I, II, or III B-Cell Non-Hodgkin's Lymphoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Drabick, Joseph J. COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: W
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 19 June 2001

STUDY OBJECTIVE
Study withdrawn.

TECHNICAL APPROACH
Study withdrawn.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Study withdrawn.

CONCLUSIONS
Study withdrawn.

Report Date: 3 May 2002 Work Unit # 01-16006

# DETAIL SUMMARY SHEET

TITLE: A Multicenter, Phase III Randomized Trial for Stage IIIB or IV NSCLC Comparing Weekly Taxol (Paclitaxel) and Carboplatin (Paraplatin) Regimen Versus Standard Taxol and Carboplatin Administered Every Three Weeks, Followed by Weekly Taxol

KEYWORDS: Phase III; NSCLC; weekly versus every three weeks; Taxol; Carboplatin

PRINCIPAL INVESTIGATOR: MAJ Carl Willis, MC

ASSOCIATES: LTC Rickey Myhand, COL Joseph Drabick, COL Alfred Brooks, MAJ Joseph Flynn

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 26 June 2001

STUDY OBJECTIVE:
To determine the overall patient survival rate for each of the two treatment regimens outlined in this study, and to see if the experimental regimen is as effective as or better than the standard treatment. The secondary objectives are to determine the time to disease progression for each regimen, to determine the objective response rate of the two treatment regimens, and to evaluate the safety and toxicity of the treatment.

TECHNICAL APPROACH
Patients will be randomized to receive either Taxol 100 mg/ml weekly for 3 weeks, 4$^{th}$ week rest with Carboplatin AUC 6 given after Taxol on Day 1 only of each cycle (1 cycle = 4 weeks) for a total of 4 cycles (16 weeks) or Taxol 225 mg/ml followed by Carboplatin AUC 6 once every 3 weeks, repeat for 4 cycles (for a total of 12 weeks). Both regimens will be followed by weekly Taxol at 70mg/m2 and will be continued until development of progressive disease, development of intercurrent illness, development of intolerable toxicity, patient refusal of further treatment, investigator decision to terminate treatment, or delay in treatment > 2 weeks (excluding week(s) of rest in treatment cycle).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Two WRAMC patients have been entered on this study since its approval 7/31/2001 (both have been entered in this reporting period). No serious or unexpected adverse events have occurred during this reporting period for either of these WRAMC patients. Only one adverse event from another facility was reported to WRAMC. It involved the hospitalization of a patient for hypoxia while receiving active treatment on protocol. The patient recovered and the adverse event was "hypoxia" deemed possibly related to study drug. One patient at WRAMC has since come off study due to progression of their disease. National accrual to the study is 307 patients. Target accrual is 444.

The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 307, if multi-site study.

CONCLUSIONS
No conclusions have been reached. Study is ongoing.

Report Date: 2 May 2002

Work Unit # 01-16007

# DETAIL SUMMARY SHEET

TITLE: An Open-Label, Multicenter, Randomized, Phase III Study Comparing Oral Topotecan/Cisplatin Versus Etoposide/Cisplatin as Treatment for Chemotherapy-naive Patients with Extensive Disease - Small Cell Lung Cancer.

KEYWORDS:

PRINCIPAL INVESTIGATOR: MAJ Carl Willis, MC
ASSOCIATES: CPT Joseph Flynn MC

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 31 July 2001

STUDY OBJECTIVE

The primary objective is to compare overall survival using Kaplan-Meier estimates in chemotherapy-naïve patients with extensive stage small cell lung cancer (SCLC) randomized to treatment with oral topotecan plus cisplatin or cisplatin plus etoposide. This trial will test the hypothesis that the regimen will prolong patient survival compared to the standard regimen. The secondary objective is to compare the response rates, response duration, time to progression, tolerability, and patient-perceived disease status and well being for patients in each treatment arm.

TECHNICAL APPROACH

This is an open-label, multicenter, randomized phase III study. Patients will be stratified according to gender, performance status (0, 1, or 2), LDH (normal or elevated), and country. Eligible patients will be randomized to one of two treatment arms: Topotecan (1.7 mg/m∫/day) administered orally on days 1-5 with Cisplatin (60 mg/m∫/day) administered intravenously on day 5 every 21 days. Or Cisplatin (80 mg/m∫/day) on day 1 with Etoposide (100 mg/m∫/day) administered intravenously on days 1-3 every 21 days (21 days = 1 course/cycle). Treatment duration will depend on the response to treatment. A maximum of 6 courses should be administered. All patients should receive at least 4 courses of treatment unless one or more of the following occur: disease progression, development of intercurrent illness, development of intolerable toxicity, patient refusal of further treatment, investigator decision to terminate treatment, or delay in treatment > 2 weeks beyond day 21.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No patients have been enrolled here at Walter Reed Army Medical Center. An expedited investigator safety report from GlaxoSmithKline reported a death on the study from another facility. The patient was NOT enrolled here at WRAMC or its affiliate. The details related to the patient's death was submitted to DCI on April 4, 2002 along with a copy of the report received from GlaxoSmithKline. No other adverse event reports have been received.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 391, if multi-site study.

CONCLUSIONS

No conclusions have been reached. The study is on going.

Report Date: 5 December 2001

Work Unit # 01-1601

# DETAIL SUMMARY SHEET

TITLE: Epstein-Barr Virus as an Etiologic Agent for Hodgkin's Disease: A Nested Case-Control Study

KEYWORDS: Pre-diagnosis serology, EBV, Hodgkin's Disease, immunology, EBER

PRINCIPAL INVESTIGATOR: Joseph Drabick COL MC
ASSOCIATES: Lynn Levin, Ph.D., M.P.H.

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 5 December 2000

## STUDY OBJECTIVES

The focus of this study is to integrate the pre-diagnosis serology in relation to the molecular status of Hodgkin's Disease (HD) cases in order to elucidate the interplay of host and viral factors in the pathogenesis of this disease. For the serologic analysis, we will conduct a nested case-control study of incident cases and matched controls identified from the Department of Defense Serum Repository (DoDSR). We expect a total of 300 cases and 900 controls. For each case, the diagnostic tissue block will be obtained from medical treatment facilities and medical centers in the Army, Navy and Air Force. Tissue blocks from all cases will be tested for EBV genome status. These data will be evaluated for consistency with three models of HD pathogenesis:

1. The EBV is solely related to EBV-genome positive HD with EBV-genome negative disease due to non-viral causes;
2. HD is a virally induced malignancy with the EBV responsible for EBV-genome positive disease and another unidentified virus(es) linked to EBV-genome negative disease;
3 The EBV plays a crucial role in the pathogenesis of essentially all HD cases but the genome is selectively lost in some patients.

## TECHNICAL APPROACH

To complete the study at WRAMC, tissue blocks are requested for a total of 24 HD cases that were either initially evaluated at WRAMC or referred to WRAMC. The blocks will be returned to the WRAMC Anatomic Pathology Service once slides are prepared at the AFIP.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been eight subjects enrolled in the study since the protocol was approved in December 2000, with two more pending. To date, the study-wide total of enrolled subjects is 299.

Pending the receipt of the last few pending cases, the data collection phase will be complete. We have already begun to return tissue blocks. The remaining blocks at WRAMC need to be sent to AFIP for slide preparation. They will then be returned to WRAMC Anatomic Pathology Department. These slides will be forwarded to Johns Hopkins to determine EBV status.

## CONCLUSIONS

As data analysis has not yet been completed, there are no conclusions to offer at this point.

Report Date: 2 October 2002 Work Unit # 1500-98

# DETAIL SUMMARY SHEET

TITLE: CALGB 9633: A Phase III Study of Adjuvant Chemotherapy After Resection for Patients with T2N0 Stage I Non-Small Cell Carcinoma of the Lung

KEYWORDS:

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 05 November 1997

STUDY OBJECTIVE
To determine if adjuvant chemotherapy can favorably alter the prognosis for high-risk patients with T2N0 NSC carcinoma of the lung. To compare failure-free survival of these patients who have and have not received adjuvant chemotherapy after surgical resection. To determine toxicity associated with adjuvant chemotherapy, and to describe pattern of recurrence.

TECHNICAL APPROACH
Eligible patients with T2N0 NSC carcinoma of the lung will be randomized after surgical resection to receive standard therapy - observation or to receive adjuvant chemotherapy with taxol and carboplatin. Chemo will be given in hematology-oncology clinic once a week x three weeks for a total of four treatments (12 wks). Chemo is IV and infusion takes one to two hours. Follow-up in clinic is every 4 mo. X 2 yrs, every 6 mo. thereafter.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is 279, if multi-site study.

Grade 4 toxicities include 1 WBC, 30 granulocytes/bands, 3 lymphocytes, 1 other hematologic, 1 vomiting, 1 diarrhea, 1 other GI, 1 alopecia, 2 dyspnea, 1 phlebitis/thrombosis, 1 malaise/fatigue, and 1 prothrombin time. Adverse event reported 4 February 2002.

Ref: CALGB Statistical Report

CONCLUSIONS
Too early.

Report Date: 7 November 2001 Work Unit # 1501-98

# DETAIL SUMMARY SHEET

TITLE: CALGB 9741: A Randomized Phase III Trial of Sequential Chemotherapy Using Doxorubicin, Paclitaxel and Cyclophosphamide or Current Doxorubicin and Cyclophosphamide Followed by Paclitaxel at 14 or 21 Day Intervals in Women with Node Positive Stage II/IIIA Breast Cancer

KEYWORDS: Chemotherapy, sequential, concurrent

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 16 December 1997

STUDY OBJECTIVE
To compare sequential chemotherapy with doxorubicin, paclitaxel and cyclophosphamide to combined doxorubicin and cyclophosphamide followed by paclitaxel for disease-free survival and overall survival, and for toxicity. To determine whether increasing the dose density of adjuvant chemotherapy (decreasing the interval between chemotherapy from 21 to 14 days) will improve overall and disease-free survival.

TECHNICAL APPROACH
Eligible patients will be randomly assigned to one of 4 groups. All will receive Adriamycin, Taxol and Cytoxan (ATC). The 4 treatment plans are: 1) sequential C q3 weeks x 4, 2) sequential A-T-C q 2 weeks x 4, 3) concurrent AC q 3 weeks x 4 followed by T q 3 weeks x 4, 4) concurrent AC q2 weeks x 4 followed by T q 2 weeks x 4. Patients randomized to q 2-week therapy will receive G-CSF during therapy; the other groups receive G-CSF at the physician's discretion. Follow-up after treatment is q 6 months x 5 years, and yearly thereafter.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of 5 WRAMC patients were entered on this protocol before it was closed to accrual in March 1999, having met its goal of 2005. During the time the study was open, no WRAMC patients have withdrawn from the study. Two adverse events have been reported during this reporting period (one death and a patient developed a second malignancy). These were reported to the WRAMC HUC. National accrual to the study was 2005 patients. Four patients continue in study follow-up.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is 2005, if multi-site study.

CONCLUSIONS
Analysis is ongoing.

Report Date: 20 November 2001 Work Unit # 1502-98

# DETAIL SUMMARY SHEET

TITLE: CALGB 9762: Clinical Pharmacology of Paclitaxel in Relation to Patient Age

KEYWORDS: Pharmacology, paclitaxel, patient age

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 27 January 1998

STUDY OBJECTIVE
To determine if there is a relationship between pharmacokinetic measurements of paclitaxel and aging. To determine if there is a relationship between the toxicities of paclitaxel and aging.

TECHNICAL APPROACH
Eligible patients with cancer for whom single agent paclitaxel treatment is appropriate will receive standard paclitaxel treatment as described in protocol with protocol specific pharmacokinetic blood samples drawn prior to therapy and at 1, 6, and 7 hours after completion of first cycle of paclitaxel. All further treatment is at physician discretion. All patients will be followed in the out -patient oncology clinic for six weeks following protocol therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Twelve WRAMC patients have been entered on this protocol. All have died of their progressive disease. Four of these were in this reporting period. National accrual to the study thus far is 151 patients; nine were within this reporting period. Projected accrual is for 120 evaluable samples. This protocol remains open at WRAMC.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 12. The total number enrolled study-wide is 151, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 18 December 2001 Work Unit # 1505-98

# DETAIL SUMMARY SHEET

TITLE: CALGB 9781: A Phase III Trial Comparing Trimodality Therapy (Cisplatin, 5-FU, Radiotherapy and Surgery) to Surgery Alone for Esophageal Cancer

KEYWORDS: esophageal, cancer, trimodality

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 24 February 1998

STUDY OBJECTIVE
To compare overall five-year survival rates between the two treatment arms. To compare treatment failure at five years between the two treatment arms. To assess and compare the toxicities of each approach.

TECHNICAL APPROACH
Eligible patients with esophageal cancer will be randomized to receive either:
1. A combination of standard dose radiation therapy and chemotherapy with Cisplatin and 5-FU, given as outpatient therapy and lasting 5 1/2 weeks. This therapy is followed in 3 to 8 weeks with surgical esophageal resection requiring an 8 to 10 day hospital stay.
2. Standard treatment consisting of surgical esophageal resection requiring an 8 to 10 day hospital stay. All patients will be followed 4x per year for 2 years, 2x per year for an additional 2 years, then annually.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
One WRAMC patient has been entered on this study before it was closed to accrual 30 March 2000. No WRAMC patients have withdrawn from the study. National accrual to this study was 56 patients. The projected accrual was for 500 patients. No adverse reactions have been reported from the CALGB during this reporting period.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 56, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 25 April 2002 Work Unit # 1506-98

# DETAIL SUMMARY SHEET

TITLE: CALGB 9720: Phase III Study of MDR Modulation with PSC-833 Followed by Immunotherapy with rIL-2 vs. No Further Therapy in Previously Untreated Patients with AML>60 Years

KEYWORDS: AML, PSC-833, rIL-2, immunotherapy

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 24 March 1998

## STUDY OBJECTIVE

To determine if the addition of PSC-833 to induction chemotherapy improves complete response rates, and if addition of PSC-833 to induction and consolidation chemotherapy improves survival for patients with AML > 60 years old. To determine if low-dose, subq rIL-2 immunotherapy with intermittent high-dose boluses after chemotherapy prolongs disease-free survival.

## TECHNICAL APPROACH

All eligible patients will be treated with a standard first line regimen utilizing ara-c, daunorubicin and etoposide (ADE). The initial study design included a randomization to ADE versus ADE plus the investigational agent PSC-833, believed to decrease drug resistance. The treatment arm utilizing the investigational agent, PSC-833, was eliminated 3/15/00 when early data analysis revealed patients receiving PSC-833 experienced greater than expected severe and life-threatening toxicities compared to those patients not receiving PSC-833. This major change to this protocol was submitted and approved by the WRAMC HUC 4/14/00. After Induction and Consolidation therapy, patients will be randomly assigned to either standard treatment, which is observation, or to maintenance therapy with rIL-2.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Three patients have been enrolled from WRAMC. All WRAMC patients have expired due to their disease. The deaths have been reported to the IRB. No deaths were due to study treatment. Two patients were off-study at the time of their death. One patient died of complications due to his leukemia while on study treatment. No new patients have been enrolled since the last APR. Accrual goals to this study have been met and effective 30 April 2002. This study is closed to enrollment.

The number of subjects enrolled to the study since last APR at WRAMC is zero, and the total enrolled to date at WRAMC is three. The total number enrolled study-wide is 640, as this is a multi-site study.

## CONCLUSIONS

No conclusions have been drawn to date.

Report Date: 1 February 2002 Work Unit # 1507-98

# DETAIL SUMMARY SHEET

TITLE: CALGB 9730: Single-Agent vs. Combination Chemotherapy in Advanced NSCLC: A CALGB Randomized Trial of Efficacy, Quality of Life and Cost-Effectiveness

KEYWORDS: NSCLC, advanced combination

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 24 March 1998

STUDY OBJECTIVE
To compare overall survival and quality of life of patients treated with paclitaxel alone or in combination with carboplatin. To determine cost-utility and cost-effectiveness of the best strategy. To compare response rates and toxicities of each arm.

TECHNICAL APPROACH
Eligible patients will be randomized to receive IV chemotherapy treatment with either single-agent taxol or with a combination of taxol and carboplatin. This treatment will be on out-patient basis, requiring six six-hour visits over 18 weeks. Quality of Life questionnaires will be administered at outset and at 2, 6, 9, and 12 months after registration to the study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Twelve WRAMC patients have been entered on this study. Nine patients have died of their progressive disease, two in this reporting period and the remaining three patients continue in study follow-up. The study group has reported no unexpected toxicities to us. The protocol was closed to accrual in December 2000. The final national accrual to the study is 584.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 12.

CONCLUSIONS
No conclusions have been reached.

Report Date: 5 October 2001 Work Unit # 1509

# DETAIL SUMMARY SHEET

TITLE: CALGB 9011: A Study of Fludarabine vs. Chlorambucil vs. Both Drugs for Chronic Lymphocytic Leukemia

KEYWORDS: fludarabine, chlorambucil, crossover study

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 November 1990

## STUDY OBJECTIVE

To compare the response rates and progression-free survival in previously untreated chronic lymphatic leukemia (CLL) patients using three therapeutic regimens; to determine whether the quality-of-life is superior in any one of the regimens; to determine whether the two drugs fludarabine and chlorambucil are non-resistant by a crossover design for patients failing to respond to the initial single agent.

## TECHNICAL APPROACH

Randomized study for eligible CLL patients comparing the new drug fludarabine with the standard treatment of chlorambucil, or with the two drugs given in combination. Length of treatment depends on patient's response, with the maximum treatment being 2 years. Fludarabine is given intravenously for 5 days every 28 days. Chlorambucil is given by mouth for 1 day every 28 days. On 02 May 94, an addendum closed the third arm of the study. In September 1994, the consent form was revised to include new toxicity data and add new subjects.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of four WRAMC patients were entered on this protocol before it was closed to accrual in December of 1994. No WRAMC patients have withdrawn from the study, and two were removed from the study treatment due to drug toxicity. One serious adverse event was reported to the IRB in February 1995. Two WRAMC patients have died from their continuing disease and the remaining two continue in study follow-up. A total of 544 patients were entered on this study nationally meeting accrual goals.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 544, if multi-site study.

## CONCLUSIONS

No conclusions have been reached.

Report Date: 1 February 2002

Work Unit # 1509-98

# DETAIL SUMMARY SHEET

TITLE: CALGB 9793: A Phase III Trial of CHOP vs. CHOP and Chimeric Anti-CD 20 Monoclonal Antibody (IDEC-C2B8) in Older Patients with Diffuse Mixed, Diffuse Large Cell and Immunoblastic Large Cell History Non-Hodgkin's Lymphoma

KEYWORDS: Lymphoma, elderly, Monoclonal Antibody Maintenance

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 31 March 1998

## STUDY OBJECTIVE

To compare CHOP treatment with or without chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in elderly patients with diffuse mixed, diffuse large cell, and immunoblastic large cell non-Hodgkin's lymphoma of B lineage with respect to response rate, the time to treatment failure, toxicity and survival. To compare the IDEC-C2B8 monoclonal antibody as maintenance therapy to observation alone after CHOP chemotherapy with respect to time to treatment failure, duration of response, toxicity and survival after an initial response to induction therapy of CHOP + IDEC C2B8. To determine if maintenance therapy with IDEC-C2B8 results in the conversion of any partial responses to a complete response.

## TECHNICAL APPROACH

All eligible patients will be randomized to receive CHOP chemotherapy with or without Anti-CD20 therapy. Therapy will be given every 21 days for a minimum of 6 cycles and maximum of 8 cycles depending upon response. Patients who achieve a complete response after 4 cycles will subsequently be randomized the second time to receive either anti-CD20 maintenance therapy or observation. Patients who achieve a partial response after 6 cycles will receive 2 additional cycles and then the same subsequent randomization. Patients who have no change in tumor measurements from cycle 4 to 6 and are in partial remission will then be randomized to maintenance therapy or observation. Patients with either stable disease, or progressive disease will be taken off study treatment and not further randomized.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No WRAMC patients have been entered on this protocol since it was approved in March of 1998. No unexpected adverse events have been reported. National accrual to the study as of June 2001 was 562. Target accrual was for 630 patients. This protocol is permanently closed at WRAMC per notice received on 17 July 2001.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

## CONCLUSIONS

No conclusions have been reached.

Report Date: 20 February 2002 Work Unit #1510-98

# DETAIL SUMMARY SHEET

TITLE: CALGB 9712: A Randomized Phase II Study of Concurrent Fludarabine+Chimeric Anti-CD 20 Monoclonal Antibody IDEC-C2B8 (Rituximab) [NSC #6887451] Induction/Consolidation vs. Fludarabine Induction/Rituximab Consolidation

KEYWORDS: Fludarabine, Rituximab, Phase II

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 28 April 1998

STUDY OBJECTIVE
1) To determine in Fludarabine treated CLL patients the complete response (CR) rate and toxicity profile of concurrent and consolidative IDEC-C2138 (arm I) and of consolidative IDEC-C2D8 therapy (arm II).
2) To assess the CR rate in patients receiving concurrent therapy with IDEC-C2B8 and Fludarabine (the induction phase of arm I).

TECHNICAL APPROACH
Eligible CLL patients will be randomly assigned to Arm I -- Fludarabine plus Rituximab induction followed by Rituximab consolidation therapy, or to Arm II -- Fludarabine induction (standard therapy) followed by Rituximab consolidation therapy. Induction therapy will last six months followed by a monitoring phase of twelve weeks. If appropriate, patients with CR, partial response, or stable disease will receive four weeks of consolidation therapy. Patients will receive prophylactic allopurinal for the first fifteen days of treatment. Patients will be entered on CALGB 9665-tissue bank companion study.

PRIOR AND CURRENT PROGRESS
This study was closed to accrual 31 January 2000. A total of eleven accruals were through WRAMC (nine from WRAMC and two from NNMC. One patient died of progressive disease. This death was reported to the IRB through an adverse events report and in last years APR. No additional adverse events have been identified during the past year. All WRAMC patients remain in study follow-up. National accrual, as previously reported, is 104 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 11. The total number enrolled study-wide is 104.

CONCLUSIONS
No conclusions have been reached. Study analysis in ongoing.

Report Date: 31 May 2002

Work Unit # 1512-98

# DETAIL SUMMARY SHEET

TITLE: CALGB 9732: A Randomized Phase III Study Comparing Etoposide and Cisplatin with Etoposide, Cisplatin and Paclitaxel in Patients with Extensive Small Cell Lung Cancer

KEYWORDS: phase III, small cell lung cancer, extensive

PRINCIPAL INVESTIGATOR: Joseph Drabick, COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 28 July 1998

STUDY OBJECTIVE:
To determine whether the addition of paclitaxel to standard chemotherapy treatment (etoposide/cisplatin) improves the survival of patients with extensive SCLC.
To compare tumor response rate and failure-free survival of patients in these two treatments groups.
To describe and compare the toxicities of patients in these two treatment groups.

TECHNICAL APPROACH
Eligible patients with extensive SCLC will be randomized to 1) standard chemotherapy: etoposide/cisplatin IV as 3 day treatment q 21 days for a total of 6 treatments, or to 2) standard chemotherapy as above with IV paclitaxel in addition on day one of each treatment. Treatment will be in Hematology-Oncology clinic.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
One WRAMC patient was entered on this protocol and has died during last year's APR reporting period. No other unexpected adverse reaction has been reported. The final national accrual to the study is 587 patients, with 198 in this reporting period.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 587, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 26 August 2002 Work Unit # 1514-99

# DETAIL SUMMARY SHEET

TITLE: CALGB 39801 Concurrent Carboplatin, Paclitaxel, and Radiation Therapy Verses Induction Carboplatin and Paclitaxel Followed by Concurrent Carboplatin, Paclitaxel, and Radiation Therapy for Patients with Unresectable Non Small Cell Lung Cancer. A Phase III Trial

KEYWORDS: non small cell lung cancer, unresectable, chemoradiotherapy

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 27 October 1998

STUDY OBJECTIVE
To determine whether the addition of two cycles of induction chemotherapy with carboplatin and paclitaxel to concomitant chemoradiotherapy utilizing carboplatin and paclitaxel leads to an increase in overall response rate, failure-free survival, and survival. To assess the pattern of failure on both treatment arms (loco-regional vs. distant failure). To assess the toxicity on both treatment arms.

TECHNICAL APPROACH
All eligible patients will be randomized to one of two treatments: 1) Chemotherapy with paclitaxel and carboplatin once a week combined with radiation therapy to the chest 5 days per week for a total of 7 weeks, or 2) chemotherapy with paclitaxel and carboplatin, once every 3 weeks for 6 weeks followed by carboplatin and paclitaxel once per week combined with radiation therapy to the chest 5 days per week for 7 weeks. Update # 1, 15 March 1999, containing editorial changes was submitted to DCI 21 April 1999.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 349, if multi-site study. Grade 4 toxicities include 1 allergy/immunology, 36 blood/bone marrow, 12 leukocytes, 23 lymphopenia, 1 transfusion – platelets, 1 supraventricular arrhythmias, 1 hypotension, 2 pericardial effusion/pericardi, 1 cardiac-ischemia/infarction, 3 thrombosis/embolism, 7 fatigue (lethargy/malaise), 1 alopecia, 1 radiation dermatitis, 11 anorexia, 10 dysphagia-esophageal related, 1 hemorrhage, 1 hemorrhage/bleeding w/grade, 2 febrile neutropenia, 1 hyponatremia, 1 hypokalemia, 1 depressed level of consciousness, 1 pleuritic pain, 1 arthralgia, 8 dyspnea, 1 hiccoughs, 1 pulmonary fibrosis, 5 pneumonitis/pulmonary infiltrate, 1 adult respiratory distress, 1 hypoxia, and 1 pneumothorax. Grade 5 toxicities include 1 hemorrhage, 1 pneumonitis/pulmonary infiltrate, and 1 pulmonary-other. This study closed to accrual effective 31 May 2002.

Ref: June 2002 CALGB Statistical Report

CONCLUSIONS
Too early.

Report Date: 5 October 2001 Work Unit # 1515-99

# DETAIL SUMMARY SHEET

TITLE: CALGB 19805 A Phase II Study of Flavopiridol (NSC # 649890) in Patients With Fludarabine Refractory B-Cell Chronic Lymphocytic Leukemia

KEYWORDS: Chronic Leukemia, refractory, investigational

PRINCIPAL INVESTIGATOR: Joseph Drabick, COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology Oncology Service INITIAL APPROVAL DATE: 24 November 1998

## STUDY OBJECTIVE

To determine the complete response rate, partial response rate, and toxicity profile to flavopiridol therapy in patients with fludarabine refractory Chronic Lymphocytic Leukemia. To determine the effects of flavopiridol on normal t-cell subsets and immunoglobulin levels in these patients.

## TECHNICAL APPROACH

All eligible patients will receive flavopiridol by a continuous intravenous infusion for 3 days, repeated every two weeks for a maximum of 12 cycles (approximately 6 months). The first cycle will be given in the hospital and subsequent cycles as an out-patient utilizing an ambulatory infusion pump. Disease reevaluation will be done at the end of 4 and 8 cycles, as well as at completion of therapy. Blood and bone marrow samples will be collected prior to any therapy and submitted to CALGB Leukemia Tissue Bank.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Seven WRAMC patients have been entered on this protocol, six in this reporting period. One of these patients has died. The remaining six patients continue in study follow-up. Seven adverse events have been reported to the HUC during this reporting period. National accrual to the study at last report was 33 patients with 23 in this reporting period. Target accrual is for 53 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 6. The total enrolled to date at WRAMC is 7. The total number enrolled study-wide is 33, if multi-site study.

## CONCLUSIONS

No conclusions have been reached.

Report Date: 27 August 2002

Work Unit # 1516-84

# DETAIL SUMMARY SHEET

TITLE: CALGB 8364: Immunological Diagnostic Studies in Adult ALL

KEYWORDS: immunology, lymphocyte, leukemia

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 October 1983

STUDY OBJECTIVE
To determine the incidence of various monoclonal antibodies' cytochemical and conventional lymphoid markers in adult acute lymphatic leukemia (ALL). To correlate the presence of the various markers with the initial and subsequent clinical characteristics of the disease, response rate, and response duration. To determine if marker status changes at relapse.

TECHNICAL APPROACH
This is a non-randomized study in which all eligible patients being entered on the ALL treatment protocol agree to allow, prior to the initiation of therapy, the submission of six air-dried unstained bone marrow smears for confirmatory cytochemical studies and 2 cc of bone marrow aspirate, along with 7 cc of peripheral blood to a designated CALGB reference laboratory. The same set of samples is again obtained at relapse.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been no publications reporting data from this study.

The number of subjects enrolled to the study since last APR at WRAMC is 1 and the total enrolled to date at WRAMC is 34. The total number enrolled study-wide is 953, if multi-site study. No grade 4 toxicities reported. This study was closed to accrual effective 15 April 1999.

Ref: CALGB Statistical Report

CONCLUSIONS
Too early. Interim analysis continues on the value of immunophenotype in ALL.

Report Date: 5 October 2001 Work Unit # 1516-99

# DETAIL SUMMARY SHEET

TITLE: CALGB 19801: A Phase II Study of 506U78 in Patients With Refractory or Relapsed T-lineage Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (LBL)

KEYWORDS: refractory disease, investigational therapy, leukemia/lymphoma

PRINCIPAL INVESTIGATOR: Joseph Drabick, COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 24 November 1998

## STUDY OBJECTIVE

To determine the complete and partial remission rates, as well as the remission duration, in patients with refractory or relapsed T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma receiving 506U78 (1.5 gram/m2/day) on an alternate day schedule (days 1,3,5). To determine the safety and toxicity associated with 506U78 administered on this schedule.

## TECHNICAL APPROACH

All eligible patients will receive the investigational drug 506U78 intravenously over 2 hours on days 1,3, and 5. Their disease will be reevaluated after 21 days. If not in remission, an identical course of treatment will be given. When remission occurs, consolidation therapy will be given. Two additional courses of the same therapy will be given as consolidation. Patients who achieve a complete response would then be candidates to receive a stem cell transplant. Those patients would be removed from this study, at that time, for transplant.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One WRAMC patient has been entered on this study in this reporting period. No adverse reactions have been reported by the CALGB. The study was closed to accrual 12 September 2001 because the accrual goal of 35 patients had been reached. Two minor editorial and administrative changes were made during this reporting period.

The number of subjects enrolled to the study since last APR at WRAMC is 1. The total enrolled to date at WRAMC is 1. The total enrolled study-wide is 35, if multi-site study.

## CONCLUSIONS

No conclusions have been made.

Report Date: 5 October 2001 Work Unit # 1517-99

# DETAIL SUMMARY SHEET

TITLE: CALGB 119801 Telephone Monitoring: Early Identification of Psychological Distress In Cancer Patients 65 or More Years Old During Active Treatment

KEYWORDS: advanced cancer, psychosocial, telephone interview

PRINCIPAL INVESTIGATOR: Joseph Drabick, COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 24 November 1998

## STUDY OBJECTIVE

To test whether telephone monitoring plus educational materials can reduce elderly cancer patient's psychological distress significantly more than the receipt of educational materials alone, through early identification of psychological problem and referral to treatment. To develop psychosocial profiles of older patients with advanced cancer who show the highest and lowest levels of psychological distress in, terms: of medical, psychosocial, and sociodemographic characteristics.

## TECHNICAL APPROACH

All eligible patients will be randomized to one of two groups. 1) Educational Materials Group: This group will be given educational materials that provide information about emotional problems which cancer patients may have and various agencies or services that are available to them. They will also be contacted by phone, by a trained psycho-oncology interviewer, three times during one year to discuss emotional and social issues. 2) Telephone Monitoring Group: This group, in addition to the educational materials, will receive a phone call from the psycho-oncology interviewer once a month for six months. The calls will last approximately 15 minutes each. Questions will ask about mood, social life issues, and physical problems. If problems are identified, follow up will be done by a WRAMC Oncology nurse, physician, social service, or psychologist, depending upon the needs. A written questionnaire will be sent prior to the phone call describing the questions that will be asked.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Eleven WRAMC patients have been enrolled on this study. Seven have been enrolled in this reporting period. No patient has withdrawn. No serious adverse events have been reported. Seven patients have died from their progressive disease. The Notice of Death has been sent to the IRB via the adverse event reporting on their treatment studies. DCI/IRB were notified via an Adverse Event Report with the CALGB Notice of Death form attached for the treatment studies the patients were on as follows: CALGB 9583 (one patient) and CALGB 9344 (one patient). National accrual to protocol is 131 patients, 51 in this reporting period. Projected national accrual is for 182 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 7 and the total enrolled to date at WRAMC is 11. The total number enrolled study-wide is 131, if multi-site study.

## CONCLUSIONS

No conclusions have been reached.

Report Date: 7 November 2001 Work Unit # 1518-99

# DETAIL SUMMARY SHEET

TITLE: CALGB 9865: Tumor Replication Error (RER) Status and Outcome In A Colon Cancer Adjuvant Chemotherapy Trial

KEYWORDS: Tissue block, Dukes C Stage, Mutations

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 15 December 1998

STUDY OBJECTIVE
To determine the relationship between disease free survival, overall survival, and tumor replication error (RER) status for individuals who have received adjuvant chemotherapy for colon cancer. To develop a database to study the relationship between family history, tumor RER status, and treatment outcome for individuals who have received adjuvant chemotherapy for colon cancer.

TECHNICAL APPROACH
Phase I – All patients who were enrolled on CALGB 8896 for Dukes C Colon Cancer who have tissue blocks available will have two tissue blocks submitted for RER analysis (one with tumor, one with normal tissue). This will include patients who are deceased. The CALGB Pathology Coordinating office will submit a list to the institution of potentially eligible cases for Phase II. This phase involves obtaining consent for completion of a family questionnaire. For deceased patients, a chart review may be obtained and data collected to correlate treatment outcome, disease relapse and survival. The institution or the patient will not receive the results of the RER analysis.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Tissue blocks from two WRAMC patients have been entered on this study since it was opened to accrual in August 1998. No WRAMC patient has withdrawn from this study, and no unexpected adverse event has been reported. National accrual to study is 206 patients with 34 in this reporting period. Projected accrual is for 350 patients. Minor revisions were made to the protocol during this reporting period.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 206, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 1 February 2002 Work Unit # 1519

# DETAIL SUMMARY SHEET

TITLE: CALGB 9192: Comparison of Chemotherapy vs. Chemohormonotherapy in Premenopausal Women with Stage II Receptor-Positive Breast Cancer

KEYWORDS: breast cancer, node-positive, receptor-positive

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 26 March 1991

## STUDY OBJECTIVE

To compare the recurrence rates, disease-free intervals and hormone receptor-positive survival for premenopausal women with lymph node-positive breast cancer given adjuvant therapy with cytoxan, Adriamycin, and 5-fluorouracil (CAF) chemotherapy alone, or chemotherapy followed by zoladex, or chemotherapy followed by zoladex and tamoxifen. To compare the relative toxicities of these three regimens and to assess their effect on blood hormone levels.

## TECHNICAL APPROACH

All eligible patients will receive a 6-month course (six cycles) of standard CAF therapy. Initially, they will be randomized to receive an additional 5 years of zoladex, receive an additional 5 years of zoladex and tamoxifen, or end therapy following CAF.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of 13 WRAMC patients were entered on this protocol before it was closed to accrual in February 1994. A total of five deaths were incorrectly reported in the last accounting period. The actual total of deaths is four patients who have died of their disease; the remaining nine continue in study follow-up. No WRAMC patients withdrew from this study. No unexpected adverse events have been reported. Total national accrual to this study was 1330 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 13. The total number enrolled study-wide is 1330, if multi-site study.

## CONCLUSIONS

Analysis is ongoing. No conclusions have been reached.

Report Date: 7 November 2001 Work Unit # 1519-99

# DETAIL SUMMARY SHEET

TITLE: CALGB 9840: A Phase III Study of Paclitaxel Via Weekly 1 Hour Infusion Versus Standard 3 Hour Infusion Every 3 Weeks with Herceptin (Trastuzumab) (NSC #688097) in the Treatment of Patients with/without HER-2/NEU-Overexpressing Metastatic Breast Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 15 December 1998

STUDY OBJECTIVE
To determine if "dose dense" treatment with paclitaxel via weekly 1-hour infusion significantly improves the response rate as compared to "standard" paclitaxel treatment for metastatic breast cancer. To evaluate the time to progression and survival of patients with metastatic breast cancer treated with either "dose dense" or "standard" paclitaxel.

TECHNICAL APPROACH
Patients will be randomized to receive either paclitaxel, 175mg/m2 over 3 hours every 3 weeks or to paclitaxel 100mg/m2 over 1 hour every week for the first 6 weeks with subsequent infusions of paclitaxel at 80mg/m2 over 1 hour. Both regimens will be given until development of progressive disease, major toxicity, or patient withdraws consent. Follow-up will be done until progression, initiation of non-protocol therapy, or death, whichever occurs first.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Five WRAMC patients have been entered on this study since its approval 15 December 1998 (three in this reporting period). Two adverse events have occurred during this reporting period; one patient has died and one patient experienced a GI bleed. These were reported to the WRAMC HUC. National accrual to the study is 293 patients with 132 in this reporting period. The new projected accrual is for 580 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 3 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is 293, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 31 August 2001 Work Unit # 1520-99

# DETAIL SUMMARY SHEET

TITLE: CALGB 9863: Phase I Study of Irmotecan (CPT- 11) in Patients with Abnormal Liver or Renal Function or with Prior Pelvic Radiation Therapy.

KEYWORDS: Phase I, Organ dysfunction, Irmotecan

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 23 February 1999

STUDY OBJECTIVE
To determine a tolerable dose of irmotecan to use in patients with ranging degrees of liver or renal dysfunction or prior pelvic radiation. To characterize the pharmacokinetics of irmotecan in patients with hepatic or renal dysfunction or prior pelvic radiation therapy.

TECHNICAL APPROACH
All eligible patients will receive a specified dose of irinotecan, determined at the time of registration, as a 90-minute infusion every 3 weeks times 4 doses. During the first treatment a total of 14 blood samples will be drawn at specific times to measure the amount of drug in the blood stream. Urine samples will be collected for the first 24 hours also. All samples will be frozen and shipped to the reference lab when all have been collected. All patients will be reevaluated after the 4 doses for response.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Two WRAMC patients have been entered on this study, one during this reporting period (January 2001). Both patients have died of their progressive disease. No unexpected adverse reactions have been reported. National accrual to the study as of June 2001 was 34 patients. The projected accrual was for 75 patients. This protocol is permanently closed at WRAMC per notice received on 17 July 2001.

CONCLUSIONS
No conclusions have been reached.

Report Date: 20 February 2002

Work Unit #1521-91

# DETAIL SUMMARY SHEET

TITLE: CALGB 9194: Comparison of Adjuvant Chemotherapy with Concurrent or Delayed Tamoxifen vs. Tamoxifen Alone in Postmenopausal Patients with Receptor Positive Stage II Breast Cancer

KEYWORDS: postmenopausal, lymph node positive, receptor positive

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 30 April 1991

## STUDY OBJECTIVE

To compare disease-free survival and overall survival of postmenopausal primary breast cancer patients with involved axillary nodes and positive estrogen and/or progesterone receptors treated with standard adjuvant therapy with long-term tamoxifen, or with chemo endocrine therapy with combined cytoxan, Adriamycin, and 5-fluorouracil (CAF) followed by long-term tamoxifen, or with concurrent chemo endocrine therapy with tamoxifen and CAF.

## TECHNICAL APPROACH

For 5 years, six courses of CAF followed by tamoxifen for 5 years, or six courses of CAF with concurrent tamoxifen for 5 years. Four addenda to this study were sent to the IRB and approved in the past year.

## PRIOR AND CURRENT PROGRESS

This study was closed to accrual in August 1995. In total, three patients from WRAMC had been entered on this study. One patient died of progressive disease. This death was reported to the IRB 14 September 1997. The other two patients from WRAMC have completed five years of Tamoxifen without adverse reactions. They continue in follow-up. Neither patient has developed recurrent disease. No unexpected adverse events were reported group-wide since the last APR.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is 1,539.

## CONCLUSIONS

No conclusions have been reached. Analysis in ongoing.

Report Date: 25 July 2002 Work Unit # 1522-84

# DETAIL SUMMARY SHEET

TITLE: CALGB 8461: Cytogenic Studies in Acute Leukemia: A Companion Study to CALGB 8011, 8323, 8321, and 8411

KEYWORDS: cytogenics, acute leukemia

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 25 September 1984

## STUDY OBJECTIVE

To determine the incidence of specific chromosome abnormalities in adult acute non-lymphatic leukemia (ANLL) and acute lymphatic leukemia (ALL).

## TECHNICAL APPROACH

All eligible patients are registered to this companion to treatment protocols. A specimen of marrow and blood is obtained at diagnosis and again at relapse.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's review last year, there have been no publications reporting data on this study. The number of subjects enrolled to the study since last APR at WRAMC is 1 and the total enrolled to date at WRAMC is 104. The total number enrolled study-wide is 4817, if multi-site study. No grade 4 toxicities reported.

Ref: CALGB Statistical Report June 2002

## CONCLUSIONS

Too early.

Report Date: 27 August 2002 Work Unit # 1523-91

# DETAIL SUMMARY SHEET

TITLE: CALGB 9111: A Trial of G-CSF vs. Placebo During Remission Induction and Consolidation Chemotherapy for Adult Acute Lymphatic Leukemia

KEYWORDS: adult acute leukemia, G-CSF

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 October 1991

## STUDY OBJECTIVE

To: 1) compare time to bone marrow recovery, infection incidence, days of hospitalization, and tolerance of non-hematopoietic organs after intensive chemotherapy for acute lymphatic leukemia (ALL) in patients given either granulocyte colony-stimulating factor (G-CSF) or placebo; 2) determine the effect of G-CSF on CR rate and duration and mortality (during neutropenia) during intensive induction and intensification; and 3) compare doses that can be given to G-CSF vs. placebo patients.

## TECHNICAL APPROACH

Eligible patients will be randomly assigned to receive subcutaneous injections of either G-CSF or placebo starting 3 days after initial chemotherapy. Injections will continue until the WBC count is normal. The pharmacist will be the only one who knows what the patients will be receiving. The study will remain blinded until after the first month. After being unblinded, patients who received G-CSF will continue to receive it during the next course of therapy. Those who did not receive it will not receive any further placebo or G-CSF. Patients will receive a series of five different cancer treatments in sequence; each uses combination chemotherapy, and one involves radiation. Total treatment time is 24 months.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There has been one manuscript published on this study.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 8. The total number enrolled study-wide is 198, if multi-site study. There was an adverse event reported 7 July 1993 and 16 September 1996. Grade 4 toxicities include 238 WBC, 199 platelets, 57 Hgb, 231 grans/bands, 174 lymphocytes, 3 hemorrhage, 12 infection, 37 bilirubin, 3 transaminase, 2 ALK Phos, 1 liver, 1 creatinine, 2 renal, 7 hypotension, 1 amylase, 7 hyperglycemia, 8 hypocalcemia, and 12 fibrinogen. Grade 5 toxicities include 1 hemorrhage, 2 infections, 1 renal, and 1 hypotension. This study was closed to accrual effective 30 July 1993 – met accrual goal and W.U. # 9311 would soon be open.

## CONCLUSIONS

This study has shown that treatment with G-CSF is effective during induction chemotherapy for ALL. Other results are still undergoing analysis.

Report Date: 03 May 2002 Work Unit # 1523-99

# DETAIL SUMMARY SHEET

TITLE: CALG13 9862 Molecular Genetic Features of Acute Lymphoblastic Leukemia

KEYWORDS:

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 22 June 1999

STUDY OBJECTIVE
To use PCR analysis to identify patients with p190 and p210 BCR-ABL positive ALL and to evaluate the clinical significance of these fusion transcripts measured at time of diagnosis. To evaluate the clinical significance of MDR as defined by BCR-ABL fusion transcripts in patients who have achieved a complete response, using both qualitative RT-PCR and quantitative (Real Time) PCR in sequential samples of both blood and bone marrow. To compare blood with bone marrow samples for the detection and quantitation of BCR-ABL transcripts in diagnosis and sequential remission samples. To pilot PCR detection and quantitation of WT-1 expression at diagnosis, remission, and at relapse in BCR-ABL positive and negative ALL, and to determine the impact of this marker on clinical outcome.

TECHNICAL APPROACH
All patients enrolled on the CALGB Leukemia treatment study (currently 19802) will be offered participation in this companion study. A total of 8 plus samples of blood and bone marrow will be collected and sent to the CALG13 Leukemia Tissue Bank in Columbus, Ohio. The number of samples is dependent upon response to therapy and if the disease returns after remission. The tests will only be drawn at a time when diagnostic blood and bone marrow samples would ordinarily be taken.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
No WRAMC patient has been entered on this protocol in this reporting period. There have been no serious adverse events reported and no WRAMC patient has withdrawn from this study. National accrual to the study is 108 patients. Projected national accrual is for 300 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 108, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 10 June 2002

Work Unit # 1524-99

# DETAIL SUMMARY SHEET

TITLE: CALGB 19802 Phase II Study in Adults with Untreated Lymphoblastic Leukemia Testing Increased Doses of Daunorubicin During Induction, and Cytarabine During Consolidation, Followed by High-Dose Methotrexate and Intrathecal Methotrexate in Place of Cranial Irradiation

KEYWORDS: ALL, Dose escalation, High-dose methotrexate

PRINCIPAL INVESTIGATOR: Joseph Drabick, COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 31 August 1999

STUDY OBJECTIVE:
To evaluate the complete response (CR) rate and toxicity in patients < 60 years of age when three days of daunorubicin are given at 60mg/m2/day in Module A and then, if tolerated, when doses of daunorubicin are escalated to 80 mg/m2/day. To evaluate CR rate and toxicity in patients > 60 years of age when three days of daunorubicin are given at 60 mg/m2/day during Module A without cyclophosphamide. To evaluate the toxicity of three days of cytarabine at 2000 mg/m2/day IV over three hours during post-remission therapy (Module B). To measure the CNS relapse rate of ALL when prophylactic intrathecal and high dose intravenous chemotherapy (Module C) replaces cranial irradiation. To target a specific serum methotrexate level at 30 hours following initiation of IV methotrexate infusion.

TECHNICAL APPROACH: All eligible patients who continue to show a response to therapy will receive a seven-course regimen of various chemotherapy agents. Doses of daunorubicin will be different for patients under 60 years than for patients over 60 years. During Course three, high doses of methotrexate will be given in place of standard cranial irradiation for CNS prophylaxis. Serum levels will be monitored to ensure adequate dosing. The seven-course therapy will take 24 months to complete. Post therapy monitoring will be done every 3-6 months for three years after treatment, then annually. Two additional companion studies are required for participation. These studies have separate consent forms but do require submission of blood and bone marrow samples for correlative science with response of the disease to therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE: Since this protocol's review one year ago, no publications reporting data from studies with similar study design. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 163. This study closed to accrual on 5 January 2001 after meeting its accrual goals. Grade 4 toxicities include 123 neutrophils/granulocytes, 21 leukocytes, 1 hemolysis, 23 hemoglobin, 6 lymphopenia, 108 platelets, 3 transfusions-platelets, 1 transfusion-pRBCs, 1 ventricular arrhythmia, 1 cardiac left ventricular, 6 hypotension, 4 edema, 1 DIC, 3 fibrinogen for leukemia, 2 fatigue, 1 endocrine-other, 8 anorexia, 3 dysphagia/esophagitis, 1 stomatitis/pharyngitis, 1 pancreatitis, 1 constipation, 1 vomiting, 1 CNS hemorrhage/bleeding with grade, 1 liver dysfunction/failure, 1 SGOT (AST), 2 SGPT (ALT), 6 bilirubin, 1 infection without neutropenia, 1 catheter-related infection, 2 febrile neutropenia, 16 infections, 5 hypocalcemia, 1 hyponatremia, 2 hyperkalemia, 1 hypokalemia, 2 hypermagnesemia, 4 acidosis, 1 alkalosis, 1 bicarbonate, 4 hyperglycemia, 1 arachnoiditis/meningismus, 1 leukoencephalopathy associated, 1 neuropathy-sensory, 1 neuropathy cranial, 6 dyspnea, 2 pleural effusion, 1 pneumonitis/pulmonary infiltra, 3 adult respiratory distress syn, 4 hypoxia, 2 creatinine, and 5 renal failure. Grade 5 toxicities include 1 CNS hemorrhage/bleeding, 1 hemorrhage/bleeding with grade, 1 febrile neutropenia, 8 infections, 1 neurologic-other, and 4 pulmonary-other. One adverse event reported for this study 21 November 2001. Ref: CALGB Statistical Report.

CONCLUSIONS Too early.

Report Date: 20 November 2001 Work Unit # 1526-92

# DETAIL SUMMARY SHEET

TITLE: CALGB 9140: A Phase III Study of CAF-Leucovorin vs. CAF for Visceral Crisis Breast Cancer

KEYWORDS: metastatic, breast cancer, leucovorin

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 02 January 1992

STUDY OBJECTIVE
To compare the response rates, duration of response, time to treatment failure, and survival of patients with metastatic breast cancer treated with cytoxan, Adriamycin, and 5-fluorouracil (CAF) versus patients treated with CAF plus leucovorin; and to compare with the toxicity experienced by the treatment groups.

TECHNICAL APPROACH
All eligible patients will be randomized to receive one of two treatment arms: (1) CAF every three weeks or (2) CAF and leucovorin every 21 days. The treatment may continue as long as one year.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of six WRAMC patients were entered on this protocol before it was closed to accrual in August 1995 having met the accrual goal of 240 patients. All six patients have died of their progressive disease. This protocol is now closed at WRAMC.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 6. The total number enrolled study-wide is 240, if multi-site study.

CONCLUSIONS
Analysis is in progress.

Report Date: 20 November 2001 Work Unit # 1527-92

# DETAIL SUMMARY SHEET

TITLE: CALGB 9190: A Trial of Postoperative Interferon in Resected High Risk Melanoma

KEYWORDS: high-dose interferon, low-dose interferon, observation

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 02 January 1992

## STUDY OBJECTIVE

To establish the efficacy of interferon alfa-2b as an adjuvant in increasing the disease-free survival and overall survival in patients at high risk for recurrence after definitive surgery for deep primary lesions or after regional lymph node recurrence.

## TECHNICAL APPROACH

Eligible patients are randomized to receive one of three treatment plans: (1) high-dose interferon for approximately 1 year, (2) low-dose interferon for approximately 2 years, or (3) observation-only frequent follow-up for 2 years, then annually. Those patients randomized to receive interferon will be trained to self-administer their subcutaneous injections at home.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Two WRAMC patients were entered on this study before it was closed to accrual in June 1995 having met its accrual goal with a national enrollment of 642 patients. Both patients continue in study follow-up. No WRAMC patients have withdrawn from the study, and no unexpected adverse events have been reported.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 642, if multi-site study.

## CONCLUSIONS

No conclusions have been reached.

Report Date: 20 November 2001 Work Unit # 1528-92

# DETAIL SUMMARY SHEET

TITLE: CALGB 9195: A Trial of Adjuvant Chemoradiation vs. Observation After Gastric Resection of Adenocarcinoma

KEYWORDS: post-gastrectomy, adjuvant therapy, observation

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 02 January 1992

## STUDY OBJECTIVE

To compare overall and disease-free survival between patients treated with gastrectomy only, and those treated with gastrectomy plus adjuvant therapy; to compare the incidence and patterns of disease failure between these two groups of patients; and to assess patient tolerance of upper abdominal chemoradiation after gastric resection.

## TECHNICAL APPROACH

Eligible patients will be randomized to receive either adjuvant chemoradiation, consisting of five courses of 5-fluorouracil and leucovorin plus one course of radiation, or to observation only. This arm would consist of close observation for symptoms of recurrence over a 2-year period, then annual follow-up thereafter.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Two WRAMC patients have been entered on this study before it was closed to accrual in July 1998 having met its accrual goal of 603 patients. The two patients remain in study follow-up. No unexpected adverse reactions have been reported. The final national accrual was 603 patients. No major changes to the protocol have been made to the protocol.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 603, if multi-site study.

## CONCLUSIONS

No conclusions have been reached.

Report Date: 5 October 2001

Work Unit # 1534-92

# DETAIL SUMMARY SHEET

TITLE: CALGB 9191: A Randomized Study of All-Trans Retinoic Acid vs. Standard Induction Therapy for Acute Promyelocytic Leukemia

KEYWORDS: induction, consolidation, crossover

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INTIAL APPROVAL DATE: 24 November 1992

## STUDY OBJECTIVE

To compare the complete remission rate and disease-free survival of trans retinoic acid (TRA) to that achieved with conventional induction chemotherapy, including Cytosine Arabinoside plus daunorubicin, in patients with previously untreated acute promyelocytic leukemia; to compare the toxicities of TRA to those of cytosine/daunorubicin as induction therapy; and to determine the value of maintenance therapy with TRA.

## TECHNICAL APPROACH

All eligible patients will be initially randomized to receive one of two induction treatments: 1) TRA orally for 45-90 days; or 2) standard chemotherapy with cytosine and daunorubicin for 7 days total. Once a complete response is achieved, consolidation therapy will be given for two courses with cytosine, one course being high dose. If the response remains, the patient is randomized again to receive either maintenance therapy with TRA or observation alone. If the leukemia returns after a response is achieved and the patient was randomized to TRA, they will crossover to receive the second therapy.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Two WRAMC patients were entered on this study before it was closed to accrual in February 1995 having met its accrual goal. Both WRAMC patients survive and continue in study follow-up. No WRAMC patients withdrew from the study, and no unexpected adverse reactions have been reported. Total national accrual to the study was 401 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 401, if multi-site study.

## CONCLUSIONS

No conclusions have been reached.

Report Date: 5 October 2001 Work Unit # 1535-92

# DETAIL SUMMARY SHEET

TITLE: CALGB 9222: A Randomized Study of Intensification Therapy for Patients under Age 60 with Acute Myelogenous Leukemia

KEYWORDS: post-remission, high-dose cytosine, sequential therapy

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 24 November 1992

STUDY OBJECTIVE
To compare two post-remission chemotherapy regimens: 1) intensification with single-agent high-dose cytosine arabinoside; and 2) three courses of sequential, potentially non-cross-resistant treatment. To confirm patient tolerance, and to continue to investigate the prognostic significance of cytogenetics and immunophenotyping in patients with acute myelogenous leukemia.

TECHNICAL APPROACH
All eligible patients will receive the same standard induction - up to two times if necessary – to achieve a complete response. Responders will then be randomized to receive either 1) six high doses of cytosine arabinoside repeated at 28-day intervals for a total of three courses, or 2) six sequential doses of high dose cytosine, followed by a second cycle of cyclophosphamide and etoposide, and then a third cycle of diaziquone and mitoxantrone with granulocyte colony-stimulating factor. Patients will then be followed for relapse or survival.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of 5 WRAMC patients were entered on this protocol before it were closed to accrual in December 1995 having met its accrual goal. Three of these have died of causes connected to their continuing disease. The remaining 2 patients continue in study follow-up. No WRAMC patients have withdrawn from the study. National accrual to this study was 474 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is 474, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 1 February 2002

Work Unit # 1541-93

# DETAIL SUMMARY SHEET

TITLE: CALGB 9153: A Trial of Cladribine in Advanced Stage, Low-Grade Non-Hodgkin's Lymphoma

KEYWORDS: low-grade, lymphoma, advanced

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 30 March 1993

## STUDY OBJECTIVE

To: 1) determine the percentage of patients with advanced, previously untreated, low-grade lymphomas who respond with complete or partial remissions to treatment with Cladribine, 2) estimate the duration of response for patients with partial and complete responses, and 3) describe the toxicity of Cladribine treatment in this population.

## TECHNICAL APPROACH

All eligible patients will be registered and will receive treatment with Cladribine intravenously as a 2-hour infusion for 5 consecutive days, every 28 days. A maximum of six cycles will be given. All patients will be reevaluated every two cycles for response.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Two WRAMC patients were entered on this protocol before it was closed to further accrual in December of 1993. No WRAMC patient has withdrawn from this study, and no unexpected adverse reactions were reported. Both WRAMC patients survive and continue to be followed for survival data only since both have had disease progression. Final national accrual to this study was 42 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 42, if multi-site study.

## CONCLUSIONS

Analysis showed this therapy to have a low level of antineoplastic activity. No conclusion has been reached.

Report Date: 20 November 2001 Work Unit # 1547-94

# DETAIL SUMMARY SHEET

TITLE: CALGB 9082 Trial Study of High-Dose CPA/CDDP/BCNU and ABMS as Consolidation to Adjuvant CAF for Patients With Operable Stage II or Stage III Breast Cancer Involving ≥ 10 Axillary Lymph Nodes

KEYWORDS: breast, autologous, bone marrow transplant

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 25 January 1994

STUDY OBJECTIVE
To determine if adjuvant chemotherapy [four CAF cycles then high-dose combination CPA/CDDP/BCNU with autologous bone marrow support (ABMS)] produces superior disease-free and overall survival compared to adjuvant chemotherapy (four CAF cycles than standard dose CPA/CDDP/BCNU) in patients with Stage II or III breast cancer in 10 or more lymph nodes. Both arms contain Tamoxifen and radiation therapy to chest walls. To compare toxicities experienced between the two programs.

TECHNICAL APPROACH
Patients entered into this study have pathologically-confirmed Stage II or IIIA breast cancer with >/= 10 lymph nodes involved. The patients are randomized to either of the two treatments. On a six-week schedule they are re-evaluated to determine response to the therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of 12 WRAMC patients were entered on this study before it was closed to accrual in May 1998. Four of these patients have died, and the remaining eight continue in study follow-up. No WRAMC patient withdrew from the protocol and no serious adverse events have occurred in this reporting period. Total national accrual to this protocol was 777 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 12. The total number enrolled study-wide is 777, if multi-site study.

CONCLUSIONS
Analysis is in progress.

Report Date: 20 November 2001

Work Unit # 1548-94

# DETAIL SUMMARY SHEET

TITLE: CALGB 9395: Phase III Intergroup Study Prospectively Randomized Trial of Perioperative 5-FU after Curative Resection, Followed by 5-FU/Leucovorin for Patients with Colon Cancer

KEYWORDS: colon cancer, chemotherapy, Dukes B3 or C

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 January 1994

## STUDY OBJECTIVE

To determine if adjuvant therapy with 1 week of 5-fluorouracil given continuously within 24 hours of a curative colon resection followed by 12 months of 5-FU/Levamisole is effective in prolonging disease-free interval and increasing survival in patients with Dukes' B3 or C colon cancer, when compared to patients who are treated with 5-FU/Levamisole only. Endpoints include treatment failure, as defined by recurrence of local/regional or distant metastasis, and survival.

## TECHNICAL APPROACH

All eligible patients will be randomized to receive or not receive 7 days of continuous 5-FU infusion starting within 24 hours of their curative surgery for colon cancer. Those patients found to have evidence of metastatic disease at the time of surgery will be removed from the study. Those patients who have pathologic classification of Dukes' B3 or C colon cancer will receive standard chemotherapy starting 35 days after their surgery; those with Dukes' B1 or 2 will be followed for evidence of recurrence. In December of this year, an addendum to the study was approved by the HUC to include CALGB 9667: Biologic Correlates to Response and Survival in Colon Cancer as a companion to this study; the consent form was modified to include this tissue block study.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Fifty-five WRAMC patients have been entered on this study before it was closed to accrual in May 2000. Thirteen of these patients have died, one within this reporting period. (Patient's death was not related to protocol therapy.) No WRAMC patients have withdrawn from the study. No modifications to the protocol have been made this year. National accrual was 854. Projected accrual was for 2000 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 55. The total number enrolled study-wide is 854, if multi-site study.

## CONCLUSIONS

Analysis is ongoing.

Report Date: 10 September 2001 Work Unit # 1551-94

# DETAIL SUMMARY SHEET

TITLE: CALGB 8869: Laboratory Studies in Breast Cancer Tissue

KEYWORDS: tissue blocks, aneuploidy, breast cancer

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 22 February 1994

## STUDY OBJECTIVE

To determine if aneuploidy provides independent prognostic information pertaining to recurrence rate of breast cancer and to explore the relationships between ploidy and clinical data regarding tumor grade and steroid receptors.

## TECHNICAL APPROACH

Paraffin tissue blocks from all patients registered to CALGB 8541 treatment protocol for Stage II breast cancer will be obtained and mailed to referenced pathology lab for subsequent review. This is a retrospective lab study and involves no risk to the patient. No consent form is required. WRAMC HUC approved update #6 on 16 January 96 to include tissue block samples from treatment studies CALGB 8642, 8741, and 8944 to those already being collected by this study.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of 57 paraffin blocks from eligible WRAMC patients have been collected and sent to referenced lab per protocol requirements, none in this reporting period. National accrual to the study is 1240 blocks as of 6/15/01. Notice was received from CALGB that the specimen acquisition goals had been met and effective 15 August 2001 was permanently closed to accrual.

## CONCLUSIONS

Analysis is ongoing.

Report Date: 20 February 2002

Work Unit # 1554-94

# DETAIL SUMMARY SHEET

TITLE: CALGB 9291: A Randomized Study of Subtotal Nodal Irradiation vs. Irradiation Plus Chemotherapy for Stages I-IIA Hodgkin's disease

KEYWORDS: radiation therapy, chemotherapy, early-stage disease

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL, MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 26 April 1994

## STUDY OBJECTIVE

To compare the progression-free and overall survival of non-laparotomized patients with clinical stage IA or IIEA Hodgkin's disease treated with subtotal nodal irradiation (3,600 – 4,000 cGy) alone to three cycles of doxorubicin and vinblastine plus subtotal nodal irradiation.

## TECHNICAL APPROACH

All eligible patients were randomized to receive one of two treatments. Treatment one was 8-9 weeks of daily (x5) radiation therapy. Treatment two was chemotherapy by vein with two drug, doxorubicin and vinblastine, over 5-10 minutes, every 14 days x 6 doses. The second group received radiation therapy in the same way that treatment one patients received it. All patients were asked to complete a quality-of-life evaluation form before treatment and an additional eight times. The questionnaire took approximately 20-45 minutes to complete. There was a change to the accrual goal, which was reported to the HUC in addendum #8 approved in October 1995.

## PRIOR AND CURRENT PROGRESS

Eight patients from WRAMC were entered on this study before it was closed to accrual in April 2000. No WRAMC patients have withdrawn from the study. All WRAMC patients completed study treatment without unexpected toxicity. No unexpected adverse events have occurred. All patients continue in routine follow-up and will continue completing a quality-of-life evaluation until 7 years post treatment. Actual national accrual was 348 patients at time of closure. Initially, the target accrual was 420 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and to total enrolled to date at WRAMC is 8. The total number enrolled study-wide is 348.

## CONCLUSIONS

The INTERGROUP study, coordinated by the Southwest Oncology Group (SWOG), was closed on the recommendation of the Southwest Oncology Group (SWOG) Data and Safety Monitoring Committee (DSMC) at the time of the second formal planned interim analysis, 4/2000. The SWOG DSMC identified that the relapse rate in the chemotherapy plus radiation therapy arm was lower that in the radiation therapy alone arm. However, overall survival was found to be about equal in either arm. WRAMC IRB was informed of these findings in June 2000. This study was published in JCO November 2001.

Report Date: 03 May 2002 Work Unit # 1557-94

# DETAIL SUMMARY SHEET

TITLE: CALGB 9344: Adjuvant High-Dose vs. Standard-Dose Cyclophosphamide, Adriamycin with/without Taxol for Node-Positive Breast Cancer

KEYWORDS: breast cancer, node positive, adjuvant

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 28 June 1994

STUDY OBJECTIVE
To determine whether higher doses of doxorubicin used as an adjuvant with cyclophosphamide in patients with early breast cancer will increase disease-free survival and overall survival. To determine whether the use of taxol as single agent after the completion of four cycles of cyclophosphamide and doxorubicin in combination will further improve disease-free and overall survival compared to the two previous drugs alone.

TECHNICAL APPROACH
All eligible patients will be randomized to one of six treatments: 1) standard dose cyclophosphamide with high-dose doxorubicin followed by taxol; 2) same two initial drugs without taxol; 3) standard cyclophosphamide with moderate dose doxorubicin with taxol afterwards; 4) same two initial drugs without taxol; 5) standard doses of cyclophosphamide and doxorubicin with taxol afterwards; or 6) standard doses without taxol. If taxol is given, there will be four courses. Tamoxifen will be given afterwards to receptor positives. The consent was recently revised to include new findings on leukemia risk with high-dose therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Sixteen patients were entered on this study from WRAMC before it was closed to accrual on 15 April 1997. Of the patients enrolled at WRAMC, three have died of their progressive disease. The remaining thirteen patients continue to be followed by the study. Final national accrual was 3170.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 16. The total number enrolled study-wide is 3170, if multi-site study.

CONCLUSIONS
Analysis continues.

Report Date: 10 June 2002 Work Unit # 1558-94

# DETAIL SUMMARY SHEET

TITLE: CALGB 9394: A Phase III Comparison of Two Schedules of Cyclophosphamide and Doxorubicin for High-Risk Patients with Breast Cancer Involving 0-3 Axillary Lymph Nodes

KEYWORDS: primary breast cancer, high-risk, 0-3 positive nodes

PRINCIPAL INVESTIGATOR: Joseph Drabick, COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 30 August 1994

STUDY OBJECTIVE
To compare disease-free survival, overall survival, and toxicity of high-risk primary breast cancer patients with 0-3 positive axillary lymph nodes treated with adjuvant high-dose chemotherapy with doxorubicin plus cyclophosphamide (AC) or high-dose sequential chemotherapy with doxorubicin followed by cyclophosphamide (AC).

TECHNICAL APPROACH
All eligible patients will be randomized to one of the two treatment arms as described above. Treatment I will consist of both drugs every 3 weeks times 6 cycles. Treatment II will consist of 4 cycles of doxorubicin at 21-day intervals followed by 3 cycles of cyclophosphamide at 14-day intervals. All post-menopausal and hormone receptor-positive women will then receive Tamoxifen for five years following completion of the chemotherapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been no publications reporting data on this study or any other with similar design.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 7. The total number enrolled study-wide is 3,000, if multi-site study. This study closed to accrual effective 1 May 1997, and met accrual goal.

Grade 4 toxicities included 74 anemia, 2 anxiety/depression, 1 bilirubin increase, 4 cardiac-EF/CHF, 3 cardiac-dysrhythmia, 1 cardiac-other, 2 convulsions, 16 diarrhea, 4 dyspnea, 2 edema, 2 fever without infection, 1 GI, 1 gastritis/ulcer, 705 granulocytopenia, 5 hematologic-other, 1 hemorrhagic cystitis, 1 hypokalemia, 2 hypotension, 4 infection, 732 leukopenia, 355 lymphopenia, 1 mucositis-other, 1 pharynx/esophagitis, 3 phlebitis/thrombosis/embolism, 1 pneumonitis/effusions/infiltrate, 1 renal failure, 1 respiratory infection, 1 skin rash/urticaria, 1 stomatitis, 141 thrombocytopenia, 1 transaminase (SGOT, SGPT), 1 vaginal bleeding, 96 vomiting, and 4 miscellaneous-other. Grade 5 toxicities include 1 infection and 1 miscellaneous-other.

Adverse event memos sent 9 June 1997 and 18 June 1999.
Ref: CALGB Statistical Report

CONCLUSIONS
Analysis is in progress.

Report Date: 03 May 2002 Work Unit # 1560-87

# DETAIL SUMMARY SHEET

TITLE: CALGB 8642: A Master Protocol to Study Single-Agent Chemotherapy vs. Standard Chemotherapy for Advanced Breast Cancer

KEYWORDS: chemotherapy, cancer, breast

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 30 June 1987

STUDY OBJECTIVE
To evaluate ability of single Phase II agents to achieve responses in previously untreated metastatic breast cancer patients.

TECHNICAL APPROACH
Randomized study in which all eligible patients receive standard cytoxan, Adriamycin and 5-fluorouracil (CAF) therapy, or a Phase II agent. Those randomized to receive a Phase II agent are treated for two cycles and then reevaluated for response or progression. If progression occurs, they are switched to CAF therapy. The next Phase II drug treatment arm, using alsamitrucin, was approved by the CALGB June 1992 for limited institutions.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 18. The total number enrolled study-wide is 365, if multi-site study.

CONCLUSIONS
The following has been reported to the IRB: This study concluded that in previously untreated metastatic breast cancer patients, the limited use of a single phase II agent prior to treatment within initial standard drugs does not result in any significant increased toxicity, decreased overall response rate, or shortened survival.

Report Date: 25 July 2002

Work Unit # 1559-94

# DETAIL SUMMARY SHEET

TITLE: CALGB 9351: A Phase II Study of High-Dose Chemotherapy in Previously Untreated Non-Hodgkin's Lymphoma

KEYWORDS: aggressive disease, high-dose CHOP

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 September 1994

STUDY OBJECTIVE

To: 1) estimate the overall response rate and determine whether dose-intensified CHOP (high-dose CHOP) chemotherapy with G-CSF can be administered with acceptable toxicity to low intermediate-, high intermediate-, and high-risk patients; and 2) determine whether it is possible to identify with early restaging gallium scans a subset of patients who are less likely to achieve a durable complete response.

TECHNICAL APPROACH

All eligible patients will receive chemotherapy with high doses of cyclophosphamide and doxorubicin and standard doses of vincristine and prednisone. Four cycles will be given at three-week intervals for a total treatment time of three months. G-CSF and an oral antibiotic will be given prophylactically for 14 days after each treatment. The first three days of treatment will be in the hospital; the remainder will be done as an outpatient.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been no reported publications for this study since last APR.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 99, if multi-site study. Grade 4 toxicities include 70 WBC, 65 platelets, 12 hemoglobin, 68 granulocytes/bands, 65 lymphocytes, 1 other hematologic, 1 hemorrhage, 2 infection, 2 diarrhea, 2 stomatitis, 1 esophagitis/dysphagia, 1 anorexia, 3 bilirubin, 1 other liver, 6 hematuria, 1 hemorrhagic cystitis, 3 dyspnea, 2 PO2/PCO2, 1 Ards, 1 dysrhythmia, 1 pain, 2 skin, 1 local, 1 hyperglycemia, 2 hyponatremia, and 1 hypokalemia. Grade 5 toxicity includes 1 other miscellaneous. This study was closed to accrual effective 31 July 1996.

Ref: CALGB Statistical Report

CONCLUSIONS

Too early.

Report Date: 27 August 2002 Work Unit # 1560-95

# DETAIL SUMMARY SHEET

TITLE: CALGB 9491: An Intergroup Study of Rectal Cancer Adjuvant Therapy, Phase III

KEYWORDS: 5-Fluorouracil bolus, prolonged infusion, pelvic radiation

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 October 1994

STUDY OBJECTIVE
To compare the effectiveness of 5-FU by bolus injection vs. 5-FU by prolonged infusion given prior to and following combined pelvic radiation therapy plus protracted venous infusion vs. 5-FU by bolus injection plus leucovorin plus levamisole given prior to and following combined pelvic radiation plus bolus 5-FU plus leucovorin in the treatment of stage B2, B3, and C rectal cancer.

TECHNICAL APPROACH
All eligible patients will be randomized to receive one of three treatments: 1) 5-FU bolus for 5 consecutive days, repeated in 4 weeks; 2) continuous 5-FU for 6 weeks intravenously through a portable pump; or 3) 5-FU bolus, similar to treatment 1, but given with levamisole and leucovorin. Radiation therapy to the pelvis is given in all three treatments. Total treatment time is about six months.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
No publications reporting data on this study or from studies with similar design.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 1917, if multi-site study.

Grade 4 toxicities include 15 cardiovascular, 2 dermatologic, 82 gastrointestinal, 279 hematologic, 11 infections, 1 lung, 3 metabolic, 1 musculoskeletal, 5 neurologic, 4 renal/bladder, and 1 secondary malignancy. Grade 5 toxicities include 3 cardiovascular, 2 gastrointestinal, 1 hemorrhage, 7 infections, and 3 lung. This study closed to accrual effective 1 August 2000 having met accrual goals.

CONCLUSIONS
Too early.

Report Date: 28 August 2002

Work Unit # 1561-95

# DETAIL SUMMARY SHEET

TITLE: CALGB 9497: Health Status and Quality-of-Life in Patients with Early Stage Hodgkin's Disease: A Companion Study to CALGB 9391

KEYWORDS: quality-of-life, early stage, Hodgkin's

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 October 1994

STUDY OBJECTIVE
To evaluate prospectively the health status and quality-of-life (QOL) of early-stage Hodgkin's disease patients receiving either subtotal nodal irradiation or short-course chemotherapy plus subtotal nodal irradiation. To describe the short-term, acute effects of two treatments for early-stage disease on patient reports of symptoms of QOL.

TECHNICAL APPROACH
All patients eligible for treatment on the treatment study #9391 will be registered to this companion study and complete questionnaires related to current health status and QOL. These questionnaires will be completed prior to treatment and at eight specified time points during their treatment. The results will be reviewed and analyzed by the Psycho-Oncology Committee at CALGB.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been no publications since last year's review.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 8. The total number enrolled study-wide is 263, if multi-site study. This study was closed to accrual effective 20 April 2000.

Ref: CALGB Statistical Report

CONCLUSIONS
Too early.

Report Date: 5 October 2001 Work Unit # 1562-95

# DETAIL SUMMARY SHEET

TITLE: CALGB 9343: Evaluation of Lumpectomy, Tamoxifen, and Irradiation of the Breast Compared with Lumpectomy plus Tamoxifen in Women 70 Years of Age or Older Who Have Carcinoma of the Breast That Is Less Than or Equal to 4 Cm and Clinically Negative Axillary Nodes

KEYWORDS: Tamoxifen, breast, lumpectomy

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 29 November 1994

STUDY OBJECTIVE
To determine the net value of radiation therapy in eligible patients with breast cancer, all of who receive Tamoxifen. To assess whether radiation therapy decreases rate of recurrence and incidence of eventual mastectomy. To estimate overall survival, disease-free survival, and breast cancer-specific morbidity for the two groups.

TECHNICAL APPROACH
Eligible breast cancer patients will be randomized to receive either a lumpectomy followed by Tamoxifen, or lumpectomy followed by radiation therapy (for approximately 6 weeks) plus Tamoxifen. Patients will be followed closely for recurrence. In the event of mastectomy subsequent to initial lumpectomy, patients will go off study and be followed for second primary and mortality.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of 13 WRAMC patients were entered on this protocol before it was closed to accrual in February 1999 having met its goal of 647 patients. One of these has died of a non-related cause in 1998; the remaining 12 continue in study follow-up. During the time the study was open, no WRAMC patients have withdrawn from the study, and no unexpected adverse events were reported. A rare side effect of treatment was reported to us by the CALGB (cataract formation). This was reported to the IRB in April 1997, and all WRAMC patients on this treatment were notified as required by the NCI and CALGB. National accrual to the study was 647 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 13. The total number enrolled study-wide is 647, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 7 November 2001

Work Unit # 1563-95

# DETAIL SUMMARY SHEET

TITLE: CALGB 9312: Phase III Comparison of Standard vs. Myeloablative Therapy for Previously Untreated Symptomatic Multiple Myeloma

KEYWORDS: myeloma, transplant, interferon

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 20 December 1994

## STUDY OBJECTIVE

1) To perform a randomized trial in newly diagnosed systemic myeloma (MM) patients, of standard therapy vs. myeloablative therapy in order to examine whether intensive therapy translates into extended survival and progression-free survival. 2) To randomize responding patients to interferon vs. no maintenance to evaluate the role of interferon in MM.

## TECHNICAL APPROACH

All eligible patients will receive standard chemotherapy (vincristine, doxorubicin, and dexamethasone) for 4 cycles. Responding patients will be randomized to receive autologous stem cell transplant with high dose chemotherapy or standard chemotherapy for 12 months. All patients will initially receive high-dose Cytoxan before transplant. After completion of transplant or chemotherapy, all patients will be randomized to observation or maintenance with interferon. This study was amended several times to afford all patients the opportunity of bone marrow transplantation at some point in their treatment.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Twenty-two WRAMC patients have been entered on this study before it was closed to accrual 1 October 2000. Twelve patients have died; four have withdrawn from study treatment, but continue to be followed for survival. Two adverse events (one death this reporting period in January of 2001) and a development of MDS were reported to HUC. Total national accrual to this study is 899 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 22. The total number enrolled study-wide is 899, if multi-site study.

## CONCLUSIONS

No conclusions have been reached.

Report Date: 20 November 2001 Work Unit # 1564-95

# DETAIL SUMMARY SHEET

TITLE: CALGB 9498: A Phase III Randomized Trial of 5-FU/Levamisole/Flucovorin vs. 5-FU/Levamisole as Adjuvant Therapy for Colon Cancer

KEYWORDS: colon cancer, levamisole, leucovorin

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 31 January 1995

STUDY OBJECTIVE
To compare the effectiveness of bolus 5-FU/leucovorin/levamisole vs. continuous infusion 5-FU/levamisole as adjuvant therapy for patients with Stage B2, C1, or C2 colon cancer. This will be measured in terms of overall survival. Disease-free survival will be secondary endpoint.

TECHNICAL APPROACH
Eligible patients will be randomized to either bolus 5-FU/leucovorin/levamisole or to infusion 5-FU/levamisole. In arm 1, cycles will be repeated at the end of 4 weeks, 8 weeks, and then every 5 weeks for a total of 6 cycles; levamisole will continue for 6 months. In arm 2, following each of the initial 2-week cycles, there will be a 1-week rest followed by a resumption of chemotherapy. Patients with progressive disease or unacceptable toxicities will be removed from the study. All patients will be followed until death.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
One WRAMC patient was entered on this protocol before it was closed to accrual in December 1999. No WRAMC patient has withdrawn from the study and no unexpected adverse reactions have been reported. The one WRAMC patient continues in study follow-up. National accrual to this study is 1044 patients. Projected accrual was for 1800 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 1135, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 11 June 2002

Work Unit # 1567-95

# DETAIL SUMMARY SHEET

TITLE: CALGB 9511: A Pilot Trial with Limited Pharmacokinetic Monitoring During Remission Induction and Consolidation Chemotherapy for Adult Acute Lymphoblastic Leukemia

KEYWORDS: PEG-Asparaginase, pharmacokinetic, ALL

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 29 August 1995

## STUDY OBJECTIVE

1) determine toxicity profile for PEG-Asparaginase given as part of intensive multi-agent chemotherapy in patients with previously untreated ALL;
2) determine incidence and significance of neutralizing antibodies, and levels of asparaginase after early treatment with PEG-Asparaginase; and
3) obtain estimate of relationship of these to outcome in ALL.

## TECHNICAL APPROACH

Eligible consenting patients with previously untreated ALL will receive aggressive chemotherapy that includes PEG-Asparaginase in place of L-Asparaginase during induction and early intensification phases of treatment (lasting 60 days), and standard chemotherapy for remaining phases of treatment (lasting 2 years). Patients will be monitored weekly during maintenance therapy, every 3 months for the following year if the patient is in remission, and every 6 months for 4 additional years.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been a couple of publications reporting data from this study.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 6. The total number enrolled study-wide is 104, if multi-site study. This study was closed to accrual effective 15 December 1997 because it met its accrual goal. Grade 5 toxicities are 1 infection, 1adult respiratory distress syndrome (ARDS) (course 2), 4 infections, 1 hepatic, 1 pulmonary, 1 renal (course 1).
Adverse events memos sent to DCI on 9/12/96, 10/31/97, 1/20/98, 1/26/98, and 11/30/99.
Ref: CALGB Statistical Report

## CONCLUSIONS

Too early

Report Date: 5 October 2001 Work Unit # 1569-96

# DETAIL SUMMARY SHEET

TITLE: CALGB 9251: A High Intensity, Brief Duration Phase II Chemotherapy Trial in Small, Non-Cleaved Lymphoma and L-3 Acute Lymphoblastic Leukemia (ALL)

KEYWORDS: high intensity, Phase II, chemotherapy

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 28 November 1995

STUDY OBJECTIVE
To determine: 1) response rate and disease-free survival of patients with category "J" NHL and L3 ALL, not associated with HIV infection, when treated with high intensity, brief duration chemotherapy; and 2) toxicity of this regimen in an HIV-negative patient population.

TECHNICAL APPROACH
All eligible patients will receive the same therapy. All drugs have been used previously to treat these diseases, but will be given at higher doses for a shorter time period. Course I (day 1-7) includes CPA (IV) and prednisone (po). Course II (day 8-12) includes IFF, Mesna, MTX, Leuco, VCR, Ara-C, Etop (IV), Dex (po), and intrathecal combination chemotherapy (day 8 and 12). This therapy is repeated for Course IV (day 50-54) and Course VI (day 92-96). Course III (day 29-33) includes CPA, MTX, Leuco, VCR, Adr (IV), Dex (po), and intrathecal combination chemotherapy (day 29 and 31). This is followed by cranial radiation therapy on days 34 to 49 in Course III only. Course III chemotherapy is repeated for Course V (day 71-75) and Course VII (day 113-117). All patients will receive first three courses at full dose and on time. In event of slow marrow recovery, later doses may be delayed.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Two WRAMC patients were entered on this protocol before it was closed to accrual in February 2000. One patient was removed due to a change in the pathologist's diagnosis. This patient suffered no adverse event as a result of study treatment and continues to be followed for survival. The second patient is no longer eligible for military care and is referred a civilian health center. National accrual to the study was 130 patients (84 NHL and 46 ALL).

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 134, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 29 November 2001 Work Unit # 1570-96

# DETAIL SUMMARY SHEET

TITLE: Cancer and Leukemia Group B

KEYWORDS: grant, NIH, cancer

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 January 1996

STUDY OBJECTIVE
This is the NIH "umbrella" grant for all CALGB studies at WRAMC. CALGB brings together more than two dozen academic institutions and their affiliates in order to conduct cancer treatment trials and related research.

TECHNICAL APPROACH
At WRAMC, through the CALGB program, over 30 active protocols are available to eligible DOD patients. All WRAMC protocol patients are followed by CALGB staff for life regardless of status of protocol enrollment. Patients are treated per individual protocol.

PRIOR AND CURRENT PROGRESS
During this reporting period, WRAMC has maintained steady enrollment to active protocols, new protocol submissions in many areas of oncology research, timely and complete patient follow-up, and up to date continuing review on all open protocols. CALGB researchers at WRAMC continue to participate in CALGB national meetings, serve on CALGB committees, publish in their fields, and provide appropriate study information to the staff and patients at WRAMC. NNMC remains an affiliate of WRAMC.

CONCLUSIONS
CALGB continues to be a healthy and growing research organization at WRAMC aspiring to provide the best study opportunities for our patients that desire them.

Report Date: 7 September 2001 Work Unit # 1573-87

# DETAIL SUMMARY SHEET

TITLE: CALGB 8762: Molecular Subtypes in Acute Lymphatic Leukemia with Philadelphia Chromosome

KEYWORDS: Philadelphia chromosome, ALL

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 27 October 1987

STUDY OBJECTIVE
To determine the incidence of pH positivity in patients with previously untreated acute lymphatic leukemia (ALL).

TECHNICAL APPROACH
Non-randomized comparison study in which all eligible patients who consent allow a sample of blood and bone marrow to be sent to a reference laboratory at the time of diagnosis, first intensification, and at relapse.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
15 WRAMC patients were entered on this study before it was closed to accrual 15 April 1999. No WRAMC patients have withdrawn from this study, and no adverse events have been reported due to the collection of study samples. Twelve WRAMC patients have died of their disease and the remaining 3 patients continue in study follow-up. Samples were collected and sent to reference lab as required by the protocol. Final national accrual to the study was 393 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 15. The total number enrolled study-wide is 393, if multi-site study.

CONCLUSIONS
While final conclusions have not been reached, analysis is ongoing and has shown correlation between chromosomal features and disease outcome and response to treatment.

Report Date: 20 February 2002

Work Unit #1573-96

# DETAIL SUMMARY SHEET

TITLE: CALGB 9334: Sclerosis of Pleural Effusions by Talc Thoracoscopy vs. Talc Slurry: A Phase III Study

KEYWORDS: Pleural Effusion, Tale Slurry, Thoracoscopy

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL, MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 23 April 1996

## STUDY OBJECTIVE

To compare a proportion of patients with successful pleurodesis at 30 days post-treatment for malignant pleural effusion (MPE) by talc slurry via chest tube or thorascopic talc insufflations. To compare the cost of treating MPE patients with these methods. To compare treatments with respect to time to recurrence of effusion, duration of drainage, extent of post treatment complications and toxicities, and patient quality-of-life and pain.

## TECHNICAL APPROACH

Eligible patients with MPE will be randomly assigned to receive either thoracoscopy with talc insufflations or talc slurry via chest tube at the bedside. Patients will be closely monitored for medical and surgical complications for 30 days, and actively followed for 6 months. Patients will complete quality-of-life instruments before treatment and 30 days after treatment. Pain will be assessed 2x per day while the patient has a chest tube in place after the procedure. Monthly follow-up visits with chest x-rays will be done for 6 months.

## PRIOR AND CURRENT PROGRESS

This study was closed to accrual by the CALGB September 1999. The study met the accrual goals. Twelve patients from WRAMC were enrolled. Eleven patients have died of progressive disease. The remaining patient continues to be followed for survival. The group has reported no unexpected adverse events during this reporting period.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 12. The total number enrolled study-wide is 348, if multi-site study.

## CONCLUSIONS

No conclusions have been reached. Analysis in ongoing.

Report Date: 7 September 2001 Work Unit # 1574-87

# DETAIL SUMMARY SHEET

TITLE: CALGB 8763: Immunoglobulin and T Cell Receptor Gene Rearrangement in Adult Acute Lymphatic Leukemia

KEYWORDS: immunoglobulin, T-cell receptor, ALL

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 October 1987

STUDY OBJECTIVE
To determine the incidence of Ig and T-cell receptor gene rearrangements from samples of patients with previously untreated adult acute lymphatic leukemia (ALL).

TECHNICAL APPROACH
Non-randomized companion study in which all eligible patients who consent allow a sample of bone marrow and blood to be sent to CALGB reference laboratory at the time of diagnosis, prior to first intensification, and at relapse.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of 10 WRAMC patients were entered on this study before it was closed to accrual in May 1996. Eight WRAMC patients have died of their progressive disease and the remaining two continue in study follow-up. No WRAMC patients have withdrawn from the study, and no adverse events have been reported as a result of the sample collection. National accrual to the protocol was 370 patients.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 10. The total number enrolled study-wide is 370, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 7 November 2001 Work Unit # 1577-80

# DETAIL SUMMARY SHEET

TITLE: CALGB 8361: Immunologic Diagnostic Studies in AML (Blood Drawing Phase; Previously CALGB 7921); A Comparative Study of Three Remission Induction Regimens and Two Maintenance Regimens for AML (Treatment Phase; Previously CALGB 8321)

KEYWORDS: immunology, oncology, leukemia

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 31 December 1981

STUDY OBJECTIVE
1) To determine the incidence of various markers in acute myelogenous leukemia (AML); 2) To correlate the presence of these markers and the surface antigen phenotype they determine with the FAB histological classification; and 3) To correlate the presence of the various markers with the initial and subsequent clinical characteristics of the disease.

TECHNICAL APPROACH
All eligible patients are registered prior to the initial therapy. From the diagnostic bone marrow procedure, 2 cc of bone marrow and 7 cc of peripheral blood are collected and sent by express mail to the CALGB reference laboratory for analysis and confirmation of classification. Samples are again obtained at relapse.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of 65 WRAMC patients were entered on this protocol before it was closed to further accrual in May 1997. Total national accrual was 2405 patients. Blood and bone marrow samples continue to be collected and sent to reference lab at times specified by the protocol. No WRAMC patients have withdrawn from the protocol, and no adverse events have been reported.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 65. The total number enrolled study-wide is 2405, if multi-site study.

CONCLUSIONS
Immunophenotyping has provided useful in the stratification of some leukemia at high risk for relapse. Analysis is ongoing.

Report Date: 05 April 2002

Work Unit # 1579-96

# DETAIL SUMMARY SHEET

TITLE: CALGB 9254: Anti-B4-Blocked-Ricin (NSC #639185) Adjuvant Post-Autologous Bone Marrow Transplant: A Phase III Study

KEYWORDS: ABB, ricin, NHL

PRINCIPAL INVESTIGATOR: Joseph P. Drabick COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 28 May 1996

## STUDY OBJECTIVE

To determine the effect on disease-free survival of Anti-B4-bR administered by 7-day continuous infusion to patients in complete remission after ABMT for B-cell NHL.

## TECHNICAL APPROACH

All eligible NHL patients who consent to this study will receive standard ABMT therapy. If they achieve complete remission, they will be randomized to receive Anti-B4-Blocked-Ricin or observation. Patients who receive ABB will receive a 7-day continuous infusion between 60 and 120 days post ABMT, and another course 14 days later. Treatment is done on an outpatient basis with frequent (6 visits) clinic monitoring. Lab studies are routine for ABMT patients with 1 extra tube for pharmacokinetic samples in patients receiving drug treatment. Patients will be followed by clinic visits every 6 months for 3 years.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of two WRAMC patients were entered on this study before it was closed to accrual in March 1997. No unexpected adverse reactions have been reported and no WRAMC patients have withdrawn from the study. Final national accrual to the study was 511 registered and 157 randomized. The study, when it closed to accrual in March 1997, was short of its projected accrual of 750 when interim analysis by the CALGB Data and Safety Monitoring Board found that it was highly unlikely that ABB would show a statistically significant benefit, even if the study were to continue to its original accrual goal.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 668, if multi-site study.

## CONCLUSIONS

Study closed since no significant benefit to patients is projected.

Report Date: 03 May 2002

Work Unit # 1584-96

# DETAIL SUMMARY SHEET

TITLE: CALGB 9665: The CALGB Leukemia Tissue Bank

KEYWORDS: leukemia, tissue bank

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 June 1996

## STUDY OBJECTIVE

To collect and store specimens from every newly diagnosed patient with acute leukemia or myelodysplasia syndrome (MDS) who is entered on a CALGB protocol for previously untreated patients.

## TECHNICAL APPROACH

All consenting eligible patients with newly diagnosed leukemia or MDS entered on a CALGB treatment protocol will have blood, bone marrow, and cell samples collected as follows: 1) pre-treatment - bone marrow aspirate (5 cc), blood (8-10 cc), 2 buccal swab samples (by twirling special brush inside cheek for 30 seconds); 2) during remission - similar blood and bone marrow samples at intervals specified in treatment protocol; and 3) at relapse - similar blood and bone marrow specimens x 1. All samples will be sent per protocol to CALGB Tissue Bank at Roswell Park Cancer Institute for use in further studies (no heritable genes).

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Thirty WRAMC patients have been entered on this protocol, one in this reporting period. Eleven of these patients have died, the remaining 19 patients continue in study follow-up. No WRAMC patients have withdrawn from the study, and no adverse events have occurred because of sample collection. All samples have been collected and sent to the appropriate reference laboratory. Minor changes have been made to the protocol. National accrual to study is 1639 patient samples, 346 in this reporting period.

The number of subjects enrolled to the study since last APR at WRAMC is 1 and the total enrolled to date at WRAMC is 30. The total number enrolled study-wide is 1639, if multi-site study.

## CONCLUSIONS

No conclusions have been reached.

Report Date: 20 November 2001 Work Unit # 1590-89

# DETAIL SUMMARY SHEET

TITLE: CALGB 8852: A Study of CHOPE in Diffuse Lymphomas

KEYWORDS: lymphoma, CHOPE, high-dose

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 31 January 1989

STUDY OBJECTIVE
To identify the maximum tolerated dose of cyclophosphamide, doxorubicin, vincristine, prednisone, and etopsoside (CHOPE) in the treatment of lymphoma, and to assess the safety of giving multiple cycles of high-dose CHOPE therapy.

TECHNICAL APPROACH
Standard doses of CHOPE will be given to the first 20-25 patients enrolled. If tolerated, the doses will be escalated for the next groups sequentially, until the maximum tolerated dose is reached.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Five WRAMC patients were entered on this study before it was closed to accrual in May 1993 having met its accrual goal with a national accrual of 227 patients. Four of these patients have died of progressive disease, the remaining one continues in study follow-up. No WRAMC patients withdrew from this study and no unexpected adverse reactions have been reported.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is 227, if multi-site study.

CONCLUSIONS
Analysis is in progress.

Report Date: 20 November 2001

Work Unit # 1591-97

# DETAIL SUMMARY SHEET

TITLE: CALGB 9583 A Phase III Two-Arm Randomized Study Comparing Antiandrogen Withdrawal vs. Antiandrogen Withdrawal Combined with Ketoconazole and Hydrocortisone in Patients with Advanced Prostate Cancer

KEYWORDS: advanced, prostate cancer, ketoconazole

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 28 January 1997

## STUDY OBJECTIVE

To compare the response proportion and duration of response to antiandrogen withdrawal alone vs. antiandrogen withdrawal combined with ketoconazole and hydrocortisone in patients with advanced hormone refractory prostatic carcinoma.

## TECHNICAL APPROACH

All eligible, consenting men will be randomly assigned to #1 stop flutamide or Casodex or #2 stop Flutamide or Casodex and start treatment with ketoconazole po tid and hydrocortisone po bid. Patients entering this will also have a bone marrow biopsy done as part of companion study CALGB 9663 (consented separately). Treatment is outpatient with clinic visits every 4 weeks. Study treatment will continue until there is clinical evidence that it is no longer effective.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Four WRAMC patients have been entered on this study before it was closed to accrual in May 2000. Three patients have died of their progressive disease and one continues in study follow-up. No WRAMC patient has withdrawn from the study, and no unexpected adverse event has been reported. National accrual to the study is 260 patients. Projected accrual was for 250. A minor change to the protocol was reported to the IRB in June 2001.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 260, if multi-site study.

## CONCLUSIONS

No conclusions have been reached.

Report Date: 18 December 2001 Work Unit # 1592-97

# DETAIL SUMMARY SHEET

TITLE: CALGB 9484 Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry

KEYWORDS: breast cancer, registry, epidemiological

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 25 February 1997

STUDY OBJECTIVE
To form a specialized registry of clinical, scientific, epidemiologic (including personal, family and environmental exposures), and psycho-social information about breast cancer patients to be used by qualified investigators in a variety of studies in order to seek new knowledge about breast cancer.

TECHNICAL APPROACH
Consenting WRAMC patients entered on CALGB breast cancer treatment protocols will donate one paraffin tissue block, and urine and blood samples as specified by protocol. The will be sent to central lab and stored for breast cancer research. Additional blood will be collected for DNA study if patient consents. This information is not available to patient or any parties outside this research project. Patients will fill out a personal and family cancer information questionnaire.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Nine WRAMC patients had been entered on this study before it was closed to accrual in September 1999. No WRAMC patient has withdrawn. One patient has died of their progression of disease in this reporting period (reported to the IRB). This study is also being closed with WRAMC IRB as there will be no further specimen retrieval.

The number of subjects enrolled to the study since last APR at WRAMC is 9 and the total enrolled to date at WRAMC is 9. The total number enrolled study-wide is 347, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 3 May 2002

Work Unit # 1594-97

# DETAIL SUMMARY SHEET

TITLE: CALGB 9760: Multidrug Resistance Studies in Acute Leukemia

KEYWORDS: resistance, multidrug, AML

PRINCIPAL INVESTIGATOR: LTC Joseph J. Drabick MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 24 June 1997

## STUDY OBJECTIVE

To study Pgp antigen expression in MDR in patients with acute leukemia at diagnosis, relapse and refractory disease. To correlate Pgp mediated MDR with pretreatment patient characteristics. To study PSC-833 Pgp modulation. To study MDR mediated by other mediators including MRP and LRP. To determine frequency of Pgp, MRP and LRP mediated MDR in adult leukemic cells, and correlate with pretreatment characteristics and with treatment outcome.

## TECHNICAL APPROACH

Bone marrow and/or peripheral blood samples as specified in the protocol are collected from consenting patients with acute leukemia at the time of diagnosis (before treatment), and at time of relapse or diagnosis of refractory disease. These samples at taken at times when the procedure is already being carried out for standard diagnostic care. The laboratory results are then correlated with clinical outcome.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Fourteen WRAMC patients have been entered on this protocol, one in this reporting period. There have been no adverse events related to specimen collection reported to the CALGB group in this reporting period. No WRAMC patients have withdrawn from the study. All samples have been collected and sent to the appropriate laboratory. National accrual to the study is 733 patients, 160 in this reporting period. Projected accrual is for 1200 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 1 and the total enrolled to date at WRAMC is 14. The total number enrolled study-wide is 733, if multi-site study.

## CONCLUSIONS

No conclusions have been reached.

Report Date: 21 February 2002 Work Unit #1595-89

# DETAIL SUMMARY SHEET

TITLE: CALGB 8961: RAS Mutations in Myelodysplasia

KEYWORDS: RAS gene, oncogenes, myelodysplasia

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 April 1989

STUDY OBJECTIVE
To determine 1) the prevalence of mutant RAS genes in myelodysplasia; and 2) if the presence of such a mutation predicts subsequent leukemic development.

TECHNICAL APPROACH
Non-randomized, non-treatment protocol in which all eligible patients are registered. Blood and bone marrow samples and slides are obtained at entry and again, when acute leukemia develops.

PRIOR AND CURRENT PROGRESS
Thirteen patients from WRAMC were enrolled on this study. It was closed to accrual in September 1996, having met its accrual goal. Twelve of the patients have expired and the remaining patient continues in follow-up. National accrual was 304 patients. No WRAMC patients withdrew from this study and no unexpected adverse reactions to the collection of these laboratory samples were reported. All blood and bone marrow samples have been collected and sent to the reference lab per protocol requirements. We will continue to follow this remaining patient and if the patient develops leukemia, samples will be collected and sent to the reference lab. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 13. The total number enrolled study-wide is 304.

CONCLUSIONS
Analysis is ongoing. To date, there have been three publications related to this study.

Report Date: 31 May 2002

Work Unit # 1596-97

# DETAIL SUMMARY SHEET

TITLE: CALGB 9640: A Comparison of Intensive Sequential Chemotherapy Using Doxorubicin Plus Paclitaxel Plus Cyclophosphamide with High-Dose Chemotherapy and Autologous Hematopoietic Progenitor Cell Support for Primary Breast Cancer in Women with 4-9 Involved Axillary Lymph Nodes

KEYWORDS: chemotherapy, breast, progenitor cell support

PRINCIPAL INVESTIGATOR: Joseph Drabick COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 29 July 1997

STUDY OBJECTIVE:
To compare induction chemotherapy followed by high dose chemo and autologous stem cell support vs. intensive sequential chemo with G-CSF support with respect to disease free survival, toxicity and overall survival in operable patients with 4-9 positive nodes.

TECHNICAL APPROACH
Eligible women will be randomly assigned to receive either 1) high-dose chemo with doxorubicin, paclitaxel and cyclophosphamide over 17 weeks with G-CSF support; or 2) standard dose chemo over 10 weeks, followed by higher dose chemo with cyclophosphamide, thiotepa, and carboplatin with autologous stem cell collection after week 10, and reinfusion 4 days after completion of high dose chemo. Both groups will be given radiation treatment 4-6 weeks post therapy, and tamoxifen therapy for 5 years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
One WRAMC patient has been entered on this protocol. No adverse reactions have been reported from the CALGB. The final national accrual to the study is 590 patients, 28 in this reporting period.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 590, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 12 June 2002 Work Unit # 1597-97

# DETAIL SUMMARY SHEET

TITLE: CALGB 9621: Phase I Study of MDR Modulation with PSC-833 with a Pilot Study of Cytogenetic Risk-Adapted Consolidation Followed by a Phase II Pilot Study of Immunotherapy with rIL-2 in Previously Untreated Patients with AML < 60 Years

KEYWORDS: PSC-833, MDR Modulation, rIL-2

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 26 August 1997

STUDY OBJECTIVE
To determine the MTD for the intensive chemotherapy used in the study. To establish the feasibility and toxicity of administering post remission therapy in a risk adapted fashion. To establish feasibility of maintenance therapy with rIL-2.

TECHNICAL APPROACH
Eligible patients with AML will receive standard induction chemotherapy plus minus PSC-833 followed by risk stratified therapy with either stem cell transplant or intensive chemotherapy, followed by immunotherapy with rIL-2. Therapy duration is 24 weeks. Patients will be followed for life.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, there have been no additional publications reported.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 10. The total number enrolled study-wide is 410, if multi-site study. This study was closed to enrollment effective March 31, 2000.

Grade IV toxicities include 2 hemorrhage, 30 infection, 2 vomiting, 13 diarrhea, 75 stomatitis, 57 esophagitis, 24 anorexia, 6 other GI, 72 bilirubin, 2 other liver, 5 transaminase, 2 BUN, 38 dyspnea, 15 pulm edema, 4 other pulmonary, 18 ARDS, 25 dysrhythmia, 2 ischemia, 25 hypotension, 1 cortical, 9 pain, 16 skin, 10 fever w/o infect., 28 malaise/fatigue, 3 hyperglycemia, 11 hypocalcemia, 7 hypokalemia, and 1 other metabolic.
Grade V toxicities include 3 hemorrhage, 18 infection, 1 other GI, 6 ARDS, 1 ischemia, 1 cortical, 1 other metabolic, and 2 other pulmonary.
Adverse event memos have been sent to DCI on 3/23/98, 9/24/98, 4/21/00, 7/11/00, 9/15/00, 1/12/01, 11/28/01, 12/5/01, and 5/3/02.

Ref: CALGB Statistical Report

CONCLUSIONS
Too early.

Report Date: 12 June 2002

Work Unit # 1598-89

# DETAIL SUMMARY SHEET

TITLE: CALGB 8952: Combination Chemotherapy for Advanced Hodgkin's Disease, Phase III

KEYWORDS: chemotherapy, Hodgkin's disease

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 29 August 1989

STUDY OBJECTIVE
To compare ABVD to the MOPP/ABV hybrid as therapy for patients with Hodgkin's disease in terms of complete response rates, disease-free survival, failure-free survival, and both intermediate and long-term toxicities.

TECHNICAL APPROACH
Randomized study in which eligible patients receive either ABVD or the MOPP/ABV hybrid combination for a minimum of six cycles unless progression is documented.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There has been one abstract published reporting data for this study.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 9. The total number enrolled study-wide is 856, if multi-site study.

Grade IV toxicities include 212 wbc, 38 platelets, 31 hemoglobin, 324 granulocytes/bands, 311 lymphocytes, 4 other hematologic, 1 hemorrhage, 11 infection, 10 vomiting, 2 diarrhea, 1 anorexia, 2 other GI, 4 bilirubin, 6 transaminase, 1 alk phos/5 nucleot, 1 liver-clinical, 1 creatinine, 1 hematuria, 1 renal failure, 11 dyspnea, 7 po2/pco2, 2 dlco, 1 fibrosis, 1 pulmonary edema, 6 non-infect. pneumon., 6 ARDS, 3 other pulmonary, 3 dysrhythmia, 2 cardiac function, 1 ischemia, 4 other heart, 4 hypotension, 3 phlebitis/thrombosis, 1 edema, 1 sensory, 1 motor, 1 cortical, 3 mood, 1 constipation, 3 pain, 1 other neurologic, 2 skin, 1 local, 2 fever w/o infection, 5 malaise/fatigue, 2 hyperglycemia, 2 hypoglycemia, 1 hyponatremia, 1 other metabolic, 2 fibrinogen, 3 prothrombin time, and 3 partial thromboplas.
Grade V toxicities include 9 infections, 1 ARDS, 9 other pulmonary, and 1 ischemia.

This study was closed to enrollment effective 10 November 1995, due to increased incidence of treatment-related deaths and second malignancy reported in one arm of the study (none at WRAMC).

Adverse event memos sent to DCI on 4/18/96 and 4/22/96.

Ref: CALGB Statistical Report

CONCLUSIONS
Too early.

Report Date: 7 September 2001 Work Unit # 1599-98

# DETAIL SUMMARY SHEET

TITLE: CALGB 9581: Phase III Randomized Study of Adjuvant Immunotherapy with Monoclonal Antibody 17-LA vs. No Adjuvant Therapy Following Resection for Stage II (Modified Astler-Coller B2) Adenocarcinoma of the Colon

KEYWORDS:

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 28 October 1997

STUDY OBJECTIVE
1) To determine whether adjuvant treatment with MoAb 17-1A will improve the probability of overall and disease-free survival, and increase disease-free intervals in patients who have undergone resection of a stage II colon cancer. 2) To evaluate a panel of prognostic markers, in order to correlate these measures with survival and disease recurrence in these patients.

TECHNICAL APPROACH
Eligible patients with colon cancer will be randomly assigned after surgery to receive either adjuvant treatment with MoAb 17-1A, or standard treatment-observation. Patients receiving adjuvant therapy will receive doses of study IV over 2 hrs in the outpatient clinic, every 4 wks for a total of 5 doses. Treated group will have weekly clinic evaluations during treatment. Both groups will be followed q 6 months for five yrs.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Four WRAMC patients have been entered on this protocol, two in this reporting period. No unexpected adverse reactions have been reported, and no WRAMC patient has withdrawn from the study. National accrual to this study is 1279; 583 patients in this reporting period. Projected national accrual is for 2100 patients. Minor editorial revisions have been made to the protocol included a change in the consent form to briefly inform participants of outcomes of other clinical trials that had used panorex as an investigational agent (reported to DCI 23 May 2001).

The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 1279, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 7 May 2002

Work Unit # 1605

# DETAIL SUMMARY SHEET

TITLE: Hemapheresis for Collection of Platelets for In Vitro Study of Platelet Cryopreservation

KEYWORDS: platelets, apheresis, storage, freezing, platelet induced clot retraction, thromboelastograph, protein phosphorylation, dynein, kinesin, nitric oxide, permeability coefficient, membrane phase transition, DMSO, blood storage bags – physical and thermal properties, dynamic mechanical analysis, glass transition temperature

PRINCIPAL INVESTIGATOR: Reid, Thomas COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 24 June 1997

## STUDY OBJECTIVE

To study the effects of storage (freezing, 4°C, 20-24°C) on *in vitro* platelet function. To study the intracellular mechanisms (e.g. contractile proteins, membrane integrity, activation) of damage during storage. To study the biochemical mechanism of platelet induced clot retraction (PICR) and platelet activation.

## TECHNICAL APPROACH

Fresh platelets are stored at 22°C for 5 days and tested for *in vitro* platelet function, emphasizing PICR. Platelet storage at 4°C with and without DMSO is studied – endpoints are preservation of functional activity. The phase transition ($T_m$ liquid crystalline → gel) is evaluated using Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), and differential scanning calorimetry (DSC).

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One hundred six potential donors have been screened. Five were considered ineligible for donation, none in the past year. Forty-five participants have withdrawn from the study since its inception due to leaving the area. Seventeen individuals are available and eligible for apheresis (25%). Two hundred three apheresis procedures have been performed. All but two were successful (99 %); none were unsuccessful in the past year. Platelet membrane integrity is damaged on cooling or freezing without cryoprotectants – DMSO preserves some platelet function. The platelet $T_m$ is approximately 15-18°C; DMSO appears to increase the $T_m$. Model membrane studies differentiate inner and outer leaflets of membrane and show that DMSO increased $T_m$. FTIR, NMR, and DSC give similar results in identifying $T_m$. To date, there has been on direct benefit to patients. The glass transition temperature and tensile module of several blood storage bags were studied.

The number of subjects enrolled to the study since the last APR at WRAMC is 23 and the total enrolled to date 99.

## CONCLUSIONS

EVA bags appear best suited for low temperature shipping and storage of blood products.

Report Date: 30 July 2001 Work Unit #1608

# DETAIL SUMMARY SHEET

TITLE: Acute Hypoxemic Respiratory Failure in Bone Marrow Transplant Patients: An Imbalance of the Immunomodulating Cascade?

KEYWORDS: Bone marrow transplantation; Acute Lung Injury; ARDS; Cytokines

PRINCIPAL INVESTIGATOR: Moores, Lisa LTC MC
ASSOCIATES: Fitzpatrick, Tom COL MC; Ling, Geoffrey LTC MC

DEPARTMENT: Medicine
SERVICE: Pulmonary & Critical Care Medicine

STATUS: C
INITIAL APPROVAL DATE: 28 October 1997

## STUDY OBJECTIVE

To determine the relationship between the inflammatory cytokine response and neutrophil activity and the development of acute respiratory failure at the time of engraftment in adult patients undergoing high-dose chemotherapy with autologous bone marrow transplantation.

## TECHNICAL APPROACH

All patients undergoing high-dose chemotherapy with autologous bone marrow transplantation at WRAMC are asked to participate in the study. If enrolled, patients have serum measurements of 6 cytokines (TNF-a, IL1-B, IL-6; IL2, IL-10, IL-8) every other day throughout the hospitalization. In addition, these same cytokines are measured from the lung via fiber optic bronchoscopy with bronchoalveolar lavage at three different times—Day 0 of chemotherapy, day of engraftment, and hospital day 21. Cell counts are also done on this fluid. Demographic features as well as information from the hospital course are collected in the data collection sheet for descriptive purposes.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There has really been no activity on this protocol over the past year. No subjects have been enrolled. Data collection is considered complete (due to difficulties with enrollment). Most of the data analysis has been completed as well, and we are set to begin the manuscript based on the initial 13 patients who were enrolled.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 13. The total number enrolled study-wide is NA, if multi-site study.

## CONCLUSIONS

Based on data from ten patients with a complete data set, it appears that IL-8 in both the lung and serum increase significantly more in patients with lung injury than those without. In addition, it appears that a more than 5-fold rise over baseline serum IL-8 3-5 days prior to anticipated engraftment might be predictive of the development of lung injury.

Report Date: 4 April 2002

Work Unit # # 1614-98

# DETAIL SUMMARY SHEET

TITLE: A Uniformed Services Comprehensive Database and Tissue Repository for the Study of Epidemiological Detection, Natural History, and New Management Strategies for Prostate Cancer

KEYWORDS: prostate, cancer, tissue

PRINCIPAL INVESTIGATOR: COL David McLeod MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 26 May 1998

STUDY OBJECTIVE

1) Create a Uniformed Services Comprehensive Database and Tissue Repository for the study epidemiological detection, natural history, and new management strategies for prostate cancer prevention and treatment. 2) Initiate a clinical project at three medical centers to demonstrate the feasibility of establishing a Tri-Service Tissue and Serum Repository at AFIP.

TECHNICAL APPROACH

This will be achieved by: 1) prospectively collecting standardized data on all prostate cancer patients treated at specified military centers beginning in 1998, and 2) samples will be obtained from radical prostatectomy specimens which will include cancerous and normal tissue. Informed consent will allow intraoperative collection of blood and tissue biopsies of the excised organ. It will allow the use of these specimens as well as the retrieval and use of their original archival biopsy tissue. Blood samples will be used to measure specific molecular markers and will be compared to clinical features.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

USAMRMC did not renew funding for this project, so this protocol is closed.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study.

CONCLUSIONS

No patients were enrolled in this protocol, thus no conclusions could be drawn.

Report Date: 13 November 2001 Work Unit # 1689

# DETAIL SUMMARY SHEET

TITLE: Chemoprevention of Prostate Cancer with Finasteride (Proscar) vs. Placebo

KEYWORDS: prostate cancer, finasteride, prevention

PRINCIPAL INVESTIGATOR: Joseph M. Flynn CPT MC
ASSOCIATES: Cheryl A. Aylesworth MAJ MC, John C. Byrd MAJ MC

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
APPROVAL DATE: 30 November 1993

## STUDY OBJECTIVE

To determine if the medication "finasteride" can prevent prostate cancer. The effect of this treatment on the quality-of-life of the participants will also be determined.

## TECHNICAL APPROACH

A total of 40-60 men aged 55 or greater who are in good health will be enrolled in the study over one to two years. The digital rectal exam (DRE) must be normal, and the prostate specific antigen (PSA) must be three or less for all participants. There will be an annual visit, a 6-month visit and two phone contacts each year for seven years. At the annual blood visit a blood sample will be taken for PSA determination and a physical exam including DRE will be done. A six-month supply of placebo or finasteride will be dispensed. Quality-of-life information will be obtained at each contact.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The study stopped accrual on 6 December 1996. Sixty-three men were randomized to the clinical trial at WRAMC. Three have transferred in and five transferred out. Five have withdrawn consent. Two subjects have died, one of pancreatic cancer and one during vascular surgery. Four of these subjects have developed prostate cancer, three within the last year. When the annual progress report was submitted last year one subject had a prostate biopsy that was pending. His prostate was biopsied due to PSA elevation, and the diagnosis was prostate cancer, Gleason 2+3=5. He had a prostatectomy and is doing well. Prostate cancer appeared as a result of the 7-year end of study prostate biopsies in two patients with normal DRE and normal PSA. Thirty of the 55 men have completed their seven years of treatment on the study, 27 of them have elected to undergo the prostate biopsies, and three of them have refused the biopsy but completed the study. The remaining twenty-five men will complete the study over the next 3 years.

Cancer of the prostate is not a serious adverse event in this study, since a large number of men in this age group get the disease. There were no adverse events caused by the study drug, either here at Walter Reed or nationwide, during the last year. No patients withdrew from the study at Walter Reed in the past year. Addendum 10 requesting a change in protocol to allow an extra blood sample to be drawn for analysis of white blood cells was approved on 20 March 2001. Addendum 11, allowing for follow up of each man after the 7 years is completed, was submitted to DCI in November 2001, along with a request for change of Principal Investigator from Dr. Joseph Flynn to Dr. Noah Schenkman.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 63. The total number enrolled study-wide is 180882, if multi-site study. The study is closed to enrollment.

## CONCLUSIONS

There have been no conclusions to date.

Report Date: 1 February 2002

Work Unit # 00-1701

# DETAIL SUMMARY SHEET

TITLE: Does Use of a Temporary Silencer Adjustable Airway Dilator Predict Outcome Using Permanent Silencer Adjustable Airway Dilator in Treatment of Obstructive Sleep Apnea

KEYWORDS:

PRINCIPAL INVESTIGATOR: Kristo, David MAJ MC

ASSOCIATES: Cteotima Andrada MS RPSGT, Christine Griffin BA, LTC Kevin McGlynn DDS, Robin Howard MA, David Bitonti DMd CDR DC USN, Scott A. Synnott DDS CPT DC USN

DEPARTMENT: Medicine
SERVICE: Pulmonary & Critical Care Medicine

STATUS: O
INITIAL APPROVAL DATE: 28 March 2000

## STUDY OBJECTIVE

To determine whether a Silencer adjustable temporary airway dilator (AD) is predicative of outcome of a permanent Silencer adjustable airway dilator in treating obstructive sleep apnea (OSA).

## TECHNICAL APPROACH

Subjects receive acoustic three-dimensional assessment of the airway, are given a temporary airway dilator to wear for two weeks, and then undergo a sleep study with the temporary AD. Next, subjects are given a permanent AD, wear it for six weeks and undergo a sleep study with the permanent AD. This study will examine whether a strong correlation exists between successful treatment of OSAHS with the temporary AD and successful treatment with the permanent AD. Additionally, the acoustic airway measurements will be examined to see if they have predictive value.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 6 and the total enrolled to date at WRAMC is 25. Of the 25 patients, 14 were studied incorrectly -- they received temporary airway dilator treatment in a neutral position (no mandibular advancement). Additionally, the permanent airway dilator, which was fabricated in Canada, was not optimally positioned in up to nine patients. In addition to these fourteen patients, six patients did not receive a sleep study and five patients were dropouts. The five patients dropped out for the following reasons: One patient lacked time and experienced lockjaw side effect in the morning after wearing oral appliance. One patient's mouth watered and did not want to take a medicinal cure for this side effect One patient had scleroderma which caused him to have pain at night. One patient's research sleep study revealed that he has central sleep apnea (exclusionary criterion), and one patient had scheduling difficulties. Also, the following AEs have occurred: Three patients have had jaw or mouth pain that appeared to be related to the oral appliance, and one patient had dental problems that are unrelated to the oral appliance. There have been no serious adverse events to date.

Due to the mistake described above with fourteen patients receiving incorrectly positioned oral appliances, an addendum was submitted 29 November 2001 and approved 30 January 2002 proposing the following changes:

> All 14 subjects will be contacted, including those who fortuitously had a positive response to AD despite neutral placement of temporary AD and improper positioning of permanent AD. They will be given a letter of explanation They will not be restudied for research purposes, but will be given the option of clinical treatment, including AD repositioning and a sleep study with the permanent AD if they so choose. The temporary device will be stopped.

The inventor of the AD, Dr. Wayne Halstrom, has written a letter stating in detail how and when to adjust the temporary and permanent ADs. The WRAMC dentist, Dr. Koudelka, has cosigned the letter and will retain a copy for reference. The original protocol will be followed.

Up to 25 new patients will be recruited and studied according to protocol and fitted according to the rules of the dental letter.

After five patients have been fitted with the permanent AD, Dr. Halstrom will visit from Canada and review the dental records (gothic arch tracings, pharyngometry, etc.) to ensure that the measurements are being done properly. Dr. Kristo and Dr. Halstrom will provide HUC and the medical monitor a written evaluation of the results of this visit.

Two recent articles that are relevant to this study are "Cephalometric and Physiologic Predictors of the Efficacy of an adjustable Oral Appliance for Treating Obstructive Sleep Apnea" and "Side Effects of Mandibular Advancement Devices for Sleep Apnea Treatment".

CONCLUSIONS

No conclusions have yet been drawn from this study.

Report Date: 31 January 2002

Work Unit # 00-1702

# DETAIL SUMMARY SHEET

TITLE: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of 12 Weeks of 2 Oral Doses (200 mg and 400 mg Once Daily) of PROVIGIL (Modafinil) as Treatment for Adults with Excessive Daytime Sleepiness Associated with Obstructive Sleep Apnea/Hypopnea Syndrome Followed by a 12-Month Open-Label Extension

KEYWORDS:

PRINCIPAL INVESTIGATOR: Kristo, David MAJ MC
ASSOCIATES: COL Arn Eliasson MC; Yvonne Taylor RN MSN CNP; Tim Andrada MS

DEPARTMENT: Medicine
SERVICE: Pulmonary & Critical Care Medicine

STATUS: O
INITIAL APPROVAL DATE: 28 March 2000

STUDY OBJECTIVE

The objectives of this study are to determine the safety and efficacy of PROVIGIL 200 mg/day (once in the morning) and 400 mg/day (once in the morning) as a treatment for excessive daytime sleepiness (EDS) in patients with obstructive sleep apnea/hypopnea syndrome (OSAHS) who need nasal continuous positive airway pressure (CPAP), and who have been characterized with regard to their actual CPAP use patterns. The primary efficacy objective will be tested by comparing the change from baseline to week 12 (or endpoint) in the Maintenance of Wakefulness Test and the Clinical Global Impression Scale between the group treated with PROVIGIL 400 mg/day and the placebo-treated group. (Note: previously, the Epworth Sleepiness Scale was the primary efficacy objective.)

TECHNICAL APPROACH

Patients using CPAP who are still experiencing excessive daytime sleepiness will be extensively screened to exclude variables such as concomitant sleep disorders, acute illness, prior Modafinil use, use of medications that might interact with Modafinil, etc. After initial screening, patients will undergo at-home CPAP testing for 2 nights to insure that their CPAP titration level is adequate to treat their OSAHS. They will also under go 14 nights of at-home CPAP testing to insure that they do have at least partial CPAP compliance. Patients who pass all of the above screening procedures are then randomized (1:1:1) to receive PROVIGIL 200 mg/day or 400 mg/day or placebo for one 12-week period. During this period, they are seen once a month for a variety of procedures, including EKG, blood labs, Maintenance of Wakefulness tests, questionnaires, etc. After completing at least 8 week of double-blind treatment, patients are eligible of an optional 12 months of open label treatment with Modafinil.

PRIOR AND CURRENT PROGRESS

There have been no amendments to the study since the last review, and the only modification is the change in the primary efficacy objectives as described above. To date, five subjects have been enrolled at WRAMC; since the last APR, no subjects have been enrolled. At present, two patients are undergoing the open-label portion of the study and one patient has completed open label. To date, there have been no serious adverse events for any WRAMC patients. The two patients who are currently in open label and the patient who just completed open label have reported decreased excessive daytime sleepiness and increased quality of life as a result of open label Modafinil usage.

Following is a list of the adverse events that have occurred at WRAMC since the last APR, along with the PI or sub-investigator's opinion as to whether the study medication caused the adverse event:

Patient 3201: Upper respiratory infection – Unlikely. Allergies – Unlikely. Dry Mouth – Possible. Conjunctival erythema -- Not related

Patient 3205: Light-headedness -- Not related. Sleeplessness – Possible. Two car accidents – Unlikely.

Patient 4306: Leg infection – Unlikely. Fatty liver – Unlikely.

Study wide, 332 patients have been enrolled to date. Eleven serious adverse events have occurred -- all of them expected.

At an investigator's meeting in November 2001, positive preliminary results were reported for the study. However, the results have not yet been finalized and published.

Quite a bit is being written about the various uses of Modafinil. However, a search of Grateful Med for the words "Modafinil" and "obstructive sleep apnea" turned up just one article written during the course of this study.

CONCLUSIONS

This study is still in progress and no findings have yet been published.

Report Date: 29 March 2002

Work Unit # 01-17003

# DETAIL SUMMARY SHEET

TITLE: Quality Management in Sleep Medicine via Telemedicine: Overseas Online Transfer of Polysomnograms via Internet File Transfer Protocol from Landstuhl Army Medical Center to Walter Reed Army Medical Center

KEYWORDS: Telemedicine, sleep medicine, quality control

PRINCIPAL INVESTIGATOR: Kristo, David LTC MC
ASSOCIATES: Eliasson, Arn COL MC; Thomas Bigott

DEPARTMENT: Medicine
SERVICE: Pulmonary & Critical Care Medicine

STATUS: O
INITIAL APPROVAL DATE: 15 May 2001

## STUDY OBJECTIVE

To compare the results of scoring and interpretation of sleep study data at the site in Landstuhl Regional Medical Center versus the scoring and interpretation results of the same online sleep study data transferred at WRAMC by a sleep specialist for quality control purposes.

## TECHNICAL APPROACH

Subjects receiving sleep studies at Landstuhl Regional Medical Center (LRMC) will have raw (unscored, uninterrupted) sleep study data sent to Walter Reed Army Medical Center (WRAMC). Transmission of sleep studies will be done via Internet, or, in case of Internet difficulties, sent on optical disk via registered mail. (Modification allowing studies to be sent via registered mail was proposed in Addendum 1.) Also, subjects will fill out three standard sleep questionnaires on the night of the study – the Berlin Questionnaire, Epworth Sleepiness Scale, and WRAMC Sleep Questionnaire – and results will be faxed to WRAMC physicians. All patient data sent to WRAMC will be identified only by patient ID study number, not name or SSN.

Physicians at both LRMC and WRAMC will independently examine each subject's sleep study. Then they will compare their results with each other. The data transferred between LRMC and WRAMC will only evaluate the technology and effective use of telemedical principles, and the content of the transferred information will in no way be used to affect clinical care decisions until the proposed study is concluded.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at LRMC is 24 and the total enrolled to date at LRMC is 24. However, no subjects have received medical interpretation from WRAMC because the files cannot be transmitted due to problems with LRMC's firewall. Addendum 1 was submitted 7 February 2002 to request permission to transfer files via optical disk by mail. We are currently awaiting approval.

No patients have withdrawn from the study and no patients have had adverse events. No recent literature regarding telemedicine and sleep is relevant to this study.

## CONCLUSIONS

No conclusions have yet been drawn from this study.

Report Date: 2 May 2002 Work Unit # 01-17004

# DETAIL SUMMARY SHEET

TITLE: A Comparison Between an Internet Communications Platform and Traditional Medical Care as a Health Care Management Model in Patients with Obstructive Sleep Apnea

KEYWORDS: telemedicine, C-PAP, obstructive sleep apnea, compliance, self-efficacy

PRINCIPAL INVESTIGATOR: Taylor, Yvonne, DrPH(c), DAC
ASSOCIATES: COL Arn Eliasson, MC; LTC David A. Kristo, MC; Tim Andrada; Paula Ephraim, LTC (Ret.)

DEPARTMENT: Medicine
SERVICE: Pulmonary & Critical Care Medicine

STATUS: O
INITIAL APPROVAL DATE: 19 June 2001

## STUDY OBJECTIVE

To compare compliance with Continuous Positive Airway Pressure regimens to treat Obstructive Sleep Apnea (OSA) between OSA patients receiving standard outpatient management and those receiving standard care augmented by a "Health Buddy" Internet health care provider interface.

## TECHNICAL APPROACH

The study design will be a randomized control trial. Two groups will be enrolled to consist of an intervention and a control group. The intervention group will receive the telemedicine management model of care and the control group will receive the traditional standard of care management model (usual care). Data will be collected from questionnaires administered at baseline and periodically through 90 days post intervention, and from the "smart card", an automated record of use that is part of the CPAP device.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Data collection of dependent variables (Nasal CPAP use, functional status and client satisfaction) will take place at the same point in time for the intervention and control group: at baseline, at the one-month clinic follow-up visit, and at the two-month terminal clinic visit. An addendum approved 15 April 2002 adds a dependent variable (self-efficacy to use nasal CPAP) to be measured at the same points in time, and also adds another observation point at one-month post-study completion. No recent literature is noted.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is N/A if multi-site study.

## CONCLUSIONS

A pilot study of ten patients is planned to begin next week. There are no study findings at this time.

Report Date: 02 May 2002

Work Unit # 01-17005

# DETAIL SUMMARY SHEET

TITLE: Comparison of F-18 FDG Coincidence PET with Tc-99m Depreotide in the Evaluation of Pulmonary Lesions

KEYWORDS:

PRINCIPAL INVESTIGATOR: Kelly, William F. CPT MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Pulmonary & Critical Care Medicine

STATUS: O
INITIAL APPROVAL DATE: 26 June 2001

## STUDY OBJECTIVE

To compare the accuracy of F-18 Fluorodeoxyglucose (FDG) Coincidence PET with Tc-99m depreotide in the evaluation of pulmonary nodule(s). Correlation will be made with biopsy pathology or radiographic stability. Accuracy of the scans will also be compared with that of physicians' estimate of malignancy and to Bayesian analysis.

## TECHNICAL APPROACH

WRAMC pulmonary physicians using history and physical examination will evaluate subjects and all available chest radiographs and CT scans. A management plan will be determined as indicated to include serial radiographic follow-up, bronchoscopic or percutaneous biopsy, surgical staging or resection. This is standard of care. Nuclear Medicine scans using F-18 FDG or Tc-99m studies will be obtained and reviewed by board-certified nuclear medicine physicians blinded to the pulmonologist's clinical impression and any pathology data. Physician estimate of PCA, Bayesian analysis estimates (for the solitary pulmonary nodules), 18-FDG coincidence results and Tc-99m depreotide results will be compared to actual pathology and to each other. Actual pathology will be defined as histology of biopsy or surgical specimen. Lesions will be defined as benign if they are radiographically stable for two years.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 21 and the total enrolled to date at WRAMC is 21 (single site study). There have been no adverse events to date and none are expected. Interestingly, there have been discordant results between the two scans in three patients (14%). Scan results often alter physician suspicion of malignancy to a small degree, but do not change management plans. These interim data are being analyzed.

## CONCLUSIONS

This first direct comparison of these two nuclear medicine lung nodule-screening tools is showing them to be discordant sometimes. Data on how such tools affect physician decision-making is being obtained. Additional study is warranted.

Report Date: 2 May 2002 Work Unit # 01-17006

# DETAIL SUMMARY SHEET

TITLE: Delivery of High Concentrations of Inspired Oxygen Using Humidified Oxygen by Nasal Cannula (Vapotherm)

KEYWORDS:

PRINCIPAL INVESTIGATOR: MAJ Melanie L. Guerrero, MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Pulmonary & Critical Care Medicine

STATUS: O
INITIAL APPROVAL DATE: 31 July 2001

## STUDY OBJECTIVE

To compare the arterial partial pressure of oxygen obtained using Vapotherm, a high-flow, humidified oxygen delivery system via nasal cannula with that using a non-rebreather mask in subjects who require chronic supplemental oxygen.

## TECHNICAL APPROACH

Most inclusion and exclusion criteria can be determined from patient records before the initial telephone call. Thus, telephone calls will be directed only to patients who are believed to meet the criteria. However, confirmation will be sought during the telephone conversation as patient records may be incomplete. Both nasal cannula and non-rebreather mask will be compared in patients with compromised lung function requiring chronic supplemental oxygen. Half of the subjects will use the nasal cannula first; the other half will use a non-rebreather mask first. There will be a washout period of sixty minutes in between, during which patients will receive their normal low-flow oxygen supplementation by nasal cannula. The order will be randomized based on random number generation from a computer program.

On the morning of testing, the protocol will be fully reviewed with the subject. Informed, written consent will be obtained. Outpatient records will be reviewed for evidence of cardiac disease. Patients' charts will also be reviewed to determine the etiology of underlying pulmonary disease. Patients will not be required to synchronize respirations with a metronome as originally planned in the study, as this is deemed unnecessary for data analysis. This is only an additional task for the patient that may be uncomfortable and unnatural in the usual breathing pattern. A PCO2 of $\geq$ 45 on the first arterial blood gas taken for study purposes would be an exclusion for further participation on the study.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No recent literature has been published concerning the study. There have been three patients enrolled since final approval of the protocol. It appears thus far that Vapotherm is superior in oxygen delivery compared to the current standard of care using a non-rebreather mask. There have been no adverse events and no patients have been withdrawn from the study.

## CONCLUSIONS

More patients are required to verify the current finding of Vapotherm as a superior oxygen delivery device over the non-rebreather mask.

Report Date: 18 December 2001

Work Unit # 01-17007

# DETAIL SUMMARY SHEET

TITLE: A Phase IV, Multicenter, Prospective, Open-Label, Observational Study to Evaluate Clinical Practice Patterns of Innohep (Tinzaparin odium Injection) in the Treatment of Acute Symptomatic Deep Venous Thrombosis

KEYWORDS: Venous thromboembolism; DVT; low molecular weight heparins

PRINCIPAL INVESTIGATOR: Moores, Lisa MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Pulmonary & Critical Care Medicine

STATUS: C
INITIAL APPROVAL DATE: 31 August 2001

STUDY OBJECTIVE
To determine physician practice patterns and settings for the use of tinzaparin, a low molecular weight heparin used in the treatment of venous thromboembolism.

TECHNICAL APPROACH
Patients with documented DVT who agree to participate are educated on the use and administration of tinzaparin. They are then started on an appropriate dose of the medication, enrolled in the coumadin clinic, and started on appropriate warfarin dosing. The tinzaparin is continued until the INR is determined to be in the therapeutic range two successive days by the coumadin clinic. During this time, demographic, treatment setting, and complication information are collected by the principal investigator. This data is forwarded to the sponsor for analysis.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The sponsor of this study, Dupont Pharmaceuticals, was purchased by another company. The new owners chose not to continue the innovate study. No patients were enrolled at WRAMC prior to closure.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is unknown, if multi-site study.

CONCLUSIONS
None. No patients enrolled.

Report Date: 1 October 2001 Work Unit # 01-1701

# DETAIL SUMMARY SHEET

TITLE: Reference Values for Impulse Oscillometry in Normal Adults

KEYWORDS: spirometry; impulse oscillometry; normal reference values

PRINCIPAL INVESTIGATOR: Hnatiuk, Oleh LTC MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Pulmonary & Critical Care Medicine INITIAL APPROVAL DATE: 21 November 2000

## STUDY OBJECTIVE

To establish reference values for impulse oscillometry in a population of normal adults.

## TECHNICAL APPROACH

Phase II prospective cohort trial. First phase to be performed at WRAMC PFT Lab and involves testing 50 asymptomatic individuals > 18 years old within the hospital staff and population with spirometry and, if normal, with an impulse oscillometer. The second phase involves identifying military posts with large active duty populations and, following local approval, testing each subject with spirometry and impulse oscillometry.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

I am not aware of any new studies with normative data for impulse oscillometry. There has been no progress on this protocol because the WRAMC PFT Lab has not received promised updated software for the impulse oscillometer from the company. According to company officials, the software was shipped from Germany to WRAMC recently and should arrive within several weeks. Also, the Sensormedics oscillometer has not gained FDA approval in the United States and only the Jaeger oscillometer will be used in the study.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0.

## CONCLUSIONS

Due to a significant delay in delivery of promised updated software, the study has not accrued any patients to date. This is expected to change shortly.

Report Date: 10 May 2002

Work Unit #1790

# DETAIL SUMMARY SHEET

TITLE: Acute Hypoxemic Respiratory Failure in Bone Marrow Transplant Patients: A Retrospective Review

KEYWORDS: acute lung injury, ARDS, bone marrow transplantation

PRINCIPAL INVESTIGATOR: Moores, Lisa LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Pulmonary & Critical Care Medicine

STATUS: C
INITIAL APPROVAL DATE: 25 April 1997

## STUDY OBJECTIVE

To determine the incidence of ALI occurring at the time of bone marrow engraftment (Engraftment Syndrome – ES) in autologous bone marrow transplant patients and to determine associated risk factors for the development of the syndrome.

## TECHNICAL APPROACH

A retrospective chart review of all autologous bone marrow transplants done at WRAMC from 1991 to July 1971. Demographic, treatment and clinical course variables were collected in Excel spreadsheet. Patients who developed ES were compared to those who did not. Chi square and Mann-Whitney-U tests were used as appropriate for statistical analysis.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Nothing to report since the APR submitted 26 January 2001.

## CONCLUSIONS

No new progress on this report.

Report Date: 15 February 2002 Work Unit # 1828

# DETAIL SUMMARY SHEET

TITLE: Light Microscopic Immunohistochemistry to Identify Leishmania on Formalin Fixed Human Tissue

KEYWORDS: leishmania, immunohistochemistry

PRINCIPAL INVESTIGATOR: G. Todd Bessinger CPT MC
ASSOCIATES: Aronson, Naomi COL MC; Krivda, Steve LTC MC

DEPARTMENT: Medicine
SERVICE: Dermatology

STATUS: C
INITIAL APPROVAL DATE: 7 January 1997

## STUDY OBJECTIVE

Identify Leishmania organisms in formalin-fixed tissues using light microscopic immunohistochemistry (IHC). Should this technique prove useful, it would provide a simple rapid test for diagnosing leishmaniasis, determining the infecting species, and thereby directing appropriate treatment.

## TECHNICAL APPROACH

Eight species-specific anti-Leishmania monoclonal antibodies will be studied as potential candidates for use in the IHC diagnosis of leishmaniasis. Each of these antibodies will be evaluated on fixed tissues known to contain Leishmania organisms (positive controls) and known not to contain Leishmania organisms (negative controls), at different antibody concentrations, and using standard technical controls. Once the assay parameters have been optimized, these antibodies will be used in the IHC technique to evaluate approximately 40 biopsied tissue specimens from individuals evaluated over the last few years for suspected leishmaniasis at WRAMC. The results of the IHC assay will be compared to the other diagnostic methods used for these specimens: H&E, culture, and animal inoculation.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Four antibodies with WHO designations IX-5H9-C10[M-3] anti-amazonensis, LXVII-1D7-B8 [M-7] anti-mexicana, VII-2C5-C5 [B-5] anti-braziliensis, and XIV-2A5-E9-E7 anti-braziliensis were used as the primary antibody in the immunohistochemistry (IHC) procedure described in the protocol. These four were chosen from the nine remaining antibodies because of their potential relevance in distinguishing between Viannia versus non-Viannia infections.

Thirteen known positive Leishmania-infected (but species-blinded), formalin-fixed skin biopsy specimens were run in the IHC assay. One slide each of the biopsy specimens was incubated with each of the antibodies listed above. In addition, another slide from each specimen was run with a saline (negative) primary antibody control and with the G2D10-pan-species (positive control) primary antibody. In a separate assay, each of the four antibodies listed above was used as a primary antibody in a similar assay using non-fixed, cultured Leishmania organisms as the target.

None of the four test antibodies recognized the formalin-fixed, infected skin biopsies. Also, none of the four significantly reacted with the cultured Leishmania organisms. The positive control antibody (G2D10), which worked so well in previous studies, only weakly recognized the amastigotes in the biopsy specimens or the cultured promastigotes.

## CONCLUSIONS

Unfortunately, despite the care in storage and the lyophilized state if the antibodies, their age may have rendered them less potent. Or, it is possible that the superior sensitivity of the pan-species anti-Leishmania antibody makes it the only one amenable to use in this type of assay.

Report Date: 11 September 2001

Work Unit # 00-1901

# DETAIL SUMMARY SHEET

TITLE: Development of HIV Specific CD+ T Cells

KEYWORDS: HIV, T Cell Lines

PRINCIPAL INVESTIGATOR: COL Naomi Aronson
ASSOCIATES: Dr. Jerome Kim

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 26 October 1999

## STUDY OBJECTIVE

Compare epitope recognition between HIV negative individuals vaccinated with gp160 MN/LAI and HIV infected individuals 2. Generate *Pneumocystis carini* specific CD4+T cell lines to assess the clonal deletion in disease progression 3. Generate *Candida albicans* specific T cell lines from archived samples.

## TECHNICAL APPROACH

Six HIV infected patients WR stage 1, 2 with CD4>400 and no history of gp160 immunization, six HIV infected patients with CD4 50-200, and twelve HIV infected patients with archived PMBC in the HIV repository from past times that they were not Candida anergic who are now Candida anergic will be enrolled. GP 160, Pneumocystis, Candida specific T-cells will be developed. Proliferation assays, T-cell repertoire by BV gene analysis and spectratyping will be performed.

## PRIOR AND CURRENT PROGRESS

Six patients have been enrolled in the first phase looking at gp 160 envelope recognition in HIV patients with CD4>400 as compared to HIV uninfected gp 160 vaccine recipients from anther WRAIR protocol. T cell lines are reported generated from all six HIV patients. This has allowed further analyses (commenced). We have enrolled six patients into the second part of the study, generating *Pneumocystis carini* specific T cell lines in HIV infected patients with a depleted (50-200) CD4 counts. Generating T cell lines for these low CD4 cell count patients, often with poorly controlled viral loads, has proven difficult, albeit some limited success has been noted.

There have been no adverse events and no early withdrawals. This is a single site study. This is a laboratory study and there is no direct benefit for the participants.

The number of subjects enrolled to the study since last APR at WRAMC is five and the total enrolled to date at WRAMC is 12.

## CONCLUSIONS

We conclude that the development of antigen specific T cell lines in the CD4>400 population is feasible and will permit us to study our scientific objectives. The development of T cell lines in those with CD4<200 is more difficult and may be hampered by uncontrolled HIV viral loads.

Report Date: 14 January 2002 Work Unit # 01-19002

# DETAIL SUMMARY SHEET

TITLE: Sodium Stibogluconate Treatment of Leishmaniasis

KEYWORDS: Leishmania, pentavalent antimonials, treatment

PRINCIPAL INVESTIGATOR: Aronson, Naomi E. COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Infectious Disease INITIAL APPROVAL DATE: 27 March 2001

## STUDY OBJECTIVE

Provide sodium stibogluconate (IND 14150) for treatment of cutaneous leishmaniasis and mucosal leishmaniasis (pentavalent antimonials currently considered the drug of choice for these infections). Provide sodium stibogluconate as a second line treatment for viscerotropic and visceral leishmaniasis (liposomal amphotericin B is the drug of choice for these types as it is FDA approved for visceral leishmaniasis).

## TECHNICAL APPROACH

Sodium stibogluconate 20 mg/kg/day will be given IV or IM for 20 days for DOD health care beneficiaries meeting inclusion and exclusion criteria, which include a parasitologic or clinicoepidemiologic diagnosis of leishmaniasis, willing to have therapy at Walter Reed Army Medical Center.

## PRIOR AND CURRENT PROGRESS

The protocol has not yet completed the myriad of sequential approvals required. It is under review at USUHS.

Elucidation of the timeline may be helpful to explain the delays. Since HUC at WRAMC, investigator provided changes to DCI 4/12/01. DCI coordinator provided memo on 5/11/01 for further changes. These proposed changes were not found to be acceptable by investigator/had been discussed in memo to DCI 4/12/01 and required conference with DCI to proceed. More changes were provided in late 5/01. 6/20/01 CIRO approval was received. 7/11/01 protocol reviewed at HSRRB meeting. HSRRB review provided to investigator 7/26/01. Requested revisions made for controversy ensuing from WRAMC DCI as to whether one of the required revisions should be made (making new assent forms for children). Once that was revolved, protocol had to go back to HUC on 10/23/01. Then the protocol had to go back to HSRRB for review. HSRRB approval received 12/27/01. Protocol approval letter was provided by WRAMC 12/27/01. Protocol was submitted to USUHS IRB for approval (requires WRAMC approval letter for submission) on 1/2/02.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

## CONCLUSIONS

The process for approval of an IND that must be evaluated by three local IRBs and CIRO is unnecessarily cumbersome. The timeliness of response and communication with investigator by DCI when changes are required to protocol and the review of those changes could be done in a more expeditious fashion. The response time of HSRRB to protocol changes of their request was also not optimal.

Report Date: 12 July 2002

Work Unit # 01-19003

# DETAIL SUMMARY SHEET

TITLE: Phase 2b Evaluation of Tetravalent Live-Attenuated Dengue Vaccines

KEYWORDS: Dengue, Challenge, Tetravalent live-attenuated vaccine, Protective immunity.

PRINCIPAL INVESTIGATOR: Sun, Wellington COL MC
ASSOCIATES: Robert Gibbons, MAJ(P) MC (WRAIR); Stephen Thomas, CPT MC; David W. Vaughn, COL MC (WRAIR); John Statler, MAJ MC; Clifton A. Hawkes, LTC MC

DEPARTMENT: Medicine; Radiology; WRAIR
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 31 July 2001

## STUDY OBJECTIVE

*Primary Objectives*

1. To evaluate the safety of giving Dengue-1 (DEN-1) and Dengue-3 (DEN-3) challenge viruses or monovalent vaccine to volunteers previously given tetravalent dengue vaccine.
2. To determine if tetravalent vaccine recipients who developed neutralizing antibody are protected from clinical disease from homologous serotype challenge virus.
3. To determine if monovalent revaccination elicits clinical illness and anamnestic antibody response in tetravalent vaccine recipients who did not develop homologous neutralizing antibody.
4. To evaluate in 2 additional flavivirus naïve volunteers if Dengue-4 (DEN-4) H-241 virus is suitable as a challenge virus that consistently causes dengue fever.

*Secondary Objectives*

1. To characterize cellular immune responses to DEN-1 and DEN-3 challenge viruses in volunteers previously vaccinated with tetravalent vaccine and volunteers without previous flavivirus exposure in order to generate hypotheses on correlates of protection.
2. To characterize cellular immune responses to monovalent dengue revaccination in volunteers previously vaccinated with tetravalent vaccine.

## TECHNICAL APPROACH

*Study Subjects:* Young (age 18-45), consenting, healthy adult volunteers who are either previous participants in live-attenuated tetravalent dengue vaccine trial (experimental groups) or have no previous exposure to flaviviruses (control group) were recruited by advertisement or by mail, email or telephone.

*Study Design*: This is a descriptive, controlled, open-label Phase 2b study. However, the assignment of the serotype of virus is masked to both the investigators and volunteers.

The Challenge arm of the study consists of 10 volunteers from previous tetravalent dengue vaccine studies conducted at the Walter Reed Army Institute of Research (WRAIR) and the Center for Vaccine Development (CVD) at the University of Maryland at College Park. Neutralizing antibody status to all four serotypes following vaccination in these volunteers is known. Up to five volunteers with serotype-specific antibody to DEN-1 or DEN-3 will be given DEN-1 or DEN-3 challenge virus, respectively.

The Revaccination arm of the study consists of up to twelve additional volunteers from the same CVD studies. For each of the six vaccine viruses used in previous tetravalent vaccine studies (2 DEN-1, 2 DEN-4, 1 DEN-2 and 1 DEN-3) two vaccinated volunteers with no antibody to that virus will be given the respective monovalent vaccine virus. Only two volunteers were recruited for this arm of the study, thus only the DEN-3 monovalent vaccine was used for this arm.

The Control arm of the study consists of up to six flavivirus-naïve volunteers. Up to two will receive either DEN-1, DEN-3 or DEN-4 challenge virus.

*Dose, Schedule and Route:* All volunteers will receive a single 0.5 ml undiluted dose of challenge or vaccine virus subcutaneously in the deltoid region.

*Study Endpoints:* 1) Presence or absence of clinical disease from challenge virus in antibody-positive vaccinated individuals. 2) Decreased viremia from challenge virus in antibody-positive vaccinated individuals. 3) Clinical safety of monovalent revaccination in antibody-negative vaccinated individuals. 4) Neutralizing antibody response after revaccination in previously antibody-negative vaccinated individuals. 5) Development of dengue fever in the control volunteers given challenge virus.

*Statistics and Analysis:* Data analysis will be primarily descriptive in this exploratory study given the small number of volunteers in each test article group. The occurrence of clinical symptoms, antibody responses and viremia will be recorded and tabulated for each volunteer and compared between the three arms of the study and between the two serotypes of challenge viruses.

*Modifications*: One modification was to allow the use of baseline chest X-rays and abdominal ultrasounds performed in December 2001. Original protocol had required all baseline labs to be done within sixty days of inoculation. This modification was necessary due to a delay of the starting date of the study from 2 January 2002 to 24 May 2002. The reason for the delay of the protocol was to allow the completion of safety testing on the DEN-1 challenge virus. There are no other modifications pertinent to WRAMC part of the protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There is no new literature on dengue challenge study in human volunteers. The number of subjects enrolled to the study is 18 and the total enrolled to date at WRAMC is 6. Study was conducted with masking of the challenge or DEN-3 vaccine virus serotype in the 12 volunteers in the Challenge and Revaccination Group. Virus assignment was unmasked to the Principal Investigator on 1 July (Day 37).

Modifications: The only modification was to allow the use of baseline chest X-rays and abdominal ultrasounds performed in December 2001. Original protocol had required all baseline labs to be done within sixty days of inoculation. This modification was necessary due to a delay of the starting date of the study from 2 January 2002 to 24 May 2002. The reason for the delay of the protocol was to allow the completion of safety testing on the DEN-1 challenge virus.

Adverse Events: There were no serious adverse events. Six volunteers, three in the Challenge Group and three in the Control Group, were hospitalized when they developed fever. One turned out to be a tooth abscess, while the remaining five were considered to be dengue fever. All volunteers recovered clinically without sequelae. Two Control volunteers, one who received DEN-4, and one who received DEN-3, developed elevations of AST/ALT. The first one developed AST of 73 IU/ml (normal 21-72) on Day 17 only. The second one developed elevated AST during Day 9 to Day 17, which peaked at 367 IU/ml on Day 13. ALT was elevated on Day 11 to Day 24 that peaked at 291 IU/ml on Day 13. All elevations returned to normal. The second one was also the only volunteer in the study to develop thrombocytopenia at 94,000 and 92,000/ml on Days 10 and 11, respectively. Of the previous tetravalent vaccinees in the Challenge arm, only volunteers who received DEN-3 challenge virus developed any AST/ALT abnormalities. Of these three, two had clinical dengue and the other was asymptomatic. One had elevated AST (peak 597 IU/ml on Day 9) from Days 6 to 16 and elevated ALT (peak 977 IU/ml on Day 9) from Days 6 to Day 24. The second had elevated AST Days 5 to 17 and elevated ALT (peak 428 IU/ml on Day 9) from Days 6 to Day 24. The third, who was asymptomatic, developed minor AST elevation of 48 IU/ml on Day 9 only. Her ALT was elevated on Day 9 to Day 11 with peak of 85 (normal 9-52 IU/ml). All abnormalities in AST/ALT's resolved by Study Day 30. No volunteers in the Challenge or Revaccination Group developed thrombocytopenia, a sine qua non of dengue hemorrhagic fever. No volunteers developed a positive tourniquet test, another indicator of capillary leakage.

CONCLUSIONS Study is ongoing. Laboratory data is yet incomplete. Conclusions are preliminary. All five volunteers challenged with DEN-1 were protected against disease. Two of five volunteers challenged with DEN-3 were protected against disease. There were no cases of dengue hemorrhagic fever in any volunteers.

Report Date: 8 August 2002

Work Unit # 01-1901

# DETAIL SUMMARY SHEET

TITLE: A Randomized, Open-Label, Phase III, International Study of Subcutaneous Recombinant IL-2 (Proleukin) in Patients with HIV-1 Infections and CD4+ Cell Counts >300/mm3: Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT)

KEYWORDS: HIV, IL-2, ESPRIT

PRINCIPAL INVESTIGATOR: Wortmann, Glenn LTC MC
ASSOCIATES: Naomi Aronson, COL MC; Richard Trotta, LTC MC

DEPARTMENT: Medicine
ERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 17 October 2000

STUDY OBJECTIVE

To compare the effects of subcutaneous recombinant interleukin-2 (SC rIL-2) and no SC rIL-2 on disease progression and death over a 5 year follow-up period in patients with HIV-1 infection and absolute CD4 cell counts of $\geq 300/mm^3$ who are taking combination antiretroviral therapy.

TECHNICAL APPROACH

This is an international, phase III, open-label, randomized trial with a total sample size of 4,000 patients. 2,000 patients will be randomized to SC rIL-2 therapy, and 2,000 patients will be randomized to no SC rIL-2 over a two-year period.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Five patients have thus far been enrolled in the study at WRAMC. Two patients have successfully completed three cycles of IL-2 with substantial improvement in their CD4 count. One patient was randomized to the standard-of-care arm and is being followed. One patient enrolled in the study and then decided not to participate, and one patient enrolled in the study and was then found ineligible secondary to a history of inflammatory bowel disease (the patient had denied a history of bowel disease during the initial interview).

There have been no adverse events at WRAMC. There have been several SAEs at other sites, and those have all been forwarded to the IRB as we received them.

Consent form has been amended on several occasions as required by the IRB.

The number of subjects enrolled to the study since last APR at WRAMC is 5 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is 3,101, if multi-site study.

CONCLUSIONS

The ESPRIT study remains open to enrollment. WRAMC will continue to recruit patients for the study.

Report Date: 6 March 2002 Work Unit # 1903-98

# DETAIL SUMMARY SHEET

TITLE: Development of New Leishmania Diagnostic and Prognostic Indicators

KEYWORDS: leishmaniasis, nitric oxide, PCR

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Wortmann, Glenn LTC MC, Weina, Peter LTC MC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 26 May 1998

## STUDY OBJECTIVE

Obtain patient samples to identify new diagnostic and prognostic indicators for leishmania diagnosis.

## TECHNICAL APPROACH

Patient with suspected leishmaniasis and normal controls will be followed prospectively and have blood drawn before therapy (or day 0 for controls) and at days 7,14 and 20 at 6-8 weeks. Urine will be collected for days 0-7 for measurement of nitrates. Skin biopsies from suspected patients will be used for PCR, leishmania culture and histopathology. Serum is obtained for measurement of soluble exoantigen and nitrates.

## PRIOR AND CURRENT PROGRESS

Twenty-three individuals have been enrolled to date: Fifteen cases and eight controls (six in last year). Two controls dropped out for noncompliance with sample collection. A third case, previously thought to have dropped out, returned for follow-up and completed protocol. No adverse events have been noted (protocol is for blood and urine collection only). A change in medical monitor and addition of associate investigator were only modifications to protocol to date.

The number of subjects enrolled to the study since last APR at WRAMC is 6 and the total enrolled to date at WRAMC is 23. The total number enrolled study-wide is n/a, if multi-site study.

## CONCLUSIONS

No results are available due to limited enrollment to date. Serum and urine samples are being collected to be run in aggregate.

Report Date: 15 May 2002

Work Unit # 1905-98

# DETAIL SUMMARY SHEET

TITLE: Evaluation of the Clinical Efficacy of Antiretroviral Resistance Testing (CERT)

KEYWORDS: HIV, antiretroviral resistance

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Wortmann, Glenn LTC MC; Hawkes, Clifton LTC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 07 July 1998

## STUDY OBJECTIVE

To determine the impact of genotypic and phenotypic antiretroviral resistance on the effectiveness of clinical care of HIV-1 infected subjects. To determine the feasibility of GeneChip HIV PRT assay and Antivirogram assays within clinical practice.

## TECHNICAL APPROACH

Local HIV patients are randomized to receive monitoring with genotypic, phenotypic (Antivirogram assay) or control (Roche Amplicor ultra sensitive PCR) viral load testing. All patients receive their viral loads at 4-month intervals. Those randomized to phenotypic or genotypic resistance testing arms, which have detectable viral loads > 1000 viral copies/ml will also have resistance testing done. Clinical changes in medications and the clinician use or non-use of the results of resistance testing to guide changes is information collected. An addendum (March 99) allows Virco therapeutic drug level monitoring for HIV drug levels in previously enrolled patients. An addendum (May 01) permits P450 polymorphism testing of cohort who enrolled and were taking the antiretroviral efavirenz.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

In the fall of 2001, a genotypic assay (Visible genetics) was FDA approved for HIV resistance testing. Additional controlled trials of resistance testing show variable conclusions. In January 2002, study investigators reviewed the data of this study in the context of an FDA approved assay and decided that is was appropriate to close the study except for data analysis. A last "termination visit" was requested of all active participants. At WRAMC, this has been completed. As of 15 May 2002, all patients have been terminated. The findings of the study include that by KM survival analysis there did not appear to be a difference in time to endpoint (virologic failure) by study arm. In the nonnucleoside and antiretroviral experienced (four or more antiretrovirals before enrollment) subgroup, the time to endpoint was significantly longer (p=.04, .01 respectively) in the phenotypic arm than the genotypic arm (p=5, .08) as compared to the standard of care (viral burden arm). At the WRAMC site, there have been fourteen serious adverse events: One death was due to homicide, and thirteen were hospitalizations. No SAE is assessed as related to this protocol.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 80. The total number enrolled study-wide is 455, if multi-site study.

## CONCLUSIONS

Use of the phenotypic resistance test in HIV patients to guide antiretroviral therapy delays the time to virologic failure in the subset of patients who are antiretroviral experienced. This suggests that phenotypic analysis of resistance may be more useful than the currently available genotypic resistance assay in heavily pretreated HIV patients who appear to be failing therapy.

Report Date: 27 September 2001 Work Unit # 1906-98

# DETAIL SUMMARY SHEET

TITLE: Preveon (adefovir dipivoxil) Expanded Access Program: Protocol GS-97-423

KEYWORDS: HIV, adefovir

PRINCIPAL INVESTIGATOR: Wortmann, Glenn LTC MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Infectious Disease INITIAL APPROVAL DATE: 07 July 1998

STUDY OBJECTIVE
To provide adefovir on a compassionate use basis to patients infected with the HIV virus that are failing or intolerant of other medications.

TECHNICAL APPROACH
To provide adefovir on a compassionate use basis to patients infected with the HIV virus that are failing or intolerant of other medications.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Four patients have been enrolled in this study, and none since the last APR. Two patients were discontinued due to non-compliance, and a third patient stopped the drug due to lack of efficacy. The fourth patient has now stopped the drug due to lack of efficacy and the company's decision to close the protocol. Multiple adverse event reports have been filed with DCI (none of which occurred at this site). This study is now closed. No patients are receiving drug, and no future patients will be enrolled.

The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 170.

CONCLUSIONS
The study is now closed.

Report Date: 27 March 2002

Work Unit # 1909-99

# DETAIL SUMMARY SHEET

TITLE: Analytical Analysis of Recombinant Malaria Proteins

KEYWORDS:

PRINCIPAL INVESTIGATOR: Diarmuid Nicholson, DAC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Infectious Diseases

STATUS: C
INITIAL APPROVAL DATE: 18 May 1999

## STUDY OBJECTIVE

Characterize malarial proteins produced in bacterial hosts with respect to purity, amino acid sequence and identify disulfide linkages.

## TECHNICAL APPROACH

Purify proteins from bacterial lysates by affinity chromatography. Characterize the proteins with MALDI-TOF and HPLC instruments.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The purified proteins have been identified and the molecular weight characterized by MALDI-TOF. The proteins have been further characterized by proteolytic digestion with Trypsin. The resulting peptides have been identified by molecular weight in the MALDI-TOF mass spectrometer. The identification of precise molecular weights made it possible to verify the recombinant protein as the expected recombinant protein. The protein has been submitted for use in vaccine trials.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is NA, if multi-site study.

## CONCLUSIONS

Mass spectrometry provides precise molecular weights that can confirm the primary structure of a protein. Enzymatic digestion of the protein can provide further characterization of the secondary structure of the protein. HPLC and gel electrophoresis can both be used to separate the protein from any contaminating proteins and proteolytic digestion can be successfully applied to separated protein band in the gel. The peptide fragments can be identified by their molecular weight in the mass spectrometer.

Report Date: 12 September 2001 Work Unit # 1976

# DETAIL SUMMARY SHEET

TITLE: Cytokine Expression in Leishmaniasis Patients Treated with Sodium Stibugluconate (Pentostam) Therapy

KEYWORDS: leishmania, Pentostam, cytokines

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Wortmann, Glenn LTC MC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 30 November 1993

## STUDY OBJECTIVE

To describe and characterize cytokine expression of patients infected with *Leishmania* when receiving sodium stibogluconate or amphotericin. Based on cytokine expression, host immune responses will be classified as T-helper 1 or T-helper type CD4 subsets. Change in TH1 and TH2 responses will be described during therapy for insight into disease pathogenesis and therapy. Specific cytokine measurements will be performed and correlated to onset of pancreatitis.

## TECHNICAL APPROACH

Patients will be followed prospectively and have blood drawn before therapy and at days 7, 14, and 20 during therapy and at 6 weeks post-treatment. Serum is obtained for measurement of soluble CD4, IL-1B and TNF-a. Peripheral blood mononuclear cells will be obtained for RNA isolation and cell culture with phorbol ester simulation. Enzyme immunoassay for specific cytokine measurement will be performed on serum and supernatant of cell cultures. Specific cytokine expression will be detected by reverse transcriptase polymerase chain reaction using specific cytokine primers. Addenda 8/99 to change assays to ELISPOT and ELISA for gamma interferon, IL4, IL 10, IL 12 and use *Leishmania* specific stimulation with various antigens and a control of Pentostam. Addenda 6/2000 to allow *Leishmania* TAQman PCR of 40 samples of banked PBMC pretreatment and if positive, at subsequent collection time points.

## PRIOR AND CURRENT PROGRESS

Recent medical literature related to this project was reviewed via Pubmed search engine. We have enrolled 45 cases and 10 controls. Enrollment has been terminated due to meeting target number. Since the last APR, there have been no amendments to the protocol. There are no reported adverse events or study withdrawals. This is a laboratory study and there is no direct benefit for the participants. Serologic cytokine measurements on collected samples have been done. The white blood cells (PBMC) were found to be nonviable and this mitigated against doing many of the assays proposed. The *Leishmania* TAQman PCR of PBMC on 40 patients were all negative. Data analysis of the results obtained form cytokine assays is ongoing.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 55.

## CONCLUSIONS

Initial studies suggest that Pentostam produced elevations in pancreatic enzymes during treatment in all patients and that this does not seem due to cytokine expression of TNF-alpha, IL-1 beta, UK-gamma. Transient increase in nitric oxide with treatment correlated with a successful outcome. TAQman PCR for *Leishmania* was negative using PBMC from forty patients.

Report Date: 14 February 2002

Work Unit #1978

# DETAIL SUMMARY SHEET

TITLE: Treatment of Leishmaniasis with Sodium Stibogluconate (Pentostam)

KEYWORDS: Pentostam, leishmaniasis

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL, MC
ASSOCIATES: Oster, Charles COL, MC; Wortmann, Glenn LTC, MC; Miller, Robert MAJ, MC; Gasser, Robert COL, MC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: C
INITIAL APPROVAL DATE: 28 June 1994

## STUDY OBJECTIVE

To provide therapy with the drug stibogluconate (Pentostam) to patients with the confirmed diagnosis of leishmaniasis.

## TECHNICAL APPROACH

Cutaneous leishmaniasis is treated with Pentostam 20 mg/kg/d for 20 days, and visceral infection for 28 days. Minor modifications to the protocol include changes in laboratory monitoring replacing P4 with P1, P2, P3 and LDH, and permitting flexibility +/- 24 hours in collection of laboratory and EKG monitors. Post treatment photos will suffice rather than measurement if cutaneous lesion appears healed. Addendum in December 1996 allowed 15 patients to have serial T-cell subset analysis. Addendum in June 1996 allowed liberalization of enrollment criteria. Addendum in April 99 to use Pentostam as a second line therapy for visceral leishmaniasis.

## PRIOR AND CURRENT PROGRESS

Forty-two persons (38 cutaneous and 2 visceral) have been treated under this protocol. Two persons (children) were treated under compassionate use of an IND. One patient enrolled in past year and terminated early due to unexpectedly elevated liver functions tests (SAE reported as requested by sponsor). There were two other early terminations – one patient left unexpectedly on the last day before receiving his 20$^{th}$ dose and one patient terminated due to toxicity (increased creatinine and pancreatitis) with uncertainty over Leishmania diagnosis. Four UAE or SAE have been reported including one death due to complications of AIDS, increased creatinine in patient discussed above, and fever, eosinophilia, and interstitial nephritis in a patient at the end of Pentostam treatment that was attributed to ibuprofen. Significant patient benefit was noted in that all patients were healed from their infection (those two who required a second treatment course were healed after the second). The number of subjects enrolled to the study since last APR at WRAMC is 1 and the total enrolled to date at WRAMC is 42.

## CONCLUSIONS

The treatment of Leishmaniasis with sodium stibogluconate is generally effective with only two relapses to date. Toxicity was noted, primarily pancreatic and musculoskeletal, but appeared reversible with drug discontinuation.

Report Date: 23 January 2002 Work Unit #1980

# DETAIL SUMMARY SHEET

TITLE: Pilot Investigation of Selected Desert Storm Veterans

KEYWORDS: Desert Storm, endogenous, retroviruses, immunologic evaluation

PRINCIPAL INVESTIGATOR: Oster, Charles COL MC
ASSOCIATES: Chung, Raymond COL MC; Gartner, Suzanne Ph.D.; Polonis, Victoria Ph.D.

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: C
INITIAL APPROVAL DATE: 14 March 1995

## STUDY OBJECTIVE

To perform a pilot descriptive evaluation of selected Gulf War veterans to include patients with neurologic findings and/or persistent fatigue, autoimmune disorder, lymphopenia, or T-cell cytopenia. To determine if there is scientific evidence for laboratory-based abnormalities which warrant further systemic investigation.

## TECHNICAL APPROACH

One blood draw (120 cc) is collected from each patient, samples are blinded, and the following are performed; immunophenotyping, whole blood smears, peripheral blood mononuclear cells (PBMC) isolation, low density cell quantitation, and PBMC and macrophage culture. The cultures are monitored for retroviral protein production [reverse transcriptase (RT) assay by classical and PCR-based methods] and for unusual morphologic changes such as the formation of multinucleated giant cells or cell fusion. Culture fluids are frozen at several time points, and patient serum, plasma, and PBMC are cryopreserved. The presence of viral RNAs in culture fluids are studied using molecular cloning and automated nucleic acid sequencing. Patient sera are analyzed for antibodies to viral proteins by immunoblotting.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 85. The total number enrolled study-wide is N/A, if multi-site study. There have been no adverse reactions to the blood collection. This study provides no direct benefit to the patients. During the past year, we have proceeded with data analysis. Two manuscripts are in preparation. The first details nucleotide sequences of a retrovirus-like reverse transcriptase gene cloned from cDNA prepared from particle-associated RNA recovered from cell-free culture fluids of cultured patient leukocytes. The second pertains to immunological abnormalities observed in patient specimens, which are suggestive of immune activation. See comment below regarding recent review of literature.

## CONCLUSIONS

We have observed an increased incidence of retroviral expression within our selected Gulf War Veteran group. Our data suggest that this expression is most likely attributable to activation of endogenous retroviruses (genetic elements carried in the germ line and exhibiting a retroviral structure), rather than infection with an exogenous agent. This retroviral expression may be either the initiator or the consequence of immune activation, and related to the immunological changes we have detected in some patients. Retroviral expression and immune activatin may serve as potential indictors and /or effectors of stress-related illness.

A putative association between human endogenous retrovirus expression and immune activation, with potential relevance to neurological disease, has recently been reported. [See Johnston JB *et al*, Monocyte activation and differentiation augment human endogenous retrovirus expression: implications for inflammatory brain diseases. Ann Neurol 50(4): 434-442, 2001.] Considering our findings in light of this, immune activation and/or endogenous retrovirus expression within the brain may also influence neuroendocrine pathways, thereby leading to the clinical symptoms associated with stress-related illness.

Report Date: 25 October 2001

Work Unit # 1984

# DETAIL SUMMARY SHEET

TITLE: The Long-Term Efficacy of BCG Vaccine: A 56-Year Follow-Up

KEYWORDS: BCG, vaccine, tuberculosis

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Santosham, Mathuram MD; Harrison, Lee MD

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 05 December 1995

## STUDY OBJECTIVE

The primary objective of this study is to determine the duration of BCG vaccine efficacy in a Native American placebo-controlled trial with vaccination in the time period 1935-1942. Other related objectives are to describe the chronic disease morbidity and mortality, and to assess risk of malignancy in this group.

## TECHNICAL APPROACH

A total of 3,287 study participants are located and Indian Health Service medical records reviewed. Death certificates are requested for all deceased. State tuberculosis and cancer registries are reviewed. Interviews are done for medical history for those without reviewed medical records.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No change in enrollment. No withdrawals. No serious or unexpected adverse events. Data collection is completed. Literature review shows that the study remains a unique observation. Statistical analysis is in final stages and draft manuscript of findings is nearing completion. The study is open for analysis only.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 3,287. The total number enrolled study-wide is n/a if multi-site study.

## CONCLUSIONS

After exclusions, and patients lost to follow-up before 1 January 1948, 2792 individuals are analyzed (1483 in BCG arm and 1309 in the placebo arm.) K-M time to TB since 31 December 1947 shows a significant divergence of the two arms with p=.003. Life table shows 36 TB cases in BCG arm and 66 in the placebo. There is no significant difference in TB mortality since 1948. Overall BCG vaccine efficacy since 1 January 1948 was 54% (CI 31.5, 69.6). Gender was important as a modifier with females receiving the BCG vaccine having about 52% less hazard of TB since 1948 than males who received BCG.

Report Date: 6 April 2002 Work Unit # 1990

# DETAIL SUMMARY SHEET

TITLE: Sodium Stibugluconate (Pentostam) Pharmacokinetics Protocol

KEYWORDS: pharmacokinetics, Pentostam, leishmaniasis

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Wortmann, Glenn LTC MC

DEPARTMENT: Medicine STATUS: O
SERVICE: Infectious Disease INITIAL APPROVAL DATE: 11 June 1997

STUDY OBJECTIVE:
To provide therapy with the drug Sodium stibugluconate (Pentostam) to patients with the confirmed diagnosis of leishmaniasis. To obtain pharmacokinetic data for patients varying in weight to provide information about the safety and appropriateness of daily dosing of sodium stibugluconate (Pentostam) at 20 mg/kg/d. A sub-objective will be to assess if daily dosing should be on the total or lean body weight.

TECHNICAL APPROACH:
Blood and urine samples are obtained before, during and after pentostam (sodium stibugluconate) therapy as specified in the protocol. Serum and urine antimony levels are determined by two assays at Ft. Detrick and Yale University. No modifications or addenda to protocol have occurred.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
Nine patients have been enrolled at WRAMC. There have been no withdrawals; all nine completed the protocol. One adverse event occurred during the entire protocol, and was a vaso-vagal episode in one volunteer post blood draw. Serum and urine antimony levels have been assayed. Pharmacokinetic modeling has been completed. Clinical correlation of toxicity and efficacy information is being correlated with the antimony levels. A draft manuscript is in progress. Data from other sites is not available to the PI. Literature review shows no new studies on similar information. There is no benefit to participants.

The number of subjects enrolled to the study since the last APR at WRAMC is 9, and the total enrolled to date at WRAMC is 9. The total number enrolled study-wide is not known, if multi-site study.

CONCLUSIONS:
Analysis to provide final interpretation of the results is pending. WRAMC participants in this CDC directed trial-provided information up to sixteen hours after infusion, which is a unique observation. Data from this study may lead to changes in recommendations as to best dosing and treatment regimens with sodium stibugluconate, the drug of choice for new world cutaneous leishmaniasis.

Report Date: 28 September 2001 Work Unit # 1994

# DETAIL SUMMARY SHEET

TITLE: Electrocortical Underpinnings of Dissociation

KEYWORDS: PTSD, dissociation, EEG

PRINCIPAL INVESTIGATOR: Engel, Charles C. LTC MC
ASSOCIATES: Cardeña, E. Ph.D.

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: C
INITIAL APPROVAL DATE: 29 October 1996

STUDY OBJECTIVE
To evaluate the relationship between presentation of trauma-related words, dissociative and anxiety reactions, and cortical and sympathetic response in a group of PTSD and non-PTSD Gulf-War veterans.

TECHNICAL APPROACH
Participants are given a battery of questionnaires that evaluate demographic information, dissociative, hypnotizability and general psychiatric symptomatology. They are then presented with a modified Stroop test, with 4 lists of words (Gulf-War related, generally positive ones, generally negative ones, neutral) while event related potentials and heart rate are monitored. They are also shown a list of trauma-related and neutral words mixed together. Demographic features as well as information from the hospital course are collected in the data collection sheet for descriptive purposes.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
None.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 25. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
This study is no longer underway. Dr. Etzel Cardeña has left USUHS and moved to University of Texas Pan Am. After being requested by DHCC to return the research records, he has agreed to return them.

Report Date: 21 August 2001 Work Unit # 1997

# DETAIL SUMMARY SHEET

TITLE: Testing for Mycoplasmal Infection: Criterion Validity and Replicability of Nucleoprotein Gene Tracking and Forensic Polymerase Chain Reaction Tests

KEYWORDS: Mycoplasma, Gulf War

PRINCIPAL INVESTIGATOR: Engel, Charles C. LTC MC
ASSOCIATES: Shyh-Ching, Lo, MD PhD, Joel Baseman PhD, Garth Nicholson PhD, Joseph Tully PhD, William Reeves MD MSPH

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: C
INITIAL APPROVAL DATE: 28 October 1997

## STUDY OBJECTIVE

The purpose of the current proposal is to study the replicability of NGT and FPCR compared to that for the more commonly used CPCR. This will be assessed mainly through two comparisons: 1) comparison of agreement for NGT and FPCR results between 3 labs newly trained in NGT and FPCR and a lab experienced at running these tests to agreement achieved with CPCR; and 2) comparison of agreement repeat NGT and FPCR results at the experienced lab to agreement achieved when experienced lab repeats CPCR.

## TECHNICAL APPROACH

As per original protocol and addenda dated 6 January 1998, 9 April 1998, and 17 December 1998.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Data analysis was completed in October 2000, and a draft report prepared. The comparisons within and between laboratories found that the reliability for all tests was no better than would be expected by chance. The USAMRMC sponsored a review of the project by the American Institute for Biological Sciences (AIBS) (AIBS report dated 26 February 2001). The AIBS acknowledged the poor reliability within and between laboratories, pointed out myriad problems associated with one laboratory, and recommended that the research project not be continued further.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 82. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

The available evidence indicates that the reliability of the tests within and between laboratories as currently operationalized is no better than expected by chance. The AIBS review recommended that no additional clinical trials or studies requiring detection of mycoplasma be undertaken until a specific, sensitive, and reliable diagnostic assay is established; that emphasis on a peer-reviewed article at this time is premature; and that study participants be informed of the study results. We concur with the recommendations, and study subjects have all been informed of their results.

Report Date: 18 February 2002 Work Unit # 00-2001A

# DETAIL SUMMARY SHEET

TITLE: Pressor Effects of Hemoglobin Based Oxygen Carrying Solution in Human Blood Vessels

PRINCIPAL INVESTIGATOR: Mongan, Paul LTC MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Anesthesia-Operative INITIAL APPROVAL DATE: 7 March 2000

STUDY OBJECTIVE: The aim of this study is to determine the effects of hemoglobin-based oxygen-carrying solutions (HBOCs) on human blood vessels.

TECHNICAL APPROACH: After surgical resection of the specimen, a small portion (1.5") of vessels that will be discarded will be taken from the specimen before its transfer to anatomic pathology. No tissue will be taken if its absence would alter the pathological reading of the specimen or potentially obscure the diagnosis. The use of the tissue at Uniformed Services University of the Health Sciences is not a standard part of patient care at USUHS and is thus research. The specimen will be placed in Krebs solution and transported to the Department of Anesthesiology research laboratory at USUHS by the PI or his designee. Vessels will be prepared and tested using routine vessel ring methodology in our laboratory. In brief, the vessels will be cleaned of excessive adherent tissue, with care being taken not to damage either the vascular endothelium or surrounding neurons in the adventitia. Blood vessels will then be cut into rings (4-5 mm in length). Multiple rings from each vessel will be tested simultaneously. These rings will be placed on stainless steel hooks and lowered into water-jacketed organ baths maintained at 37°C and filled with Krebs-Ringer solution of the following composition (in mM); NaCl, 119; KCl, 4.7; CaCl2, 2.5; KH2PO4, 1.2; MgSO4, 1.2; NaHCO3, 25; and glucose, 5.6. Each vessel will be stretched to its optimal length as determined by the tension response to serotonin (5-HT) measured by a Grass FT10 force transducer. After a 90 min equilibration period, phenylephrine (PE) or 5HT concentration response relationships will be determined. After washing and return to basal tension, vessels will be contracted with increasing concentrations of HBOCs (10-8M to 6x10-6 M). Data will be expressed as a percent of the maximum tension developed in response to a maximum effective dose of PE or 5-HT. To determine the endothelial independent activity of the HBOCs, we will remove the endothelium by gently scraping the luminal wall of the blood vessel. The effectiveness of the removal of functional endothelium will be verified by the absence of a relaxant response to acetylcholine (Ach, 10-6M). These scraped rings will then be used to examine the direct actions of HBOCs on vascular smooth muscle activity. Clarification of the mechanism of changes in tension related to the HBOC will be done by incubating the vessel rings with specific blockers of nitric oxides synthase, soluble guanyl cyclase, endothelial phoshpodiesterase, endothelin, cAMP, IP3, pathways and KATP channels. After study, excess tissue will be appropriately disposed of as medical waste according to USUHS guidelines. Genetic testing will not be done.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
No new information. No progress has been made in the past year due to an inability to procure additional equipment to support these studies. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

CONCLUSIONS:
None to report. While this remains a worthwhile venture to foster academic productivity in an area related to combat casualty care by utilizing available human vessels for testing HBOCs, the lack of institutional commitment by WRAMC and/or USUHS to purchase the necessary equipment makes it unlikely that any progress will be made on this project.

Report Date: 18 February 2002 Work Unit # 00-2002A

# DETAIL SUMMARY SHEET

TITLE: Developing a Control Population for Alternative Phenotyping for Malignant Hypothermia Using Peripheral B Lymphocytes

KEYWORDS:

PRINCIPAL INVESTIGATOR: Mongan, Paul LTC MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: C
SERVICE: Anesthesia-Operative INITIAL APPROVAL DATE: 14 March 2000

## STUDY OBJECTIVE

The objective of this proposal is to develop normal values for a control population to compare with MH susceptible populations for MH phenotyping using peripheral B lymphocytes. The central hypothesis of this proposed research is that functional abnormalities in skeletal muscle type isoform RYR1-mediated $Ca^{2+}$ regulation is a ubiquitous phenomenon in MH susceptible individuals. This abnormality can be demonstrated not only in skeletal muscles, but in other cells which the RYR1. The rationale for the proposed research is based on our recent findings in peripheral B cells. Firstly, B cells express the RYR1 that appear to function as a $Ca^{2+}$ responses release channel during B cell activation. Secondly, our preliminary studies also indicate that the $Ca^{2+}$ responses of B cells to the RYR1 activating agents caffeine ($p<0.0001$) or 4-chloro-m-cresol ($P<0.05$) are significantly greater in MH susceptible than in MH negative individuals. In the present study, we propose to study $Ca^{2+}$ signaling in B cells with the RYR activating agent caffeine or 4-chloro-m-cresol in B cells to develop a normal control population to which we can compare MH susceptible (MHS) individuals. We will enroll normal patients and compare $Ca^{2+}$ responses in B cells with results obtained from MHS patients.

Specific Aim:

1. To develop normal values for the $Ca^{2+}$ response in B cells to caffeine and 4CmC in a normal control population.
2. To validate the $Ca^{2+}$ response with precise fluorimetric measurements.

## TECHNICAL APPROACH

We will test the $Ca^{2+}$ response of B cells to caffeine and 4CmC in normal individuals. Stock solutions for caffeine and (100 mM) and 4CmC (100 mM) will be freshly made in HBSS and DSMO, respectively. Changes in $[Ca^{2+}]i$ will be directly measured in B cells by measuring the fluorescence intensity if fluo-3-loaded cells (Sei and Arora 1991; sei et al. 1991). This technique requires no cell separation. Cells ($2 \times 10^6$)/ml) will be loaded with 1 mM fluo-3 (Molecular Probes, Inc.) by incubation in subdued light (60 min, 25°C0 with acetoxy-methyl ester. The cells are permeant to this form of the dye and intracellular esterases hydrolyze the fluo-3 ester to the active and impermeant fluo-3 form in the cytoplasm. Fluo-3-loaded cells will then be stained with either phycoerythrin (PE)-conjugated CD4, CD8, leu12, or LeuM3 mAB. Cells will then be washed three times with HBSS and re-suspended in 1 ml of HBSS and analyzed by FACScan (Becton-Dickinson). Forward and right angle scatter signals will be displayed on a linear scale, with the forward scatter adjusted to gate cells from debris. For dual color analysis of intracellular fluo-3-fluorescence (excitation at 488 nm with emission at 525 nm) and PE (excitation at 488 nm, with emission at 585 nm) signals will be detected after separation with 530 (FL-1) and 585 (FL-2) band pass filters respectively. FL-1 fluorescence is recorded as a log amplified signal but displayed as a linear signal, whereas FL-2 (PE) fluorescence is recorded and displayed as a log amplified signal. Cross-over of FL-1 fluorescence into the FL-2 detection window will be compensated by analog subtraction at the preamplifier stage. The FL-1 signal for fluo-3 will be calibrated by transporting in saturating $Ca^{2+}$ with ionomycin

(Molecular Probes) to obtain the minimum signal ($F_{min}$). The $[Ca^{2+}]i$ can be calculated from the fluo-3-fluorescence intensity using the formula: $[Ca^{2+}]i = Kd\ (F- F_{min})/ (F_{max}- F)$, where $[Ca^{2+}]i$ = intracellular ionized calcium concentration; Kd = 400 nM for the intracellular dye. Previous experiments indicate that $Ca^{2+}$ response in $CD4^+T$, $CD8^+T$, B cells and $LeuM3^+$ monocytes was clearly detectable within mixed mononuclear cell preparations.
Precise quantitative confirmation of the flow cytometric analysis $[Ca^{2+}]i$ measurements will be performed by fluorescence scanning techniques after CD magnetic bead reverse isolation of the B-cell population. This technique is more sensitive and precise for $[Ca^{2+}]i$ measurements than flow cytometry. However, due to the complexity of isolation and setup, this measurement technique would not be suitable for a screening test. It can, however, support the results and applicability of the flow cytometry tests.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Unfortunately, the current information available indicates that this line of investigation will not lead to a better diagnostic screening test for Malignant Hyperthermia and associated disease states. B cells have a variable expression of RYR1 and thus cannot be a reliable test for MH. Therefore, we will need to terminate this project.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

CONCLUSIONS
Further work on the development of a noninvasive test for MH with B cells is not warranted.

Report Date: 18 September 2002 Work Unit # 01-20002a

# DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Comparison of One-Needle Versus Multiple-Needle Technique for Lumbar Medial Branch Block

KEYWORDS: medial branch block, facet joint, injection, low back pain

PRINCIPAL INVESTIGATOR: MAJ Steven P. Cohen MC
ASSOCIATES: Milan Stojanovic, MD, Massachusetts General Hospital, Boston, MA

DEPARTMENT: Surgery
SERVICE: Anesthesia-Operative

STATUS: C
INITIAL APPROVAL DATE: 18 September 2001

STUDY OBJECTIVE:
Part I: To determine whether or not using one needle from one skin entry point to block several medial branch nerves is as effective as using the more common method of using one needle and a different skin entry point for each nerve blocked.

TECHNICAL APPROACH:
All patients with suspected facet joint arthropathy who consented underwent medial branch blocks under either the single needle or multiple needle approach. In those patients who obtained good temporary relief as measured by a pain diary, on their next visit they underwent medial branch blocks using the other technique. Patients with good relief from both blocks proceeded to undergo radiofrequency denervation of the nerves.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
We have had a preliminary report describing our technique accepted for publication in Clinical Journal of Pain. Stojanovic MP, Zhou Y, Hord D, Vallejo R, Cohen SP. A new technique for medial branch block: The one needle approach. Accepted to Clin J Pain 6/02. In Press.

The number of subjects enrolled to the study since last APR at WRAMC is 12 and the total enrolled to date at WRAMC is 12. The total number enrolled study-wide is 20 (8 at Mass General), if multi-site study.

CONCLUSIONS:
Since the MGH investigators still need 5 more patients, a statistical analysis has not been performed. However, based on our results, it appears that using the 'single-needle approach' is quicker to perform, less painful to the patient, and based on contrast spread, is equally effective as a test to diagnose facet joint arthropathy as the 'multiple needle approach'. The PI has now PSC'd and the study is closed at WRAMC.

Report Date: 21 September 2001 Work Unit # 01-2001a

# DETAIL SUMMARY SHEET

TITLE: Comparison of Two Plasminogen Activators in Reducing Bleomycin Induced Pulmonary Fibrosis in the Rat

KEYWORDS: animal, rat, pulmonary fibrosis model, ARDS, hydroxyproline, bleomycin pulmonary injury, fibroproliferation, rtPA, rhUK

PRINCIPAL INVESTIGATOR: Mongan, Paul LTC MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Anesthesia-Operative

STATUS: O
INITIAL APPROVAL DATE: 3 October 2000

## STUDY OBJECTIVE

To compare and contrast anti-fibrinolytic agents in reducing lung fibrosis using the rat bleomycin lung fibrosis model.

## TECHNICAL APPROACH

The experimental design is a block randomized control study (control injury and therapy) of the effect of the treatments rTPA and rhUK in reducing fibrosis in a rat bleomycin model of ARDS. In brief, sixty adult male Sprague-Dawley rats weighing 240-280 gm will be block randomized into five groups. Twelve rats will serve as the sham injury and control vehicle therapy group (0.3 ml phosphate-buffered saline (PBS) control). The additional forty-eight rats will be subjected to a standard intratracheal bleomycin lung injury protocol and randomized to one of four intratracheal treatments of rTPA (250 or 500 mcg in 0.3 ml PBS), rhUK (12,500IU), or delivery vehicle controls (0.3 ml PBS).

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Due to problems in moving money to USUHS to cover per diem costs prior to starting animal work, the schedule would not permit any work to be accomplished before the end of the fiscal year. No new pertinent literature is available.

## CONCLUSIONS

None to report.

Report Date: 17 May 2002 Work Unit # 2078A

# DETAIL SUMMARY SHEET

TITLE: In Vitro Diagnosis of Malignant Hyperthermia With 4-Chloro-M-Cresol and Ryanodine
KEYWORDS:

PRINCIPAL INVESTIGATOR: Mongan, Paul LTC MC
ASSOCIATES: Dr. Sheila Muldoon, MAJ John Armstrong, CPT Lynn Giarrizzo, CPT Grant Lynde, Saiid Bina, Ph.D

DEPARTMENT: Surgery STATUS: C
SERVICE: Anesthesia and Operative INITIAL APPROVAL DATE: 25 May 1999

## STUDY OBJECTIVE

Our objective is to determine if 4-Chloro-M-Cresol (4-CmC) and ryanodine would be useful adjunctive agents to be used as our supplemental tests for the diagnosis of malignant hyperthermia (MH). The contracture response of normal skeletal muscle obtained from volunteers without MH or any other neuromuscular disease to 4-CmC and ryanodine will be characterized.

## TECHNICAL APPROACH

The muscle specimens for the ryanodine and 4-chloro-M-Cresol (4-CmC) contracture tests will be obtained from a total of 15 consenting subjects between the ages of 18 and 60 years scheduled for elective surgery at Walter Reed (WRAMC) or the National Naval Medical Center (NNMC). The location of the surgery dictates the muscle group to be sampled. Patients undergoing lower extremity surgery such as total hip or total knee arthroplasty will have the muscle taken from the vastus muscle group. Patients undergoing abdominal surgery will have the muscle specimen taken from the rectus abdominis. Patients with a history of malignant hyperthermia (MH), neuromuscular disorders or any neuromuscular disease are excluded from participation. As an added precaution to the prevention of enrollment of individuals with neuromuscular disease, a screening creatine phosphokinase (CPK) is obtained. An elevated CPK excludes the volunteer from participation. The type of anesthesia used during the surgery will not influence the results of the tests and will be determined by the anesthetizing team. Shortly after initial approval of the protocol at Walter Reed, approval for this study was obtained at NNMC, and an addendum to the protocol was submitted to and approved by DCI to that effect.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is 2, if multi-site study. No enrollment in the past year.

## CONCLUSIONS

Due to inactivity and lack of time for the investigators to pursue this investigation, the PI requests that the study be closed.

Report Date: 17 March 2002

Work Unit # 00-2001

# DETAIL SUMMARY SHEET

TITLE: Cytotoxic T Lymphocyte Recognition of Epithelial Cancers

KEYWORDS:

PRINCIPAL INVESTIGATOR: LTC George E. Peoples MC/ LTC (P) Craig Shriver MC (acting)
ASSOCIATES: CPT Gayle Ryan MC; CPT Bryan Fisk MC; Dr. Vasantha Srikantan

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 4 April 2000

## STUDY OBJECTIVE

To collect discarded tissue, blood, and body fluids in order to investigate the cellular immune response to epithelial cancers in order to identify common tumor antigens that may serve as the target of immunotherapeutics such as vaccines.

## TECHNICAL APPROACH

Patients with known epithelial malignancies such as ovarian, breast, lung and prostate who are having blood drawn, malignant pleural effusions or ascites removed, or surgical removal of large tumors are identified by their providers. These providers contact us to inform us of tissue or body fluids that are to be discarded. Prostate patients who have been enrolled in the serum bank CPDR trial have been identified since the cellular components of their blood draw are discarded. The patients are consented unless the samples are collected without patient identification. The lymphocytes and/or tumor cells are isolated and stored for future studies.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

We have not enrolled any new patients into this study since the last APR. We want to keep this protocol open in order to assess the feasibility of investigating the use of peptide cancer vaccine immunotherapy as an adjuvant to surgical and chemotherapy of lung cancer. No consented patient has asked for his or her sample to be removed from study.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 48.
Review of recent literature reveals no new findings in this field.

## CONCLUSIONS

There are no new conclusions since the last APR.

Report Date: 30 May 2002 Work Unit # 00-2002

# DETAIL SUMMARY SHEET

TITLE: Sentinel Lymph Node (SLN) Evaluation in Colorectal Cancer (CRC)

KEYWORDS:

PRINCIPAL INVESTIGATOR: LTC George E. Peoples MC

ASSOCIATES: COL Daniel Otchy MC; LTC (P) Craig Shriver MC; LTC Carol Adair MC; CPT Darin Cox MC; CPT Dwight Kellicut MC

DEPARTMENT: Surgery STATUS: O
SERVICE: General Surgery INITIAL APPROVAL DATE: 18 April 2000

## STUDY OBJECTIVE

To determine the feasibility and usefulness of sentinel lymph node (SLN) biopsy in colorectal cancer (CRC).

## TECHNICAL APPROACH

The surgery performed for these patients is standard. The blue dye is injected intramurally around the tumor either in vivo or ex vivo. The blue nodes are labeled as sentinel and submitted separately to pathology.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

We have completed our ten patient pilot trial in which the use of isosulfan blue was injected ex vivo. Additionally, we performed sentinel lymph node injections in vivo with seven patients. We were able to find sentinel nodes in all 17 patients. The average number of SLN was 5.5 with no differences between injection techniques (ex vivo vs. in vivo). Of the 17 patients, 10 had negative nodes and 7 had positive nodes on their final pathologic report. The SLN accurately predicted the nodal basin in all 17 patients. There were no false negatives. Most importantly, four patients (23%) were upstaged as a result of the serial step sectioning and immunohistochemical staining of the SLN. Therefore, in the pilot trial, we demonstrated a 23% upstaging of the group, or a doubling of the positive nodes found utilizing this new staging technique. We will continue to accrue patients. We have not seen any reactions to the isosulfan blue dye. The technique appears to work just as well ex vivo (n=10) as in vivo (n=7). There are 2 reports from the same group on the utility of SLN in CRC, but this technique is not widely used yet. CALGB is starting a limited access feasibility trial of SLN in CRC in which we have been invited to participate.
The number of subjects enrolled to the study since last APR at WRAMC is 4 and total enrolled to date at WRAMC is 17.

## CONCLUSIONS

The SLN technique is feasible and would appear to improve staging in CRC from our limited preliminary results.

Report Date: 25 April 2002

Work Unit # 00-2003

# DETAIL SUMMARY SHEET

TITLE: Evaluation of Neutrophil Activation in Diabetes After Carotid Endarterectomy

KEYWORDS:

PRINCIPAL INVESTIGATOR: CPT Scott Rehrig MC
ASSOCIATES: David Gillespie, LTC MC

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 18 April 2000

## STUDY OBJECTIVE

Diabetes is a known risk factor for increased morbidity and mortality following most surgical procedures and traumatic injuries. The primary hypothesis in this study is that in diabetes surgical intervention alone alters the neutrophil (PMN)-endothelial cell interaction, which may play a role in the increased organ injury observed in these patients. The aim of this study is to evaluate the effect of non-insulin dependent (NIDDM) diabetes on neutrophil cell adhesion molecule expression and hydrogen peroxide production in the context of a surgical procedure.

## TECHNICAL APPROACH

Patients were informed of the protocol and consented prior to their operation. Patients served as their own controls. Preoperative blood was collected prior to procedure through an indwelling line placed for the purpose of intraoperative monitoring. A second blood draw was obtained intraoperatively via the same indwelling catheter one hour after skin incision. The third and final collection was obtained within twenty minutes upon arrival to post anesthesia care unit, via indwelling catheter. The samples were then transported to USUHS at room temperature. Red blood cells were lysed using 1x lysis buffer for twenty minutes. The samples were then centrifuged, red cells decanted, and the neutrophil pellets were washed in buffered saline. To determine expression of CD18 and CD11b, the isolated neutrophils were exposed to anti-human CD18 and CD11b antibody for fifteen minutes on ice. The amount of hydrogen peroxide produced by neutrophils was then maximally stimulated oxidative burst. After incubation, the cells were rewashed and suspended in PBS for flow cytometric analysis. The neutrophils were identified on forward and right angle scatter of a 488nm argon laser on an EPICS XL. The cellular fluorescence of each of three measures (DCF, CD11b, and CD18) were measured with logarithmic amplification and expressed as percent positive cells compared to cells stained with isotype control antibody.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This protocol utilizes flow cytometry to measure neutrophil function in diabetic surgery patients. This instrument requires very specialized training for its operation and subsequent interpretation of data. Unfortunately, Dr. Fleming is no longer an associate investigator. She represented the main technical resource for the flow cytometry. As a "fallback", we attempted to utilize the flow cytometry resources at the DCI lab, but due to technical and logistical problems, were not successful. As a result, the study has been on hold. Dr. Gillespie, staff vascular surgeon, will be assuming the role of principal investigator, as I am due to graduate and PCS to Fort Campbell, KY. Dr. Gillespie is currently TDY at Landstuhl Army Medical Center, Germany. Upon his return in the early summer of 2002, he plans to seek new immunology support and expertise for the flow cytometer in hopes of continuing the study. The number of subjects enrolled to the study since last APR at WRAMC is 0, and the total enrolled to date at WRAMC is 5.

## CONCLUSIONS

Study is currently on hold until new PI returns from overseas commitment.

Report Date: 25 March 2002 Work Unit # 00-2004

# DETAIL SUMMARY SHEET

TITLE: Phase 1b Trial of HER-2/neu Peptide (E75) Vaccine in Patients at High Risk for Recurrence after Surgical Extirpation of Prostate Cancer

KEYWORDS: Vaccine, Her2 neu, prostate cancer

PRINCIPAL INVESTIGATOR: LTC George E. Peoples MC/ LTC(P) Craig Shriver MC (acting)
ASSOCIATES: CPT Gayle Ryan, CPT Jennifer Gurney, CPT Raj Bannerji

DEPARTMENT: Surgery STATUS: O
SERVICE: General Surgery INITIAL APPROVAL DATE: 23 May 2000

## STUDY OBJECTIVE

1) Assess safety and document local and systemic toxicity to the peptide vaccine (E75+ GM-CSF).
2) Determine maximum tolerated dose (MTD) and optimal biologic dose (OBD) for the peptide vaccine.
3) Evaluate the in vivo cellular immune response to the peptide vaccine.
4) Evaluate time to recurrence in the vaccinated patients vs. matched controls.

## TECHNICAL APPROACH

Eligible patients are identified and offered study participation after referral from their urologist. Consenting patients are tested for HLA A2 type: A2+ patients receive vaccine, A2- patients are observed clinically q3 months for 18 months. Patients assigned to vaccine are skin tested to assess immunologic intactness and then vaccinated q 3 to 4 weeks x 6 with blood draw before each vaccine to assess peptide-specific immune response. Patients are observed with serial vital signs for one hour after each vaccine and at 48 hours for delayed hypersensitivity reaction. Vaccinated patients return for a final blood test and skin test four weeks after series is complete, and followed clinically q3 months for 18 months.

Vaccine is given by intradermal injection 0.5 cc x 2 with a dose escalation scheme for three patients at 100 mcg of peptide, three patients at 500 mcg of peptide, and three at 1000 mcg of peptide -- with this dose for remaining patients if well tolerated. This study was amended to add FDA administrative changes and to add a group of intermediate risk patients thus expanding enrollment.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

During this reporting period, the protocol has been amended to add a group of patients with a modified vaccination schedule and to include dose reduction for patients with vaccine reactions. The number of subjects enrolled to the study since last APR at WRAMC is 7 and the total enrolled to date at WRAMC is 23 (13 vaccinated and 10 on observation arm). Dose escalation has been completed. Adjustment to vaccination schedule is now being implemented. One patient was withdrawn from further vaccination after an adverse reaction, but remains under study observation. Five adverse events have been reported to the IRB (WRAMC and USUHS) in this reporting period: three large local reactions (grade II), one serious flu type reaction (grade II) and one secondary malignancy (BCC). No patients have suffered any sequellae from these reactions.
Review of current literature reveals little new information. None of the information has an effect on the direction of this study.

## CONCLUSIONS

No clinical conclusions have been reached.
Dimer Assay: We tested and implemented the HLA-A2 dimer assay as a means to monitor the in vivo immune response to peptide vaccinations. The dimer assay showed good correlation with standard immunologic assays and has become part of our standard battery of immunologic tests for patients receiving E75 peptide vaccination.

Report Date: 25 March 2002

Work Unit # 00-2005

# DETAIL SUMMARY SHEET

TITLE: Phase 1b Trial of HER-2/neu Peptide (E75) Vaccine in Breast Cancer Patients at High Risk for Recurrence after Surgical and Medical Therapies

KEYWORDS: Vaccine, Her2 neu, Breast cancer

PRINCIPAL INVESTIGATOR: LTC George E. Peoples MC; LTC (P) Craig Shriver MC (acting)
ASSOCIATES: CPT Gayle Ryan, CPT Jennifer Gurney, CPT Raj Bannerji

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 23 May 2000

STUDY OBJECTIVE

1) Assess safety and document local and systemic toxicity to the peptide vaccine (E75).
2) Determine maximum tolerated dose (MTD) and optimal biologic dose (OBD) for the peptide vaccine.
3) Evaluate the in vivo cellular immune response to the peptide vaccine.
4) Evaluate time to recurrence in the vaccinated patients vs. matched controls.

TECHNICAL APPROACH

Eligible patients are identified and offered study participation after referral from their oncologist or radiation oncologist. Consenting patients are tested for HLA A2 type: A2+ patients receive the vaccine; A2- patients are observed clinically Q3 months for 18 months. Patients assigned to vaccine are skin tested to assess immunologic intactness and then vaccinated q 3 to 4 weeks x 6 with blood draw before each vaccine to assess peptide-specific immune response. Patients are observed with serial vital signs for one hour after each vaccine and at 48 hours for delayed hypersensitivity reaction. Vaccinated patients return for a final blood test and skin test 4 weeks after series is complete, and then are followed clinically Q3 months for 18 months. Vaccine is given by intradermal injection 0.5 cc X 2 with a dose escalation scheme for 3 patients at 100 mcg of peptide, 3 patients at 500 mcg of peptide, and 3 at 1000 mcg of peptide -- with this dose for remaining patients if well tolerated. This study was amended to: 1) add FDA changes; 2) add a group of intermediate risk patients; and 3) clarify recruiting procedures and approve a telephone script and patient letter for use in patient recruiting.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

During this reporting period, the protocol has been amended to add a group of patients with a modified vaccination schedule and to include dose reduction for patients with vaccine reactions.

The number of subjects enrolled to the study since last APR at WRAMC is 16, and the total enrolled to date at WRAMC is 26 (10 vaccinated, 15 being observed, 1 withdrew before assignment). Dose escalation has been completed. Adjustment to vaccination schedule is now being implemented. The total number enrolled study-wide is 28. One patient withdrew consent before beginning active study participation due to family objections to her taking part. One patient withdrew from active vaccination after an adverse event, but remains under study observation. Two adverse drug reactions (grade II) occurred at WRAMC and one large local vaccine reaction occurred at CBCP site in Windber, PA during this reporting period. No patients have suffered sequellae. These reactions were reported to IRB at WRAMC and USUHS. Review of the current literature reveals little new information. No information has an effect on the direction of this study.

CONCLUSIONS: No clinical conclusions have been reached.
Dimer Assay: We tested and implemented the HLA-A2 dimer assay as a means to monitor the in vivo immune response to peptide vaccinations. The dimer assay showed good correlation with standard immunologic assays and has become part of our standard battery of immunologic tests for patients receiving E75 peptide vaccination.

Report Date: 3 May 2002

Work Unit # 00-2006

# DETAIL SUMMARY SHEET

TITLE: Creation of a Retrospective and Prospective Database of Patients Evaluated and Treated for Breast Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Peoples, George E. LTC MC
ASSOCIATES: Shriver, Craig LTC (P) MC; Maniscalco-Theberge, Mary COL MC; Arciero, Cletus CPT MC

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 25 July 2000

STUDY OBJECTIVE

1. To collect data beginning on DCI approval of this protocol on all patients 18 and older who present to the General Surgery clinic at WRAMC with breast cancer.
2. To utilize this database to analyze the diagnosis treatment and treatment outcomes for patients undergoing treatment for breast cancer. Analysis will include but not be limited to: risk factors for developing breast cancer, effectiveness of various modalities of treatment, risk of recurrence.

TECHNICAL APPROACH

The patients are identified by the CBCP nurse case-managers in the Comprehensive Breast Center. These patients are counseled and consented to be a part of this prospective clinical database. The nurses and physicians seeing the patient collect the information on data forms; then CBCP data managers enter the data into the database. The patients are assigned unique CBCP numbers to protect their confidentiality. The identifier code is kept secured in the CBCP Director, Dr. Shriver's office. He is the only person having access to the code.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 44 and the total enrolled to date at WRAMC is 89. The total number enrolled study-wide is 89, if multi-site study. There have been no adverse events and no patients have withdrawn from the study.

A review of the literature revealed no publications within the last year reporting data from studies of a similar design.

CONCLUSIONS

This protocol is progressing as planned.

Report Date: 13 February 2002

Work Unit # 01-20003

# DETAIL SUMMARY SHEET

TITLE: A Prospective Randomized Phase III Study Comparing Radiofrequency Ablation Versus Cryosurgical Ablation for the Treatment of Malignant Liver Tumors

KEYWORDS:

PRINCIPAL INVESTIGATOR: Peoples, George LTC MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 23 January 2001

STUDY OBJECTIVE:
To evaluate any differences in morbidity, disease-free survival, or overall survival in patients with metastatic liver cancer treated with ablative technologies.

TECHNICAL APPROACH:
After randomization, patients undergo radiofrequency ablation or cryoablation, (intra-op), of liver mets. End points include post-op morbidity, and disease-related survival.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
No randomized trials had been previously reported, and none have been recently reported either, evaluating these two common liver ablative techniques.

The number of subjects enrolled to the study since last APR at WRAMC is 3 and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
Only three patients enrolled to date. After approval of APR, we will continue enrolling appropriate patients. Many patients don't meet inclusion criteria because they have too many lesions in the liver being treated.

Report Date: 15 May 2002 Work Unit # 01-20004

# DETAIL SUMMARY SHEET

TITLE: A Randomized, Double-Blind, Multi Center, Comparative, Phase III Study Of Intravenous BMS-284756 With Or Without Oral BMS-284756 Follow Up Versus IV Piperacillin/Tazobactam With Or Without Oral Amoxicillin/Clavulanate Follow-Up In The Treatment Of Complicated Skin And Skin Structure Infections

KEYWORDS: skin and skin structure infections, Piperacillin/Tazobactam, placebo, clinical trials, Amoxicillin/Clavulanic Acid

PRINCIPAL INVESTIGATOR: CPT Christopher Swiecki, MC

ASSOCIATES: MAJ Michael Woll, MC

DEPARTMENT: Surgery STATUS: C
SERVICE: General Surgery INITIAL APPROVAL DATE: 23 January 2001

STUDY OBJECTIVE:
The primary objective of this study is to demonstrate the clinical efficacy of BMS-284756 600 mg IV QD (optional switch to BMS-284756 600 mg PO QD), by showing a non-inferior clinical cure rate relative to that of a standard regimen of piperacillin/tazobactam 3.375 gm IV Q6H (optional switch to amoxicillin/clavulanate 500 mg PO Q8H) in the treatment of complicated skin and skin structure infections.

TECHNICAL APPROACH
Patients diagnosed with complicated skin and skin structure infections requiring initial IV therapy will be screened for inclusion in the study. If they meet the inclusion criteria, they are enrolled and randomized to receive either BMS-284756 with piperacillin/tazobactam placebo or the standard treatment regimen of piperacillin/tazobactam 3.375 gm IV with matching BMS-284756 placebo for treatment of their skin infection. Total therapy will be for a minimum of 2 days up to 14 days and will be based on the subject's clinical response to the therapy at the investigators judgment. Blinding is performed by the pharmacy. Switch to oral medications is made when the patient's clinical status allows it. The endpoint is resolution of symptoms or when the investigator determines the treatment is not effective. The Test of Cure visit (TOC) will include a wound culture (if clinically indicated), a blood and urine lab workup, physical exam and a clinical evaluation of signs and symptoms of the primary infection to assess the efficacy of the treatment.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
No subjects have been enrolled at this time. The total number of subjects to be randomized study wide will be 430 at 74 different sites in effort to obtain 300 evaluable subjects. Several safety reports regarding potential adverse events related to the study drug have been published and are to be filed with DCI.

CONCLUSIONS
No conclusions have been reached at this time. The Clinical Project Manager informed the WRAMC site that they had been trying to get the WRAMC site up and running since October 2000. However, due to the tight timelines, they have not been able to move forward with the WRAMC site.

Report Date: 18 May 2002

Work Unit # 01-20005

# DETAIL SUMMARY SHEET

TITLE: Comparison of Doppler Flow Characteristics of the Superior Mesenteric Artery to Invasive Pulmonary Artery Catheterization in Critically Ill Patients

KEYWORDS: Doppler, SMA blood flow

PRINCIPAL INVESTIGATOR: CPT Jimie Anderson MC
ASSOCIATES: LTC Goff

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 22 May 2001

## STUDY OBJECTIVE

To describe blood flow in critically ill patients using noninvasive duplex ultrasound and pulmonary artery catheter (PAC) measurements.
To explore whether changes in hemodynamic status influence resistance index, pulsatility index, SMA diameter and flow using duplex ultrasound.
To explore whether a relationship exists between blood flow recorded by duplex ultrasound and blood flow recorded by pulmonary artery catheter.
PI anticipates finding a decreased SMA flow during hypovolemic shock.

## TECHNICAL APPROACH

Prospective, nonrandomized, one group, pilot study. Subjects in this study will essentially be used as their own controls because all patients/subjects eligible for study will have both ultrasound and PAC measurements done.

Methodology: Subjects will be recruited preoperatively when the use of PAC is anticipated (a probable significant blood loss) or postoperatively if PAC is inserted. The decision for the use of pulmonary artery catheter (PAC) will be made by the primary team. No patient will have a PAC placed or extended for the purpose of this study. Patient will consent prior to elective surgery or in the ICU. Preliminary data will be collected from patient medical records such as sex, age, body mass index, pertinent past medical history, diagnosis, fasting status, and vasoactive drug use. This data will be placed in the database. This data must be collected because it may affect measurements between patients. Patient will be given an ID number. No name, hospital ID, or SSN will be placed in the database. Pertinent past medical history includes diseases that may contribute to false vascular readings, such as hypertension, diabetes, peripheral vascular disease, cardiomyopathy, congestive heart failure, mesenteric occlusive disease, renal insufficiency, or hepatic insufficiency. Data will then be collected from all consecutive PAC measurements between the hours of 0500 and 2300, until the sample size has been achieved. Any interventions based on PAC readings will be recorded. Possible interventions include fluid boluses, blood transfusion, antibiotics, vasoactive drug use, or discontinuation. No additional PAC readings for the purpose of the study will be obtained. One of the investigators will perform duplex ultrasound within ten minutes of the PAC measurements, allowing minimal disruption of normal routine. After consent and initial data is obtained, the ultrasound transducer will be placed on the subxiphoid abdomen with a minimal amount of conducting gel. The superior mesenteric artery (SMA) can be easily identified by ultrasound arising parallel to the aorta, distal to the celiac trunk, and proximal to the renal arteries. To maximize reproducibility, and minimize interobserver variability, the SMA duplex sonographic methods described by Perko et al will be used. A 3-4 MHz probe will be used to display the long axis of SMA at 60 degrees of isonation. The diameter will be assessed during systole. B mode and spectral trace parameters will be obtained 1 cm from its origin using a combination of color flow and pulsed wave doppler to measure the velocity and resistance to flow.

A total of four repeat ultrasound measurements will be taken and recorded in our database. PAC measurements are typically done every four hours. There are exceptions. For example, open hearts are done more frequently. The number of measurements may be less in accordance with the duration of PAC, as judged by the primary care team. For example, a patient who underwent a CABG will require frequent measurements immediately out of the operating room until stabilized; then every 2-4 hours until the following morning. At that time, if the postoperative course was uneventful, the cardiothoracic surgeon discontinues the catheter the next morning. In this example, a measurement will be obtained after the patient is moved to the ICU, then again if a change in hemodynamic parameters occurred during the initial stabilization period, and then again every 2-4 hours when repeat pulmonary artery catheter measurements are obtained...until the catheter is discontinued or a maximum of four measurements are obtained.

Each study will take approximately 10-15 minutes. Possible limitations include obesity, overlying bowel gas, and recent abdominal surgery. Thin body habitus, no abdominal incision, and great experience should be associated with faster scanning times. A completion ultrasound will be obtained after the pulmonary artery catheter is discontinued. The use of ultrasound in this study will have no impact on clinical decisions.

Data Collection: Patient information collected on data sheet will include sex, age, body mass index, pertinent medical history, diagnosis, fasting status, and use of vasoactive agents. In addition, pertinent labs to include any lactate level, arterial blood gas, and hemoglobin measurements will be documented that corresponds to a particular measurement. No additional labs will be ordered for this study; only existing lab data will be used. Cardiac output, cardiac index, systemic vascular resistance, pulmonary artery pressure, mean arterial blood pressure, stroke volume, central venous pressure, mixed venous saturation, and heart rate will be collected from the pulmonary artery catheter measurements and entered in our database.

Corresponding ultrasound measurements to include pulsivity index, resistance index, SMA diameter, and systolic and diastolic flow velocities from four encounters will also be entered into the database. SMA flow will be calculated.

Sample Size/Data Analysis: This pilot study will contain a total of twelve in the study sample (ten subjects determined a priori sample size plus two subjects to account for missing data or dropouts). Permission is requested to enroll up to 25 subjects in order to obtain the total sample size. Descriptive statistics will be presented for all demographic variables, pulmonary artery catheter measurements, and SMA duplex measurements. Where appropriate, bar graphs, line graphs, and "box-n-whisker" plots will be presented for study variables. PI will keep track of how many decided not to participate in the study and the reason for non-participation, if known.

Given the descriptive statistics that will be reported here, an interesting and related question is the following: To what extent do the data for each outcome variable resemble a normal distribution? An answer to this question may assist the PI in the future development of a clinical trial by suggesting which outcome variables to include in a future study. For the continuous data collected in the study, the nonparametric, Kolmogorov-Smirnov (K-S) one-sample test is useful to evaluate the null hypothesis that the cumulative distribution of a cardiac output (and separately for each multiple measurement) is similar to that of a normal distribution. For nominal, dichotomous data (e.g. gender), the nonparametric, binomial test will be used to evaluate a similar null hypothesis. For nominal data with multiple levels, (e.g. race), the nonparametric, chi-square goodness-of-fit test will be used to evaluate a similar null hypothesis. All tests will be two-tailed, and SPSS will be the statistical software package used in data analysis.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
No recent changes in the literature. No results available for analysis.
The number of subjects enrolled to the study since last APR at WRAMC is 0, and the total enrolled to date at WRAMC is 0.

CONCLUSIONS No results available for analysis.

Report Date: 13 May 2002

Work Unit # 01-20006

# DETAIL SUMMARY SHEET

TITLE: Tissue and Blood Library Establishment for Molecular, Biochemical, and Histologic Study of Breast Disease

PRINCIPAL INVESTIGATOR: LTC Craig Shriver MC

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 22 May 2001

STUDY OBJECTIVE

1. Acquisition and banking of breast tissue, lymph nodes and/or blood from informed and consenting donors.
2. Experimental analysis of DNA, RNA, and/or proteins isolated from donor tissues for molecular, biochemical, immunological and/or histopathological analysis.
3. Establishment of an integrated and relational database for tissue/serum and patient clinical characteristics that will provide the resources necessary to achieve the following future goals:
   a. Identify single nucleotide polymorphisms (SNPs) present in DNA from diseased breast tissue (as defined by histologic criteria) as compared to breast tissue without disease, lymph nodes with and without metastatic deposits, and/or DNA derived from patient leucocytes.
   b. Identify differences in RNA and protein expression associated with breast disease (as defined by histologic criteria) as compared to normal breast tissue and lymph nodes with and without metastatic deposits.
   c. Correlate SNPs and differences in RNA and protein expression associated with diseased breast and nodal tissue (as defined by histologic criteria) with the corresponding clinical patient database.
   d. Identify factors within patient serum and/or blood-derived cellular components that correlate with patient risk factors or clinical status as defined in the corresponding clinical patient database.

TECHNICAL APPROACH

Methodology: The approach to collection of the samples to be achieved is as follows, based on the grouping of the patients presenting (corresponding to the subjects groups in section 9a above). Patients already diagnosed with breast cancer: This group will consist of patients who already have undergone a breast biopsy of any type, at WRAMC or another institution (after confirmation of the pathology diagnosis at that other institution), which has confirmed a cancer diagnosis that requires further surgical therapy as per the consensus recommendation of the multidisciplinary breast conference. Approximately 8cc of blood will be obtained from a peripheral venous access line that has been placed for the administration of anesthetic or fluids. Once the breast tissue is surgically removed, as clinically indicated, the specimen(s) will be taken to the pathology laboratory where a licensed pathologist will ensure that the tissue is adequate for routine pathology analyses (diagnosis, margin status assessment, and other indicated purposes). If appropriate, an FNA (fine needle aspiration) utilizing a 22 gauge needle/syringe setup will be performed on the breast and/or lymph node specimen(s), and the cytologic contents placed in standard solution, centrifuged, and flash frozen prior to placing them in the freezer. Then, and only then, if any actual excess tissue (cancerous or benign) remains, samples of that tissue will be harvested for archiving in the tissue bank. This archival tissue will be divided and placed into vials, labeled with a code number after all patient identifiers are removed, and flash-frozen in liquid nitrogen. It will then be placed into the CBCP Tissue Bank freezer at temperatures down to -180°C. Blood samples will be centrifuged prior to separation and flash freezing of the serum and non-serum contents, and placed into the -180°C freezer. This tissue will remain in the freezer at the WRAMC site for at least a two week period of time, or longer if needed, to fulfill the requirement set in section (ii) below. During this time, no analyses will be performed on the specimen – this period of time will be known as the "Fail-Safe" time period. The Fail-Safe time period is intended to allow the diagnostic testing they determine is necessary to patient care. After the pathologist determines with final certainty, by the publishing of the official final pathologic report with no outstanding addenda, that there is no diagnostic pathologic requirement for the

frozen specimen(s) on that patient (identified only by code with the logbook as noted above) will be released to the CBCP for research analyses. This will include transfer of the tissues to offsite locations for specialized studies (to include functional genomics, proteomics, immunulogic analyses).

The serum and non-serum contents of the blood will, after appropriate labeling and removal of all patient identifiers, linked only to the patient via the codebook, be either held in the freezer indefinitely or transferred to one of the CBCP offsite research facilities for immunologic or proteomic analysis. The cytologic aspirate will likewise, after appropriate labeling and removal of all patient identifiers, linked only to the patient via the codebook, be either held in the freezer indefinitely or transferred to one of the CBCP offsite research facilities for molecular, proteomic, immunologic, and/or histopathologic analysis.

All consenting adult patients presenting to the Breast Center or the Women's Imaging Center at WRAMC with evidence of breast disease for which a breast tissue biopsy (to include ductal lavage, open breast biopsy, tru-cut biopsy, image-directed biopsy) is clinically indicated. After consent is obtained, patients will fill out the standard questionnaire and then be taken to procedure or surgery. Approximately 8cc of blood will be obtained from a peripheral venous access line that has been placed for the administration of anesthetic or fluids. If no IV access is clinically indicated, consenting patients will have the blood drawn using standard sterile techniques from a peripheral vein. Once the breast tissue is surgically removed, as clinically indicated, the specimen(s) will be taken to the pathology laboratory analyses (diagnostic, margin status assessment, and other indicated purposes). If deemed appropriate, an FNA utilizing a 22-gauge needle/syringe setup will be performed on the specimen, and the cytologic contents placed in standard solution, centrifuged, and flash frozen prior to placing them in the freezer. To clarify, this will be on a specimen already removed from the patient, now in the hands of the pathologist, who will take a 22 gauge or equivalent needle on a syringe and make several passes into the biopsy specimen in order to retrieve and store individual cells (cytology) that in no way will negatively affect the actual standard pathologic analysis. Then, and only then, if any actual excess tissue (cancerous or benign) remains, samples of that tissue will be harvested for tissue archiving in the tissue bank. This archival tissue will be divided and placed into vials, labeled with a code number after all patient identifiers are removed, and flash-frozen in liquid nitrogen; it will then be placed into the CBCP Tissue Bank freezer at temperatures down to -180°C. Blood samples will be centrifuged prior to separation and flash freezing of the serum and non-serum contents, and storage at -180°C.

This tissue will remain in the freezer at the WRAMC site for at least a two week period of time, or longer if needed to fulfill the requirement set in section (ii) below, where no analyses will be allowed to be performed on it – this period will be know as the "Fail-Safe" time period. The intent of the fail-safe time period is to allow the diagnostic pathologists to request that the banked tissue be brought back out of freezer and thawed for diagnostic testing if it is determined to be necessary for any reason. After the pathologist determines with final certainty, by the publishing of the official final pathologic report with no outstanding addenda, that there is no diagnostic pathologic requirement for the frozen specimen(s), then the archived specimen(s) on that patient (identified only by code with the logbook as noted above) will be released to the CBCP for research analyses. This will include transfer of the tissues to offsite locations for specialized studies (to include functional genomics, proteomics, and immunologic analyses).

The serum and non-serum contents of the blood will, after appropriate labeling and removal of all patient identifiers, linked only by to the patient via the codebook, be either held in the freezer indefinitely or transferred to one of the CBCP offsite research facilities for molecular, immunologic biochemical, histological, and/or proteomic analysis. The cytologic aspirate will likewise, after appropriate labeling and removal of all patient identifiers, linked only to the patient via the codebook, be either held in the freezer indefinitely or transferred to one of the CBCP offsite research facilities for immunologic or proteomic analysis.

All consenting adult patients presenting to the WRAMC plastic surgery clinic for elective reductive mammoplasty are screened by routine clinical measures of mammography (if indicated) and clinical breast examination. If they are found to have no contra-indication to said procedure, have been appropriately counseled by a licensed Plastic or General Surgeon, and if they are patients who still desire elective reduction mammoplasty, consent is obtained, patients will fill out the standard questionnaire, and are taken to surgery. Approximately 8cc of blood will be obtained from a peripheral venous access line that has been placed for the administration of anesthetic or fluids. Once the breast tissue is surgically

removed, as clinically indicated, the specimen(s) will be taken to the pathology laboratory where a licensed pathologist will ensure that the tissue is adequate for routine pathology analyses (diagnosis, margin status assessment, and other indicated purposes). If appropriate, an FNA (fine needle aspiration) utilizing a 22 gauge needle/syringe setup will be performed on the breast and/or lymph node specimen(s), and the cytologic contents placed in standard solution, centrifuged, and flash frozen prior to placing them in the freezer. Then, and only then, if any actual excess tissue (cancerous or benign) remains, samples of that tissue will be harvested for archiving in the tissue bank. This archival tissue will be divided and placed into vials, labeled with a code number after all patient identifiers are removed, and flash-frozen in liquid nitrogen. It will then be placed into the CBCP Tissue Bank freezer at temperatures down to -180°C. Blood samples will be centrifuged prior to separation and flash freezing of the serum and non-serum contents, and placed into the -180°C freezer. This tissue will remain in the freezer at the WRAMC site for at least a two weeks, or longer if needed to fulfill the requirement set in section (ii) below, where no analyses will be allowed to be performed on it. This period will be know as the "Fail-Safe" time period. After the pathologist determines with final certainty that there is no diagnostic pathologic requirement for the frozen specimen(s), the archived specimen(s) on that patient will be released to the CBCP for research analyses. This will include transfer of the tissues to offsite locations for specialized studies (to include functional genomics, proteomics, immunologic, and histopathologic analyses).

The serum and non-serum contents of the blood will, after appropriate labeling and removal of all patient identifiers, linked only by to the patient via the codebook, be either held in the freezer indefinitely or transferred to one of the CBCP offsite research facilities for functional genomics, proteomics, and/or immunologic analysis.

Primary uses of the tissue and serum specimens: The known primary uses under this protocol for the acquired tissues and serums/blood fall into seven major subsections. These are:

Tissue Banking
BioImaging/Microscopy
Gene Expression Profiling
Sequencing
Genotyping
Pharmacogenomics
Protein Expression Profiling

At the end of each of the above seven laboratory workflows, the data will be QA'd, analyzed using powerful genomics/proteomics software tools, and placed into the CBCP database/data warehouse. QA of the data involves using software tools that interrogate the fields of the data that come out of the workflow stations. This is to ensure the data has consistency, and is within expected or know ranges. Any data found to be outside of expected ranges is not necessarily flawed but is then identified for closer analysis by researchers.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

An Addendum dated 1 November 2001 was approved by the HUC on 6 November 2001. There have been no adverse events with this minimal risk protocol and no patients have withdrawn from the study. The number of subjects enrolled to the study since last APR at WRAMC is 233 and the total enrolled to date at WRAMC is 233. The total number enrolled study-wide is 343, as a multi-site study (Windber). A review of the literature revealed no publications within the last year reporting data from studies of a similar design.

CONCLUSIONS

The study is ongoing.

Report Date: 13 May 2002 Work Unit # 01-20007

# DETAIL SUMMARY SHEET

TITLE: Creation of a Blood Library for the Analysis of Blood for Molecular Changes Associated with Breast Disease and Breast Cancer Development

KEYWORDS:

PRINCIPAL INVESTIGATOR: LTC Craig Shriver MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: General Surgery INITIAL APPROVAL DATE: 22 May 2001

## STUDY OBJECTIVE

The objectives of this protocol are therefore:

1. Acquisition and banking of blood serum from informed and consenting donors.
2. To characterize gene and protein expression profiles and single nucleotide polymorphisms associated with breast disease and breast cancer development.
3. Identify factors within patient serum and/or blood-derived cellular components that correlate with patient risk factors or clinical status as defined in the corresponding clinical patient database.

## TECHNICAL APPROACH

*Methodology: Blood collection and processing workflows:* Patients will be categorized into the appropriate groups and about 8-12 ml of venous blood collected by a phlebotomist or nurse. Before blood draw, the PI or designee (a trained breast care case manager) would provide a consent form and explain the study to the patient. The patient will sign the consent form if willing to participate. All consenting patients will be assigned a unique CBCP identification number, which will not reveal patient identity. The blood will be drawn and a portion of it placed in PAX-gene blood tubes (Quigen, Inc.), which stabilizes the RNA for up to seven days. Plasma and serum will be processed within two hours by spinning blood down and aliquoting into separate tubes, after which they will be stored in the CBCP laboratory freezer. On a weekly scheduled basis, samples will be transferred to the CBCP Genomics/Proteomics Center at the Windber Research Institute where the following procedures will be carried out:

*RNA, DNA and Protein from blood isolation from blood*: RNA will be purified from blood collected in PAXgene RNA tubes using the RNA Test Kit (PAXgene™, Qiagen Inc., CA). RNA will then be employed for other down stream analysis after determining concentration with a DNA/RNA calculator. DNA will be isolated from blood using the QIAamp DNA blood kit. This involves lysing the blood in appropriate buffer and loading this on a spin column. DNA gets bound to the silica gel-based membrane and pure DNA eluted in water or low-salt buffer. Protein will be isolated from plasma or serum samples using an extraction buffer (50mM Tris HCL, pH 7.5 and 0.1% Nonidet P-40) as described below. Approximately two volumes of buffer per volume of the sample are centrifuged at 14,000rpm/15minutes at room temperature. The supernatant is transferred to a fresh tube and about twice its volume of isopropanol added. The mixture is allowed to stand at room temperature for 15-20 minutes before centrifugation as described above. The supernatant is discarded and precipitate reconstituted in the Tris buffer. Total protein concentration will be determined by the Bradford protein assay procedure.

*Primary uses of the blood and serum specimens:* The known primary uses under this protocol for the acquired serum and blood fall into six major subsections:

1. Serum/Blood Repository Banking – this includes sample definition and receiving, flash freezing/labeling/storage, OCT embedding (placing the blood cells in a special preservative that protects the RNA/DNA during prolonged freezing), labeling (putting identifier codes on each tissue
2. sample for subsequent tracking), storage, and inventory/tracking. The inventory and tracking of all samples will be done electronically with barcodes and sample tracking software – initially the software will be Freezerworks™ to be followed by our own developed software module by Cimmaron Inc. that will be integrated with our laboratory analysis software GenoMax™.
3. Gene Expression Profiling – blood samples will undergo RNA isolation by Northern Analysis and RT-PCR, and mRNA selection by RT-PCR, subsequent cDNA synthesis and cDNA Library construction, DNA spotting, hybridization and array scanning, image processing and data analysis, for eventual gene expression profile identification.
4. Sequencing – after plasmid isolation, DNA will undergo PCR setup, thermal cycling, PCR clean-up, Capillary electrophoresis, and Sequence Analysis.
5. Genotyping – blood will undergo DNA quantification followed by PCR set-up, thermal cycling, SNP (single nucleotide polymorphism) reaction clean-up, capillary electrophoresis set-up, genotype calling, and genotype QC.
6. Pharmacogenomics – blood will undergo RNA isolation, mRNA selection, cDNA synthesis, probe labeling, probe clean-up, probe fragmentation, suppression hybridization, array scanning, image processing, data analysis, and gene expression profile identification.
7. Protein Expression Profiling – after sample clean-up, serum and blood will undergo 1D- and 2D-Electrophoresis, Gel staining, Image acquisition and processing and analysis, and Gene expression Profile identification.

At the end of each of the above seven laboratory workflows, the data will be QA'd, analyzed using powerful genomics/proteomics software tools, and placed into the CBCP database/data warehouse. QA of the data involves using software tools that interrogate the fields of the data that come out of the workflow stations, to ensure the data has consistency and is within expected or know ranges. Any data found to be outside of expected ranges is not necessarily flawed, but is then identified for closer analysis by researchers.

Data will be stored in the CBCP server(s) and/or data warehouse (being developed with NCR Inc.), initially on CBCP sites at WRAMC, USUHS, or WRI, and eventually at the CBCP Data Warehouse in Fort Detrick, Maryland (as part of our MANVT initiative, funded separately). The MANVT initiative is a Medical Are allow for the near-real time interaction between all of the four main CBCP sites (WRAMC, USU, Windber network) that would link all of the sites, as well as allow for creation of a data warehouse (situated at least in part at Fort Detrick, MD, or to have a significant redundancy backup there).

Further information regarding various techniques to be used in the above workflows:
*Molecular analysis of blood*: DNA and RNA isolated from the blood samples will be used for other down stream processes such as polymerase chain reaction (PCR) amplification using gene specific primers targeting mutant specific alleles of genes of interest, quantitative RT-PCR (qRT-PCR) for assessment of the transcriptional profiles of specific genes. Proteins in all samples of the different patient categories will be displayed and identified using 2D-DIGE technologies. Altered proteins will be isolated and sequenced using MALDI/TOF and/or LS-MS-MS and the relevant genes/proteins identified in the human genome sequence database. Disease specific changes will be characterized at the DNA level by cloning, sequencing, and analysis of the genes and regulatory elements. The genomic DNA of patients will be analyzed to determine changes that may have occurred during disease progression or those present only in particular categories of patients as compared to controls. The expression patterns of 500-1000 genes associated with biochemical processes implicated in cancer will be monitored in parallel using microarray technology. The genes being arrayed will include known specific genes implicated in the development of breast cancer, as well as generalized genes (cell cycle regulators, protein shuttle genes, stress-related genes)

that conceivably are involved in oncogenic pathways. Briefly, complementary DNA (cDNA) clones representing genes of interest will be spotted on microscopic glass slides and hybridized with differentially labeled cDNA populations synthesized from mRNAs. Such changes would identify potential markers or provide disease specific targets for treatment. Single nucleotide polymorphisms (SNPs) of known gene variants located in coding regions of genes of interest and variants that cause amino acid changes will be characterized. SNPs linked with breast cancer will be identified and then used as diagnostic and predictive markers.

*Immunoassays:* Quantitative measurement of protein levels in plasma or serum will be carried out using ELISA kits (R & D Systems Inc., Minneapolis, MN). Active and total protein will be measured by an activity assay (e.g. AP Biotrak, Amersham Pharmacia Biotech, Piscataway, NJ). All procedures will be as per manufacturer instructions.

*SDS-Page*: SDS-Page will be carried out using the Phastgel System (Amersham Pharmacia Biotech, Piscataway, NJ). The procedure involves adding 3µl of loading buffer (950µl Bio-Rad Laemmli sample buffer and 50µl β-mercaptoethanol) to the protein sample, incubating at 95°C for five minutes, snap cooling on ice before separation on 12.5% homogenous or 10-25% gradient gel. Molecular weight markers and known control samples will be electrophoresed simultaneously as positive and negative controls.

*Western blot/analysis*: Electrophoresed proteins will be transferred into nitrocellulose membrane using the Phast System followed by western analysis using the Western Light Plus Protein detection kit (Tropix Inc., MA) and specific primary antibodies. Blots will be exposed to radiographic films (Kodak Biomax) and presence of protein identified by signals captured on the radiographic films. Signals will be digitized and quantified.

*Statistical analysis*: Data obtained from the above laboratory analysis will be collated and statistically analyzed. Primary analysis will be comparison of gene and protein expression pattern across the different patient categories.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

An addendum dated 1 November 2001 was approved by the Human Use Committee on 6 November 2001. A new consent form was approved at that time. There have been no adverse events with this minimal risk protocol, and no patients have withdrawn from the study. A review of the literature revealed no publications within the last year reporting data from studies of a similar design.

The number of subjects enrolled to the study since last APR at WRAMC is 140, and the total enrolled to date at WRAMC is 140. The total number enrolled study-wide is 140, if multi-site study.

CONCLUSIONS

The study is ongoing and progressing as planned.

Report Date: 24 September 2001

Work Unit # 01-2001

# DETAIL SUMMARY SHEET

TITLE: Creation of a Database of Patients at a High Risk for Breast Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Shriver, Craig LTC(P) MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 30 November 2000

STUDY OBJECTIVE
This is a prospective database for patients who are seen in the CBCP Risk Reduction clinic, who have an increased risk of developing breast cancer based on a computerized analysis of their individual risk factors.

TECHNICAL APPROACH
For consenting patients, they are asked to fill out a questionnaire that details many items of their personal and family breast cancer risk history. They are assisted in filling out the questionnaire by one of our nurses in the CBCP. For future visits, they fill out a shorter version in order to garner any information of risk factors that might have changed in the interim.

PRIOR AND CURRENT PROGRESS
The number of subjects enrolled to the study since last APR at WRAMC is 77 and the total enrolled to date at WRAMC is 77. There have been no serious or adverse events.

CONCLUSIONS
Enrollment is going well. No data analysis has been undertaken to date.

Report Date: 18 October 2001

Work Unit # 01-2002

# DETAIL SUMMARY SHEET

TITLE: A Prospective, Randomized, Double-Blind, Multicenter Trial Assessing the Safety and Efficacy of Sequential (Intravenous/Oral) BAY 12-8093 (moxifloxacin) 400mg Every 24 Hours Compared to Intravenous Piperacillin/Tazobactam 3.375 grams Every Six Hours Followed by Oral Amoxicillin/Clavulanic Acid Suspension 800 mg Every Twelve Hours for the Treatment of Patients With Complicated Intra-Abdominal Infections.

KEYWORDS: moxifloxacin, complicated intra-abdominal infections, Piperacillin/Tazobactam, Amoxicillin/Clavulanic Acid

PRINCIPAL INVESTIGATOR: MAJ Michael M. Woll MC
ASSOCIATES: CPT Christopher Swiecki MC

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 12 December 2000

STUDY OBJECTIVE

To prove that sequential IV/Oral Moxifloxacin therapy is not worse than treatment with IV Piperacillin/Tazobactam as an adjunct to surgical treatment of complicated intra-abdominal infections.

TECHNICAL APPROACH

Patients diagnosed with complicated intra-abdominal infections are screened for inclusion in the study. If they meet the inclusion and exclusion criteria, they are enrolled and undergo either surgical exploration or Interventional radiology fluid aspiration. The infected material is split and half is sent to our lab for routine bacteriologic testing and the other half is sent to a central lab (Covance Laboratories, Indianapolis, IN). Once enrolled, patients receive either IV Moxifloxacin 400mg QD or IV Piperacillin/Tazobactam 3.375 grams IV q 6 hours. Blinding is performed by the pharmacy. Switch to oral medications is made when the patient's clinical status allows it. The endpoint is resolution of symptoms. Serial blood chemistry measurements are made at the time on enrollment, day of IV to PO switch, and at the Test of Cure visit (TOC).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Only two subjects have been enrolled at WRAMC to date. There have been no adverse events at WRAMC. Two patients at other institutions in the study have developed pseudomembranous colitis. There was one death. Pseudomembranous colitis is a potential complication of any antibiotic therapy. The consent has been amended to specifically address pseudomembranous colitis.

The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 215 if multi-site study.

CONCLUSIONS

Based on the limited data, Moxifloxacin is equal to Piperacillin Tazobactam followed by Amoxicillin/Clavulanate in terms of safety and efficacy.

Report Date: 30 November 2001

Work Unit # 2076

# DETAIL SUMMARY SHEET

TITLE: Gamma Probe Assisted Detection of Micrometastasis in Well-Differentiated Thyroid Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Shriver, Craig LTC MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: C
INITIAL APPROVAL DATE: 25 November 1997

## STUDY OBJECTIVE

To determine if the gamma probe can be used to identify micrometastasis to cervical lymph nodes in well-differentiated thyroid cancers.

## TECHNICAL APPROACH

Patient ingests a small amount of radioactive iodine pre-operatively and during thyroidectomy a gamma-detecting probe is used to assess lymph nodes for evidence of iodine-containing cells (thyroid cancer mets).

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of five patients have been accrued to the protocol. One patient has accrued in the last 24 months. There have been no unexpected complications. There is not enough data to state whether the technique is viable.

## CONCLUSIONS

Accrual was slower than initially expected, mainly due to lack of dedicated research personnel for this particular study. However, there were no unexpected adverse events. The technique itself, while hypothetically feasible, needs further study. Due to poor accrual we are closing the study at WRAMC.

Report Date: 21 September 2001 Work Unit # 2078-99

# DETAIL SUMMARY SHEET

TITLE: Characterization of the Perioperative Serum Cytokine Elaboration in Patients Undergoing Hepatic Resection Cryoablation

KEYWORDS:

PRINCIPAL INVESTIGATOR: Ward, David T, MAJ, MC
ASSOCIATES: CD Shriver, LTC, MC

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: C
INITIAL APPROVAL DATE: 20 October 1998

## STUDY OBJECTIVE

To characterize the temporal elaboration of serum inflammatory mediators in patients undergoing hepatic resection or cryoablation.

## TECHNICAL APPROACH

Serial blood samples are drawn perioperatively and then the serum is withdrawn and preserved for eventual cytokine analysis.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 3 and the total enrolled to date at WRAMC is 12. The total number enrolled study-wide is N/A, if multi-site study. There have been no adverse events.

## CONCLUSIONS

We have closed the study to accrual. We have met our target enrollment. We characterized the system cytokine response to hepatic cryoablation.

Report Date: 3 December 2001

Work Unit # 2079-99

# DETAIL SUMMARY SHEET

TITLE: Intraductal Carcinoma of the Breast Treated by Conservative Surgery: Insights Based on Histopathologic Evaluation Using Computer Graphic Three-Dimensional Reconstruction

KEYWORDS: breast, DCIS, cancer, CT

PRINCIPAL INVESTIGATOR: Shriver, Craig LTC MC
ASSOCIATES: Gayle, Ryan CPT MC

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: C
INITIAL APPROVAL DATE: 15 December 1998

STUDY OBJECTIVE
Determine the extent of involvement of the ducts of the breast in DCIS using a novel imaging modality

TECHNICAL APPROACH
Tissue breast biopsy is performed in the usual fashion and after standard pathology analysis; a computerized 3-dimensional reconstruction is generated to assess the involvement of the ductal system of the breast in a more analytical fashion.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
Shortly after opening this protocol, there was a change in the way pathological analyses are performed and accrual was difficult. By the middle of this year the technique became superfluous, so we were not really accruing patients. We therefore desire to close this study.

Report Date: 16 April 2002 Work Unit # 2080-99

# DETAIL SUMMARY SHEET

TITLE: Alteration in Colonic Motility Secondary to Inflammatory Bowel Disease

KEYWORDS: radiotherapy, prostate cancer

PRINCIPAL INVESTIGATOR: Anderson, Jimmie CPT MC
ASSOCIATES: Terez Shea-Donohue, PhD, Lawson, Steve CPT MC

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 20 April 1999

## STUDY OBJECTIVE

This study was designed to evaluate changes seen in the innervations of the colon affected by inflammatory bowel disease. Specifically to determine the 1) *in vitro* changes in the neutral control of colonic smooth muscles responses undocked by inflammation in both affected and unaffected sites and 2) contribution of nitric oxide to changes in the control of smooth muscles in colitis.

## TECHNICAL APPROACH

At the time of operation for either resection due to colon cancer of inflammatory bowel disease a portion of colon is harvested with the enlistment of the pathologist to ensure all material needed for pathologic diagnosis is obtained. This portion of the colon is then transported to Dr. Shea-Donohue's laboratory, Department of Medicine, USUHS in oxygenated Kreb's solution. The mucosa is then stripped using micro dissection organ baths at 37 degrees C, gassed with 95% 02/5% c02 and rinsed every ten minutes throughout the experiment. One end of the tissue is connected to stationary mounting point at the bottom of the bathe and connected to a Grass FT03 force displacement transducer. Prior to addition of drugs or to nerve stimulation the muscle strips are pre-stretched to their optimal length (Lo) for generation of active tension. Lo is defined as that degree of stretch that gives a maximal contraction to cetycholine. Recordings of Isometric tension development at Lo will be made on a bench top polygraph. Muscle strips will be exposed to no cumulative concentrations of drugs with at least thirty minutes before addition of the next concentration. Concentration responses to agonist and antagonist are expressed as tension generated per surface area (mN/cm2).

## PRIOR AND CURRENT PROGRESS

There has been little in the literature on the physiology of the nervous system in ulcerative colitis. A MEDLINE search from 01JAN01 through current using "ulcerative colitis nerve" as the search reveals only one relevant recent publication. It does not address the functional neuropathy we have studied.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 10. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

UC abiates the enteric neuronal control of mucosal permeability and increases contraction frequency contributing to the diarrhea in UC. The enhanced extrinsic motor inhibitory pathway seen in UC may be an attempt at compensation for this damage. The enteric neuropathy found in UC may be the primary lesion in ulcerative colitis leading to diarrhea.

Report Date: 19 November 2001 Work Unit # 00-2101

# DETAIL SUMMARY SHEET

TITLE: Intraoperative Carotid Duplex: A Prospective Study of the Clinical Significance of Residual Defects Following Carotid Endarterectomy

KEYWORDS: intraoperative, carotid, duplex

PRINCIPAL INVESTIGATOR: LTC James M. Goff
ASSOCIATES: LTC Patricio Rosa; LTC (P) Sean D. O'Donnell MC; LTC David L. Gillespie MC; MAJ Neal Hadro MC; Margaret Kidwell, RVT

DEPARTMENT: Surgery
SERVICE: Peripheral Vascular Surgery

STATUS: O
INITIAL APPROVAL DATE: 18 January 2000

## STUDY OBJECTIVE

To compare the rate of neurologic events, restenosis, reoperation and death in patients who undergo carotid endarterectomy and in whom: 1) the intraoperative carotid duplex is normal and no repair is performed, 2) the intraoperative carotid duplex shows a minimal abnormality that is not repaired, 3) the intraoperative duplex shows an abnormality that is repaired, and 4) the carotid artery was opened only once versus two or more times.

## TECHNICAL APPROACH

This is a prospective observational study. Patients who are eligible for carotid endarterectomy undergo the standard medical and preoperative evaluation to ensure that there are no contraindications to surgery. This includes a thorough history and physical, labs, x-rays, EKGs, and consultations as dictated by their medical condition. Once scheduled for surgery, they are approached regarding their willingness to participate in the study. Informed consent is obtained. A datasheet is initiated on the patient to record demographic data, risk factors for atherosclerotic vascular disease, history of chronic medical problems, and previous vascular surgery. In the operating room, the findings of the initial duplex, any further surgical management decision should the duplex be abnormal, findings if re-explored, number of times re-opened and final duplex findings prior to leaving the operating room are recorded.

The intraoperative carotid duplex is standardized as follows. An ATL HDI 3000 machine, with a 10 MHz CL-10-5 sterile probe and sterile gel or saline to obtain acoustic coupling is used, with the probe in direct contact with the artery, using an incident angle of 60 degrees. Care is taken to avoid the presence of bubbles between the probe and artery or pressure against the artery. B-mode is first used to longitudinally scan the CCA, beginning proximal to the proximal endpoint of the endarterectomy and continuing into the ICA as far as accessible. The proximal endpoint of the endarterectomy and the clamp site in the CCA are then examined longitudinally and in transverse views in B-mode, followed by color flow and spectral analysis and measurement of the peak systolic velocity. The distal endpoint and the clamp site in the ICA are examined next, in color and with spectral analysis, with measurement of the peak systolic and end diastolic velocities and particular attention paid to the presence of mosaicism, spectral broadening or lack of acoustic window. In the cases in which the presence of a prosthetic patch precludes direct visualization of the distal endpoint, the most proximal portion of the ICA distal to the patch will be examined. The ECA will then be examined in B-mode followed by spectral analysis and measurement of the peak systolic velocity. The velocities recorded will be those that are the highest within the area of interest. Color pictures are obtained of the CCA at the proximal endpoint, the ICA at the distal endpoint and of the proximal ECA. If a defect is identified, minor or major, its characteristics, namely dimensions, location and associated velocities, are recorded, and a photograph obtained. This is repeated each time that a defect is identified. If a defect is identified which requires reoperation, once it has been repaired, a new study will be initiated, covering all the areas usually covered in the completion study, as if this was the first time the carotid artery is closed. This new study is recorded into the Vascular Database as a separate study. The amount of time required to perform each study is recorded separately by annotating in the

space provided in the datasheet the time of the day when the study was initiated and when it was completed. The attending surgeon will proceed with termination of the operation when the intraoperative duplex is normal or shows a minor abnormality as defined by our protocol in the section on background and significance, or re-exploration versus termination if a major defect is present. The patients are divided into three groups: 1) patients with normal duplex, 2) patients with a minor defect on the duplex, and 3) patients with an abnormal finding on the duplex. Any changes in the neurologic exam as noted by the care team is recorded. The patients are followed with the standard post-operative duplex schedule at 6 months, and yearly after that. This is modified following the standard management algorithm as dictated by abnormal findings if any. The endpoints of the study are: 1) a carotid duplex of the operated side that remains stable for one year and does not meet criteria for reoperation, 2) the occurrence of a transient ischemic attack, amaurosis fugax or stroke in the cerebral distribution of the operated side, 3) the occurrence of criteria for reoperation of the operated side, namely, neurologic symptoms in the distribution of the ipsilateral carotid artery associated to a lesion considered to be hemodynamically significant or a possible source of embolic material, and restenosis compatible with 60% or greater diameter reduction, 4) death, 5) two years from the time of the operation elapse. The current standard of care at Walter Reed AMC is for patients to undergo an intraoperative duplex following their CEA. The attending surgeon then chooses to revise the procedure or not based on the duplex findings and his choice of intraoperative neurologic assessment. The vascular surgeons in Walter Reed do not currently have a uniform, agreed upon definition of what would constitute a minor defect. The change in the current standard of care is that a uniform definition is agreed upon, and the attending surgeon is expected to abide by this definition when considering whether to re-explore the carotid or not. This definition is supported by the medical literature. The research is the observation of any immediate and long-term difference in outcome among the three groups of patients.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 42 and the total enrolled to date at WRAMC is 68. There have been no adverse events. No patients have withdrawn from the study. Review of the recent literature shows that there have been 4 studies in the last year that have addressed intraoperative duplex scanning. Panneton et al (Intraoperative duplex ultrasound during carotid endarterectomy, Vasc. Surg., 2001; 35:1-9) performed a retrospective review of 149 patients who underwent intraoperative duplex and classified the defects as normal, minor and requiring no revision, or major and requiring revision. The rate of defects requiring repair was 11%. This study is remarkably similar in its results to our own retrospective review of intraoperative duplex (Intraoperative carotid duplex: the fate of patients found to have residual defects following carotid endarterectomy, WU# 21000E-99) and suffers from the same problems that our respective study attempts to answer. Panneton's study only included the 149 patients in which an intraoperative duplex was performed and did not study the 183 additional carotid endarterectomies that were performed in their institution during the same time period. Surprisingly, their highest stroke rate was in those patients who had normal intraoperative studies. Additionally, they did not answer the question of restenosis and the fate of unrepaired external carotid artery defects that our prospective study will answer. Mansour et al (Decreased recurrent carotid stenosis by routine patching and intraoperative scanning, Am Surg, 2001; 67:328-332) focused their attention at restenosis rate when routine patching and duplex were used together and concluded that recurrent stenosis was lower when compared to their previously reported study. They attempted to answer only one question that is also a question in our study, restenosis, and their rate of restenosis is dramatically lower that the rate reported in the literature. The remaining two studies did not study intraoperative duplex as we have proposed (one included a small number of intraoperative studies lumped together with intraoperative arteriograms to study when a repeat postoperative duplex should be performed and the other used intraoperative duplex to assess trainee technical competence in the performance of the carotid endarterectomy). None of the current studies described above has attempted, in a prospective fashion, to answer all of the questions proposed by our study.

CONCLUSIONS

Thus far, minor defects noted on intraoperative duplex do not appear to increase the incidence of stroke, death, or restenosis in the small group of patients studied to date. If this finding continues, minor defects following carotid endarterectomy could be safely followed, reducing the risk to the patient associated with reopening the artery and decreasing the operative and anesthesia time.

Report Date: 28 August 02

Work Unit # 00-2102

# DETAIL SUMMARY SHEET

TITLE: Clinical And Pathophysiologic Efficacy of SEPS The Endoscopic Treatment Of Incompetent Perforating Veins of The Lower Extremity In Patients With Chronic Venous Insufficiency (CEAP classes 4-6)

KEYWORDS: gene expression, skin, venous ulcer

PRINCIPAL INVESTIGATOR: David L. Gillespie, LTC MC
ASSOCIATES: Bader B. Fileta BS, MT(ASCP), AACC; Audrey S. Chang PhD; Jeffrey Anderson, Marcos Rojkind MD, PhD

DEPARTMENT: Surgery
SERVICE: Peripheral Vascular Surgery

STATUS: O
INITIAL APROVAL DATE: 25 July 2000

## STUDY OBJECTIVE

Determine if the addition of SEPS (subfascial endoscopic perforator surgery) to a treatment regimen including conventional surgery and compression therapy alters patient outcomes. Parameters to be observed during the study include:

a) rate of ulcer healing
b) ulcer recurrence
c) post-operative pain and disability
d) post-operative wound complications
e) venous hemodynamics as measured by duplex derived valve closure times and air plethysmography
f) improved overall quality of life as measured by SF 36. This will be the first study to address these critical questions.

Compare the physical characteristics under confocal microscopy of fibroblasts grown in tissue culture from areas of diseased lower extremity skin to normal skin of the thigh before SEPS and 6 months after SEPS. Examine the effect of correcting lower extremity venous hypertension on the expression of the matrix metalloproteases MMP-1, MMP-2, MMP-9, MMP-13 and the inhibitor of metalloprotease activity TIMP-1 in fibroblasts grown from areas of diseased lower extremity skin to normal skin of the thigh before SEPS and 6 months after SEPS.

## TECHNICAL APPROACH

In this study skin biopsies are obtained from patients undergoing venous surgery. Total RNA and protein are isolated. The RNA is then reverse transcribed using the First Strand cDNA Synthesis Kit (Boerhinger Mannheim, Indianapolis, IN) using primers specific for MMP-1, MMP-2, MMP-9, MMP-13 and TIMP-1. RT-PCR product is then separated over 2% agarose gel containing ethidium bromide (0.5 &g/&ml) and visualized by UV irradiation and will be photographed using a Polaroid documentation system.

Western blots are performed using monoclonal mouse anti-human antibodies MMP-1, MMP-2, MMP-9, MMP-13 and TIMP-1 will be used as the primary antibodies (Oncogene Science, Cambridge, MA). Goat anti-mouse horseradish peroxidase coupled antibodies will be used as secondary antibodies. Scanning densitometry is then performed (NIH imager v.1.57) to quantify the amount of these proteins in each sample. Activity of these enzymes is then performed using gel substrate zymography.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Prior work in our lab has demonstrated alterations in matrix metalloprotein expression and activation exists in patients with venous insufficiency when compared to controls. In addition we have found that the

activation of these matrix-remodelling proteases varies by location in the leg. Based on these observations and a review of the literature, we propose to not only examine the differences in clinical benefit and physiologic changes but we also propose to use this opportunity to look for changes in dermal fibroblast expression of these matrix metalloproteases. Specifically we are interested in looking at the expression of MMP-1 MMP-2, MMP-9 MMP-13 and TIMP-1 in dermal biopsies of normal skin in the thigh to diseased dermal fibroblasts of the lower leg in patients with chronic venous insufficiency CEAP class 4-6.

More recent data from our lab has shown that the increase in matrix metalloproteinases in the ankle skin of these patients is associated with a corresponding increase in both inhibitors of MMPs namely TIMP-1 and inducers of MMP expression such as the extracellular matrix metalloproteinase inducer CD147/EMMPRIN.

The most major progress that we have made in our laboratory has been our success in growing fibroblasts from skin biopsies of patients with severe chronic venous insufficiency. Thus far we have been successful in placing both normal fibroblast from thigh skin biopsies and abnormal wound skin biopsies from a total of 5 patients into culture. The next phase of our research will be to characterize these cells and then begin to look at the expression of MMP.

The number of subjects enrolled to the study since last APR at WRAMC is 7 and the total enrolled to date at WRAMC is 26. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS

We have enrolled 26 patients to date. PCR and Western Blot analysis have been performed on twenty of these patients specimens looking for the expression of CD147/EMMPRIN, MMP-1,8 and TIMP-1. This data is currently undergoing statistical analysis. The six other patients' samples have been grown in cell culture in preparation for upcoming experiments..

Report Date: 7 September 2001

Work Unit # 01-2101

# DETAIL SUMMARY SHEET

TITLE: Percutaneous Arterial Closure After Diagnostic and Interventional Endovascular Procedures: A Prospective Randomized Evaluation of the Perclose Device in Patients with Peripheral Vascular Disease

KEYWORDS: Suture Mediated Closure Device, Peripheral Vascular Disease

PRINCIPAL INVESTIGATOR: Starnes, Benjamin MAJ MC
ASSOCIATES: O'Donnell, Gillespie, Goff, Rosa, Chang

DEPARTMENT: Surgery
SERVICE: Peripheral Vascular Surgery

STATUS: O
INITIAL APPROVAL DATE: 24 October 2000

## STUDY OBJECTIVE

1. To evaluate the complication rate comparing percutaneous closure versus manual compression in patients with peripheral vascular disease at a single institution.
2. To assess with Color-Flow Duplex Ultrasonography the effects (change in vessel diameter or peak systolic velocity) on the common femoral artery after suture-mediated percutaneous closure in patients with peripheral vascular disease.
3. To determine if sheath size has a positive or negative effect on successful outcome of the suture-mediated percutaneous closure device in patients with peripheral vascular disease.
4. To assess time to hemostasis, time to ambulation and length of stay after suture-mediated percutaneous closure following diagnostic or interventional arteriography.
5. To assess technical limitations, if any, associated with a suture-mediated percutaneous closure device used specifically in patients with peripheral vascular disease.

## TECHNICAL APPROACH

No amendments or modifications have been made to the technical approach of the protocol.

Subjects: All patients undergoing arteriography by the Peripheral Vascular Surgery Center at WRAMC will be offered inclusion in this study. 374 patients will be recruited. Age and gender will not be a discriminator for inclusion. Patients presenting to the Vascular Surgery Clinic generally range from 55 to 85 years of age. An additional subset population of 24 patients being evaluated for aortic endografting for a diagnosis of abdominal aortic aneurysm will be studied to evaluate the utility of this device in patients receiving larger sheath sizes. The total number of patients studied will therefore by 398 (374 + 24).

Study Design: This study will be a prospective randomized control trial comparing a novel percutaneous suture-mediated closure device with the conventional method of manual pressure. Patients will be divided into those undergoing only diagnostic arteriogram ("D") vs. those undergoing diagnostic arteriogram followed by intervention ("I"). These patients will have the identifier "D" or "I" associated with their case. At the end of each procedure, the patient will be randomized to receive either device "+" or manual compression "-".

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been no recent publications on the use of this device in patients with peripheral vascular disease. As far as the investigators know, this will be the first study to date describing the use of this device in patients with peripheral vascular disease. The number of subjects enrolled to the study since last APR at WRAMC is 86 and the total enrolled to date at WRAMC is 86. There have been no unexpected adverse reactions outside of those normally associated with the device. One patient was withdrawn from the study because it was felt that use of a suture medicated closure device was not in the best interest of the patient. She had received "Reopro" (abciximab) after carotid stenting and manual compression was not an option.

## CONCLUSIONS

Early review of the data suggests that this device is indeed safe and effective in-patients with peripheral vascular disease with the added benefit of improved patient comfort decreased length of stay.

Report Date: 3 January 2002 Work Unit # 2125

# DETAIL SUMMARY SHEET

TITLE: Post-Sclerotherapy Pigmentation. Can Early Microthrombectomy Prevent It? A Controlled Trial in Varicose Vein Patients

KEYWORDS: varicose veins, sclerotherapy, pigmentation, thrombectomy

PRINCIPAL INVESTIGATOR: J. Leonel Villavicencio MD
ASSOCIATES:

DEPARTMENT: Surgery STATUS: C
SERVICE: Peripheral Vascular Surgery INITIAL APPROVAL DATE: 25 February 1997

## STUDY OBJECTIVE

To investigate the effects of microthrombectomy (thrombus extrusion) on the development of post-sclerotherapy pigmentation.

## TECHNICAL APPROACH

Patients with venous spiders (1 mm or less) and varicose veins 1-3 mm will be randomly treated with a sclerosing agent. A selected area of the lower extremity will be divided into two equal halves. One week after sclerotherapy, one half will be thrombectomized and the other one will be left as control. Photographs will be taken before the injection, one-week and 16 weeks after. Two independent investigators will score the photographs. The study includes a total of 100 patients, 50 at WRAMC and 50 at NNMC.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The total number of patients enrolled to date is 100. The number of completed patients who received treatment is 98. Two patients are pending final photographs that will be taken in mid January 2002. At this time, the study will be completed in both centers, WRAMC and NNMC. The photographic scoring by two independent reviewers will also be completed by the end of January 2002 at both centers. Three patients have been lost to follow-up (changed address due to new military assignments), and one withdrew voluntarily. The reason for withdrawal was that the patient was unhappy with longer-than-expected waiting time to be treated. There was one protocol violation consisting of performing microthrombectomy in the entire treated area instead of only in the randomized one half as stated in the protocol. This information is clearly stated in the CRF # 403. There was one expected adverse event (EAE) in patient 323 who had a 1 $cm^2$ area of skin necrosis on the right thigh after a well placed and properly performed intravascular injection of the appropriate sclerosing agent concentration. The lesion healed uneventfully in the course of five weeks. From a total of fifty patients enrolled, there were 42 Caucasians, 3 Hispanics, one Asian, and four Afro-Americans.

The number of subjects enrolled to the study since last APR at WRAMC is 29 and the total enrollment to date at WRAMC is 50. The total number enrolled study-wide is 100.

## CONCLUSIONS

The analysis of the photographic scoring performed by the two independent reviewers who received a training session in the photographic and clinical assessment of results will be completed by the end of January 2002. At this time, the statistician will review and analyze the data and will provide us with the results. Data is being entered into a data base prepared by Dr. Kao from the Department of Preventive Medicine and Biostatistics of the Uniformed Services University of the Health Sciences. We will review the results and will discuss the findings. We have the purpose to write a manuscript for publication as soon as the information is completed.

Report Date: 7 December 2001

Work Unit # 2130-99

# DETAIL SUMMARY SHEET

TITLE: Does Protease Gene Expression Vary by Location in the Lower Extremity in Patients with Primary Varicose Veins or Chronic Venous Insufficiency as Compared to Controls?

KEYWORDS: MMP, varicose veins

PRINCIPAL INVESTIGATOR: Gillespie, David LTC MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Peripheral Vascular Surgery

STATUS: O
INITIAL APPROVAL DATE: 2 February 1999

## STUDY OBJECTIVE

1. Compare the expression of MMP-1, MMP-3, MMP-7, MMP-13, and tryptase in varicose veins as compared to non-varicose veins.
2. To quantify and localize these protein levels comparing the upper thigh vein to lower leg vein.
3. To compare their enzymatic activity.

## TECHNICAL APPROACH

In this study, segments of greater saphenous vein are obtained from patients undergoing CABG or varicose vein surgery. These veins are processed and both total RNA and total protein isolated. The RNA is then reverse transcribed using the First Strand cDNA Synthesis Kit (Boerhinger Mannheim, Indianapolis, IN) using primers specific for MMP-1, 3, 7, 13, and tryptase. RT-PCR product is then separated over 2% agarose gel containing ethidium bromide (0.5 &g/&ml) and visualized by UV irradiation and will be photographed using a Polaroid documentation system.

Western blots are performed using monoclonal mouse anti-human antibodies MMP-1, MMP-3, MMP-7, MMP-13, and tryptase as the primary antibodies (Oncogene Science, Cambridge, MA). Goat antimouse horseradish peroxidase coupled antibodies will be used as secondary antibodies. Scanning densitometry is then performed (NIH imager v.1.57) to quantify the amount of these proteins in each sample. Activity of these enzymes is then performed using gel substrate zymography are prepared.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 9 and the total enrolled to date at WRAMC is 30. All specimens have been processed for RNA and protein extraction. We are in the process of completing the final Western Blots for the MMP1 assay. We were able to amplify MMP-1, MMP-13, and tryptase mRNA from both proximal and distal segments of all greater saphenous veins studied. MMP-3 mRNA, however, was not found in either segment of any of the veins examined. A semiquantitative analysis of RT-PCR products comparing the ratio of MMP-1, MMP-13, or tryptase mRNA to GAPDH mRNA showed no difference between cases and controls. Western Blot analysis revealed larger quantities of MMP-1 in varicose veins compared to non-diseased veins from CABG patients ($48.0 \pm 36.7$ D.I. versus $12.5 \pm 6.8$ D.I., $p=0.036$). We also found that the greater amounts of MMP-13 and tryptase in varicose veins compared to control approached statistical significance. Investigation into the regional variation of proteases revealed there to be lower amounts of MMP-1 in distal as compared to proximal vein segments ($37.9 \pm 35.0$ D.I. versus $44.1 \pm 41.6$ D.I., $p=0.01$). Similarly, we found significantly less MMP-13 in distal segments of varicose veins as compared to the proximal segments ($152.8 \pm 130.0$ D.I. versus $206.7 \pm 173.3$ D.I., $p=0.006$).

## CONCLUSIONS

This study revealed that MMP-1 is increased in varicose veins when compared to controls. In addition, we found that there is regional variation of MMP-1 and MMP-13 in diseased varicose veins. Lower leg veins had reduced amounts of these proteolytic enzymes when compared to veins of the upper thigh.

Report Date: 15 April 2002 Work Unit # 2131-99

# DETAIL SUMMARY SHEET

TITLE: Is the Bacterium Chlamydia Pneumoniae a Possible Inciting Agent for the Development of Atherosclerosis of the Carotid or Coronary Arteries?

KEYWORDS: infection, atherosclerosis

PRINCIPAL INVESTIGATOR: Gillespie, David LTC MC

DEPARTMENT: Surgery STATUS: C
SERVICE: Peripheral Vascular Surgery INITIAL APPROVAL DATE: 6 April 1999

## STUDY OBJECTIVE

1. To investigate whether there is Chlamydia pneumoniae DNA within the atheromas of coronary or carotid atherosclerotic plaques of patients.
2. To characterize this with serologic evidence of Chlamydia pneumoniae.

## TECHNICAL

Atherosclerotic plaques were collected from a total of 9 patients undergoing carotid endarterectomy. These specimens were compared to 72 coronary artery atherosclerotic plaques collected from tissue banked post mortem specimens by the Cardiovascular Pathology Department at AFIP.

Carotid atherosclerotic plaques were collected after patients underwent carotid endarterectomy for ≥ 60% internal carotid artery stenosis. These specimens were placed in M1-99 tissue buffer and then stored at -70° C. DNA was extracted from these specimens in order to search for evidence of C. pneumoniae DNA fragments using polymerase chain reaction (PCR) analysis. All 81 specimens were examined using a set of primers that were chosen to amplify the major outer membrane protein gene of C. pneumoniae- (OMP-1). Sixteen of these 81 specimens were further examined using a second primer set designed to amplify a fragment of C. pneumoniae DNA obtained by a restriction digestion using the Pst-1 endonuclease. Amplification products were visualized by agarose gel electrophoresis. Confirmation of the PCR products was accomplished using Southern hybridization to a digoxigen-labelled probe. The presence of DNA was confirmed by human cellular oncogene (Her-2) analysis. A purified C. pneumoniae (from TWAR strain) was used in each PCR run as positive control.

Human DNA was identified in all cases using Her-2 analysis. Controls for C. pneumoniae (TWAR) were also positive in all cases. All 81 specimen studied by PCR for the OMP-1 gene however, were negative. Similarly none of the subset of 16 DNAs were amplified by the primers for the 474 bp Pst I fragment of the C. pneumoniae genome.

We submitted this for publication to the Journal but were told that due to the overwhelming evidence in the literature that C. pneumoniae is present we need to do more work. We have been re-analyzing our data using a more sensitive assay and are in the process of completing this work.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 9 patients. Previous APRs had counted all atherosclerotic plaques both carotid atheromas obtained from patients covered in this consent form and coronary atheromas which were postmortem specimens owned by AFIP. There have been no complications or adverse events associated with this study.

## CONCLUSIONS

We have confirmed other centers findings of that approximately 10% of atheromas obtained from carotid or coronary arteries have Chlamydia pneumonia DNA within them. The implications remain to be elucidated.

Report Date: 11 January 2002

Work Unit # 00-2301

# DETAIL SUMMARY SHEET

TITLE: Evaluation of Digital Fundus Images as a Diagnostic Method for Surveillance of Diabetic Retinopathy

KEYWORDS: Diabetes mellitus, Eye, Retina, Telemedicine, Vision

PRINCIPAL INVESTIGATOR: Robert M. Bauer MAJ MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Ophthalmology

STATUS: O
INITIAL APPROVAL DATE: 14 December 1999

STUDY OBJECTIVE:
The objective of this study is to assess accuracy in diagnosis of diabetic retinopathy by review of digital non-mydriatic fundus images and compare results with those obtained by opthalmoscopic examination of the same patients.

TECHNICAL APPROACH:
Fundus images are obtained from diabetic patients using a nonmydriatic digital fundus camera. The images are transferred from the camera to a viewing station by T1 connection. Images are evaluated for signs of diabetic retinopathy by recognition of presence and extent of physical findings as outlined by the Early Treatment of Diabetic Retinopathy Study and used commonly in clinical practice to determine treatment guidelines. The level of agreement of such findings ascertained by clinical examination is compared statistically with findings from review of the digital images by kappa analysis.

PRIOR AND CURRENT PROGRESS:
The start of this research has been delayed for twenty-two months. This delay is attributed to three specific problems: 1) It took seven months for the purchase request of the imaging system for this protocol to be processed through WRAMC Telemedicine Directorate. 2) Ophthalmic Imaging Systems, Inc. (OIS) was unable to equip the requested digital camera with a compatible CCD because a vendor had back-ordered the device. No other compatible CCD was available. OIS delivered the equipment for this system to our research site approximately nine months after receipt of the purchase request. 3) The CPU for the image-viewing unit malfunctioned shortly after its receipt at the research site and it was returned for repairs. We expect to receive the repaired viewing station 28 January 2002 approximately six months after it was sent to OIS for repair.

CONCLUSIONS:
This research has been delayed for an extensive period of time due to circumstances beyond the control of the investigators. We expect the equipment to be operational by the end of this month. We expect that when we begin enrolling patients the study can be completed within a period of approximately two months.

Report Date: 1 March 2002 Work Unit # 00-2302

# DETAIL SUMMARY SHEET

TITLE: Expression of Markers of Vascular Proliferation in Human Choroidal Neovascular Membranes

KEYWORDS: neovascularization, retinal degeneration

PRINCIPAL INVESTIGATOR: Prem S. Subramanian MAJ MC
ASSOCIATES: Thomas P. Ward LTC (P) MC

DEPARTMENT: Surgery
SERVICE: Ophthalmology

STATUS: O
INITIAL APPROVAL DATE: 4 April 2000

## STUDY OBJECTIVE

To identify cellular markers of neovascularization by determining the expressive of putative vasogenic and tumourigenic genes in surgically excised choroidal neovascular membranes.

## TECHNICAL APPROACH

Please see the original protocol for technical details. The strategy remains harvesting mRNA from surgical and eye bank specimens; this mRNA then will be used in RT-PCR to determine expression levels of the genes of interest (VEGF, TGF-beta, 67-kd laminin receptor, alpha-beta integrin). The PCR technique has been modified to allow the use of fluorescent-tagged primer sequences that may be used in an automated thermocycler to obtain direct quantitation of amplified products. All analyses are to be performed in the DCI labs.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

As noted in our prior APR (FY01), it has become increasingly difficult to enroll patients in this study since the advent of a new non-surgical, perhaps more effective, treatment for choroidal neovascularization (CNV). This treatment, photodynamic therapy, has become the most popular method for treating CNV. Submacular surgery is performed much less commonly than even two years ago. As noted below, no new subjects have been enrolled in this study. We await the possible enrollment of patients from an outside site (as noted in the prior year's APR). If a sufficient number of patients can be enrolled from this center, then the study will be continued. If not, then we will have no choice but to terminate the study due to our inability to obtain surgical specimens.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 1, if multi-site study. There have been no adverse events reported.

There has been only one relevant study published in this area of research in the past year. Hangai *et al.* (Invest Ophthalmol. Vis. Sci. 2001 42:1617-1625) reported expression of angiogenic factors *Ang1* and *Ang2* from RPE cells in response to VEGF stimulation *in vitro*. These factors also co-localized with VEGF in human CNV specimens examined with confocal immunomicroscopy. This study provides further evidence of growth factor expression in conjunction with CNV.

## CONCLUSIONS

None.

Report Date: 5 February 2002

Work Unit # 01-23001

# DETAIL SUMMARY SHEET

TITLE: Telemedical Examination of Eyelid Lesions: Correlation of Remote Diagnosis With In-Person Clinical Exam and Pathologic Analysis

KEYWORDS:

PRINCIPAL INVESTIGATOR: Weichel, Eric D. CPT MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Ophthalmology

STATUS: O
INITIAL APPROVAL DATE: 3 April 2001

STUDY OBJECTIVE:
The purpose of this study is to compare the diagnostic accuracy of remote video examination of eyelid lesions with live exams and final pathologic diagnosis.

TECHNICAL APPROACH:
Patients presenting to the Ophthalmology Service desiring removal of an eyelid lesion will either be examined by video or in-person analysis after reading and signing the informed consent. The investigators will randomize the subjects to either sequence A (in-person exam followed by video exam) or sequence B (video exam followed by an in-person exam). The sham controls who refuse biopsy of their eyelid lesion but agree to participate in the video portion of the study (denoted sequence C) will have a video of their eyelid lesion. The video examination includes four static images. The video exam of the eyelid is performed using a three dimensional camera.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since the last APR, we have found no recent literature to support any amendments or modifications to this research study. We have enrolled fifteen subjects since the last APR with the total enrollment of fifteen patients. No study patient has experienced an adverse event or been withdrawn from the study.

CONCLUSIONS:
We are currently actively enrolling patients into this study with a goal of seventy patients.

Report Date: 26 April 2002 Work Unit # 01-2335-99a

# DETAIL SUMMARY SHEET

TITLE: Night Vision Goggle and Night Firing Range Performance After Myopic Excimer Laser Keratorefractive Surgery in U.S. Army Personnel

KEYWORDS: Refractive surgery, laser, excimer laser, lamellar, photorefractive keratectomy, contrast sensitivity, visual performance, night vision, night vision goggles

PRINCIPAL INVESTIGATOR: Bower, Kraig LTC MC

DEPARTMENT: Surgery
SERVICE: Ophthalmology

STATUS: O
INITIAL APPROVAL DATE: 21 November 2000
MASTER PROTOCOL APPROVAL DATE: 20 April 1999

STUDY OBJECTIVE

- Evaluate visual performance in Night Vision Goggles (NVG) before and after excimer laser refractive surgery. Performance measurements will include high and low contrast targets viewed with and without optical correction.
- Determine the safety of LASIK and PRK in terms of maintenance of best-corrected NVG visual resolution of both high and low contrast targets under a full range of night sky conditions. The magnitude and duration of any transient post-operative changes in best-corrected NVG performance will be evaluated.
- Evaluate the efficacy of PRK and LASIK by assessing improvement of uncorrected NVG visual performance.
- Evaluate whether any measured post-operative NVG performance changes affect the ability to perform a specific task, as determined by performance testing on the night firing range before and after excimer laser refractive surgery.
- Evaluate subjective responses to the surgery to determine satisfaction and complaints with respect to glare, night vision, and halos.

TECHNICAL APPROACH

This study is an observational-only, non-intervention sub-protocol to the Master Protocol (WRAMC WU#2335-99; HSRRB Log # A-10105.0). It is a two-year prospective non-randomized investigation of night vision goggle and night firing performance using a three-group (PRK surgical treatment, LASIX surgical treatment, or no surgical treatment), longitudinal design with measurements taken at four points in time (initial or month 0, and months 1, 3, and 9 after the initial measures). The initial, baseline measures (obtained pre-operative as part of the master protocol for the surgically-treated subjects and abstracted from the master protocol database, and at the initial data collection for control subjects) will consist of a one time only measure of the key variables. The subsequent measures will consist of 3 evaluations made at 1, 3, and 9 months following the surgical procedure or, for the control group, following the baseline measures. The NVG measures specific to this protocol will be made at baseline and at 1, 3 and 9 months post- baseline. All baseline pre-operative evaluation and all study follow-up evaluations will be conducted at Walter Reed, except for NVG acuity and night firing to be conducted at the Night Vision Laboratory, Fort Belvoir. The specific goal of this NVG sub-study is to evaluate the effect of two types of refractive surgery on performance with night vision goggles and the M-16 on the night firing range over time as compared to no surgical intervention.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is N/A, if multi-site study. A literature search was performed and no new relevant articles were found.

CONCLUSIONS: None.

Report Date: 26 April 2002

Work Unit # 01-2335-99b

# DETAIL SUMMARY SHEET

TITLE: Prospective Evaluation of Keratorefractive Surgery in Army Aviator Trainee

KEYWORDS: Refractive surgery, laser, excimer laser, lamellar, photorefractive keratectomy, contrast sensitivity, flight performance, pilot performance, night vision goggles, night flight

PRINCIPAL INVESTIGATOR: Bower, Kraig LTC MC
ASSOCIATES: LTC Jeff Rabin, LTC Corina van de Pol

DEPARTMENT: Surgery
SERVICE: Ophthalmology

STATUS: O
INITIAL APPROVAL DATE: 25 September 2001
MASTER PROTOCOL APPROVAL DATE: 20 April 1999

## STUDY OBJECTIVE

- Conduct a prospective evaluation of the efficacy and safety of refractive surgery (photorefractive keratectomy or PRK; laser in-situ keratomileusis or LASIK) in Army helicopter pilot trainees.
- Compare flight and visual performance of two keratorefractive surgical treatment modes in pilot trainees: PRK and LASIK.
- Identify factors which predict performance and/or compromise safety during flight training by evaluating the following variables prospectively: mode of refractive surgery, initial refractive error, degree of astigmatism, corneal thickness, pupil size (normal and low light), initial level of visual performance (visual acuity, contrast sensitivity, night vision goggle resolution) under simulated day and night conditions.
- Make formal recommendations on the efficacy and safety of keratorefractive laser surgery for Army aviator training, to include selection criteria and mode of treatment to achieve optimal flight and visual performance, and maximum safety.

## TECHNICAL APPROACH

This sub-protocol is a two-year prospective study of the efficacy and safety of keratorefractive surgery in Army helicopter pilot trainees. Two treatment modes (PRK and LASIK) and a control group will be utilized. If the subject meets FDME vision standards at 1 month post-operative (uncorrected visual acuity of 20/50 or better in each eye, corrected visual acuity of 20/20 or better in each eye, not more than -0.75 D in any meridian; no complications), then IERW training will commence at a time no sooner than 3-months post-operative, pending the granting of an Exception to Policy and acceptance into the IERW program. Pre- and post-operative visual and flight performance parameters will be measured.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Subject enrollment has been on hold pending final approval of the sub-protocol, and establishment of a fully operational refractive laser center at WRAMC. Now that those tasks are accomplished, we will begin subject enrollment, probably in June 2002.

A literature search was performed and no new relevant articles were found.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study.

## CONCLUSIONS

None.

Report Date: 26 April 2002 Work Unit # 01-2335-99c

# DETAIL SUMMARY SHEET

TITLE: Operational Assessment of Refractive Surgery for Rated Army Aviators: A Prospective Evaluation

KEYWORDS: Refractive surgery, laser, excimer laser, lamellar, photorefractive keratectomy, contrast sensitivity, flight performance, pilot performance, night vision goggles, night flight

PRINCIPAL INVESTIGATOR: Bower, Kraig LTC MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Ophthalmology

STATUS: O
INITIAL APPROVAL DATE: 25 September 2001
MASTER PROTOCOL APPROVAL DATE: 20 April 1999

STUDY OBJECTIVE

- Test the null hypothesis that refractive surgery does not significantly impact visual or flight performance of experienced Active Army Aviators by conducting a prospective evaluation of the military occupational-specific impact of photorefractive keratectomy (PRK) and laser in-situ keratomileusis (LASIK) on both visual and flight performance of experienced Active Army Aviators.
- Identify vision-related pre-operative factors (e.g., initial refractive error, degree of astigmatism, wavefront aberrations, corneal curvature or thickness, pupil size, initial level of visual performance) which may predict performance and/or compromise safety of flight.
- Make formal recommendations on the efficacy and safety of keratorefractive laser surgery for experienced Army aviators, to include selection criteria and mode of treatment, which insure optimal flight and visual performance, with maximum safety.

TECHNICAL APPROACH

This protocol is a two-year prospective study of the efficacy and safety of keratorefractive surgery in rated Army aviators. Forty subjects will undergo PRK and forty subjects who will undergo LASIK. Subjects will be UH-60 pilots who will complete pre- and post-operative visual and detailed flight performance testing at USAARL. At WRAMC, subjects will complete pre-operative and post-operative visual and ocular testing and the keratorefractive procedure. The study will evaluate standard, FDA-approved PRK and LASIK procedures to determine whether PRK and/or LASIK are compatible with the Army Aviation environment, and safe and effective for rated Army Aviators.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Study enrollment ready to begin now that we have approval and an operational laser center. Expect that first subjects will be enrolled in June 2002.

A literature search was performed and no new relevant articles were found.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS

None.

Report Date: 28 May 2002

Work Unit # 2328

# DETAIL SUMMARY SHEET

TITLE: The Effect of Differing Enucleation Techniques on Cure Rate and Survival Time of Patients with Uveal Malignant Melanoma: A Comparison of Standard Enucleation, "No-Touch" Enucleation and Enucleation with Stabilization of Intraocular Pressure

KEYWORDS: melanoma, enucleation, eye

PRINCIPAL INVESTIGATOR: Ward, Thomas MAJ MC
ASSOCIATES: McLean, Ian MD

DEPARTMENT: Surgery
SERVICE: Ophthalmology

STATUS: T
INITIAL APPROVAL DATE: 05 March 1996

## STUDY OBJECTIVE

This study seeks to determine whether the surgical technique employed for enucleation of an eye containing a uveal malignant melanoma has any effect on cure or survival. The three methods to be compared are standard enucleation, "no-touch" enucleation, and enucleation with stabilization of intraocular pressure (STOP).

## TECHNICAL APPROACH

The Registry of Ophthalmic Pathology at the AFIP has accessioned all cases utilizing "no-touch" enucleation and STOP enucleation. These cases will be compared to a registry database of standard enucleation. The National Death Index (NDI) will be queried, at AFIP expense, to determine mortality. The results will be analyzed utilizing multivariate analysis (Cox's proportional hazards model). In addition, both cure and survival time will be estimated by regression analysis.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study was administratively terminated at the 28 May 2002 Human Use Committee meeting for failure to submit a completed Annual Progress Report.

## CONCLUSIONS

This study was administratively terminated at the 28 May 2002 Human Use Committee meeting for failure to submit a completed Annual Progress Report.

Report Date: 10 September 2001 Work Unit # 2334-99

# DETAIL SUMMARY SHEET

TITLE: 5 Fluorouracil-Induced Dacryostenosis and Lid Malposition

KEYWORDS:

PRINCIPAL INVESTIGATOR: Eisman, Andrew MAJ MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Ophthalmology

STATUS: C
INITIAL APPROVAL DATE: 24 November 1998

## STUDY OBJECTIVE

To determine the prevalence of 5-Fluorouracil induced dacryostenosis and lid malposition in a cohort of patients receiving systemic 5-FU for at least three months.

## TECHNICAL APPROACH

No changes or addenda have been required or submitted. The approach remains the same as in the original protocol.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 3 and the total enrolled to date at WRAMC is 28. The total number enrolled study-wide is 52, if multi-site study. Twenty-four were enrolled in Philadelphia, PA before arrival at WRAMC.

## CONCLUSIONS

The prevalence rates of the following ocular abnormalities were calculated: ocular irritation 5.8%, blepharitis 3.8%, conjunctivitis 3.8%, keratitis 3.8%, eyelid dermatitis 5.8% cicitricial ectropion 1.9%, tearing 26.9%, punctal-canalicular stenosis 5.8%, and blurred vision 11.5%. African Americans developed tearing at a significantly higher rate when compared to Caucasians ($p=0.022$, Two Sided Fisher Exact Test.) Three patients developed permanent complications that will require surgery for correction. Of the 7 patients who developed a single abnormality, 6 developed tearing and one developed eyelid dermatitis. All of the eight patients who had multiple findings developed tearing as one of their abnormalities.

Report Date: 26 April 2002 Work Unit # 2335-99

# DETAIL SUMMARY SHEET

TITLE: Initial Evaluation of Excimer Laser Keratorefractive Surgery in US Army Personnel

KEYWORDS: Refractive surgery, laser, excimer laser, lamellar, photorefractive keratectomy, contrast sensitivity

PRINCIPAL INVESTIGATOR: Bower, Kraig LTC MC
ASSOCIATES: LTC Jeff Rabin, MAJ Prem Subramanian, MAJ Robert Bauer

DEPARTMENT: Surgery
SERVICE: Ophthalmology

STATUS: O
INITIAL APPROVAL DATE: 20 April 1999

## STUDY OBJECTIVE

The objective of this study is to conduct a prospective clinical trial to evaluate the safety and efficacy of the VISX Excimer Laser System for the treatment of naturally occurring low to moderate myopia, with or without low levels of astigmatism, in U.S. Army personnel.

## TECHNICAL APPROACH

Master protocol modifications approved. Separate sub-protocols approved:

a. Night Vision Goggle and Night Firing Range Performance After Myopic Excimer Laser Keratorefractive Surgery in U.S. Army Personnel
b. Prospective Evaluation of Keratorefractive Surgery in Army Aviator Trainee
c. Operational Assessment of Refractive Surgery for Rated Army Aviators: A Prospective Evaluation

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since the last APR we have worked primarily on obtaining approval of our sub-protocols (see above) as well as completing the installation of the new WRAMC Center for Refractive Surgery. No treatments have been performed under this protocol pending the new center's opening. Now that the center is fully operational, subject enrollment will resume.

A literature search was performed and no new relevant articles were found.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 19. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

No new conclusions since last APR.

Report Date: 24 August 2001 Work Unit # 00-2401

# DETAIL SUMMARY SHEET

TITLE: The Effect of Pedicle Screw Fit Using Image-Guided Techniques

KEYWORDS:

PRINCIPAL INVESTIGATOR: Lehman, Ronald CPT MC
ASSOCIATES:

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: C
INITIAL APPROVAL DATE: 05 October 1999

## STUDY OBJECTIVE

To assess the effect of pedicle screw fit using image guided surgery techniques.

## TECHNICAL APPROACH

A cadaveric study that will assess the accuracy of pedicle screw placement with and without the use of Stealth 3-D imaging.

## PRIOR AND CURRENT PROGRESS

Because of technical challenges the original methodology had to be modified. The cadaveric spines were evaluated by DEXA and CT scan. The frameless stereotactic system could not be adequately calibrated to perform the study as originally anticipated. After discussion with DCI, the decision was made to revise the previous study and use the cadaveric specimens to evaluate the biomechanics of S1 sacral pedicle screws. We also obtained an additional four specimens free of charge from the Spine Course as outlined in the addendum to this protocol. The current study consisted of ten fresh frozen cadaveric sacra that were harvested and evaluated with dual energy X-ray absorptiometry (DEXA) to assess bone mineral density (BMD). Matched 7.5-mm stainless steel pedicle screws were then randomly assigned by side (left versus right) and placed bicortically or tricortically under direct visualization using the same insertion site and technique. Maximum insertional torque was recorded for each revolution of the screw with a digital torque wrench (TQJE1500, Snap-On Tools Corp., Kenosha, WI)

## CONCLUSIONS

Maximum bicortical S1 screw insertion torque averaged 5.22 ± 0.83 (SE) in-lbs. compared to the maximum tricortical S1 screw insertion torque of 10.34 ± 1.94 (SE) in-lbs. This resulted in a 99% increase in maximum insertional torque ($p=0.005$) utilizing the tricortical technique. Mean BMD was 940 ± 0.25 mg/cm$^2$ (507-1428 mg/cm$^2$). The BMD correlated with maximal insertional torque for the tricortical technique ($r=0.806$, $p=0.005$), but not with the bicortical technique ($r=0.48$, $p=0.16$).

Tricortical S1 pedicle screw fixation (directed into the sacral promontory) results in an average 99% increase in peak insertional torque ($p=0.005$) compared to bicortical S1 pedicle screw fixation (paralleling the endplate). Tricortical pedicle screw fixation directly correlates with BMD.

Report Date: 17 August 2001

Work Unit # 00-2402

# DETAIL SUMMARY SHEET

TITLE: A Comparison of Standard Intraoperative Fluoroscopy vs. Fluoroscopy Using FluoroNav Stereotactic System

KEYWORDS:

PRINCIPAL INVESTIGATOR: Polly, David LTC MC
ASSOCIATES:

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: O
INITIAL APPROVAL DATE: 26 October 1999

## STUDY OBJECTIVE

The primary objective of this study is to determine the amount of x-ray radiation used during the placement of spinal instrumentation with standard intraoperative fluoroscopy vs. fluoroscopy using the FluoroNav Stereotactic system.

## TECHNICAL APPROACH

The investigator will perform the spinal fusion surgery using standard methods as determined by the investigator. The first ten procedures will be performed without the use of the FluoroNav system. The next twenty procedures will be performed with the use of the FluoroNav system. To allow surgeons to become familiar and comfortable with the system, the first ten of the twenty procedures with the FluoroNav will be treated as the learning curve. In the event the FluoroNav system experiences operational difficulty, standard fluoroscopy will be used.

During all procedures, the amount of time required to place all instrumentation will be recorded on the case report form. The beginning of instrumentation placement will be deemed as the placement of the first awl, curette, probe or drill that begins the exposure of the bone for subsequent instrumentation placement. The beginning should be announced to the OR personnel responsible for recording time. The end of the instrumentation placement will be deemed as the placement of the last surgical instrument or confirming fluoroscopic image of implant(s), if taken. This point in the procedure should also be announced for recording purposes.

At the end of the procedure, the amount of radiation exposure as measured by the C-arm manufacturer's timing mechanism shall be recorded on the case report form. Also, other operative facts such as total OR time and number of implants placed will be recorded.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

To date, data has been collected on the ten procedures where FluoroNav was not used and five of the twenty procedures using FluoroNav have been completed and the data recorded.

The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 15.

## CONCLUSIONS

Although the study is in progress and any conclusions would be premature at this time, issues with the FluoroNav equipment have impacted the enrollment of patients.

Report Date: 17 October 2001 Work Unit # 00-2403

# DETAIL SUMMARY SHEET

TITLE: The Relationship of Femoral Notching, Osteoporosis, and Supracondylar Fractures

KEYWORDS: femoral notching, total knee arthroplasty, osteoporosis

PRINCIPAL INVESTIGATOR: Scott B. Shawen, MAJ, MC
ASSOCIATES: William Klemme, LTC, MC; John Xenos, LTC, MC; Philip J. Belmont, Jr., MAJ, MC; Joseph Orchowski, MAJ, MC, Timmie Topoleski, Ph.D.

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: C
INITIAL APPROVAL DATE: 30 November 1999

STUDY OBJECTIVE:
To examine the effect of femoral notching, osteoporosis, and distal femoral geometry on femoral torsional strength.

TECHNICAL APPROACH
- Obtain cadaveric femurs for study (13 paired femurs)
- Perform DEXA scan to the proximal/distal femur to determine bone mineral density
- Take radiographs of femurs to rule out evidence of bony tumor
- Randomize femurs into "notched" and "un-notched" groups
- Perform CT scans of femurs to determine cortical thickness, bone diameter, and amount of notching
- Perform mock total knee replacement surgery to femurs, notching selected specimens
- Embed specimens in fixtures and perform torsional testing for strength (N-m)
- Dispose of specimens
- Analyze data utilizing Student's t-test and correlation values
- Review data and statistics with biostatistician

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Study has been completed. No recent literature since last APR relating to this area. Statistics completed. Manuscript ready for submission for publication.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 26.

CONCLUSIONS
Femoral notching significantly decreases femoral torsional strength. This can be predicted by evaluating the bone mineral density as well as distal femoral geometry. The most predictive test alone was distal femoral bone density. By adding the distal polar moment of inertia (calculation based on distal femoral geometry) to the bone mineral density, the ability to predict the torsional strength is improved.

Report Date: 9 April

Work Unit # 00-2404

# DETAIL SUMMARY SHEET

TITLE: The Radioscaphoid Interval. A Sensitive Indicator of Early Perilunar Instability

KEYWORDS: Wrist, Instability, Radiographic correlation

PRINCIPAL INVESTIGATOR: Kenneth Taylor, MAJ MC
ASSOCIATES: Philip Belmont CPT MC, Scott Shawen CPT MC, Christopher Litts MAJ MC

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopedic Surgery

STATUS: O
INITIAL APPROVAL DATE: 18 April 2000

## STUDY OBJECTIVE

To establish the diagnostic sensitivity and specificity of the radioscaphoid interval in determining early peripheral carpal instability.

## TECHNICAL APPROACH

Patients presenting to the WRAMC Orthopaedic Hand Surgery clinic with physical examination consistent with carpal instability, and matched controls meeting inclusion/exclusion requirements are being enrolled in this study. Measurement from plain film radiographs, clinical examination data and subsequent inoperative findings are recorded as previously outlined in the DCI-approved protocol. There have been no changes to the methodology of this study.

## PRIOR AND CURRENT PROGRESS

There have been no significant additions to the orthopaedic literature concerning the topic of this study. In order to assure blinded assessment by the investigator, no radiographic measurements have been performed to date as only subjects in the treatment group have been enrolled. We will begin enrolling age and sex-matched subjects in accordance with the procedures outlined in the protocol. No subjects have withdrawn from the study and there have been no adverse effects. Currently, ten subjects have been enrolled. Of these, seven have had surgery and three are being followed clinically. Enrollment has not affected patient care, as the operative surgeon will also be blinded to the results of additional radiographic measurements made for the purpose of this study.

The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 10. The total number enrolled study-wide is 10, if multi-site study.

## CONCLUSIONS:

Subjects will continue to be enrolled in accordance with DCI-approved protocol.

Report Date: 7 June 2002

Work Unit # 00-2405

# DETAIL SUMMARY SHEET

TITLE: MOSS-Miami and VertiGraft 2 Open-Label Study # 199901

PRINCIPAL INVESTIGATOR: Polly, David LTC MC

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopedics Surgery

STATUS: O
INITIAL APPROVAL DATE: 22 August 2000

STUDY OBJECTIVE The VertiGraft2 with the MOSS®-MIAMI® Spinal Fixation System has been approved by the FDA for treatment of spondylolisthesis and it is commercially available. The purpose of this study is to assess the performance of the implant using a transforaminal lumbar interbody infusion (TLIF) procedure and report the outcomes. The basis of comparison for this study is the historical controls from prior surgeries and previous WRAMC experience.

TECHNICAL APPROACH Preoperative Evaluation: Within three months prior to the surgical intervention procedure, the study subject must be evaluated using the standard health status survey (SF-36) and the Oswetry Disability Index. All procedures in this protocol are normal standard of care. The research part of this study comes from the data collection information from the SF-36, the Oswestry Disability Index and the Clinical Evaluation sheets. Surgical Procedure: On the date of the surgery, the Operative Case Report Form will be completed to include all relevant and required surgical data. Postoperative Evaluations: The study subject is allowed to ambulate when able to do so without undue discomfort and at the discretion of the Investigator. The study subject will be discharged when afebrile and ambulating comfortably, as soon as deemed appropriate by the Investigator. Radiographic Evaluation: In addition to the radiographic evaluation performed prior to surgery, all subjects will be evaluated postoperatively by radiograph. The films will be evaluated on the basis of the standard for fusion ratings. The criteria for the standards are: a score of 0 = no fusion procedure performed, 1 = obvious Pseudoarthrosis, 2 = Possible Pseudoarthrosis, 3 = Fusion status uncertain, 4 = Probable fusion and 5 = Fusion (included sentinel sign and/or bridging trabecular bone). The radiographic views required include: A-P and lateral views at all time frame points. The flexion and extension views will be done at the twelve-month and the twenty-four month follow-ups. In addition to these radiographic views, a CT scan will be performed at the three-month follow-up. These views are normal standard of care to all patients. There have been no modifications to this study.

PRIOR AND CURRENT PROGRESS The number of subjects enrolled to the study since last APR at WRAMC is 6 and the total enrolled to date at WRAMC is 29. There have been no amendments or modifications to the study. One patient voluntarily withdrew. There have been three adverse events. One patient was in a motor vehicle accident at 12 weeks post-op with no significant adverse sequelae present. The second patient had an intra-operative pedicle fracture of her right L5 pedicle. A routine CT was done to verify that the screw placement was still okay. At three weeks post-op, her 100-pound dog jumped on her; her pain worsened. She returned to the clinic for evaluation. Her screw displaced further and she went back to the OR to have the screw removed. This is unrelated to the protocol; it is a sequelae of pedicle screw fixation, which is FDA approved for this indication. The third patient had an adverse event during the 2-level TLIF surgery. On the L5-S1 right side while seating the VertiGraft 2, the laminate separated (split) the graft. The VG2 seemed well positioned, provided structural support as desired, and would have been difficult to remove or alter and therefore was left in place and surgery continued. A bone graft substitute (cancellous chips) was placed into the disc cavity. No untoward effects noted.

CONCLUSIONS This study needs one more enrollee to reach the new modified enrollment goal. All patients appear to be healing. Many have experienced substantial clinical improvement. There have been no fusion failures. One patient has not experienced significant pain relief.

Report Date: 19 September 2002

Work Unit # 00-2406

# DETAIL SUMMARY SHEET

TITLE: The Porous-Coated Anatomic Total Hip Prosthesis, Inserted Without Cement; Results After 15 Years in a Prospective Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Xenos, John S. LTC MC
ASSOCIATES:

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: O
APPROVAL DATE: 12 September 2000

STUDY OBJECTIVE:
To report the minimum 15-year results of a consecutive series of 100 primary uncemented total hip arthroplasties using a first generation design.

TECHNICAL APPROACH
Clinical information including SF-36 General Health Questionnaire and plane radiographs are obtained on each patient in routine follow-up evaluation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 55.

CONCLUSIONS
The femoral component has exceeded expectations with no loosening of a stem determined to be bone ingrown at earlier follow-up intervals. The acetabular component has a failure rate similar to other first generation uncemented designs.

Report Date: 15 February 2002 Work Unit # 01-24003

# DETAIL SUMMARY SHEET

TITLE: Hip Arthroscopy in Young Active Adults Retrospective Case Series Report

KEYWORDS:

PRINCIPAL INVESTIGATOR: Andersen, Romney MAJ MC
ASSOCIATES:

DEPARTMENT: Orthopaedics and Rehabilitation STATUS: C
SERVICE: Orthopaedic Surgery INITIAL APPROVAL DATE: 2 January 2001

STUDY OBJECTIVE:
Assess the results of hip arthroscopy done at Walter Reed Army Medical Center

TECHNICAL APPROACH
Review results as assessed by modified Harris Hip Score and SF-36.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
Enrollment complete, surveys returned and data tabulated. Publication draft is currently under revision by staff. No adverse events. No recent literature updates of significance.

The number of subjects enrolled to the study since last APR at WRAMC is 24 and the total enrolled to date at WRAMC is 24. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS:
Hip arthroscopy is of limited value in patients undergoing MEB or workman's compensation claims. This finding differs from previous studies.

Report Date: 19 November 2001

Work Unit # 01-24004

# DETAIL SUMMARY SHEET

TITLE: An Observational Study to Record Process Measures and Analyze Cost Related to Iliac Crest Bone Graft Harvest for Spinal Fusion

PRINCIPAL INVESTIGATOR: LTC (P) David W. Polly, Jr. MC
ASSOCIATES: LTC (P) William R. Klemme MD, LTC Timothy R. Kuklo MD JD, Eileen Bronfman RN MA, CPT Aman Dhawan MD

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: O
INITIAL APPROVAL DATE: 2 January 2001

## STUDY OBJECTIVE

A prospective, observational study of posterior iliac crest bone harvesting is ongoing using process measures to establish a normative bone harvesting database for future comparative studies and analysis of bone graft substitutes. The objectives of the study are:
Establish a normative data set of the parameters of iliac crest bone graft harvest recording.
Time expended in performing the graft.
The amount of bone harvested.
The amount of blood lost.
The equipment and disposable supplies used in the procedure.
This will establish a baseline for comparing the use of autologous bone graft to emerging alternatives.

## TECHNICAL APPROACH

Beginning in February 2001, autogenous posterior iliac crest bone graft harvest was obtained from fourteen patients (ten males and four females) under supervision of a fellowship trained spine surgeon. Bone graft was obtained using the "trephine curettage" technique through a separate incision from the primary surgery. Data collection included estimated blood loss for the procedure and the harvest proper, total time for the harvest, and total bone harvested as measured after packing using a calibrated specimen cup.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Autogenous iliac crest bone graft is currently the "gold standard" when attempting an arthrodesis in various clinical scenarios. In spine surgery, autogenous iliac crest bone graft (ICGB) is one of the most commonly performed procedures, as iliac crest is the most common donor site. Various authors have reported the potential dangers, biomechanical consequences, as well as the associated complications including superficial or deep infection, sensory loss, nerve and/or arterial injury, peritoneal perforation, and sacroiliac instability. The incidence of minor complications ranges from 4% to 20.6%, with major complications ranging from 0% to 8.6%. Because of this morbidity, bone graft substitutes are emerging. The theoretical advantages include decreased operative time, and ease of use with great versatility in size, shape, and volume of graft needed. Economic efficacy and clinical benefit of these substitutes will need to be established before these bone substitutes become standard of care. A critical analysis of both ICBG harvesting and bone graft substitutes is needed.

The number of subjects enrolled to the study since last APR at WRAMC is 14 and the total enrolled to date at WRAMC is 14. The total number enrolled study-wide is 14 if multi-site study.

## CONCLUSIONS

Iliac crest bone harvest adds time and contributes blood loss to the index procedure. Average volume of bone harvested during posterior iliac crest bone grafting is 37 cc. These process measures must be taken into consideration in light of the emerging field of bone graft substitutes as they contribute to patient complications and cost.

Report Date: 15 February 2002 Work Unit # 01-24005

# DETAIL SUMMARY SHEET

TITLE: Prospective Cohort Analysis of Hip Arthroscopy in Young Active Adults with Two Years Follow-up

KEYWORDS:

PRINCIPAL INVESTIGATOR: Anderson Romney C., MAJ MC
ASSOCIATES:

DEPARTMENT: Orthopaedics and Rehabilitation STATUS: O
SERVICE: Orthopaedic Surgery INITIAL APPROVAL DATE: 6 February 2001

STUDY OBJECTIVE:
Assess the results of hip arthroscopy done at Walter Reed Army Medical Center on a prospective basis.

TECHNICAL APPROACH:
Patients undergoing hip arthroscopic surgery have pre and post operative questioners administered to assess the results of the surgery. No change to the protocol has occurred.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
No recent literature updates of significance. No modifications to the study. No adverse events. No patients withdrawn from study.

The number of subjects enrolled to the study since last APR at WRAMC is 4 and the total enrolled to date at WRAMC is 4.

CONCLUSIONS:
None yet.

Report Date: 7 February 2002

Work Unit # 01-24006

# DETAIL SUMMARY SHEET

TITLE: Adolescent Idiopathic Scoliosis Overhang Curve

PRINCIPAL INVESTIGATOR: Polly, David W. LTC MC

DEPARTMENT: Orthopaedic Surgery and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: O
INITIAL APPROVAL DATE: 10 April 2001

## STUDY OBJECTIVE

The main objective of this exploratory study is to help develop and define the necessary radiographic (process) and clinical (patient) outcome measures involving current surgical techniques for the treatment of single overhang adolescent idiopathic scoliosis (AIS) curves to perform a scientifically valid prospective investigation. To reflect current surgical techniques, consecutive cases of single overhang AIS curves treated surgically from 1 July 1996 to 1 April 1999 will be collected from spinal deformity centers with appropriate case volume, research capabilities, and study commitment. To achieve this goal, the pilot study will develop the infrastructure to: 1) Classify single "overhang" AIS curves reliably by different scoliosis surgeons, and 2) to ensure that participating spinal deformity centers will be able to fulfill the above requirements with an appropriate case volume to participate in a prospective investigation. A secondary objective of this exploratory study is to obtain preliminary data on currently available surgical approaches to treat these single "overhang" AIS, thoracic thoracolumbar and lumbar curve patterns, investigating the following questions: 1) Are levels truly saved using anterior versus posterior current techniques?, 2) Which technique(s) provide the best correction, balance, cosmesis, and patient satisfaction?, 3) Is there one technique associated with increased morbidity over others?, 4) Are the cost profiles of the current techniques available and similar?, 5) How does sagittal plane alignment influence the results? It is hoped that information from this secondary objective will help provide specific and detailed objectives for the future prospective investigation.

## TECHNICAL APPROACH

An exploratory study. X-ray films will be measured from the patient's immediate post-op and one-year and two-year follow-ups. Graphic illustrations of the measuring techniques will be given to each participating physician. These techniques are the standard accepted techniques as agreed upon the Scoliosis Research Society.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

To date, the software for measuring the scoliosis films has been developed and participating sites that have received their IRB approval are actively capturing the images electronically for measurement. Three spine surgeons have finished Phase 1 of the validation of the software. Phase 1 consisted of the three spine surgeons measuring thirty sets of radiographs manually (pre-op AP, Lateral, Right Side-Bending, Left Side-Bending, post-op AP, and Lateral) two times each. Patient identifiers were blinded and each patient was then assigned a number and data was recorded on the Radiographic Assessment form. The forms were sent to PhDx for statistical analysis. Phase 2 consists of measuring the same numbered radiographs digitally on the computer and transmitting that information to PhDx for statistical significance. The end result will be to compare manual to digital for validation of the software. Once validated, the software will be rolled out to participating IRB approved sites to commence with the retrospective review of adolescent idiopathic scoliosis patients. Because this is a retrospective review of available scoliosis films, there are no adverse events to report.

The number of subjects enrolled to the study since last APR at WRAMC is 30 and the total enrolled to date at WRAMC is 34. The total number enrolled study-wide is 70 if multi-site study.

## CONCLUSIONS

In all but one measurement, (Sagittal T2-T5), the manual measurement technique provided a reliable and reproducible means of validating measurement methods between the surgeons.

Report Date: 25 February 2002 Work Unit # 01-24007

# DETAIL SUMMARY SHEET

TITLE: A Multi-Center Study to Evaluate the Safety of Efficacy of DePuy AcroMed Titanium Surgical Mesh and Moss-Miami Spinal System Pedicle Screws

PRINCIPAL INVESTIGATOR: Polly, David W. LTC MC
ASSOCIATES: Kuklo, Timothy R. LTC MC

DEPARTMENT: Orthopedic Surgery and Rehabilitation STATUS: O
SERVICE: Orthopedic Surgery INITIAL APPROVAL DATE: 24 April 2001

STUDY OBJECTIVE: Determine the clinical success of the Titanium Surgical Mesh and MOSS-Miami Pedicle Screws in the treatment of one or two adjacent levels of degenerative disc disease in the lumbar spine. Instrumentation for this procedure is used at the levels above and or below the motion segment or segments. In addition, the clinician will be allowed to instrument at an additional level if the clinician deems it necessary. The maximum number of levels allowed to be instrumented will be four.

- Determine the rate of healing (radiolographically apparent fusion) for subjects implanted with Titanium Surgical Mesh and MOSS-Miami Pedicle Screws.
- Determine the comparative success rates of the DePuy AcroMed Titanium Surgical Mesh and MOSS-Miami Pedicle Screws compared with Lumbar I/F Cage® with VSP® Spine System.
- Identify possible intra-operative complications.
- Identify possible long-term complications

TECHNICAL APPROACH:
Preoperative Evaluation: Subjects will be asked to participate in the study following the surgeon's determination that the study criteria. The subject will be asked to sign the informed consent form following explanation and discussion of the study with the investigator. Women of childbearing age must take a blood pregnancy test before starting this study. If this test is positive, you cannot take part in this study. Once the consent form is signed the subject is enrolled in the study. The Case Report Form should be completed verifying that the investigator determined that the subject satisfied all the inclusion and exclusion criteria. (Sample Case Report Forms detailing the required data collection are provided in the Investigator Manual.) The Subject will be prepared for surgery in accordance with accepted medical practice. The appropriate history, physical examination and x-ray work will be done. The preoperative evaluation must occur within three months of the planned surgery. The preoperative evaluation is to be documented on the Demographic Case Report Form. In addition, the subject will be asked to complete the Oswestry Disability Index and the SF36 within three months prior to the surgery. The clinical coordinator will administer these research tools. The research part of the study involves the data collection from the SF-36 (a measure of health status), the Oswestry Disability Index, the Clinical Evaluation sheets and the safety and efficacy of the Titanium Surgical Mesh and MOSs-Miami Pedicle Screws versus the Lumbar I/F (Interbody Fusion) Case with the VSP Spine System using the TLIF/PLIF surgical technique. The VSP Spine System and the Lumbar I/F are outside controls use by DePuy.

Preoperative Evaluation Data Collection
Patient demographics and history: (CRF Demographic to be completed within 3 months prior to surgery

- Age
- Gender
- Height/Weight
- Smoking status
- Duration of pain (back, leg)
- Previous surgeries/treatments

Clinical Assessment:
- Pain and function status (Oswestry)
- Pain at back, leg (5 point scale)
- Work status
- Patient satisfaction questionnaire (SF36)

Radiographic Assessment:
- Anteroposterior
- Lateral
- Flexion/Extension

The preoperative evaluation must be completed no greater than three months prior to surgery.

Surgical Procedure: The surgical procedure will be done on an in-patient basis as is customary for lumbar fusion surgery. The surgical approach will include PLIF and TLIF per surgeon preference as both are considered open posterior approaches (see Investigators Manual for surgical procedures). Postoperatively, the patient will be allowed to ambulate according to the individual surgeon's judgment. Subjects will receive standard postoperative care. Subjects should avoid bending, lifting, stooping and twisting for the first three months and avoid heavy lifting for the first six months. Throughout the study, the occurrence of complications and adverse events will be identified and documented by the Study Investigator and reported to the sponsor. Based on the Study results, or if deemed necessary by the clinical Investigator or reviewing IRB, the Sponsor will amend the Study protocol, or if warranted, terminate subject enrollment. Any additional procedures must be documented.

Intraoperative/Immediate Postoperative Assessment and Data Collection
- Date of surgery
- Operative time
- Estimated blood loss
- Blood replacement
- Levels fused
- Device used (size and quantity)
- Complications

Surgical procedures subsequent to the original surgery will be categorized as follows:
- A revision is a procedure that adjusts or in any way modifies the original implant configuration. This may include adjusting the position of the original configuration or replacing part or all of the assembly.
- A removal is a procedure where one or more components of the original implant configuration are removed without replacement.
- A re-operation is any surgical procedure at the involved spinal level(s) that does not remove, modify, or add any components of the assembly.
- A supplemental fixation is a procedure in which additional instrumentation not under study in the protocol is implanted.
- Any implant that is removed will be returned to the Sponsor for evaluation. Retrieved implants should be stored in formalin and returned to the sponsor (see Investigator Manual).

Postoperative Evaluation: Clinical postoperative evaluations will be performed at 3 months, 6 months, 12 months and 24 months. Clinical evaluation will include pain and function, pain at donor site, pain medications, reflexes, sensory function, motor functions and work status. Clinical evaluation scales are provided below. Data will be collected and recorded on the Follow up CRF. All complications (device and non-device), re-operations and revisions will also be recorded at each visit on CRF Medical Event Form. At the 12 and 24-month evaluations, subjects will be asked to complete the SF-36 questionnaire. There have been no modifications to this study.

PRIOR AND CURRENT PROGRESS: We have one adverse event reported. The number of subjects enrolled to the study since APR at WRAMC is 7 and to total enrolled to date at WRAMC is 7. The total number enrolled study-wide is 52, if multi-site study.

CONCLUSIONS: Unchanged.

Report Date: 19 April 2002 Work Unit # 01-24008

# DETAIL SUMMARY SHEET

TITLE: Functional and Clinical Outcome Following Arthroscopically Assisted Anterior and Posterior Cruciate Ligament Reconstruction in a High-Demand Patient Population

KEYWORDS: Anterior/Posterior Cruciate Ligament, Outcomes

PRINCIPAL INVESTIGATOR: Taylor, Kenneth F. MAJ MC
ASSOCIATES: Kevin L. Kirk CPT MC, Kevin P. Murphy LTC MC

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: O
INITIAL APPROVAL DATE: 26 June 2001

## STUDY OBJECTIVE

To describe the clinical and functional outcomes of arthroscopically assisted anterior and posterior ligament reconstruction in a physically active population.

## TECHNICAL APPROACH

Retrospective chart review, clinical survey, and examination of the above patient population. No modifications in approach from initial protocol.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

To the investigator's knowledge there have been no recent investigations of multi-ligamentously injured knees in an active population published in the literature. Findings thus far appear to demonstrate a quicker return to pre-injury activity level in patients who have undergone reconstruction with allograft ligaments compared to those who have had autograft reconstructions. This finding is also corroborated by the higher return to duty rates of the active duty patients with allograft reconstructions. Overall, the present results indicate a high patient satisfaction with the surgery was well as a large majority able to return to pre-injury function.

The number of subjects enrolled to the study since last APR at WRAMC is 16 and the total enrolled to date at WRAMC is 16. This is not a multi-site study.

## CONCLUSIONS

Current conclusions are the following:

1) Arthroscopically assisted ACL/PCL reconstruction allows a majority of patients to return to high levels of activity following surgery.
2) Allograft reconstruction allows quicker return to pre-injury activity level and had higher retention of active duty soldiers than autograft reconstruction.
3) Arthroscopically assisted ACL/PCL reconstruction is an excellent option for patients with multiple knee ligament injury.

Report Date: 14 June 2002

Work Unit # 01-24009

# DETAIL SUMMARY SHEET

TITLE: Effects of Alendronate Sodium (FOSAMAX) on Spinal Fusion in the Rabbit Model

PRINCIPAL INVESTIGATOR: Ronald A. Lehman, Jr., CPT, MC
ASSOCIATES: Timothy R. Kuklo, LTC MC; Rebecca Cockman-Thomas, LTC, VC; Jerry Cowart, DVM

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopedic Surgery

STATUS: O
INITIAL APPROVAL DATE: 14 August 2001

STUDY OBJECTIVE:
Alendronate sodium will not have a positive effect on bone healing by virtue of its specific inhibition of osteoclast-mediated bone resorption.

TECHNICAL APPROACH:
Our goal is to perform bilateral intertransverse process fusion surgery using bilateral autologous iliac crest bone graft spinal fusion (as described by Boden, et. al., 1994) on skeletally mature (3-5kg) NZW rabbits. Postoperatively, we will randomly assign equal numbers to two experimental groups. Preoperative posteroanterior and lateral radiographs will be taken to help exclude specimens with underlying disease. Group 1- saline control will receive a daily postoperative dose of saline per os, while Group 2 – alendronate sodium group will receive 100ug in daily oral doses of equal volume (20-40cc) to that of the saline group. All groups will receive single daily doses by gavage of the prescribed compound for 8 weeks. After the 8-week period the animals will be humanely sacrificed and several analyses performed. At the time of sacrifice we will radiograph the lumbar spine of each rabbit. The radiographs will be viewed and the fusion mass graded in a blinded fashion as fused or not fused

Assessments will be made of the incorporation of the bone graft and that status of the fusion. This will be determined on radiographs as having a continuous trabecular pattern within the fusion mass on either (or both) sides between the adjacent transverse processes. Incorporation of the bone graft will be graded as resorbed, minimally remodeled, moderately remodeled, or fully remodeled. Bone graft will only be placed between the transverse processes, and not between the intervening vertebral bodies. After radiography, the lumbar spine and fusion mass will be excised and grossly inspected. Gross size of each fusion will be noted. At this time manual palpation of the fusion mass will be performed. Two trained individuals, blinded to the treatment group, will evaluate the fusion mass as solid (no movement) or not solid (movement present) at the level of the joint fused. The location of the motion will be noted when present. Only levels that have had graft incorporation and no motion in the fusion mass will be defined as fused. Histological analysis will be performed by a veterinary pathologist. The quality of the fusion will be graded at the level by assigning a histologic score from zero to seven as described by Emery et al. The area of focus will be at the superior and inferior transverse process and bone graft incorporation sites. The superior and inferior sites will be sampled, and their scores averaged. Then, the right and left scores will be averaged and a mean score assigned to each rabbit. The lumbar spine at the level of the arthrodesis will be prepared for histologic analysis.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
All rabbits have been operated upon and the first set of 10 will be euthanized on 20 June 2002 according to the protocol. The next set of 20 will occur the first week of July and then the last set of 20 two weeks later. Manual palpation and radiographic analysis will be performed at that time. We will then contact the histologists and veterinary pathologists to perform the histologic staining which will take approximately 4 months. At that point we will begin collecting the data and writing the manuscript. There have been several articles published recently which will contribute to our study. Recent investigations have shown that the effect of Alendronate Sodium has been shown to increase the effects of the osteoblasts as well as

the osteoclasts, thereby increasing bone formation in fracture healing.

We have had nine animals drop out of the study to date. Following is a list of the complications for each animal.

- Preanesthesia (replaced with animal from AFIP resources)
- Postoperative infection (unknown source)
- Complications secondary to gavaging of the rabbits (1-swallowed half of syringe, 2-punctured lungs)
- Postoperative hind leg paralysis (most commonly reported complication in literature)

All animals were euthanized according to ICUC and AFIP protocol.

Four animals were replaced by AFIP for occurrences deemed under their control/error. Therefore, we currently have 45 animals in the study.

CONCLUSIONS:
Our study has progressed well since final approval for the funding was obtained in March. However, we have had approximately a 10% drop out rate with more than half the experiment still to perform. We may need to order more rabbits for the study in order to obtain statistical significance. We will determine this after the analysis of these fifty animals. The relevance to this study is extremely significant. Therefore, if more animals are needed, it would be prudent to continue with an addendum to procure additional funding. We anticipate that most of the data collection will be completed by December 2002. We will then analyze the data and make a determination if additional resources will be necessary.

Report Date: 24 October 2001

Work Unit # 01-2401

# DETAIL SUMMARY SHEET

TITLE: Quantitative Analysis of the Neovascularization of Distraction Osteogenesis from the End of Distraction to Bone Maturity Correlated with Bone Histology, Mechanical Properties, and Radiography

KEYWORDS: neovascularization, distraction osteogenesis

PRINCIPAL INVESTIGATOR: Roxanne Wallace CPT (P) MC
ASSOCIATES: Kathleen McHale COL MD, Bahman Rafiee MD, Nozomu Inoue MD PhD

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: O
INITIAL APPROVAL DATE: 12 March 2001

## STUDY OBJECTIVE

The capillary density of the distraction gap will increase from zero at the time of osteotomy to that of normal mature bone at the end of consolidation. The radiographic, mechanical, and histological properties at each interval will correlate with the increase in capillary density.

## TECHNICAL APPROACH

We have delayed performing the corrosion casting. We performed post mortem DEXA and CT scans of the tibia.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Not applicable.

## CONCLUSIONS

The following abstract has been prepared from the data.

Distraction Osteogenesis: A Densitometric, Biomechanical, and Histological Study
Purpose: To evaluate the utility of DEXA in predicting mechanical strength of post distraction callus.
Materials and Methods: Thirty New Zealand white rabbits underwent unilateral tibial callus distraction with an external fixator across a mid-diaphyseal osteotomy. Included were a seven-day post-operative latency period, ten days of distraction at 0.5mm B.I.D., and zero, seven, fourteen, twenty-eight, or fifty-six days of post-distraction consolidation before sacrifice. Tibiae were removed and stripped of soft tissue. Anteroposterior plain radiographs and DEXA scans were taken. Specimens were embedded and torqued to failure. Plain radiographs were taken. A callus defect index was generated by finding the ratio of incomplete columns of ossification to width of callus.
Results: The DEXA-derived bone mineral density (BMD) demonstrated a moderate correlation to torsional strength while the cartilaginous defect as present (r=.78,.88), a significant positive correlation with torsional strength after the cartilaginous defect was 80% ossified (r=.97), and less of a correlation once callus remodeling began (r=0.6).
Conclusions: In the early post distraction period when cartilaginous or fibrocartilaginous defects interrupt the longitudinal continuity of osseus trabeculae strength only moderately correlates with density. After these defects ossify, the density-contributing substance is distributed within the material uniformly such that it can distribute stress throughout itself and strength correlates with density. This is the optimal time period to use DEXA to predict strength. However, once remodeling begins, there is again a non-uniform distribution of osseus trabeculae resulting in no correlation between density and strength.

Report Date: 22 July 2002 Work Unit # 01-24010

# DETAIL SUMMARY SHEET

TITLE: Biomechanics of Anatomic Versus Straight Forward Technique of Thoracic Pedicle Screw Placement: A Cadaveric Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Lehman, Ronald A. CPT MC
ASSOCIATES: COL David W. Polly Jr. MC, LTC Timothy R. Kuklo MC JD, Robin S. Howard MA

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopedics Surgery

STATUS: C
INITIAL APPROVAL DATE: 14 September 2001

## STUDY OBJECTIVE

This will be a randomized experimental study in a cadaveric model comparing the maximal insertional torque and force to failure of an anatomic versus a straight-ahead insertion technique of pedicle screws in the thoracic spine.

## TECHNICAL APPROACH

Experiments will be conducted on cadaveric spines (T1-T12) obtained from donors without history of tumor or metabolic bone disease, excluding osteoporosis. Soft tissues will be dissected, leaving only the osteoligamentous column intact. Vertebrae will be excluded from the study if radiographs detect tumor, previous fracture, or previous hardware. Each spine will be scanned using DEXA (Hologic QDR-2000, Boston, MA). The specimens will be mounted in an acrylic water-filled container at a depth of 15 cm to place the spine in a supine anatomic position. The DEXA scans will be performed in the AP and lateral planes yielding estimates for a BMD in milligrams per square centimeter. The specimens will be stored at –20 degrees Celsius until time of experimentation. They will be thawed at room temperature for 18 hours before use. An experienced spine surgeon, with extensive clinical experience in the use of pedicle screws, will place all of the pedicle screws.

The surgeon will locate the entry point for the screw with a pedicle awl and the cortex will be breached. A 0.45mm Kirschner Wire (K-wire) will then be placed under direct visualization. The depth of the pedicle will then be measured and screw length determined. The screw will be sized to ensure adequate length that the dorsal cortex of the vertebrae will not be engaged during placement of the pedicle screw. A 4.5 mm cannulated tap will then be utilized to breech the posterior cortex to the neurocentral junction. The concept of "tapping" is similar to using a nail to begin a hole before attempting to place a screw into a wall. It is difficult to begin the screw without a prefabricated hole. Thus, tapping involves using a screw-like device to enlarge the diameter of the pedicle hole, so that the larger pedicle screw can be inserted. The K-wire will then be removed and a 5.0 mm monoaxial TSRH pedicle screw (Sofamor-Danek; Memphis, TN) will then be placed using either the straightforward or the anatomic technique. Both of the insertion techniques will utilize the "all-in technique" of insertion of the pedicle in the coronal place.

Insertion technique will be randomly assigned to vertebrae side using a computer program based on random number generation. Randomization will include blocking on vertebral level as follows: Starting with T1/T2, each consecutive pair of vertebrae will have one vertebrae with the anatomic technique on the left side and the penetration depth to the total distance from the screw entrance site to the anterior cortex. Each screw length will be chosen so that it would most approximate 80% of the pedicle screw axis length when this variable is controlled. The largest size pedicle screw will be utilized when this variable is controlled. Mediolateral screw angulation is the angle measured in the coronal plane of a line bisecting the vertebral body and the line of the long axis of the screw. The mediolateral screw insertion angle can be controlled within narrow limits within a given vertebral body. The mediolateral insertion angle will be chosen so that it would most closely approximate the average pedicle angle for the various vertebral levels: 5° for T10-T12.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Average BMD was 632 ± 0.25 mg/cm² (471-794 mg/cm²). The MIT for the straightforward technique was 2.58 ± .14 (SE) in-lbs while the anatomic trajectory averaged 1.86 ± 0.14 (SE) in-lbs. The insertional torque at the neurocentral junction for the ST technique averaged 1.89 ± .17 (SE) in-lbs. (73% of MIT), while the AT trajectory averaged 1.39 ± .11 (SE) in-lbs (75% of MIT). POS for the ST technique was 610.87 ± 49.73 (SE) in-lbs., while the POS of the AT averaged 480.52 ± 53.79 (SE) in-lbs. Thus, the straightforward technique (paralleling the endplate) results in a 39% increase in MIT (p=0.0005), and a 36% increase in MIT at the neurocentral junction (p=0.007). Additionally, the average insertional torque at the neurocentral junction for the straightforward trajectory was equivalent to the MIT for the anatomic trajectory. A 27% increase in POS (p=0.034) was seen with the straightforward technique. BMD did not correlate with peak insertional torque for either technique (p=0.118), but did correlate with POS for both the AT (p=0.025) and ST techniques (p=0.027).

The number of spines used in the study since last APR at WRAMC is ≤3 and the total used to date at WRAMC is ≤3.

CONCLUSIONS

The straightforward technique results in a 39% increase in MIT (p=0.0005) and a 27% increase in POS (p=0.034) over the anatomic trajectory. The neurocentral junction provides approximately 75% of the MIT in the thoracic spine. BMD directly correlates with pullout strength, but not with insertional torque.

Report Date: 15 July 2002 Work Unit # 01-24011

# DETAIL SUMMARY SHEET

TITLE: The Biomechanical Effects of Various Tapping Techniques with Insertion of Thoracic Pedicle Screws: A Cadaveric Study

KEYWORDS: Thoracic Pedicle Screws; tapping, insertional torque

PRINCIPAL INVESTIGATOR: Kuklo, Timothy R. LTC MC
ASSOCIATES: Lehman, Ronald A. CPT MC

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedics Surgery

STATUS: C
INITIAL APPROVAL DATE: 14 September 2001

## STUDY OBJECTIVE

This will be a controlled experimental study in a cadaveric model comparing the maximal insertional torque and force to failure of various tapping techniques prior to insertion of pedicle screws in the thoracic spine. The maximum insertional torque is related to pullout strength of the various techniques.

## TECHNICAL APPROACH

Experiments will be conducted on cadaveric spines (T1-T12) obtained from donors without history of tumor or metabolic bone disease, excluding osteoporosis. Soft tissues will be dissected, leaving only the osteoligamentous column intact. Vertebrae will be excluded from the study if radiographs detect tumor, previous fracture, or previous hardware. Each spine will be scanned using DEXA (Hologic QDR-2000, Boston, MA). The specimens will be mounted in an acrylic water-filled container at a depth of 15 cm to place the spine in a supine anatomic position. The DEXA scans will be performed in the AP and lateral planes yielding estimates for a BMD in milligrams per square centimeter. The specimens will be stored at -20° Celsius until time of experimentation. They will be thawed at room temperature for 18 hours before use. An experienced spine surgeon, with extensive clinical experience in the use of pedicle screws will then place all of the pedicle screws.

The surgeon will locate the entry point for the screw with a pedicle awl and the cortex will be breached. A 0.45mm Kirschner Wire (K-wire) will then be placed under direct visualization. The depth of the pedicle will then be measured and screw length determined. The screw will be sized to ensure adequate length that the dorsal cortex of the vertebrae will not be engaged during placement of the pedicle screw. A 4.5mm cannulated tap will then be utilized to breech the posterior cortex to the neurocentral junction. The K-wire will then be removed and a 5.5mm monoaxial TSRH pedicle screw (Sofamor-Danek; Memphis, TN) will then be placed using a standardized technique. Placement will be randomized left to right in a predetermined randomization process. This process will be repeated for each pedicle screw with the exception of the size of the pedicle screw. For example, if we use a 4.5 cannulated tap we would then place either a 4.5 mm screw "line-to-line", a 5.0 mm screw (undertap by 0.05 mm), or a 5.5 screw (undertap by 1 mm).

The percent length will be determined as a ratio of screw penetration depth to the total distance from the screw entrance site to the anterior cortex. Each screw length will be chosen so that it would most closely approximate 80% of the pedicle screw axis length when this variable is controlled. The largest size pedicle screw will be utilized when this variable is controlled. Mediolateral screw angulation is the angle measured in the coronal plane of a line bisecting the vertebral body and the line of the long axis of the screw. The mediolateral screw insertion angle can be controlled within narrow limits within a given vertebral body. The mediolateral insertion angle will be chosen so that it would most closely approximate the average pedicle angel for the various vertebral levels: 5° for T10-T12. In the first part of the experiment, each vertebra will be instrumented with Sofamor CD screws. Each screw length was chosen so that it would most closely approximate 80% of the pedicle screw axis length. The sagittal insertion angle used in all specimens is 0°.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

BMD averaged 732 g/cm² (620-884 g/cm²) for Group 1, and 614 g/cm² (533-697 g/cm²) for Group 2. In Group 1, the average MIT was 1.37 ± 0.08 (SE) in-lbs. for line-to-line tapping and 2.61 ± 0.19 (SE) in-lbs. For 1 mm undertapping, a 93% increase in MIT ($p<0.0005$). In Group 2, the average MIT was 1.22 ± 0.08 (SE) in-lbs. For 0.5 mm undertapping and 1.79 ± 0.16 (SE) in-lbs. For undertapping by 1 mm, a 47% increase in MIT ($p=0.03$).

| | **Tapping Technique** | **MIT (in-lbs.)** | **% Increase** |
|---|---|---|---|
| Group 1 (BMD=614 g/cm²) (range 620-884 g/cm² | Line-to-Line (5.0 mm tap) | 1.37 ± 0.08 (SE) | N/A |
| | 1 mm Undertap (4.0 mm tap) | 2.61 ± 0.19 (SE) | +93% ($p<0.0005$, $r=0.718$) |
| (BMD=614 g/cm²) (range 533-697 g/cm²) | 0.5 mm Undertap (4.5 mm tap) | 1.22 ± 0.08 (SE) | N/A |
| | 1 mm Undertap (4.0 mm tap) | 1.79 ± 0.16 (SE) | +47% ($p+0.06$, $r=0.651$) |

BMD correlated with undertapping by 1 mm in Group 1 ($p<0.005$), but not with undertapping by 0.5 mm ($p=0.087$), although there appeared to be a trend in osteoporotic specimens. There were no noted differences in MIT between thoracic regions/levels, despite small differences in thoracic pedicle widths ($p=0.192$).

CONCLUSIONS

Undertapping the thoracic pedicle by 1 mm increases MIT by 47% ($p=0.03$) when compared to undertapping by 0.5 mm, and by 93% ($p<0.0005$) when compared to tapping line-to-line.

Report Date: 5 December 2001 Work Unit # 01-2402

DETAIL SUMMARY SHEET

TITLE: Preoperative and Postoperative EMG Analysis of Rotator Cuff Tears: Clinical Outcome Correlation with MRI Findings, Size and Repairability

KEYWORDS:

PRINCIPAL INVESTIGATOR: Doukas, William LTC MC
ASSOCIATES: Andersen, Romney MAJ MC, Pasquina, Paul MAJ MC

DEPARTMENT: Orthopaedics and Rehabilitation STATUS: O
SERVICE: Orthopaedic Surgery and PM & R INITIAL APPROVAL DATE: 30 November 2000

STUDY OBJECTIVE:
Assess the innervation status of the rotator cuff muscles preoperatively and post operatively to see if any change is seen after the repair of the muscles.

TECHNICAL APPROACH:
See original protocol, no changes to original protocol

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
We have assessed eleven patients so far in the study. The patients are at varying stages in the study. No patient has completed the study, as it will take 2 years for each patient. This is the first APR and all eleven patients have been assessed in this reporting period. There have been no amendments since the protocol was approved. There have been no adverse events. This is not a multi-center study. Four patients have been removed from the study for the following reasons:

- Two patients had surgery that showed no rotator cuff tear.
- One patient improved with physical therapy decided not to have surgery.
- One patient self removed from study for unknown reasons.

The number of subjects enrolled to the study since last APR at WRAMC is 11 and the total enrolled to date at WRAMC is 11.

CONCLUSIONS:
No conclusions have been drawn to this date.

Report Date: 6 September 2001

Work Unit # 2496

# DETAIL SUMMARY SHEET

TITLE: PRO OSTEON Implant 500 Coralline Hydroxyapatite Bone Void Filter for Use in Filling the Iliac Crest Bone Donor Site

KEYWORDS: bone graft, spinal fusion, hydroxy appetite

PRINCIPAL INVESTIGATOR: Polly, David LTC MC
ASSOCIATES:

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: C
INITIAL APPROVAL DATE: 29 October 1996

## STUDY OBJECTIVE

Bone substitutes are being developed for various applications. Coralline hydroxy appetite is commercially available for use in the human body. Its capacity to induce bone formation in the human body has not been well documented. This study is designed to document the effect of HA on bone formation.

## TECHNICAL APPROACH

For spinal fusions, bone is harvested from the iliac crest. Previous work done at WRAMC has shown that the donor site does not regenerate bone. In this study, half of the patients have the donor site backfilled with HA, half have no backfill. They are followed with imaging studies.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 12. The total number enrolled study-wide is n/a, if multi-site study.

## CONCLUSIONS

The sponsor is in the process of completing study. A site visit on 11 September 2001 will close the study.

Report Date: 1 October 2001 Work Unit # 00-2501

# DETAIL SUMMARY SHEET

TITLE: Spectro-Temporal Properties of Auditory-Visual Integration for Understanding Spoken Language

KEYWORDS: Speech Recognition, Auditory-Visual, Sensory Integration

PRINCIPAL INVESTIGATOR: Kenneth W. Grant
ASSOCIATES: Steven Greenberg, Ph.D., International Computer Science Institute, Berkeley, CA

DEPARTMENT: Surgery
SERVICE: Army Audiology and Speech Center

STATUS: O
INITIAL APPROVAL DATE: 30 November 1999

STUDY OBJECTIVE:
To determine the effects of across-modality temporal asynchrony on the recognition of nonsense syllables and sentences. This protocol was amended to test four hearing-impaired subjects on nonsense syllable recognition.

TECHNICAL APPROACH
Speech sentence materials and nonsense syllables were filtered into two or four narrow spectral slits with at least one octave separation between adjacent slits. In the main condition, the audio signal consisted of two filtered speech bands making up the low and high end of the speech spectrum (i.e., 298-375 Hz and 4762-6000 Hz). The visual channel consisted of a video image of female speaker of American English (head, neck, and shoulders) speaking each of the different speech tokens. The stimuli were presented audiovisually with a range of temporal asynchrony conditions between audio and visual stimulus components (-400 ms – audio leading to 400 ms – video leading) being tested. The subject task was to either press a designated area on a touch screen terminal, write down on paper, and or speak back verbatim what s/he heard. Touch screen responses are stored on computer for later analyses.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is 6 and the total enrolled to date at WRAMC is 13.
Nine normal-hearing subjects and four hearing-impaired subjects have completed the protocol using sentence materials and nonsense syllable materials with no adverse effects reported. Results have been tallied and plotted and presented to the study sponsor (The International Computer Science Institute, Berkeley, CA). An initial report of a portion of these data pertaining to nonsense syllable recognition was presented at the International Hearing Aid Research Conference, Lake Tahoe, CA (August 2000). A second report pertaining to results obtained with sentence materials was presented to the Auditory-Visual Speech Processing (AVSP) 2001 Conference, Aalborg, Denmark, (September).

CONCLUSIONS
Spectrally sparse audio comprised of two narrow bands of widely separated speech, or speechreading information, provides modest intelligibility when presented alone in the absence of the other modality. However, this same information can, when combined across modalities, provide good intelligibility (63% average accuracy for sentence materials, 90% for nonsense syllables). When the audio signal leads the video, intelligibility falls off rapidly as a function of modality asynchrony. When the video signal leads the audio, intelligibility is maintained for asynchronies as long as 200 ms. For eight out of nine subjects, the highest intelligibility is associated with conditions in which the video signal leads the audio (often by 80-120 ms). It is believed that this tolerance to video leading conditions, and intolerance to audio leading conditions, is a combination of evolutionary factors (light traveling faster than sound), neural conduction factors (auditory conduction times greater than visual conduction times), and linguistic factors (visual speech information related to place of articulation evolves over a relatively long time window of approximately 200 ms).

Report Date: 8 January 2002

Work Unit # 00-2502

# DETAIL SUMMARY SHEET

TITLE: Efficacy of Endobronchial Adhesives in Experimental Lung Volume Reduction

KEYWORDS: Endoscopic, cyanaocrylate, volumetric lung reduction

PRINCIPAL INVESTIGATOR: LtCol Eric Mair
ASSOCIATES: CPT Cote, MAJ Lane

DEPARTMENT: Surgery
SERVICE: Otolaryngology – Head and Neck

STATUS: C
INITIAL APPROVAL DATE: 7 December 1999

STUDY OBJECTIVE:
Study the safety and effectiveness of endoscopic cyancrolate volumetric lung reduction (ECVLR0 of the right upper lobe in a goat model. This protocol studies a new non-surgical minimally invasive alternative for treatment of severe chronic obstructive pulmonary disease.

TECHNICAL APPROACH:
Under general anesthesia, the right upper lobe bronchus is bronchoscopically occluded with a biocompatible cyanoacrylate in hopes of reducing lung volume. No change from protocol; see original protocol for details.

PRIOR AND CURRENT PROGRESS:
Ten goats underwent rigid bronchoscopy and application of the bioadhesive via an angiocatheter into the tracheal bronchus. Follow-up endoscopy and radiographs were performed at one week and three month intervals. Bronchial cultures and histopathologic data were obtained.

Each animal underwent successful occlusion of the tracheal bronchus opening. Two goats died prematurely due to pneumonia. The eight remaining goats were found to have partial and complete atelectatic lobar collapse on radiographic and necropsy examination. Culture results included three cases of Pseudomonas aeruginosa and two cases of Streptococcus mutans. Evidence of a distal glue plug at necropsy appeared to correlate positively with excellent clinical course and lobar collapse on radiologic exams. Incomplete occlusion or partially dislodged plugs appeared to negatively affect clinical course with subsequent development of lobar pneumonia.

CONCLUSIONS:
Endoscopic bronchial occlusion with a bioadhesive can achieve effective lobar collapse in an animal model.

Report Date: 7 January 2002 Work Unit # 00-2503

# DETAIL SUMMARY SHEET

TTTLE: Auditory-Visual Integration for Improved Human/Machine Interaction

KEYWORDS:

PRINCIPAL INVESTIGATOR: Grant, Kenneth Ph.D. DAC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: C
SERVICE: Army Audiology & Speech Center INITIAL APPROVAL DATE: 22 February 2000

## STUDY OBJECTIVE

This is a multi-year umbrella grant submitted to the National Science Foundation (NSF). The primary goals of the grant are to characterize in detail the pattern of co-modulated activity shared in common between the visible speech articulators and the acoustic output associated with the speech utterance under a variety of background conditions and to apply the insights and quantitative data obtained to improve the performance of both automatic speech recognition and speech synthesis.

## TECHNICAL APPROACH

To achieve the various goals outlined in the proposal several study areas have been identified. These are:

1. Identify the parts of a talking face that are primarily responsible for shielding the acoustic speech signal from background noise,
2. Determine the robustness of bimodal masking protection by substituting animated and synthetic objects for natural faces and speech sounds,
3. Computationally model the human behavioral results on speech detection in noise by developing new procedures for integrating visible speech information with acoustic speech signals based on recent research pertaining to the importance of the low-frequency modulation spectrum for intelligibility, and
4. Develop software "agents" (talking avatars) that can be used to assist human/computer interactions via integration of appropriate visual movement and synthesized speech.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study did not receive funding and has been withdrawn. No studies have been initiated.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study.

## CONCLUSIONS

This study did not receive funding and has been withdrawn. No studies have been initiated and none are planned.

Report Date: 12 April 2002

Work Unit # 00-2504

# DETAIL SUMMARY SHEET

TITLE: Radiofrequency Ablation of Oral Lymphangiomas, A Pilot Study

KEYWORDS: Radiofrequency Ablation, Lymphangiomas

PRINCIPAL INVESTIGATOR: Benjamin Cable, MAJ MC
ASSOCIATES: Eric Mair, LtCol MC

DEPARTMENT: Surgery
SERVICE: Otolaryngology – Head and Neck

STATUS: C
INTIAL APPROVAL DATE: 18 April 2000

STUDY OBJECTIVE
To determine the efficacy of radiofrequency ablation techniques in the treatment of patients with oral lymphangiomas.

TECHNICAL APPROACH
Pilot study, single therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

CONCLUSIONS
Protocol to be closed as PI and associate investigator are leaving WRAMC.

Report Date: 2 May 2002 Work Unit # 00-2505

# DETAIL SUMMARY SHEET

TITLE: Investigation of Alternative Sclorotherapy Agents for Injection Snoreplasty Palatal Stiffening Using the Beagle Canine Model: Pilot Study.

KEYWORDS: snoring, beagle, palatal stiffening, sclerotherapy

PRINCIPAL INVESTIGATOR: CPT Scott E. Brietzke, MC, USA
ASSOCIATES: LtCol Eric Mair MC

DEPARTMENT: Surgery
SERVICE: Otolaryngology – Head and Neck

STATUS: C
INITIAL APPROVAL DATE: 6 June 2000

## STUDY OBJECTIVE

The objective of this study is to investigate the use of hyper tonic saline, ethyl alcohol, tetracycline, and palatal implants as potential palatal sclerotherapy/stiffening agents for the treatment of snoring as compared to the current agent in use, Sotradecol. Each agent's efficacy as a palatal stiffening agent will be investigated and compared to Sotradecol using a previously employed canine model. Agents that cause significant palatal mucosal breakdown will be ruled out as potential agents for use in humans.

## TECHNICAL APPROACH

Each animal is to undergo three separate procedures during which the snoring level will be measured. The first will be a baseline snoring measurement that will be immediately followed by a palatal injection of the selected sclerothrapy agent (Isotonic saline, Sotradecol®, Hypertonic saline, Ethyl alcohol, or tetracycline). The volume will be predetermined and standardized (2.0 cc) as will be the initial injection technique: a single submucosal injection in the midline soft palate. The animals will be recovered and a period of 3-4 weeks will elapse between procedures. The first two procedures will involve baseline measurements and a palatal injection, and the third will be a measurement followed by palatal harvest. During this time, the animal's weight and oral intake will be carefully monitored on a daily basis as will the injection site and neck incisions.

## PRIOR AND CURRENT PROGRESS

All animal work is complete. Twenty dogs total (four in each group and five groups) were included. There have been no addenda. Ethanol has been shown to be equivalent to 3% Sotradecol (the positive control group). This has led to an ethanol human use protocol. This animal data are to be submitted along with the human use data as part of a single manuscript.

## CONCLUSIONS

The animal work included in this study was the founding basis for a successful human use protocol. Submission for publication is pending completion of the human use study.

Report Date: 2 July 2002 Work Unit # 00-2507

# DETAIL SUMMARY SHEET

TITLE: Auditory Supplements of Speechreading

KEYWORDS: Audiovisual Speech Perception, Speechreading, Hearing-Impaired

PRINCIPAL INVESTIGATOR: Grant, Kenneth Ph.D. DAC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: O
INITIAL APPROVAL DATE: 1 August 2000

STUDY OBJECTIVE
This is a five-year NIH application describing a research program to further understand the benefits and limitations of auditory-visual speech recognition in normal and hearing-impaired individuals. The proposed studies include examinations of the effects of aging, hearing status, and visual acuity on speech recognition in noise and reverberation.

TECHNICAL APPROACH
Methods will include identification and discrimination of speech sounds (nonsense syllables, words, and sentences) with and without visual cues (i.e., speechreading). Speech signals will be presented in a variety of background noises and under conditions of room reverberation to simulate typical real-world conditions encountered by normal ad hearing-impaired individuals. Special purpose equipment to measure various aspects of static and dynamic visual acuity will be employed to determine if elderly subjects are placed under additional processing demands due to deteriorating peripheral vision, especially for motion detection.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
None. This grant is under revision and has not yet been awarded. No studies have been initiated.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

CONCLUSIONS
None.

Report Date: 01 August 2002 Work Unit # 00-2509

# DETAIL SUMMARY SHEET

TITLE: The Determination of a Suitable Animal Model for Teaching Endoscopic Surgery of the Paranasal Sinuses Based on CT Imaging, Endoscopic Examination and Anatomical Skull Analysis.

KEYWORDS:

PRINCIPAL INVESTIGATOR: Casler, John D. LTC MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Otolaryngology-Head and Neck INITIAL APPROVAL DATE: 12 September 2000

STUDY OBJECTIVE
To determine a suitable animal model for teaching endoscopic surgery of the paranasal sinuses based on CT Imaging, endoscopic examination and anatomical skull analysis.

TECHNICAL APPROACH
To acquire the specimens outlined in this protocol through tissue-sharing of animals sacrificed in other studies. These specimens will be imaged and studied in the fashion described in the protocol.

PRIOR AND CURRENT PROGRESS
The specimens for this study are currently being acquired.

CONCLUSIONS
The study is ongoing and making progress.

Report Date: 21 November 2001

Work Unit # 01-25003

# DETAIL SUMMARY SHEET

TITLE: Complex Sound Segregation by Hearing-Impaired Listeners

KEYWORDS:

PRINCIPAL INVESTIGATOR: Lentz, Jennifer, Ph.D., DAC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: W
INITIAL APPROVAL DATE: 10 July 2001

STUDY OBJECTIVE
Study withdrawn by P.I.

TECHNICAL APPROACH
Study withdrawn by P.I.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Study withdrawn by P.I.

CONCLUSIONS
Study withdrawn by P.I.

Report Date: 30 July 2001 Work Unit # 01-2501

# DETAIL SUMMARY SHEET

TITLE: Performance of Directional Microphone Hearing Aids in Everyday Listening Situations

KEYWORDS:

PRINCIPAL INVESTIGATOR: Cord, Mary MA DAC
ASSOCIATES: Surr, Rauna MS, DAC; Walden, Brian, PhD, DAC

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: C
INITIAL APPROVAL DATE: 3 October 2000

STUDY OBJECTIVE:
Difficulty understanding speech in the presence of background noise is a common complaint of hearing aid users and a primary reason for dissatisfaction with hearing aids. Directional microphones are one of the few options available on wearable hearing aids that can improve speech understanding in noise. A number of studies have demonstrated this advantage in the laboratory. The extent to which this advantage is realized in the real world is less clear. The following specific questions were addressed in this investigation: 1) Do patients who are fit with switchable omnidirectional/directional hearing aids use the directional option in daily living, and if so, how much? 2) Do experienced users of these hearing aids recognize the characteristics of everyday listening situations that provide the greatest performance advantages for directional microphones? 3) How frequently are such listening situations encountered in everyday life?

TECHNICAL APPROACH:
Clinic patients who had obtained binaural switchable omnidirectional/directional microphone hearing aids were contacted for a telephone interview. Those who reported regular use of their hearing aids and indicated at least occasional use of both microphone configurations were mailed two questionnaires designed to assess performance with each microphone type in daily life.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
112 patients were contacted by telephone. 22 (20%) reported less than four hours per day of hearing aid use. 26 (23%) were not switching between the two microphone configurations for various reasons (e.g., don't know what the different settings of their hearing aids were, didn't notice any difference between omnidirectional and directional, only use default setting). 57 (51%) reported regular use of their hearing aids and at least occasional use of both microphone configurations and were mailed the two questionnaires described below. 48 subjects completed and returned the questionnaires. The number of subjects enrolled to the study since last APR at WRAMC is 112 and the total enrolled to date at WRAMC is 112. No subjects have withdrawn from the study.

CONCLUSIONS:
Questionnaire results revealed that patients found the directional microphone to be most helpful in noisy situations where the signal is in front of the listener and the signal source is relatively near. As the noise becomes more diffuse and/or reverberation increases, the directional microphone is felt to be less helpful. Patients found the omnidirectional microphone to be most helpful in situations where the location of the signal was other than front, and noise was absent. These patient reports are consistent with the signal processing provided by each microphone type and suggest that patients can identify listening situations in their everyday life which should favor one or the other. In everyday life, subjects encounter fewer situations that favor directional microphone use than those which favor omnidirectional microphone use. However, the frequency with which situations which favor one or the other microphone mode are encountered was not related to overall hearing aid satisfaction or satisfaction with either microphone configuration.

Report Date: 7 September 2001

Work Unit # 01-2502

# DETAIL SUMMARY SHEET

TITLE: Performance of Custom-Fit Versus Fixed Format Hearing Aids for Precipitously-Sloping High-Frequency Hearing Loss

KEYWORDS: Hearing aid, disposable, fixed format, custom-fit, speech recognition, benefit, satisfaction, real ear aided response

PRINCIPAL INVESTIGATOR: Walden, Brian Ph.D. DAC
ASSOCIATES: Therese C. Walden, Au.D.; Mary T. Cord, M.A.

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: C
INITIAL APPROVAL DATE: 14 November 2000

## STUDY OBJECTIVE

To determine the magnitude of real-ear response differences between custom-fit hearing aids and the best match fixed-format hearing aids in patients with precipitous high-frequency hearing loss. To determine the frequency with which these differences may translate into significant differences in hearing aid performance and satisfaction within the subject sample. To compare coupler and real-ear response measures for these two hearing aid fittings in this patient population.

## TECHNICAL APPROACH

This study compared the real-ear response provided by custom-fit hearing aids to the closest matching fixed-format disposable hearing aids in patients with precipitous high-frequency hearing loss. Laboratory and field measures of aided performance were obtained to compare patient performance with the custom-fit and fixed-format hearing aids. In addition, coupler versus real-ear response differences was compared for the two hearing aid types.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Preliminary behavioral studies with the SDHA, using standard tests of speech recognition and field measures of hearing aid performance, suggested that it could provide significant benefit to patients with mild-to-moderate hearing loss (Preves, 2000; Staab & Preves, 2000). An electroacoustic assessment of the SDHA revealed that its frequency response was broader and smoother, and it had lower levels of circuitry noise, than comparison instruments that included fully digital and digitally programmable devices (Moore, Stone, & Alcantara, 2001). Additionally, Sweetow (2001) and Fabry (2001) reported on their experiences fitting the SDHA with large samples of patients. Both encountered significant problems with patient discomfort and feedback, despite reporting good sound quality and performance with the device.

Fifteen hearing-impaired patients recruited from the clinic population of the Army Audiology & Speech Center have been enrolled in the study to date and no additional subjects will be recruited. There have been no adverse events, nor did any patients enrolled subsequently withdraw from the study.

Results revealed that relatively close approximations to the real-ear aided responses of the custom-fit instruments were possible for most subjects using only seven fixed acoustical formats. The differences that existed in the aided responses between the two instrument types did not result in significant differences for aided speech recognition, nor for field ratings of aided performance, although patient satisfaction was rated lower for the disposable hearing aids. Additionally, the real-ear to coupler difference was greater for the disposable hearing aid, presumably due to its deeper insertion into the ear canal.

CONCLUSIONS

1. When compared to their own custom-fit hearing aids, patients will obtain comparable speech recognition performance (HINT), subjective aided performance in everyday listening (APHAB), and satisfaction (SADL) with the SDHA format that most closely matches the frequency response of their own instruments.

2. Greater real-ear gain can be achieved with the SDHA compared to typical fits with custom CIC or canal instruments (for comparable 2-cc coupler gain).

3. For patients with predominantly high-frequency hearing losses, custom fitting to precise prescriptive targets may not be essential. Rather, it appears that most can be fit equally well with a limited number of fixed electroacoustic configurations.

4. Participants generally report the sound quality of the SDHA to be at least equal to custom-fit instruments.

5. The larger RECD observed for the SDHA is attributable to its very deep insertion in the ear canal. A more shallow insertion does not provide this advantage.

6. The SDHA can be fit to most ears, using one of the three tip sizes currently available.

7. Retention of the deep insertion can be a problem in some patients, and the SDHA may gradually work its way out after several hours of use. Overcoming this problem can be clinically challenging and time consuming.

8. Feedback can be a problem with some patients, even with a deep insertion.

Report Date: 4 October 2001

Work Unit # 01-2565a

# DETAIL SUMMARY SHEET

TITLE: Dead Regions in the Cochlea and Their Influence on Speech Processing

KEYWORDS: cochear processing, inner hair cells, hearing loss, amplification

PRINCIPAL INVESTIGATOR: Summers, Van Ph.D. DAC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: O
INITIAL APPROVAL DATE: 7 November 2000

## STUDY OBJECTIVE

To test for regions of dead inner hair cells in cochleas of listeners with high-frequency hearing loss. To examine the influence of high-frequency amplification on speech recognition performance for hearing-impaired listeners with and without dead inner-hair-cell regions.

## TECHNICAL APPROACH

The study involves three psychoacoustic tasks (masked thresholds in threshold equalizing noise, psychophysical tuning curves, and frequency modulation detection) aimed at identifying listeners with regions of dead inner hair cells or nonfunctioning neural channels in the cochlea. The second portion of study involves tests of speech recognition under various amplification conditions to determine the benefit of amplifying frequencies associated with these "dead regions".

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Data collection is ongoing. The psychoacoustic tasks have been generally successful in identifying listeners with and without regions of dead inner cells, although these results have shown some instances of inconsistency across tasks. The speech recognition results collected to this point provide little evidence that the presence or absence of dead inner hair cell regions will influence what amplification strategy is most likely to benefit a given hearing-impaired listener.

The number of subjects enrolled to the study since last APR at WRAMC is 18 and the total enrolled to date at WRAMC is 18. None of the subjects have withdrawn form the study. There have been no adverse reactions from subjects nor has any subject withdrawn form the study. There is no benefit to the subjects.

## CONCLUSIONS

The listeners tested in this study have near-normal low-frequency hearing and steeply sloping high-frequency hearing loss. The data collected to this point suggest that these listeners show little benefit from either the broadband amplification generally provided by hearing aids or lowpass amplification aimed at avoiding amplification of frequencies associated with dead regions. The presence of dead inner hair cell regions does not appear to influence of this general pattern.

Report Date: 29 April 2002 Work Unit # 01-2570a

# DETAIL SUMMARY SHEET

TITLE: Spread of Masking by Harmonic Complexes in Normal Hearing and Hearing Impaired Listeners

KEYWORDS: Masking, Schroeder-phase, harmonics

PRINCIPAL INVESTIGATOR: Leek, Marjorie R. Ph.D, DAC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: O
INITIAL APPROVAL DATE: 12 June 2001

## STUDY OBJECTIVE

To determine the influence of acoustic waveform shape on the upward spread of masking from low frequencies to high frequencies within harmonic complexes. Excessive acoustic interference across frequency for waveforms shaped like vowel sounds might be involved in some of the difficulties experienced by hearing-impaired people while listening to speech sounds in noisy environments.

## TECHNICAL APPROACH

Masking by harmonic complexes will be measured in a two-alternative forced choice procedure with signal frequencies ranging from 1000 to 4000 Hz. Signal frequencies at and below 2000 Hz fall within the passband of the masker, while higher frequencies measure masking outside the masker passband. Masking will be measured at three masker levels, and for maskers constructed with component phases in positive and negative Schroeder phases. Masking will also be measured for a Gaussian noise with the same frequency passband as the harmonic complexes.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Data collection has been initiated on this study. Twelve subjects were enrolled during the past year, and that is the total enrollment to date. Ten subjects completed the study, one is still participating in data collection, and one subject chose to withdraw because of difficulty finding time to attend the experimental sessions. There have been no adverse reactions. There is no direct benefit to the subjects from participating in this study.

The number of subjects enrolled to the study since last APR at WRAMC is 12 and the total enrolled to date at WRAMC is 12.

## CONCLUSIONS

Upward spread of masking by harmonic complexes increased with increasing stimulus intensity. The positive Schroeder-phase masker was less effective at masking on-frequency signals than negative Schroeder-phase masker; however, the reverse was true for signal frequencies signals higher than the masker band. More upward spread of masking was found for hearing-impaired subjects, but the reversals in masking effectiveness due to masker phase were also observed in those listeners. These findings may reflect a change in phase in the low-frequency skirts of the auditory filters underlying masking effects, and an interaction between the masker waveforms and neural tuning curves.

Report Date: 23 November 2001 Work Unit # 2550

# DETAIL SUMMARY SHEET

TITLE: Neuromotor Control of Speech Rate During Syllable Repetition

KEYWORDS: speech rate, orofacial, EMG

PRINCIPAL INVESTIGATOR: McClean, Michael PhD, DAC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: C
INITIAL APPROVAL DATE: 03 January 1996

STUDY OBJECTIVE:
To determine how orofacial muscle activity and movement vary with rate of syllable repetition, and to apply resulting physiologic data to development of a realistic computer model of the neuromotor mechanisms underlying speech rate control.

TECHNICAL APPROACH:
Acquisition of experimental data on orofacial motor control during speech involves the use of an electromagnetic movement recording system to study the kinematics of the lip, tongue and jaw during speech. Surface electrodes are used to obtain electromyographic (EMG) recordings of associated activity in lip and jaw muscle. During the past year, the planned work on computer simulation was discontinued due to limited resources. The methodology for acquiring physiologic data on speech rate control was modified to incorporate a more precise method of speech rate manipulation. This involved computer generation of rate targets based on temporally modified versions of individual's natural speech.

PRIOR AND CURRENT PROGRESS
During the past year, kinematic and EMG data were acquired on an additional three subjects using the new method of targeting rate variation. This brings the total number of subjects for the project to six. There have been no adverse events at any time during this protocol, and no subjects have withdrawn from the study. We have now acquired very extensive physiologic datasets on three subjects using the new method of rate targeting. We will not acquire any additional data on this protocol. It is anticipated that analysis of existing datasets will provide a substantial contribution to current understanding and future studies of rate control. The number of subjects enrolled to the study since last APR at WRAMC is three, and the total enrolled to date at WRAMC is six.

CONCLUSIONS
Work on this project has demonstrated the feasibility of acquiring simultaneous EMG and movement data on lip and jaw movements during speech while precisely controlling percent modulation of speech rate in individual speakers. This should provide a much stronger technical basis for future studies of rate control. Ongoing data analysis will provide the first quantitative descriptions of physiologic correlates of speaking rate at precise levels of utterance duration.

Report Date: 24 January 2002 Work Unit # 2565

# DETAIL SUMMARY SHEET

TITLE: Auditory Processing and Sensorineural Hearing Loss

KEYWORDS: hearing loss, active mechanism

PRINCIPAL INVESTIGATOR: Summers, Van Ph.D, DAC
ASSOCIATES: Leek, Marjorie Ph.D, DAC

DEPARTMENT: Surgery
SERVICE: Army Audiology and Speech Center

STATUS: O
INITIAL APPROVAL DATE: 14 March 1997

## STUDY OBJECTIVE

This work unit is a grant proposal; submitted to the National Institute of Health to obtain funding. The grant involves a physiological process in the inner ear referred to as the active mechanism. The research examines 1) a possible psychoacoustic means of evaluating active mechanism status in individual listeners and 2) the role of the active mechanism in improving signal detection and speech recognition in selected competing sounds.

## TECHNICAL APPROACH

Each of the proposed experiments involves auditory testing of normally hearing and hearing-impaired listeners. The basic task of the subjects is similar to procedures used clinically to evaluate hearing. Subjects listen to sounds (both speech and non speech) over earphones while seated in a sound-treated booth. They make responses indicating their detection or identification of these sounds by touching specific areas on a touch screen terminal.

## PRIOR AND CURRENT PROGRESS

Three experimental studies described in the NIH grant have been completed under individual work unit numbers. No patients have been or will be enrolled under this work unit number for these three experiments. An addendum to this work unit number was approved by the Human Use Committee on 20 June 2000 which allows the remaining experiments described in the NIH grant to be carried out under this work unit number (experiments 5-8 in the grant) a revised consent form appropriate to these experiments was approved at that time. We have completed experimental programming and pilot testing for experiment 7 in the grant and are currently collecting data for this experiment under this work unit number. This experiment examines how background sounds. The number of subjects enrolled under this work unit number since last APR at WRAMC is four and the total enrolled to date at WRAMC is four.

## CONCLUSIONS

Data collected to this point replicate the literature in indicating that normal hearing listeners have much less difficulty in recognizing speech masked by a fluctuating background signals (either a single competing talker or the same competing signal played backwards) than by continuous noise with little amplitude modulation. A current finding, which has not been previously reported is that the difference in performance between the fluctuating and continuous background conditions, appears to be level dependent: the performance difference is reduced at high presentation levels. This pattern of results is consistent with the idea that the cochlear active mechanism contributes to the difference in speech recognition performance for fluctuating vs. continuous maskers. The influence of the active mechanism is reduced with increases in presentation level, which may partially account for more similar performance across the two-masker types at high levels.

Report Date: 2 July 2002

Work Unit # 2570

# DETAIL SUMMARY SHEET

TITLE: Hearing Loss and the Perception of Complex Sounds

KEYWORDS: hearing impairment, frequency resolution, time perception

PRINCIPAL INVESTIGATOR: Leek, Marjorie PhD
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: O
INITIAL APPROVAL DATE: 26 August 1997

## STUDY OBJECTIVE

Patients with hearing loss have difficulty understanding speech in noise because of much functional impairment within the ear, including reductions in the ability to carry out precise spectral and temporal analyses of sound. Studies in this program of research explore these analytic abilities in hearing-impaired and in normal hearing people, with the ultimate goal of increasing the benefits derived by hearing-impaired patients through the use of hearing aids.

## TECHNICAL APPROACH

All of the experimental techniques used in these studies involve earphone presentation of sounds to a subject, who indicates his perception through the use of a touch-screen terminal. Experiments often require listeners to detect a low-intensity sound buried in noise or ask listeners to judge whether two sounds are the same or different. Acoustic stimuli are generated to test specific hypotheses concerning functional effects of hearing loss.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This is an NIH grant that contains a number of experiments. During the past year, we have completed data collection, and have begun writing a manuscript on a study measuring perception of dynamic intensity contours by hearing-impaired listeners. We have also begun computer programming for two new experiments that will soon be underway. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 43. There have been no adverse reactions and no patients have withdrawn from these studies. There is no direct benefit to patients who participate in this study.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 43. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

In determining the shape of dynamic contours in temporal waveforms (i.e., discriminating damped sounds from ramped sounds), performance improves with stimulus level for both normal hearing and hearing impaired listeners, but more rapidly for the latter group. There may be a trade-off between the loss of compression in damaged cochleas, which might improve the perception of these contours, and poorer performance related to the reduction in modulation depth due to the sensitivity loss in hearing impaired listeners.

Report Date: 7 October 2001 Work Unit # 2572

# DETAIL SUMMARY SHEET

TITLE: Determining the Prevalence of Occult Carotid Disease in Patients with Head and Neck Squamous Cell Carcinoma Using Color Flow Duplex Imaging

KEYWORDS: carotid artery stenosis, head and neck, squamous cell carcinoma, prevalence

PRINCIPAL INVESTIGATOR: CPT Christopher R. Cote, MC
ASSOCIATES: COL John Casler, MC; MAJ James Goff, MC

DEPARTMENT: Surgery
SERVICE: Otolaryngology-Head & Neck Surgery

STATUS: C
INITIAL APPROVAL DATE: 28 October 1997

## STUDY OBJECTIVE

This study was conducted to determine whether patients with HNSCCA have an increased rate of occult ASCAD compared to the general population.

## TECHNICAL APPROACH

*Study Design:* A cross-sectional study was performed to identify the prevalence of clinically significant ASCAD in the specific population of patients with a diagnosis of HNSCCA using noninvasive color flow duplex imaging. In addition, the demographic variables and risk factors for head and neck cancer and for carotid disease, as identified in the literature, were recorded with the use of a questionnaire.
*Methods:* Forty-nine patients with a diagnosis of HNSCCA completed the questionnaire and then had a duplex screening exam.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The most common risk factor identified was tobacco smoking in 41 of 49 patients (84%). ASCAD was identified in one patient (2%). The stenosis in that patient was less than 60 percent.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 50. The total number enrolled study-wide is 50, if multi-site study.

## CONCLUSIONS

We conclude from this study that even though patients with HNSCCA usually have risk factor(s) associated with ASCAD, the rate of occult ASCAD was not different than that found in the general population. Thus routine screening of HNSCCA patients with color flow duplex imaging to detect occult ASCAD is not warranted.

Report Date: 4 April 2002

Work Unit # 2577-98

# DETAIL SUMMARY SHEET

TITLE: Influences of Masker Phase on Detection of Brief Signals

KEYWORDS:

PRINCIPAL INVESTIGATOR: Summers, Van Ph.D.DAC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: C
INITIAL APPROVAL DATE: 05 May 1998

## STUDY OBJECTIVE

Outer hair cells within the cochlea are thought to be the physiological source of an active mechanism that alters the internal representation of an input signal in important ways. In the presence of sensorineural hearing loss, the influence of the active mechanism is reduced or eliminated due to outer hair damage. This experiment involves a signal detection task, which may provide a psychoacoustic means of evaluating active mechanism status in individual listeners.

## TECHNICAL APPROACH

Normal-hearing and hearing-impaired listeners are individually tested. The experimental task measures the signal-to-masker detection thresholds for brief tonal signals masked by broadband harmonic complexes that differ only in phase structure ("positive" and "negative" Schroeder phase). Differences in masking effectiveness between the two harmonic complexes and variability in performance based on the temporal position of the probe within each masker are examined.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Data collection has been completed. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 17. The total number enrolled study-wide is NA, if multi-site study.

Presentations describing various aspects of the findings were made at the Joint meeting of the Acoustical Society of America and European Acoustics Association in Berlin, Germany, March 1999 and at the meeting of the Association for Research in Otolaryngology in St. Petersburg, FL, February 2000. Two articles based on this protocol have been published (Journal of the Acoustical Society of America, 2000; Hearing Research, 2001). There have been no adverse reactions from subjects and there is no benefit to the subjects. Ten subjects served in all of the experimental test conditions. Scheduling constraints required that seven subjects serve in only a subset of the test conditions.

## CONCLUSIONS

For normally hearing listeners, the temporal location of the probe signal within the positive-Schroeder masker had a large influence on masking effectiveness. The effect was greatest in testing at moderate presentation levels and diminished at high level. This effect was also greatly reduced in hearing-impaired listeners at all test levels. The results are consistent with active mechanism influences on performance by normal hearing listeners tested at moderate levels with this influence being reduced at high levels and in the presence of cochlear damage.

Report Date: 1 October 2001 Work Unit # 2584-99

# DETAIL SUMMARY SHEET

TITLE: A New Treatment For Xerostomia In Postirradiated Head & Neck Cancer Patients

KEYWORDS:

PRINCIPAL INVESTIGATOR: Criswell, Mark MAJ MC
ASSOCIATES: Sinha, Christopher LTC MC

DEPARTMENT: Surgery STATUS: C
SERVICE: Otolaryngology-Head and Neck INITIAL APPROVAL DATE: 29 October 1996

STUDY OBJECTIVE
To study the benefits of the Vapotherm MT-4000 personal humidifier in patients with xerostomia from radiation treatment of head and neck cancer

TECHNICAL APPROACH
No addenda

PRIOR AND CURRENT PROGRESS
Data collection is complete. Data analysis is ongoing. Twelve total subjects were enrolled in the previous year and in total. Three subjects were withdrawn. Two of these were at patients' requests because of logistical difficulties in arranging the required three clinic visits within the required timeframe, due to their work schedule and commute. One patient was disenrolled because his dementia prevented him operating the equipment after several attempts. There have been no adverse consequences for any subjects.

CONCLUSIONS
Data analysis indicates the Vapotherm device has no significant advantage over a standard bedside humidifier. The study is now completed.

Report Date: 22 August 2001

Work Unit # 2585-99

# DETAIL SUMMARY SHEET

TITLE: Neuromotor Basis of Stuttering (NIH Grant DC03659 R01)

KEYWORDS: speech, stuttering, orofacial movement, voice

PRINCIPAL INVESTIGATOR: Michael D. McClean PhD
ASSOCIATES: Charles M. Runyan PhD & Stephen M. Tasko PhD

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: O
INITIAL APPROVAL DATE: 27 October 1998

STUDY OBJECTIVE The goals of the proposed research are an enhanced understanding of the neuromotor basis of stuttering and the development of improved forms of speech therapy for persons who stutter. Given the complexity of this speech production system, it is logical that we develop improved methods for evaluating speech pattern generating function while controlling for different sources of input such as phonetic patterning and emotional response. This approach is taken in the present research through analyses of speech structure movements and voice acoustics. A central issue concerns how different muscle systems (e.g. tongue and jaw) are controlled and coordinated. A general hypothesis underlying much of the work is that there are subgroups of individuals whose pattern generating function for speech reflects different motor strategies, and these strategies have varying levels of instability. Specific hypotheses will address the association of orofacial and respiratory movements, and voice acoustic measures in normal speakers and persons who stutter, the effects of speech therapy on speech motor output, and the temporal-spatial characteristics of orofacial and respiratory movement, and voice acoustics during disfluency. The research should provide an improved basis for clinical categorization of persons who stutter and better understanding of changes in motor performance related to speech therapy.

TECHNICAL APPROACH The above issues and hypotheses are being studied through analysis of lip, tongue, jaw, rib cage, and thoracic movements, and voice acoustics in individuals with a history of stuttering and a group of normal speakers. Electromagnetic and inductive plethysmographic systems are used to record speech structure movements while subjects produce a small set of speech utterances at varying rates and vocal intensities, a reading passage, and monologue. Wide ranges of clinical-behavioral measures of speech performance are obtained in stutter subjects. Persons who stutter will be tested prior to and following an intensive program of stuttering therapy.

PRIOR AND CURRENT PROGRESS Substantial progress has been made during the past year towards addressing the specific aims of this protocol. Major refinements were made in the data reduction and measurement procedures for processing kinematic and acoustic signals. Progress has been made principally in studies pertaining to the coordination orofacial with respiratory and laryngeal systems among nonstutterers, effects of stuttering treatment on speech kinematics, and speech rate control processes in stutterers and nonstutterers. During the past year, data were acquired on an additional 49 subjects (28 normal controls and 21 stutterers), with repeated testing being performed on 31 of these 49. There have been no adverse reactions, and no subjects have withdrawn from the study.
The number of subjects enrolled to the study since last APR at WRAMC is 49 and the total enrolled to date at WRAMC is 83. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS Analyses of speech coordination in normal speakers provide indirect evidence that the neural coupling with the laryngeal and respiratory systems is greatest for the jaw compared with other orofacial structures. Work on stuttering treatment indicates that stutterers showing large reductions in severity display tend to reduce orofacial speeds and vocal intensity following treatment.

Report Date: 6 February 2002 Work Unit # 2585-99

# DETAIL SUMMARY SHEET

TITLE: Neuromotor Basis of Stuttering (NIH Grant DC03659 R01)

KEYWORDS: speech, stuttering, orofacial movement, voice

PRINCIPAL INVESTIGATOR: Michael D. McClean PhD
ASSOCIATES: Charles M. Runyan PhD & Stephen M. Tasko PhD

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: C
INITIAL APPROVAL DATE: 27 October 1998

STUDY OBJECTIVE The goals of the proposed research are an enhanced understanding of the neuromotor basis of stuttering and the development of improved forms of speech therapy for persons who stutter. Given the complexity of this speech production system, it is logical that we develop improved methods for evaluating speech pattern generating function while controlling for different sources of input such as phonetic patterning and emotional response. This approach is taken in the present research through analyses of speech structure movements and voice acoustics. A central issue concerns how different muscle systems (e.g. tongue and jaw) are controlled and coordinated. A general hypothesis underlying much of the work is that there are subgroups of individuals whose pattern generating function for speech reflects different motor strategies, and these strategies have varying levels of instability. Specific hypotheses will address the association of orofacial and respiratory movements, and voice acoustic measures in normal speakers and persons who stutter, the effects of speech therapy on speech motor output, and the temporal-spatial characteristics of orofacial and respiratory movement, and voice acoustics during disfluency. The research should provide an improved basis for clinical categorization of persons who stutter and better understanding of changes in motor performance related to speech therapy.

TECHNICAL APPROACH The above issues and hypotheses are being studied through analysis of lip, tongue, jaw, rib cage, and thoracic movements, and voice acoustics in individuals with a history of stuttering and a group of normal speakers. Electromagnetic and inductive plethysmographic systems are used to record speech structure movements while subjects produce a small set of speech utterances at varying rates and vocal intensities, a reading passage, and monologue. Wide ranges of clinical-behavioral measures of speech performance are obtained in stutter subjects. Persons who stutter will be tested prior to and following an intensive program of stuttering therapy.

PRIOR AND CURRENT PROGRESS The above issues and hypotheses are being studied through analysis of lip, tongue, jaw, rib cage, thoracic movements, and voice acoustics in individuals with a history of stuttering and a group of normal speakers. Electromagnetic and inductive plethysmographic systems are used to record speech structure movements while subjects produce a small set of speech utterances at varying rates and vocal intensities, at reading passages, and at monologues. Wide ranges of clinical-behavioral measures of speech performance are obtained in stutter subjects. Persons who stutter will be tested prior to and following an intensive program of stuttering therapy.

CONCLUSIONS Considerable progress has been made during the course of this work towards achieving the specific aims as stated in the original NIH grant application. A unified experimental procedure was developed for acquisition, measurement, and analysis of orofacial and respiratory kinematics, and voice acoustics, during speaker productions of an extensive speech sample. Substantial progress has been made on correlational studies relating the activity levels of different speech muscle systems, the effects of stuttering treatment of speech kinematics, and speech rate control in stutterers. Since the last APR, there have been no new subjects recruited for this study. There have been no adverse reactions, and no subjects have withdrawn from the study. The number of subjects enrolled to the study since last APR at WRAMC is zero. The total enrolled to date at WRAMC is 83.

Report Date: 15 November 2001

Work Unit # 2587-99

# DETAIL SUMMARY SHEET

TITLE: Spectral Shape Discrimination by Normal-Hearing and Hearing Impaired Listeners

KEYWORDS: spectral shape, hearing loss, complex sounds

PRINCIPAL INVESTIGATOR: Lentz, Jennifer Ph.D.
ASSOCIATES: Leek, Marjorie Ph.D.

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech

STATUS: C
INITIAL APPROVAL DATE: 12 January 1999

STUDY OBJECTIVE:
The perception of sounds with different spectral characteristics is one of several important auditory cues to the accurate understanding of speech. These spectral characteristics may be distorted by damage to the inner ear (cochlea), which produces a loss in auditor sensitivity. The role that this damage plays in the discrimination of sounds with different spectra is evaluated in normal-hearing and hearing-impaired listeners. A second part of the protocol is concerned with hearing aids, which can amplify different regions of the spectrum depending on a person's hearing loss. We also will assess whether listeners place more emphasis on amplified spectral regions after wearing a hearing aid for several months.

TECHNICAL APPROACH:
Listeners will hear two short, multi-tonal masking stimuli presented consecutively over headphones. These sounds will have similar spectral characteristics, but a signal tone will be added in-phase to a single component of one of the sounds. The listener is asked to indicate on a touch-screen terminal which sound included the signal. The intensity of the signal necessary for detection will be determined for several combinations of masking frequencies. Weighting analysis techniques will be used to evaluate whether a listener uses frequency region distant from the signal to aid in its detection.

PRIOR AND CURRENT PROGRESS
Data collection and analysis are complete. Results were presented at two national meetings in February 2000 and August 2000, and two papers have been submitted to a major technical journal. Seven normal-hearing and thirteen hearing-impaired subjects have been enrolled in the study. There have been no adverse reactions. One subject withdrew from the study because he chose not to continue.

The number of subjects enrolled to the study since last APR at WRAMC is 3 and the total enrolled to date at WRAMC is 20.

CONCLUSIONS
The data indicate that hearing-impaired listeners show small differences from normal-hearing listeners in the way they process spectral information. Peripheral loss of frequency resolution in impaired ears may cause these listeners to direct their attention to portions of the power spectrum where spectral information may be more readily represented.

Report Date: 6 February 2002 Work Unit # 2588-99

# DETAIL SUMMARY SHEET

TITLE: Variations in Orofacial Reflexes with Stuttering Severity

KEYWORDS: orofacial reflexes, stuttering, lip, jaw, speech

PRINCIPAL INVESTIGATOR: McClean, Michael Ph.D.
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: C
INITIAL APPROVAL DATE: 29 June 1991

## STUDY OBJECTIVE

Short-latency reflexes can be evoked in lip and jaw muscle by innocuous mechanical stimulation at the corner of the mouth during static posturing of the lips, tongue, and jaw. The goal of this research is to determine whether the relative excitability of these reflexes varies systematically across individuals showing different levels of stuttering severity.

## TECHNICAL APPROACH

Subjects will include 44 adults divided into four groups of approximately 11 according to stuttering severity (nonstutterers, mild, moderate, severe). Surface electromyographic (EMG) recordings will be obtained of lip and jaw muscle while subjects maintain static postures within the orofacial system. A servo-controlled motor operating under position feedback will be used to apply small amplitude (0.8 mm) mechanical stretches at that point in a postero-lateral direction. Signal averages of lip and jaw muscle EMG will be generated using stimulus onset as a trigger. Reflex amplitudes first will be quantified as percent modulation of prestimulus EMG. Percent modulation of EMG on individual muscles will be used to calculate ratios of lip to jaw EMG for both excitatory and suppression responses.

## PRIOR AND CURRENT PROGRESS

No work on this protocol has been carried out since the last progress report. No subjects have been run on this protocol in this or previous years. Thus, there have been no adverse reactions, and no subjects have withdrawn from the study.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is -, if multi-site study.

## CONCLUSIONS

The protocol is now closed.

Report Date: 26 July 2002

Work Unit # 2591-99

# DETAIL SUMMARY SHEET

TITLE: Complex Sound Analysis by Persons with Impaired Hearing (Application for NIH NRSA Post Doctoral Fellowship)

KEYWORDS: hearing loss, complex sounds, sound segregation

PRINCIPAL INVESTIGATOR: Leek, Marjorie PhD DAC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: O
INITIAL APPROVAL DATE: 14 September 1999

## STUDY OBJECTIVE

The perception of specific sounds in a complex background of sounds is an important aspect to communication. Often times we communicate in the midst of a rich acoustic environment in which many sounds are present with vastly different temporal and spectral characteristics. It is well-known that a healthy auditory system has the ability to distinguish different sound sources from one another and attend to a particular sound source amid multiple sound sources, but less is known regarding the abilities of a damaged auditory system to make use of the prevalent cues in a complex acoustic scene. The main goal of this research protocol is to assess the abilities of hearing-impaired listeners to segregate sounds in a 2-source environment and compare their abilities with those of normal-hearing listeners. We will assess whether the damage to the cochleas in hearing-impaired listeners limits their ability to distinguish one sound from another using certain cues.

## TECHNICAL APPROACH

Listeners will hear four short, multi-tonal stimuli presented over headphones. The first two sounds will be played simultaneously. Next, the two sounds will be played again, but one of those sounds will have different spectral characteristics. The listener is asked to indicate on a touch-screen terminal which sound (the third sound or the fourth sound) was changed. Depending on the characteristics of the sounds, listeners will hear the first two simultaneously-presented sounds as either one sound or two sounds. If the listeners hear the two sounds as if they were one, the task will be extremely difficult to do. However, if the listeners hear the two sounds separately, they will easily distinguish which sound changes across the presentations. Different aspects of the sounds will be changed to evaluate when the two sounds are heard as a single sound or heard as two sounds. In some experiments, the onset times of the two sounds will be varied. Sensitivity will be measured as a function of onset time difference. In other experiments, the sounds will be modulated at different rates, and sensitivity will be measured as a function of modulation rate difference.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Experimental programming for the portion of this protocol dealing with the ability of onset differences within a complex sound to help listeners hear spectral differences is completed, and we are currently beginning data collection. No results can be reported yet. The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 4.

## CONCLUSIONS

The preliminary data obtained so far suggests that onset differences between a distracter tone and the target complex sound on the order of 100 ms may help listeners separate distracter from target, and perceive changes in the spectrum of sound.

Report Date: 15 April 2002 Work Unit # 2635-99

# DETAIL SUMMARY SHEET

TITLE: Monitoring for Donor-Specific Hyporesponsiveness Following Renal and Pancreatic Allotransplantation

KEYWORDS: Kidney Transplant

PRINCIPAL INVESTIGATOR: Allen Kirk, LCDR, MC
ASSOCIATES: S. John Swanson, COL, MC

DEPARTMENT: Surgery
SERVICE: Organ Transplant

STATUS: O
INITIAL APPROVAL DATE: 22 June 1999

STUDY OBJECTIVE:
Primary Protocol Objective:
The primary objective of this protocol is to develop methods of evaluating patients after transplantation that detect donor-specific immune hypo-responsiveness or tolerance.

Secondary protocol objectives include:
1. To monitor patients clinically and generate base-line data on donor specific immune responses that occur following transplantation with conventional immunosuppression. These observations will be used as a comparison for future trials using novel immunomodulatory regimens.
2. To correlate long-term patients and graft outcome with findings from the techniques developed. While this study is not powered to clinically correlate these techniques, it is hoped that pilot data can be obtained during assay development indicating that immune hypo-responsiveness to donor antigen results in improved graft survival. Formal study of this will involve subsequent protocol development.

TECHNICAL APPROACH:
An unlimited number of transplant patients will be enrolled. In addition, up to 20 normal, non-uremic volunteers will be enrolled to establish a normal baseline for peripheral blood assays. Samples received from transplant patients prior to transplant will serve as uremic controls.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 168. Expected serious adverse events were submitted to the NIDDK IRB during this review period.

CONCLUSIONS:
This protocol is currently open to accrual. This protocol is a standard of care protocol that provides transplant relevant tissue and blood samples for assay development. This protocol is not used for the study of investigational agents. A total of 168 patients have been enrolled, eleven since the last Continuing Review. The marked decrease in enrollment during this reporting period reflects the fact that we have accrued most of the normal tissue donors required and have begun transplanting most recipients under investigational protocols in the past year. Of the patients enrolled to date, 99 are healthy volunteers, 22 are long-term post-transplant patients transplanted elsewhere, and 47 are patients who proceeded to renal transplantation at the Clinical Center. Two grafts have been lost after the first year (one kidney and one pancreas) secondary to rejection.

There have been two deaths associated with this protocol. One patient died secondary to intraoperative complications from retroperitoneal fibrosis and never proceeded to transplant. The second patient death,

secondary to myelodysplasia, occurred during this reporting period. This patient died after receiving a bone marrow transplant performed on a different protocol. This was reported as an SAE under the bone marrow transplant protocol.

This study has provided TAB investigators with important information on the natural history of allotransplant function, immune function, and intragraft histology under the standard of care, and as such, has served as a reference point for contemporaneous investigational agent protocols. This trial has also provided tissue allowing TAB investigators to develop a novel real-time polymerase chain reaction assay for characterization of the transcriptional events occurring as a result of allograft reperfusion, and immune attack. This assay has served as the topic of a Cooperative Research and Development Agreement (CRADA) with Applied Biosystems. Additional information has been obtained through the analysis of cytokine gene polymorphisms. Correlates between outcome and polymorphism have aided to the design of investigational protocols. This protocol is also valuable in maintaining the expertise of the transplant program in standard of care immunosuppression. NIDDK investigators outside of TAB have enrolled these patients in multiple renal pathophysiology trials, thus this protocol has provided the NIH with a patient population (renal transplant recipients) unavailable elsewhere in the Clinical Center.

The protocol needs to be maintained to continue to provide biopsy and peripheral blood samples for transcriptional and polymorphism studies. It is also necessary to maintain some level of competence in standard transplant methods, and to provide a reference point for graft outcome to which investigational therapies can be compared.

Report Date: 15 April 2002 Work Unit # 2636-99

# DETAIL SUMMARY SHEET

TITLE: Live Donor Renal Donation for Allotransportation

KEYWORDS: Kidney Donor

PRINCIPAL INVESTIGATOR: Allen Kirk, LCDR, MC
ASSOCIATES: S. John Swanson, COL, MC

DEPARTMENT: Surgery
SERVICE: Organ Transplant

STATUS: O
INITIAL APPROVAL DATE: 22 June 1999

STUDY OBJECTIVE: This protocol is designed to identify candidates for renal donation and provide donor kidneys for patients undergoing renal transplantation as part of protocol related studies at the NIH Clinical Center. This protocol will also be used to facilitate the procurement of donor blood and bone marrow in support of transplant studies involving the evaluation of donor specific immune reactivity.

TECHNICAL APPROACH: The eligible population will be adults without preexisting renal disease who are willing to donate a kidney to a family member or close friend who is enrolled in a clinical transplant protocol at the NIH Clinical Center. Patients will be considered providing they are in good general health. While each patient is evaluated individually, symptomatic cardiac disease, cerebrovascular disease, or peripheral vascular disease will generally lead to the exclusion of the candidate. Also, most contagious infectious diseases contraindicate donation, although this is dependent in large part on the infectious status of the recipient. For example, an individual with Hepatitis C would not be acceptable for general donation but might be able to donate to another individual with the same strain of hepatitis C virus.
Patients will not be selected according to race and gender. However, because some of the disorders under study have different demographic characteristics, the patient populations will not be expected to be evenly balanced (e.g. refractory hypertension). By international convention, children are not allowed to be used as living organ donors regardless of whether their guardians consent. For this reason, only adults will be considered for donation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 83, if multi-site study. There has been one Serious Adverse Event reported to the NIDDK IRB since the last Continuing Review and is summarized as post-operative incisional hernia.

CONCLUSIONS:
This protocol is currently open to accrual. A total of 83 patients have been enrolled in this protocol; forty since the last Continuing Review. Of the patients enrolled, 46 have proceeded to renal donation, and 37 have been medically excluded. All patients remain alive and well with good renal function.

Living related and unrelated kidney donation provides over 50% of the organs for renal transplant protocols, and remains an invaluable source of organs for tolerance protocols. Living donation is the preferred organ source for transplantation and eliminates many variables that confound the interpretation of transplant protocols. Patients that have been accrued under this protocol and have gone on to become actual donors have all done well post-operatively with minor expected complications. Forty-five grafts have functioned immediately, while one graft has had delayed function attributable to acute tubular necrosis. The recipient of this graft is off dialysis and recovering renal function at home. In the past year, we have instituted the laparoscopic technique for donor nephrectomy in keeping with the standard of care for this procedure.

Report Date: 21 November 2001

Work Unit # 00-2801

# DETAIL SUMMARY SHEET

TITLE: Mentor Saline Filled Testicular Prosthesis Adjunct Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 18 January 2000

## STUDY OBJECTIVE

To provide access to this device while the core study data are submitted and reviewed by the Food and Drug Administration (FDA). Once the Mentor Saline filled testicular Prosthesis is cleared for market via the Pre-market Approval (PMA) process, enrollment of subjects into the Adjunct Study will be halted. This control study will collect tracking information on subjects enrolled into the study and information on the incidence and severity of adverse events.

## TECHNICAL APPROACH

Enrollment is done through patient screening in the Urology Clinic or referred to us from other urology departments in the military. Male military health care beneficiaries age 18 years of age or older who are indicated for testicular prosthesis implantation (in cases of testicular agenesis or following surgical removal of the testis) either unilaterally or bilaterally are enrolled.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The protocol was approved January 2000. There are 16 patients enrolled to date at WRAMC and 151 study wide. Enrollment is continuing at this time. All adverse events have been reported.

The number of subjects enrolled to the study since last APR at WRAMC is 6 and the total enrolled to date at WRAMC is 16. The total number enrolled study-wide is 151, if multi-site study.

## CONCLUSIONS

None at this time.

Report Date: 20 December 2001 Work Unit # 01-28001

# DETAIL SUMMARY SHEET

TITLE: SWOG: Selenium and Vitamin E Cancer Prevention Trial (SELECT), Phase III Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: Dean, Robert LTC MC; Flynn, Joseph CPT MC; McLeod, David COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 20 February 2001

## STUDY OBJECTIVE

Primary objective is to assess the effect of selenium and vitamin E alone and in combination on the clinical incidence of prostate cancer. Secondary objectives are: to assess the effect of these two drugs alone and in combination on the incidence of other cancers including lung, colorectal and all other cancers combined; and to assess the effect of the study drugs along and in combination of prostate cancer free survival, lung cancer free survival, colorectal cancer free survival, cancer free survival, overall survival, and serious cardiovascular events. Quality of life, molecular epidemiology, pathological biomarkers, and diet supplement, nutrient intake, and plasma nutrients will also be assessed.

## TECHNICAL APPROACH

A total of 150 to 400 men who are in good health will be enrolled at WRAMC over a period of five years. The study will last a total of seven to twelve years for each man, depending upon the date of enrollment. The digital rectal exam (DRE) must be normal, and the prostate specific antigen (PSA) must be at or below 4 ng/ml. African American men must be at least fifty years old; all other races fifty-five years old. The men are ineligible if any previous history of hemorrhagic stroke or have had a malignancy other than basal or squamous cell carcinoma within the last five years, or are on coumadin for any reason. There will be two visits required per year: an annual visit with DRE and blood draw for PSA, a six-month supply of study drug will be dispensed, and a general health assessment done. The second visit at six months after enrollment will be for general health assessment and medication dispensing. The men enrolled have the choice of participating in several sub-studies, which involve the collection of toenails, blood, and prostate tissue (only if biopsy is indicated by rise in PSA or abnormal DRE) for current and future research of prostate cancer.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The original protocol was approved for enrollment as of 17 July 2001. An amendment for submission of a news release brochure was approved 31 August 2001. No literature has been released to date. No patients have been enrolled at WRAMC because of delayed contract negotiations between the Henry M. Jackson Foundation and Southwest Oncology Group. Many men want to join this prevention study; ten have been screened and will be ready to enroll in January 2002. There have been no study-wide adverse events reported.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is approximately 1000. The goal for nationwide enrollment is 32,000 over a five-year period.

## CONCLUSIONS

There have been no conclusions to date.

Report Date: 30 January 2002

Work Unit # 01-28002

# DETAIL SUMMARY SHEET

TITLE: A Pilot Study to Evaluate the Safety and Feasibility of Thermal Ablation with Thermo Rods ™ for Residual Prostate Cancer Following External Beam Radiation Therapy.

KEYWORDS:

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 20 March 2001

## STUDY OBJECTIVE

The primary objective is to evaluate the safety of a course of thermal ablation treatment with Thermo Rods ™ to treat residual prostate cancer following external beam radiation therapy. The secondary objective is to obtain preliminary data, as a follow-up to this study, regarding the effect of thermal ablation with Thermo Rods ™ on PSA levels over time.

## TECHNICAL APPROACH

This is an open, multi-center, non-randomized, uncontrolled pilot study to evaluate the safety and feasibility of thermal ablation with Thermo Rods ™ for residual prostate cancer following external beam radiation.

## PRIOR AND CURRENT PROGRESS

This protocol received final approval on March 20, 2001. Several sponsor-initiated changes to the protocol have been submitted to the WRAMC IRB for approval. The sponsor has reported no adverse events or patient withdrawals. The number of subjects enrolled to the study since last APR at WRAMC is 0 . The total number enrolled study-wide is 11 if multi-site study. Screening is continuing at our site at the present time.

## CONCLUSIONS

None at this time.

Report Date: 27 March 2002 Work Unit # 01-28003

# DETAIL SUMMARY SHEET

TITLE: AMS002.2: Evaluation of the Safety and Tolerability of Transurethral Dehydrated Alcohol Injection for the Treatment of Benign Prostatic Hyperplasia

KEYWORDS:

PRINCIPAL INVESTIGATOR: COL David McLeod MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 15 May 2001
(Six Month Review)

STUDY OBJECTIVE
The primary objectives of this study are to monitor the occurrence of side effects and complications associated with transurethral injection of dehydrated alcohol into the prostate and establish a dose range that provides improvement in symptoms with minimal side effects.
The secondary objectives are to evaluate the improvement in lower urinary tract symptoms (LUTS) in men with Benign Prostatic Hyperplasia (BPH) following transurethral intraprostatic injection of dehydrated alcohol and to assess the impact of treatment on patient sexual function and quality of life.

TECHNICAL APPROACH
This is a phase I-II study to evaluate the safety and tolerability of transurethral dehydrated alcohol injection for the treatment of benign prostatic hyperplasia.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This protocol received final approval on May 15th 2001. As a result of a sponsor-reported serious adverse event, which occurred at another site, and discussions with the FDA on 10 August 2001, this protocol was placed on clinical hold and enrollment was suspended. The adverse event has been reported to the WRAMC IRB. No other adverse events have been reported.

On 4 March 2002 the sponsor announced that the FDA released this study from clinical hold. On 22 March 2002 we received the revised protocol incorporating the FDA requirements and are in the process of preparing the paperwork to submit to DCI for approval.

A literature search was performed and no new relevant articles were found.
The number of subjects enrolled to the study since the last APR is at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total enrolled study-wide is 56 if multi-site study.

CONCLUSIONS
None at this time.

Report Date: 30 September 2002 Work Unit # 01-28003

# DETAIL SUMMARY SHEET

TITLE: AMS002.2: Evaluation of the Safety and Tolerability of Transurethral Dehydrated Alcohol Injection for the Treatment of Benign Prostatic Hyperplasia

KEYWORDS:

PRINCIPAL INVESTIGATOR: COL David McLeod MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 15 May 2001
(Six Month Review)

STUDY OBJECTIVE
The primary objectives of this study are to monitor the occurrence of side effects and complications associated with transurethral injection of dehydrated alcohol into the prostate and establish a dose range that provides improvement in symptoms with minimal side effects.

The secondary objectives are to evaluate the improvement in lower urinary tract symptoms (LUTS) in men with Benign Prostatic Hyperplasia (BPH) following transurethral intraprostatic injection of dehydrated alcohol and to assess the impact of treatment on patient sexual function and quality of life.

TECHNICAL APPROACH
This is a phase I-II study to evaluate the safety and tolerability of transurethral dehydrated alcohol injection for the treatment of benign prostatic hyperplasia.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This protocol received final approval on 15 May 2001. As a result of a sponsor-reported serious adverse event, which occurred at another site, and discussion with the FDA on 10 August 2001, this protocol was placed on clinical hold and enrollment was suspended. The adverse event has been reported to the WRAMC IRB. On 4 March 2002, the sponsor announced that the FDA released this study from clinical hold. On 22 March 2002, we received the revised protocol incorporating the FDA requirements and submitted the addendum to DCI for approval. The addendum was approved on 27 August 2002.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to-date at WRAMC is 0. The total enrolled study-wide is 75 if multi-site study.

CONCLUSIONS
None at this time.

Report Date: 23 April 2002

Work Unit # 01-28004

# DETAIL SUMMARY SHEET

TITLE: An Exploratory Comparison Between Lemonade and Potassium Citrate: The Impact on Urine pH and 24 Hour Urine Parameters

KEYWORDS:

PRINCIPAL INVESTIGATOR: MAJ Kevin Gancarczyk MC
ASSOCIATES: LTC Noah Schenkman MC

DEPARTMENT: Surgery
SERVICE: Urology Service

STATUS: O
INITIAL APPROVAL DATE: 26 June 2001

## STUDY OBJECTIVE

To explore the effects of lemonade on 24-hour urinalysis parameters, in patients with a history of nephrolithiasis, compared to the standard urinary alkalinizing agent, potassium citrate.

## TECHNICAL APPROACH

This is a self-controlled, pilot study to examine the changes in a 24 hour urine specimen in a small collection of subjects, who are treated sequentially on (1) Dietary treatment, (2) Lemonade, and (3) Potassium citrate tablets. The subjects and the investigators will be not be blinded. Subjects will be instructed to maintain a low sodium, low protein diet that is helpful in preventing stone formation for the duration of the study. Appropriate female subjects will have a pregnancy test done at the beginning of the study, although none of the treatments have any known teratogenic effects. There have been no modifications since the protocol was approved.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A literature search was performed and no new articles were found.

The number of subjects enrolled to the study since last APR at WRAMC is 6 and the total enrolled to date at WRAMC is 6. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

We will continue to recruit patients until the original goal of 20 patients is realized. Future research goals would include performing a prospective and randomized study to determine if lemonade is just as effective as potassium citrate in the prevention of stone formation.

Report Date: 30 May 2002

Work Unit # 01-28005

# DETAIL SUMMARY SHEET

TITLE: An Open Label, Multicenter, Ascending, Single Dose Study Investigating the Pharmacokinetics, Pharmacodynamics, and Safety of FE200486 in Prostate Cancer Patients

KEYWORDS:

PRINCIPAL INVESTIGATOR: McLeod, David G. COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: W
INITIAL APPROVAL DATE: August 2001

STUDY OBJECTIVE
Study withdrawn by P.I.

TECHNICAL APPROACH
Study withdrawn by P.I.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Study withdrawn by P.I.

CONCLUSIONS
Study withdrawn by P.I.

Report Date: 30 May 2002 Work Unit # 01-28006

# DETAIL SUMMARY SHEET

TITLE: An Open Label, Multicenter, Extension Study Investigating the Long-Term Safety and Tolerability of Repeat Doses of FE200486 in Prostate Cancer Patients

KEYWORDS:

PRINCIPAL INVESTIGATOR: McLeod, David G. COL MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: W
SERVICE: Urology INITIAL APPROVAL DATE: August 2001

STUDY OBJECTIVE
Study withdrawn by P.I.

TECHNICAL APPROACH
Study withdrawn by P.I.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Study withdrawn by P.I.

CONCLUSIONS
Study withdrawn by P.I.

Report Date: 2 April 2002

Work Unit # 01-2857-98a

# DETAIL SUMMARY SHEET

TITLE: Outcome Comparison of Radical Prostatectomy Pathologic Specimens

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 1 May 2001
(Master Protocol Approval Date: 26 May 1998)

## STUDY OBJECTIVE

It is hypothesized that the step-sectioning of whole mounted prostate specimen would enhance the ability to discover violation of surgical margins and extra-capsular extension, resulting in decreased recurrence (biochemical and clinical) in patients with negative margins, and greater identification of patients with positive margins.

## TECHNICAL APPROACH

We have reviewed the articles related to outcomes of radical prostatectomy and prognostic factors affecting the outcomes by using PubMed and manual literature search to get the hypothesis stated above. A SQL script will be written to query the CPDR prostate cancer database (WU #2857-98) for data from the data fields listed below. The data set will be divided into two groups based on the processing methods of radical prostatectomy specimens: Whole mount group in which the specimen were processed with whole-mounted and step sectioning (2.25 mm thick) technique; and non-whole mount group in which the specimen were processed with traditional hand slicing (2-5 mm thick) and partial sampling method. Comparison of pathological findings of the radical prostatectomy specimen between the whole-mounted group and non-whole mount group will be performed, and the relationship between the pathological findings and disease-free survival will be analyzed using the stated statistical methods below.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A literature search was performed and no new relevant articles were found. The study query of the CPDR National Database revealed 249 patients from Walter Reed who had close step-sectioning/whole mounting. These were compared to a sample of 682 patients who had standard processing. The sloe-step sectioning patients had a higher detection rate of extra prostatic extension. In men who were found to be organ-confined prostate cancer on close-step sectioning, the three-year disease free survival was significantly greater than those who were "organ confined" by standard processing. These results were generated primarily by Alok Desai, a visiting medical student from George Washington University, working closely with CPDR researchers. The publication of this work is being submitted to DCI for approval.

The number of subjects enrolled to the study since last APR at WRAMC is 249 and the total enrolled to date at WRAMC is 249. The total number enrolled study-wide is 931, if multi-site study.

## CONCLUSIONS

Close-step sectioning and whole mounting of radical prostatectomy specimens provides a more accurate assessment of pathologic stage. For standard processed radical prostatectomy specimens, there is a higher false staging such that many men thought to have "organ confined" disease actually have subtle extraprostatic extension that is only detected by the close-sectioning/whole mount technique.

Report Date: 27 March 2002 Work Unit # 01-2857-98b

# DETAIL SUMMARY SHEET

TITLE: Study of CPDR Multicenter Database to Develop Nomograms on % of Positive Biopsy Cores, Gleason Sum, and Pre-Biopsy PSA to Predict Pathologic Stage in Radical Prostatectomy Patients

KEYWORDS:

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: Gancarczyk, Kevin J MAJ MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 5 June 2001
(Master Protocol Approval Date: 26 May 1998)

## STUDY OBJECTIVE

The goal of this study is to develop predictive nomograms based on % of core biopsies positive for prostate cancer, highest biopsy Gleason sum, and pre-treatment (or pre-biopsy PSA) to predict final pathologic stage variables in men who have undergone radical prostatectomy and whose data has been maintained in the Center for Prostate Disease Research (CPDR) multicenter database (W#2857-98).

Secondary goals will be to recreate CPDR nomograms identical to the methodology of Partin et.al. using their three prognostic factors and to determine how well the Partin, et.al. nomograms predicted our CPDR cases.

## TECHNICAL APPROACH

The clinical and pathological data of all men entered into the Center for Prostate Disease Research's (CPDR) database, which is a Department of Defense Multi-center Tri-service Longitudinal National Database that had diagnosis by transrectal ultrasound and biopsy (TRUS/BX) and undergone radical prostatectomy as primary therapy for prostate cancer between January 1990 and January 2001 will be reviewed. Only those men that have complete information in regards to clinical stage, race, age, pre-treatment PSA, TRUS/BX data and pathologic stage will be analyzed. Required TRUS/BX data include total number of cores taken, total number of cores positive for prostate cancer and highest Gleason score. The study is limited to men that had between 6-12 cores taken and defined the percentage of biopsy cores positive as the total number of cores positive for prostate cancer divided by the total number of cores taken. All of the radical specimens were staged according to the 1992 TMN classification and only those with pathology Gleason Sum available were used. Any patient that had neoadjuvant hormonal therapy or are missing any of the aforementioned data of interest will be excluded.

Once the patients are identified a bivariate analysis will be performed using chi square method for PSA, clinical stage, highest biopsy Gleason Sum, race, age, and percentage of biopsy cores positive for prostate cancer to determine the most significant predictors of pathologic outcome. The main objective of this study is to produce a clinically useful probability nomogram, in order to accomplish this we first have to determine the pathological stage stratification of the percent of biopsy cores positive. Biopsy cores taken ranging from 6- 12 to encompass the multiple biopsy schemes that are currently in practice, nine subgroups will be initially formed: $< 20\%$, $\geq 20$ to $< 30$, $\geq 30$ to $<40$, $\geq 40$ to $< 50$, $\geq 50$ to $< 60$, $\geq 60$ to $< 70$, $\geq 70$ to $<80$, $\geq 80$ to $< 90$, $\geq 90$ to 100 (16-20). Next the four possible pathologic outcomes: organ confined (OC), capsule positive (Cap +), seminal vesicle positive (SV +) and node positive (N+) will be applied to these groups. Then based on similar pathologic outcomes the final subgroups will be identified. Next, the significant predictors will be entered into a stepwise logistic regression model to determine their independent predictive significance.

Once the three most significant independent predictors of pathology at the time of radical prostatectomy with their subgroups are identified, a probability nomogram will then be created with each patient only having one pathologic outcome and a confidence level greater than 95%.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A literature search was performed and no new relevant articles were found. Using the CPDR database a total of 4,608 patients were identified who underwent RRP. Of those, only 1,527 patients met all inclusion/exclusion criteria. The % of cores positive was found to be a significant predictor of pathologic stage. A nomogram using % cores positive, pre-treatment PSA, highest biopsy Gleason Sum were used to predict pathologic stage. A manuscript has been submitted to Urology and is currently undergoing revisions prior to publication. Future plans include using the % core positive to predict PSA recurrence and disease free survival.

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is 1527. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS

Biopsy quantification of prostate biopsy cores is an independent predictor of pathologic stage of cancer after radical prostatectomy.

Report Date: 29 March 2002

Work Unit # 01-2857-98c

# DETAIL SUMMARY SHEET

TITLE: Development of Internet-Accessible Prediction Models for Prostate Cancer Diagnosis, Treatment and Follow-up

KEYWORDS:

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 7 August 2001
(Master Protocol Approval Date: 26 May 1998)

STUDY OBJECTIVE

(1) Analyze the CPDR database by integrating the most powerful prognostic variables with the following regression models: logistics regression, Cox proportional regression, and artificial neural networks (ANN).

(2) Build clinical models predicting probability of prostate cancer in the diagnosis phase, optimal primary treatment in the treatment phase and the optimal recurrence treatment in the follow-up phase.

(3) Implement these models into software and post it on the web accessible by patients and physicians as tools for public education, patient self-testing, and physicians decision making reference.

TECHNICAL APPROACH

A data warehouse will be designed, and web applications to support the prediction models will be developed. Unix operating system, Oracle servers, and SAS will be used to support the web applications and data mining.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A literature search was performed and no new relevant articles were found.

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is 5001. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS

The study is ongoing – no conclusions have been gained as of this APR.

Report Date: 22 May 2002 Work Unit # 01-2871-98a

# DETAIL SUMMARY SHEET

TTTLE: Characterization of Novel Prostate Specific Gene, PCGEM1

KEYWORDS: tissue, prostate, cancer

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 20 February 2001
MASTER PROTOCOL APPROVAL DATE: 21 July 1998

STUDY OBJECTIVE

1. Characterization of PCGEM1 Structure and Function
2. Mechanisms of Regulation of PCGEM1 Expression
3. Analysis of PCGEM1 Expression in Prostate Cancer

TECHNICAL APPROACH

1. Characterization of PCGEM1 Structure and Function: A comprehensive analysis of PCGEM1 cDNA clones has revealed that PCGEM1 represents a novel cDNA sequence, which may belong to the emerging group of functional non-coding mRNAs. PCGEM1 cDNA as well as the native PCGEM1 mRNA will be analyzed to determine if PCGEM1 functions as a non-coding RNA or one of the short ORFs of the PCGEM1 cDNA encode PCGEM1 protein. PCGEM1 mRNA will be analyzed for its subcellular localization e.g., nuclear localization of PCGEM1 mRNA or absence of PCGEM1 mRNA in polyribosomes will further support its non-coding nature. Anti-peptide antibodies will be raised against PCGEM1 ORFs to detect PCGEM1 encoded protein, if any. The short ORFs derived from the PCGEM1 cDNA will be expressed in NIH3T3 cells as observed with the full length PCGEM1 cDNA. Cell growth regulating functions of the PCGEM1 will be characterized by over expression of PCGEM1 in NIH3T3 cells or immortalized normal prostate epithelial cells and by inhibiting the expression of PCGEM1 sequence LNCaP prostate cancer cells. Deletion mutagenesis will define the regions in PCGEM1 sequence critical for PCGEM1 biologic functions. The cDNA sequence of PCGEM1 homologs from non-human species will determine conserved regions of PCGEM1.

2. Mechanisms of Regulation of PCGEM1 Expression: The prostate tissue specificity and androgen regulation of PCGEM1 suggests for normal functions of PCGEM1 in development and/or maintenance of the prostate gland. Genomic clones of PCGEMI1 will be characterized by DNA sequencing. The PCGEM1 promoter sequence will be identified and characterized by DNA sequencing. The PCGEM1 promoter sequence will be identified and characterized by transfecting PCGEM1 reporter-reporter constructs in LNCap cells treated with or without androgens. Once the PCGEM1 promoter is identified, it will be analyzed for the sequence elements for the presence of androgen response elements (ARE). Deletion mutagenesis of the promoter sequence followed by reporter gene assays will be performed to define the sequences that confer prostate tissue specificity or androgen regulation. Using in situ hybridization assays, the cell type specificity of the PCGEM1 expression will be established in frozen OCT embedded and paraffin embedded tissue sections of the normal and tumor regions of the human prostate.

3. Analysis of PCGEM1 Expression in Prostate Cancer: Preliminary analysis of paired normal and tumor specimens revealed PCGEM1 over expression in tumor specimens of about half of CaP patients. Role of PCGEM1 expression in prostate cancer progression will be evaluated in CWR22 xenograft model derived tumors representing androgen sensitive and androgen refractory tumors. PCGEM1 expression will also be analyzed in matched normal and tumor tissue of 100 prostate cancer patients using laser capture micro dissection (LCM) and quantitative RT-PCR. Analysis of PCGEM1 expression by in situ RNA

hybridization in representative specimens will complement the RT-PCR assays. We will examine whether PCGEM1 over expression is associated with specific pathologic stage, cancer recurrence after radical prostatectomy and the clinical stage of the disease. To address the PCGEM1 expression in the context of multifocal CaP, PCGEM1 expression will be analyzed in the sections of the whole-mounted prostate from cancer patients.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since the last APR, COL Moul replaced Col McLeod as the Principal Investigator on this project.

A literature search has been performed and there are no new articles to report.

The experimental approach used is laser capture microdissection (LCM) coupled with RT-PCR. Preexisting OCT embedded frozen prostate tissues containing normal and tumor regions from radical prostatectomy specimens of prostate cancer patients will be used. Matched tumor and normal cells from each patient will be obtained using LCM.

Quality control experiments to ensure optimization of LCM, RNA preparation, and semiquantitative RT-PCR assay conditions were established. LCM analysis on specimens derived from 78 patients was completed and RNA was prepared. PCGEM1 expression was determined by RT-PCR assays for 35 patient tissues and needs to be completed for the remaining 43 patient tissues.

The number of subjects enrolled to the study since last APR at WRAMC is 78 and the total enrolled to date at WRAMC is N/A. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
None at this time.

Report Date: 17 May 2002

Work Unit # 01-2871-98b

# DETAIL SUMMARY SHEET

TITLE: The Use of Transformed Prostate Cell Lines CPDR7, CPDR8, CPDR9, to Evaluate the Capacity of T Lymphocytes to Recognized Prostate-Derived Antigens

KEYWORDS:

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 10 April 2001
MASTER PROTOCOL APPROVAL DATE: 21 July 1998

STUDY OBJECTIVE

The CPDR7, CPDR8 and CPDR9 cell lines will be used as target cells in cytoxicity *in vitro* assays to determine whether peptide-specific CTL can recognize naturally processed antigen.

TECHNICAL APPROACH

CPDR7, CPDR8, CPDR9 immortalized prostate cancer cell lines will be used as targets in the cytoxicity assays in addition to t2 cells. This will specifically help to demonstrate that naturally processed antigens can be lysed by CTL to peptides.

***Day 0** Generation of Dendritic Cells (DC):* Monocytes are purified by plating 10 X $10^6$ PBMC in 3 ml of complete medium (RPMI-1640 plus 5% AB hum serum, non-essential AA sodium pyruvate, L-glutamine and gentamycin) in each well of a 6-well plate. After two hours at 37° C, the non-adherent cells are removed by gently shaking the plates and aspirating the supernatants with a Pasteur pipette and vacuum. The wells are washed for a total of three times with medium (3 ml) to remove most of the non-adherent and loosely adherent cells. Check the plates in the inverted microscope and if contaminating T cells are still present, remove them by gently flushing medium onto the bottom of the wells with a transfer pipette and removing one more time the supernatants. Add 3 ml of complete medium to each well containing 50 ng/ml of GM-CSF and 1,000 U/ml of IL-4. These DC will be ready to use for CTL induction cultures after 6-7 days. IF the cell cultures become too yellow, remove ½ of medium and feed with fresh medium containing cytokines. On day 6, DC can be induced to maturate by adding fresh medium containing poly I:C (Sigma) to a final concentration of 20 µg/ml.

***Day 7 (part A)** Induction of CTL with DC and peptide:* The DC are harvested and washed 1X with PBS-HAS (human serum albumin) and re-suspended in PBS with 1% HSA. The DC are counted and pulsed with 40 µg/ml of synthetic peptides corresponding to prostate antigens (PSA, PSMA, etc...) at a cell concentration of 1~2x $10^6$/ml in PBS-HSA in the presence of 3 µg/ml $\beta_2$ microglobulin for four hours at 20°C (room temperature) with constant mixing in rocking platform. While the DC are bring pulsed, $CD8^+$T-cells are purified with Miltenyi immunomagnetic beads by positive selection as described above for CD14+cells and will be used for as responders. CD8-depleted cells can be re-frozen for used as monocytes for re-stimulation with antigen (day 14). Typically to obtain enough cells for one 48-well plate culture, 200 to 250x$10^6$ PBMC are processed to obtain 24x$10^6$ CD8+cells. Re-suspend the CD8 positive cells after washing them, at 2x$10^6$ cells/ml and keep at 4°C until further use. After the 4 hr peptide pulsing incubation, the DC are irradiated (4,200 rads), washed 1 time with RPMI-HS medium (RPMI + 5% human AB serum) and diluted at 1 X $10^5$ cells/ml.

***Day 7 (part B)** Setting up T-cell priming cultures:* 0.25 ml cytokine-generated DC (@1x$10^5$ cells/ml) are co-cultured with 0.25 ml of CD8 T-cells (@ 20x$10^5$ cells/ml) in each well of a 48-well plate in RPMI-HS and in the presence of 10 ng/ml of rIL-7.

***Day 8*** Add rIL-10 to a final concentration of 10 ng/ml.

***Day 14*** *Restimulate the induction cultures with peptide pulsed adherent cells in individual wells of the 48-well plate:* Plate $2x10^6$ PBMC (washed with DNAse and irradiated ~4,200 rads) in 0.5 ml of the complete medium per well. Incubate for 2 hours at 37°C to allow monocytes to adhere to bottom of plates. Wash off non-adherent cells by gently flushing the cells with PBS 2% FCS and pulse adherent cells with 10 µg/ml of peptide in the presence of 3µg/ml $\beta_2$ microglobulin (in 0.25 ml of PBS-FCS per well) for 2 hours at room temperature in rocking platform. The peptide solution from each well is aspirated. One-half of the media is aspirated from the CD8+ cells and fresh media. The cells are re-suspended individually and transferred to the wells containing the "dry" peptide-pulsed adherent cells.

***Day 15*** Add 100 µl of medium containing rIL-10 and rIL-4 (1:100) so final concentration of cytokines is 10 ng/ml and 2000 U/ml.

***Day 16 or 17*** Add 100 µl fresh medium containing rIl-2/ml (final of 50 IU) to each well.

***Day 21*** Re-stimulate the entire cultures again. Repeat procedures from day 7 to 17

***Day 28-29*** Perform either a cytoxicity (5 hr $Cr^{51}$ release) assay or ELISA for individual wells using a single E/T ratio (use 75% of the cells from each well, and do not count the effectors). Targets used are: T2, T2-pulsed with peptide (10µg/ml the night before). In addition, the CTL will be tested for activity against the CPDR7, CPDR8 and CPDR9 cell lines to demonstrate that these cells can recognize naturally processed antigens. CPDR 7, CPDR 8 and CPDR 9 cell lines will be used as targets in cytoxicity assays, by labeling with 51Cr.

**To continue growing positive wells, the cultures must be re-stimulated with peptide and APC every 7 days as described above or expanded by REM.

NOTE: Peptides have been provided to you diluted in 100% DMSO plus 0.1%TFA at 20 mg/ml. A total of 5 mg are in each vial, sufficient for several experiments. Dilute in medium for pulsing APC or targets only the amount required. You can store peptide stocks at –20°C and freeze-thaw several times (up to 10) without problem.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A literature search was performed and no new relevant articles were found. Since the last APR, COL Moul replaced COL McLeod as the Principal Investigator on this project. The final approval letter was dated 3 May 2001. The acquisition of the necessary materials for this protocol is in progress, but no work has begun on this project. Reporting a count of subjects enrolled on this protocol is not applicable, as this protocol uses three cell lines, CPDR7, CPDR8 and CPDR9 that were developed under the master protocol WU # 2871-98 "Creation of a Tissue Library for the Molecular Biologic Study of Patients with Prostate Cancer".

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is N/A. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS

There are none at this time.

Report Date: 17 May 2002 Work Unit # 01-2871-98c

# DETAIL SUMMARY SHEET

TITLE: Characterization of Prostate Specific G-Protein Coupled Receptor (PSCR) in Prostate Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 7 August 2001
MASTER PROTOCOL APPROVAL DATE: 21 July 1998

STUDY OBJECTIVE

PSGR will be analyzed for its biologic and biochemical functions and expression. Tumor tissues, well characterized for pathology and clinical information, will be used to evaluate the prognostic utility of PSGR overexpression in prostate tumor development and/or progression.

TECHNICAL APPROACH

Year 1

Task 1: Prepare polyclonal antibodies against PSGR synthetic peptides.
Task 2: Bacterial expression of full length and partial PSGR protein and generation of antibodies against bacterially expressed/purified PSGR antigens
Task 3: Evaluate PSGR expression vectors (AdPSGR and plasmid-expression vectors) for analysis of biologic and biochemical functions in prostatic epithelial cells
Task 4: Characterize anti-PSGR antibodies by immunoprecpitations, Western blot and immunfluorescence/immunocytochemistry for detection of the PSGR protein in PSGR transfectants and bacterially expressed PSGR protein.
Task 5: Cell biologic characterization of prostatic epithelial cells harboring expression vectors of PSGR. Evaluation of PSGR transfectants in cell cycle and apoptosis assays. Analysis of the PSGR transfectants in colony forming, soft agar and cell proliferation assays.
Task 6: Screening and characterization for PSGR expression in prostate cancer cell lines.
Task 7: Prepare RNA from laser microdissected matched normal and tumor specimens of 50 prostate cancer patient and analyze for PSGR expression by quantitative RT-PCR using TaqMan chemistry and ABI 7700 system (50 samples per year)

Year 2

Task 1: Characterization of the genomic clone of PSGR and sequence analysis of putative promoter sequence.
Task 2: Analyze promoter sequence of PSGR using luciferase reporter gene assays and transient transfections of prostate cancer cells and CoS cells.
Task 3: Follow up on the cell biologic characterization of PSGR transfectants.
Task 4: Study the membrane localization of the PSGR protein.
Task 5: Analysis of biochemical properties of PSGR: dissection of the signal transduction pathways.
Task 6: Optimize and analyze the analysis of PSGR protein by immuno-histochemistry in prostate tissues determine cell type specificity and get the tissue array ready. If antibodies do not work, this line of experiment will be discontinued.
Task 7: Prepare RNA from laser microdissected matched normal and tumor specimens of 50 prostate cancer patients and analyze for PSGR expression by quantitative RY-PCR using TaqMan chemistry and ABI 7700 system (50 samples per year)

Year 3

Task 1: Analysis of PSGR expression in prostate tissues by *in situ* RNA hybridization and immunohistochemistry
Task 2: Analyze tissue microarray of 425 prostate cancer patients for PSGR protein expression.
Task 3: Prepare RNA from laser microdissected matched normal and tumor specimens of 50 prostate cancer patient and analyze for PSGR expression by quantitative RT-PCR using TaqMan chemistry and ABI 7700 system (50 samples per year).
Task 4: Complete clinico-pathologic correlation and statistical analysis of the PSGR expression (both by quantitative RT-PCR and immunohistochemistry) in specimens from prostate cancer patients.
Task 5: Follow up on the biochemical characterization of PSGR functions.
Task 6: Utilizing deletion mutagenesis approach, characterize the cell/tissue specificity conferring cis-acting sequences in the promoter region and study the enhancer elements, if any.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A literature search was performed and no new relevant articles were found.

Since the last APR, COL Moul replaced COL McLeod as the Principal Investigator on this project. The final approval letter for this protocol is dated 13 February 2002. Work on this protocol has not yet been initiated.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
None at this point in time.

Report Date: 2 April 2002

Work Unit # 02-2857-98d

# DETAIL SUMMARY SHEET

TITLE: Assessing the Predictive Accuracy of Prostate Cancer Prognostic Factors Using Traditional Statistical Methods and Artificial Neural Networks

KEYWORDS:

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 2 October 2001
(Master Protocol Approval Date: 26 May 1998)

STUDY OBJECTIVE

The purpose of this study is to assess the accuracy of prostate cancer prognostic factors in predicting response to therapy and post-therapy recurrence using traditional statistical methods and artificial neural networks.

TECHNICAL APPROACH

A disk containing the data set without identifying any patient confidentiality information (SSN, Last name, First name, Address, for example) but with a unique randomly selected code number will be supplied to the Collaborator, Harry B. Burke, M.D., Ph.D., and a CPDR staff from CPDR Headquarters, who will analyze the data in terms of recurrence, cancer-specific, and all-cause mortality. The area under the receiver operating characteristic curve will assess predictive accuracy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A literature search was performed and no new relevant articles were found.
The final approval letter for this protocol is dated 22 March 2002 and was received by this office 2 April 2002. Therefore, no work has been done on this protocol.

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 12,500, if multi-site study.

CONCLUSIONS

No conclusions have yet been made.

Report Date: 3 April 2002 Work Unit # 02-2857-98e

# DETAIL SUMMARY SHEET

TITLE: Statistical Modeling Using Pre-Operative Prognostic Variables in Predicting Extracapsular Extension, Positive Margins and Outcome After Radical Prostatectomy for Prostate Cancer: Retrospective Study Using the CPDR Prostate Cancer Database

KEYWORDS:

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 9 October 2001
(Master Protocol Approval Date: 26 May 1998)

STUDY OBJECTIVE
The objective of this study is to perform statistical analysis on a group of patients that have undergone radical prostatectomy for prostate cancer. The outcome of this analysis will establish the important preoperative variables that predict disease-free survival after surgery. These variables will then be used to develop a simple equation to predict outcome after radical prostatectomy, capsular penetration and probability of positive margins.

TECHNICAL APPROACH
The CPDR database of radical prostatectomies at WRAMC between 1985-2000 will be used. 1,085 patients and their data are currently available. Only those patients that have accurate clinical follow-up and variable data will be included in the study. A separate model that employs the number of positive biopsies in place of clinical stage will be performed. More specifically, we will incorporate the number of biopsies (1-6) positive for cancer instead of the clinical stage category in one of the prediction models.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A literature search was performed and no new relevant articles were found.
No current progress. This protocol has not yet received final approval.
The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is N/A.

CONCLUSIONS
Pending.

Report Date: 28 March 2002

Work Unit # 02-2857-98f

# DETAIL SUMMARY SHEET

TITLE: A Deterministic Computer Model of Prostate Cancer Progression Following Radical Prostatectomy

KEYWORDS:

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 8 January 2002
(Master Protocol Approval Date: 26 May 1998)

STUDY OBJECTIVE
To compare the Net Gain/Loss Years (NGLY-theoretical) using a computer model to the actual Net Gain/Loss in Life Years (NGLY-actual)

TECHNICAL APPROACH
Anonymous data sets will be sent to New Mexico Health Sciences Center, and a computer model will be run for each data set. The data will be analyzed and compared.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A literature search was performed and no new relevant articles were found.
Final approval was just received 6 February 2002. Work has not yet begun on this protocol.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

CONCLUSIONS
This study is ongoing and no conclusions have been drawn as of the date of the APR.

Report Date: 13 November 2001 Work Unit # 2801

# DETAIL SUMMARY SHEET

TITLE: Establishment of a Serum Bank for the Future Detection of New Prostate Cancer Markers in Serum of Patients with Prostate Cancer, Benign Prostate Conditions and No Prostate Disease

KEYWORDS: serum, prostate, future

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Moul, Judd COL MC

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 06 December 1994

STUDY OBJECTIVE
Primarily to establish a serum bank. Serum will be obtained from patients with prostate cancer, benign prostate disorders and no prostate disease to use in the evaluation of new markers of disease.

TECHNICAL APPROACH
Thirty ccs of blood will be drawn and spun down, and the serum will be frozen for use in the future.

PRIOR AND CURRENT PROGRESS
There have been no adverse reactions reported from this protocol.

The number of subjects enrolled to the study since last APR at WRAMC is 415 and the total enrolled to date at WRAMC is 1735. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
None at this time.

Report Date: 31 October 2001

Work Unit # 2802

# DETAIL SUMMARY SHEET

TITLE: Center for Prostate Disease Research Prostate Cancer Radical Prostatectomy Follow-Up Questionnaire

KEYWORDS: prostate cancer, survey, outcomes

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 13 December 1994

## STUDY OBJECTIVE

To conduct a large patient self-reporting questionnaire study of urinary, sexual, and quality-of-life morbidity after radical prostatectomy for prostate cancer in the military health care system.

## TECHNICAL APPROACH

Researchers will: 1) design and validate a questionnaire to assess incontinence, impotence, urinary stricture, quality-of-life and recurrence in radical prostatectomy patients; 2) generate an accurate list of radical prostatectomy patients from military hospitals; 3) mail questionnaires; and 4) tabulate data and analyze results.

## PRIOR AND CURRENT PROGRESS

This study is complete and produced two publications related to patient self-reported sexual and urinary outcomes after radical prostatectomy for prostate cancer.

The number of subjects enrolled to the study since last APR at WRAMC is zero, and the total enrolled to date at WRAMC is 1069.

## CONCLUSIONS

Radical prostatectomy during the era from the 1980s to the mid 1990s produced substantial urinary and sexual morbidity.

Report Date: 12 November 2001

Work Unit # 2804

# DETAIL SUMMARY SHEET

TITLE: Medical Therapy in Benign Prostate Hyperplasia: Full-Scale Trial

KEYWORDS: prostate, medical therapy, BPH

PRINCIPAL INVESTIGATOR: Schenkman, Noah LTC MC
ASSOCIATES: Rueda, Maria COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 31 January 1995

## STUDY OBJECTIVE

To determine the effectiveness of medical therapy (finasteride and/or doxazosin) to treat, delay or prevent the symptomatic progression of benign prostatic hyperplasia (BPH) and to assess differences over time between treatment groups. To investigate prognostic indicators and biologic parameters regarding response to therapy. To gain insight into biologic and physiologic natural history of prostate growth.

## TECHNICAL APPROACH

The study is multi-center, placebo-controlled, double-masked clinical trial in which patients who have been diagnosed with symptomatic BPH are randomly assigned to either of three drug treatment arms or a placebo control once all entrance criteria have been fulfilled. All patients are monitored closely and will undergo follow-up evaluation quarterly for efficacy, adverse events and overall mortality. The protocol was approved 5 May 1995 and addenda were approved 28 June 1995, 29 October 1996, 28 October 1997, 5 February 1998, 28 April 1998 and 20 July 2001.

## PRIOR AND CURRENT PROGRESS

Enrollment started December 1995 and ended January 1998. A total of 165 participants were randomized in the full-scale trial and 24 in the pilot study at WRAMC. Enrollment study wide is 3047. The following is a breakdown in status of the enrollees at WRAMC:
Pilot Study 24 subjects, 2 deaths, 9 other inactives. 4 subjects off both medications, 4 had progression of BPH, 2 developed prostate or bladder cancer.
Full Scale Trial 165 subjects, 5 deaths, 11 inactives. 17 off both medications, 2 off doxazosin only and 3 off finasteride only. 18 have developed prostate or bladder cancer.
In the last year the serious adverse events have been 2 joint replacements, 1 abdominal aortic aneurysm, 1 TIA, 3 TURPS, 2 cardiac incidents, 3 prostate cancers and 2 other cancers. The 2 deaths were from the aortic aneurysm and a cardiac incident. None were attributed to the study medications. Adverse events for the total study are not available at this time.
The inactive rate increased by 3 subjects, all for health reasons.
The full-scale trial will continue until 30 November 2001. The amendment dated 13 October 2000 provided an option to the subjects of remaining on the study medications until unblinding in April 2002.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 189. The total number enrolled study-wide is 3047.

## CONCLUSIONS

Baseline data has been presented at past American Urological Society meetings and will be presented at future meetings. Ancillary studies are being submitted for use of tissue accrued from the biopsy subset and after review of submissions these will be prioritized and approved. There are no conclusions to date.

Report Date: 24 June 2002 Work Unit # 2809

# DETAIL SUMMARY SHEET

TITLE: Multicenter Prospective Cohort Study to Evaluate the Safety and Effectiveness of the American Medical Systems (AMS) Ambicor ™ Inflatable Penile Prostheses

KEYWORDS: Ambicor, implant, prostheses

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 29 August 1995

STUDY OBJECTIVE
To evaluate the ability of the AMS penile prosthesis to provide an erection suitable for sexual intercourse (device function) as determined by PE and patients self report. Safety will be evaluated by measuring rates of complications and the occurrence of medical conditions associated with the device.

TECHNICAL APPROACH
After patients have made a decision to have an Ambicor ™ implant, they are informed about the study. Pre-study/screening lab work must be completed prior to surgery. After surgery, the patient cannot use the device for sexual intercourse for six weeks. Follow-up exams will be at 6 weeks, 6 months, 1 year, and 18 months post-implant. Patients will complete questionnaires at these visits. Complications, associated medical conditions, and other adverse effects will be followed for 18 months.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A literature search was done and there are no new results to report.

The number of subjects enrolled to the study since last APR at WRAMC is 1 and the total enrolled to date at WRAMC is 19. The total number enrolled study-wide is 140, if multi-site study. No adverse events have been reported. Enrollment is continuing.

CONCLUSIONS
None at this time.

Report Date: 28 September 2001 Work Unit # 2812

# DETAIL SUMMARY SHEET

TITLE: A Randomized, Double-Blind Comparative Trial of Bicalutamide (Casodex) vs. Placebo in Patients with Early Prostate Cancer

KEYWORDS: prostate cancer, Casodex

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Moul, Judd COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 28 November 1995

STUDY OBJECTIVE
The primary objective is to compare two years of adjuvant bicalutamide 150 mg monotherapy with placebo in terms of clinical progression and overall survival. The secondary objectives are to compare two years of adjuvant bicalutamide 150 mg monotherapy with placebo in terms of time to treatment failure and tolerability and to investigate the association of serial measurement of serum PSA and treatment outcome following two years of adjuvant bicalutamide therapy vs. placebo.

TECHNICAL APPROACH
This is a double-blind, randomized clinical trial evaluating bicalutamide (Casodex) 150 mg monotherapy vs. placebo as adjuvant therapy with early prostate cancer.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Enrollment was completed in 08/97. 3,292 patients were enrolled in this study nationwide. Twenty-four (24) patients were enrolled at WRAMC. We have received no new adverse reports from other sites. All serious and unexpected adverse events from WRAMC have been reported. Twenty-two (22) patients have completed the active part of the study and are being followed for survival and disease progression per protocol. Five (5) patients have started on second line therapy as a result of disease progression. One (1) patient has voluntarily withdrawn from the study and is lost to follow-up and one (1) patient was lost due to death.

CONCLUSIONS
Study is ongoing. No conclusions at this time.

Report Date: 02 January 2002

Work Unit # 2813

# DETAIL SUMMARY SHEET

TITLE: A Phase II Study to Determine the Effects of Finasteride and Flutamide on Patients with Rising PSAs Who Have Had Radical Prostatectomy, Radiation or Cryoblation Treatment for Localized Primary Prostate Cancer

KEYWORDS: finasteride, flutamide, prostate

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: McLeod, David COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 27 February 1996

STUDY OBJECTIVE

To determine in patients with Stage A, B, C, or D1 cancer of the prostate: 1) the likelihood of response in order to assess whether daily finasteride and daily flutamide should be advanced to other studies; 2) toxicity of daily finasteride with daily finasteride; and 3) the likelihood of potency maintenance in patients who were potent before the study.

TECHNICAL APPROACH

Patients will receive flutamide and finasteride daily and will be followed for two years. If the patient remains responsive to the study drugs, they will remain on the lower dose and be followed for five years. If a patient has three consecutive rises in the PSA, the flutamide will be increased to full dose and the patient will be followed for survival data for five years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Enrollment was completed in August 1997. All patients have completed the 2-year trial and are in the 5-year survival phase. Fourteen patients have continued to respond to low dose hormonal therapy, two patients have advanced to full dose hormonal therapy, eight patients have discontinued therapy due to inability to tolerate drug for expected side effects, twelve patients have discontinued due to progression with rising PSA or other medically required issue, one patient is lost to follow-up, and two patients died.

The number of subjects enrolled to the study since last APR at WRAMC is zero, and the total enrolled to date at WRAMC is 39. The total number enrolled study-wide is 200, if multi-site study.

CONCLUSIONS

Combination flutamide and finasteride appears to be well-tolerated and effective in short-term reduction of serum PSA for a majority of men with serologic recurrence after prior local therapy. Further study is needed to determine long-term efficacy of this combination low dose hormonal therapy.

Report Date: 21 November 2001 Work Unit # 2827

# DETAIL SUMMARY SHEET

TITLE: A Phase II Study to Determine the Effects of Flutamide on Patients with Rising PSAs Who Have Had Radical Prostatectomy, Radiation, or Cryoblation Treatment for Localized Primary Prostate Cancer

KEYWORDS: prostate, cancer, flutamide

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 28 January 1997

STUDY OBJECTIVE
To determine whether or not the use of low dose flutamide alone in patients with PSA – only recurrent prostate cancer should be advanced to the other studies; mainly a phase III randomized trial. This study is also designed to determine the toxicity of 250 mg flutamide and to determine the likelihood of those patients who were potent upon enrolling into the study to maintain their potency.

TECHNICAL APPROACH
Patients receive flutamide daily and are followed for two years.

PRIOR AND CURRENT PROGRESS
Twenty-nine patients have been enrolled in this study at WRAMC. All adverse events have been reported. A total of 14 patients have been dropped from the study: six patients for diarrhea (an expected side effect), four had progression of disease and were advanced to full hormonal therapy, one for anxiety, one died, and two moved. All patients have experienced gynecomastia (also an anticipated side effect). The fifteen patients remaining on the study are tolerating the drug and continue to respond. Seven patients have completed the two-year study period and will be followed for survival for five years per protocol. Average nadir for this study is 0.9 (2 of 20 reached <0.1) at three months. This study remains open to enrollment.

The number of subjects enrolled to the study since last APR at WRAMC is 7 and the total enrolled to date at WRAMC is 29.

CONCLUSIONS
None to date.

Report Date: 28 September 2001

Work Unit # 2832

# DETAIL SUMMARY SHEET

TITLE: Retrospective Study of CPDR Multicenter Database to Develop Nomograms Based on Sextant Positive Biopsy Cores, Gleason Sum and Pre-Biopsy PSA to Predict Pathologic Stage In Radical Prostatectomy Patients

KEYWORDS: prostate cancer, nomograms, pathology

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: McLeod, David COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 19 November 1997

## STUDY OBJECTIVE

The goal of this study is to develop predictive nomograms based on number of sextant biopsies positive for prostate cancer, highest biopsy Gleason sum, and pre-treatment (or pre-biopsy) PSA to predict final pathological stage variables in men who have undergone radical prostatectomy and whose data has been maintained in the CPDR database.

Secondary goals will be to recreate CPDR nomograms identical to the methodology of Partin et al using their three prognostic factors and to determine how well the Partin, et.al. nomograms predicted our CPDR cases.

## TECHNICAL APPROACH

The CPDR prostate cancer database is being used to perform the retrospective study. Patients who have had radical prostatectomy and who have the known preoperative variables of PSA value, biopsy Gleason sum (worst), clinical stage category, and sextant biopsy numbers of cores positive and post-operative pathologic stage are the study subjects. Multivariable logic regression is used to construct nomograms of these factors to predict final stage.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study has been completed. Using the CPDR database, 1506 patients met the study criteria and were used to develop nomograms based on pretreatment PSA level, prostate biopsy highest Gleason grade, and percent of prostate biopsies positive for cancer to predict final post-operative surgical stage. In multivariable analysis, PSA, Gleason grade, and percentage of biopsy cores positive for cancer were independent predictors of stage.

The number of subjects enrolled to the study since last APR at WRAMC is 1506 and the total enrolled to date at WRAMC is 1506. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

This WU# has been closed, but the study is continuing under WU# 01-2857-98b. A manuscript reporting the nomograms to predict final stage using PSA level, biopsy Gleason grade, and percent positive biopsy cores will be submitted to DCI for clearance for future publication under WU# 01-2857-98b.

Report Date: 2 October 2001 Work Unit # 2834

# DETAIL SUMMARY SHEET

TITLE: Retrospective Review of Three-Dimensional (3D) Computerized Tumor Volume Determination in Radical Prostatectomy Specimens From Black and White Patients

KEYWORDS: prostate, computerized, tumor volume

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: McLeod, David COL MC, Bauer John MAJ MC

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 24 November 1997

STUDY OBJECTIVE
The goal of this study is to compare tumor volume and characteristics of whole-mount radical prostatectomy specimens between black and white prostate cancer patients.

TECHNICAL APPROACH
This is a retrospective study of the CPDR Prostate Cancer Database examining the tumor volume measurements and tumor locations derived from our whole-mount radical prostatectomies performed by AFIP since April 1993.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The study is ongoing. Using the 280 3-D models reported in the October 2000 APR, we have now examined tumor location comparing black and white patients. These have been done in two ways: the 3-D model biopsy simulator and the actual tumor location in examination of the whole prostate mounts. In general, black and white men with clinically localized prostate cancer have similar tumor location, however, black patients have a slight propensity to have antior tumors. A manuscript to report these results is being prepared and will be submitted to DCI within 3 months.
The number of subjects enrolled to the study since last APR at WRAMC is 128 and the total enrolled to date at WRAMC is 310. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
This study is ongoing and additional models will be processed from the whole-mounted prostate under the Tissue Protocol WRAMC WU# 2871-98 to determine if tumor location between black and white men becomes even less pronounced as screening/early detection becomes more accepted in military health care.

Report Date: 2 October 2001 Work Unit # 2836

# DETAIL SUMMARY SHEET

TITLE: Three-Dimensional Ultrasonic Visualization Prostate Cancer

KEYWORDS: ultrasound, 3-D modeling, prostate

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: Spevak, Marianne; Zorn, Burkhardt LTC MC; McLeod, David COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 25 November 1997

## STUDY OBJECTIVE

The general objective is to validate current, biopsy-based results indicating that power spectrum analysis of radio-frequency (RF) ultrasonic echo signals from the prostate can distinguish cancerous from non-cancerous prostate tissue in three dimensions (3-D) over the full volume of the prostate. The specific objective is to correlate whole-mount histology obtained from radical prostatectomy specimens with 3-D tissue-typing images derived from RF echo signals obtained immediately prior to prostatectomy.

## TECHNICAL APPROACH

Patients enrolled in this study will already be scheduled for radical prostatectomy. These examinations will use standard TRUS instrumentation and procedures to acquire RF-echo signal data within a week of surgery. RF echo-signal data will be acquired using a currently available B&K Medical systems transrectal prostate scanner. This scanner will be interfaced with a data-acquisition computer using an interface module and digital hardware identical to current units currently utilized in Riverside Research Institutes' (RRI) collaborative study with MSKCC. The examining urologist will acquire RF data from approximately 20, evenly spaced, parallel transverse scan planes for each patient. Sectioning of prostatectomy specimens will be performed by pathologists at AFIP in planes corresponding to the scan planes of the pre-surgical TRUS examination. The pathologist will demonstrate lesion boundaries directly on digital images of each whole-mount section using available image-manipulation software. RRI will process RF data using RRIs current off-line method to generate color-encoded, volume renderings of the prostate. The volume renderings will be compared with whole-mount histology performed on excised glands. Comparisons will be made between computer-generated depictions of lesions and lesion properties determined from histology. This comparison will be based on tumor borders demarcated by the pathologist on images of each section and will assess tumor shape, volume, number of foci, etc. In addition, staging based on lesion features depicted by the 3-D images will be compared to clinical and pathological staging; relative performance will be expressed as ROC curves.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No patients have been enrolled on this protocol. Recruitment and screening continues for the protocol. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

None at this time.

Report Date: 02 January 2001 Work Unit # 2837

# DETAIL SUMMARY SHEET

TITLE: NPCP 2200: A Comparison of Leuprolide with Leuprolide and Flutamide in Previously Untreated Patients with Clinical Stage D2 Cancer of the Prostate

KEYWORDS: leuprolide, flutamide, prostate cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 26 February 1985

STUDY OBJECTIVE
To try to determine if the antiandrogen flutamide will increase the efficacy of leuprolide.

TECHNICAL APPROACH
Patients are randomized to receive leuprolide and flutamide or leuprolide and placebo. At the time of progression, the blind is broken, and patients not receiving flutamide will be given drug.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Although this study was permanently closed on 07/01/87, we continue to follow 2 patients for survival. One patients remains in leuprolide and remains stable without adverse events. The other patient is followed by phone contact and he is reported to be stable and without complaints.

CONCLUSIONS
None. The two patients will continue to be followed for survival.

Report Date: 02 January 2002

Work Unit # 2840-98

# DETAIL SUMMARY SHEET

TITLE: Agent Orange Exposure in Vietnam Veterans and the Risks of Prostate Cancer

KEYWORDS: agent orange, prostate, cancer, Vietnam

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 10 February 1998

## STUDY OBJECTIVE

Using a case control design, this study will evaluate the relationship between exposure to Agent Orange and other herbicides and the risk of prostate cancer among the Vietnam veterans who served in the Army. This study also will be able to determine risk based on the level of exposure to Agent Orange.

## TECHNICAL APPROACH

This is a case controlled study – Subjects will be identified through the CPDR multi-center database (those patients with prostate cancer) and a registry of Vietnam vets maintained at the DVA (controls). Once the study population is identified, a computer assisted telephone survey (CATI) will be conducted. A dietary questionnaire will be mailed to those individuals who complete the telephone survey.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Interviews began in August 1999. 962 have been completed, 214 cases, and 748 controls. 800 dietary questionnaires have been mailed to study participants, with 500 of the questionnaires completed and returned by the study participants. The associate investigator and the statistician are in the process of analyzing the data. No additional subjects will be enrolled until the data is evaluated.

## CONCLUSIONS

None at this time.

Report Date: 27 February 2002 Work Unit # 2841-98

# DETAIL SUMMARY SHEET

TTTLE: Association of 6q Allelic Losses in A Subset of Primary Human Prostate Cancer

KEYWORDS: prostate, cancer, chromosome

PRINCIPAL INVESTIGATOR: Dean, Robert LTC MC
ASSOCIATES: Moul, Judd COL MC; McLeod, David COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 10 February 1998

## STUDY OBJECTIVE

To examine human prostate tumor cell for loss of heterozygosity (LOH) on Chromosome 6q and its role as a possible marker of prostatic cancer recurrence after radical prostatectomy.

## TECHNICAL APPROACH

A retrospective review of 200 patients who underwent a radical prostatectomy at WRAMC between 1986 and 1994 will have prostatic tissue analyzed for loss of heterozygosity on chromosome 6q16.3-6q21. A retrospective analysis will be performed to uncover statistical correlations with LOH chromosome 6q and demographic information, path stage and grade as well as recurrence using the CPDR database (WU#2898/2894).

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Genomic DNA from tumor and normal prostate tissues from radical prostatectomy specimens of 38 patients were analyzed by polymerase chain reaction (PCR) for thirteen polymorphic microsatellite loci on 6q. Allelic losses of one or more polymorphic loci were detected in 11 of 38 patients (29%). Six of 11 tumors showing any 6q deletion were found to have allelic losses at D6S300 and D6S1056 loci.

## CONCLUSIONS

This study revealed a 1.5 megabase interval between D6S300 and D6S1056 at 6q16.3-6q21 as the minimal region of deletion, which may contain the putative tumor suppressor gene involved in prostate tumorigenesis. One of the tumor samples demonstrated homozygous deletion at a distal location D6S314 (6q23-6q24) suggesting another locus potentially associated with CaP. Although the relationship of 6q loss of heterozygosity (LOH) with various clinicopathologic variables, i.e., cancer recurrence or pathologic stage, did not reveal a statistically significant association, the risk of 6q LOH to non-organ confined (pT3) disease was five fold higher than for organ confined disease. An additional manuscript/abstract is being worked on at this time. It will be submitted to DCI for approval prior to submission.

Report Date: 06 August 2001

Work Unit # 2843

# DETAIL SUMMARY SHEET

TITLE: ECOG EST 1887: A Phase III Trial of Cystectomy Alone vs. Neoadjuvant M-VAC+Cystectomy in Patients with Locally Advanced Bladder Cancer

KEYWORDS: cisplatin, cystectomy, bladder cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 25 October 1988

## STUDY OBJECTIVE

To compare the survival in patients with locally advanced bladder cancer that are treated with cystectomy alone to those who are treated with M-VAC (methotrexate/vinblastine/adriamycin/cisplatin) followed by cystectomy in a randomized Phase III neoadjuvant trial, and to qualify the "tumor downstaging" effect of neoadjuvant M-VAC.

## TECHNICAL APPROACH

This is a randomized, multicenter, Phase III trial for patients with T2-T4a, N0, M0 transitional call carcinoma of the bladder with or without squamous differentiation. Patients are randomized to radical cystectomy or M-VAC plus radical cystectomy.

## PRIOR AND CURRENT PROGRESS

This protocol has been closed to enrollment since 1995. Since this is an ECOG study, we continue to follow patients for survival. One patient was currently being followed for survival, but at this time he is lost to follow-up. Since this is the only patient we were following, we are closing the study at this time.

## CONCLUSIONS

None at this time.

Report Date: 21 December 2001 Work Unit # 2843-98

# DETAIL SUMMARY SHEET

TTTLE: Statistical Modeling Using Pre-Operative Prognostic Variables in Predicting Extrascapsular Extension, Positive Margins and Outcome After Radical Prostatectomy for Prostate Cancer: Retrospective Study Using the CPDR Database

KEYWORDS: prostate, cancer, survival

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: C
SERVICE: Urology INITIAL APPROVAL DATE: 02 February 1998

STUDY OBJECTIVE
The objective of this study is to perform statistical analysis on a group of patients who have undergone radical prostatectomy for prostate cancer. The outcome of this analysis will establish the important preoperative variables that predict disease-free survival after surgery. These variables will then be used to develop a simple equation to predict outcomes after radical prostatectomy, capsular penetration and probability of positive margins.

TECHNICAL APPROACH
We will query the CPDR Database for those patients who underwent radical prostatectomies at WRAMC between 1985-1995. 573 patients and their data are currently available, only those that have accurate clinical follow-up and variable data will be included in this study. The variables that will be studied are: age, race, pre-treatment PSA, pre-treatment PAP, clinical stage, highest biopsy Gleason sum, highest biopsy glandular differentiation, and highest biopsy nuclear grade. A separate model that employs the number of positive biopsies in place of clinical stage will be performed. Cox proportional hazards model will be used to assess the simultaneous influence of possible predictor variables on the time to disease recurrence after radical prostatectomy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This was a study performed by Dr. John Bauer, a Urology resident, working with CPDR statisticians. Using preoperative clinical state, PSA Level, biopsy Gleason grade, and ethnicity, an equation was developed to predict pathologic stage and risk of recurrence.

The number of subjects enrolled to the study since last APR at WRAMC is zero, and the total enrolled to date at WRAMC is 573.

CONCLUSIONS
Pre-operative prognostic factors can be used to predict outcome after radical prostatectomy.

Report Date: 24 January 2002

Work Unit # 2846-98

# DETAIL SUMMARY SHEET

TITLE: Assisting the Predictive Accuracy of Prostate Cancer Prognostic Factors Using Traditional Statistical Methods and Artificial Neural Networks

KEYWORDS: prostate cancer, neural network analysis

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 12 March 2000

## STUDY OBJECTIVE

The purpose of this study is to assess the accuracy of prostate cancer prognostic factors in predicting response to therapy and post-therapy recurrence using traditional statistical methods and artificial neural networks.

## TECHNICAL APPROACH

Predicting natural history, therapy and post-therapy response require that natural history, therapy-dependent, and post-therapy prognostic factors be identified and assessed by a statistical model. Our group has examined both anatomic-cellular putative prognostic factors, for example, stage, grade, angiogenesis, Ki-67, and PSA and molecular-genetic putative prognostic factors, for instance, p53, bcl-2, and CD-34. The goal of this study is to assess these factors in terms of their utility as natural history, therapy and post-therapy prognostic factor using both traditional statistical methods, for example, logistic regression and proportional hazards methods, and artificial neural networks.

## PRIOR AND CURRENT PROGRESS

Preliminary neural network computer analysis was performed using data from the CPDR database. The key investigator, Dr. Harry Burke, moved to a new University during the study, which hampered the collaboration. As a result not definitive results were obtained and no conclusions are possible.

The number of subject enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2715.

## CONCLUSIONS

No conclusions were possible from this project. The key collaborator has now relocated to George Washington University here in Washington DC and a new protocol to continue the work started under this protocol is in the final approval stage at DCI. This will allow us to study the greatly expanded CPDR Triservice Multicenter National Prostate Research Database.

Report Date: 28 March 2002 Work Unit # 2852-98

# DETAIL SUMMARY SHEET

TITLE: Comparisons of Disease Progression in pT3 Prostate Cancer Receiving Adjuvant or Salvage Radiotherapy Following Radical Prostatectomy

KEYWORDS: pT3, prostate cancer, radiotherapy

PRINCIPAL INVESTIGATOR: Petroski, Rayford MAJ MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: C
SERVICE: Urology INITIAL APPROVAL DATE: 05 May 1998

## STUDY OBJECTIVE

To assess the outcomes of men undergoing external beam radiation therapy (XRT) after having radical prostatectomy (RP). To determine whether patients receiving radiation therapy prior to developing a detectable PSA post-operatively have a longer time to PSA recurrence that those patients receiving radiation therapy after developing a detectable PSA.

## TECHNICAL APPROACH

Retrospective chart review using the CPDR database (Work Unit Numbers 2857-98 and 2898). We will query to find those patients with pT3 disease who have been treated with XRT, assessing the outcome based on immediate (adjuvant) or delayed (salvage) radiotherapy.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of 619 (48 from NNMC and 571 from WRAMC) patients who underwent RP between January 1,1989 and June 30,1996 were identified through the WRAMC database. Of these, 239 were pT3 patients, 82 of whom received XRT. Data was available on 26 patients receiving adjuvant XRT and 35 patients receiving salvage XRT. Kaplan-Meier Product Limit Estimates (KMPL) were used to assess the time to biochemical (PSA) recurrence.

A literature search was performed and no new relevant articles were found. Several papers are in the process of being written, and will be submitted to DCI for approval when submitted for publication.

The number of subjects enrolled to the study since last APR at WRAMC is 61 and the total enrolled to date at WRAMC is 61. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

This study documents the response rate of adjuvant and salvage radiation after radical prostatectomy in our population and confirms other findings that Gleason scores, stage and post-prostatectomy PSA predicts response rates to radiation. This study also has new findings of the deleterious effect of radiation on post-prostatectomy incontinence.

Report Date: 27 November 2001

Work Unit # 2854-98

# DETAIL SUMMARY SHEET

TITLE: ECOG EST 3886: Randomized Phase III Evaluation of Hormonal Therapy vs. Observation in Patients with Stage D1 Adenocarcinoma of the Prostate Following Pelvic Lymphadenectomy and Radical Prostatectomy

KEYWORDS: zoladex, orchietectomy, adenocarcinoma/prostate

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 05 February 1998

STUDY OBJECTIVE
To determine the time to progression and survival in patients with histologically confirmed Stage D1 prostate cancer following radical prostatectomy and pelvic lymphadenectomy treated with no immediate hormonal therapy compared to those treated immediately with hormonal therapy.

TECHNICAL APPROACH
This is a multicenter randomized Phase III trial. Patients can be randomized to hormonal therapy or observation. Those patients randomized to observation may be registered to receive hormonal therapy if their disease progresses. All patients that progress on hormonal therapy will be followed off study drug. This study was closed to enrollment in 1993.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is zero and the total enrolled to date at WRAMC is one. The total number enrolled study-wide is 87. One patient was randomized to the hormone therapy (zoladex) arm of the study. We continue to follow this patient for survival. This is an ECOG protocol and ECOG no longer provides drug for this study. The patient has experienced no side effects.

CONCLUSIONS
None.

Report Date: 3 April 2002 Work Unit # 2857-98

# DETAIL SUMMARY SHEET

TITLE: Multicenter Prostate Cancer Database for the Center for Prostate Disease Research (CPDR) with Patterns of Care, Outcome and Prognostic Analysis

KEYWORDS: CPDR, prostate, cancer

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 26 May 1998
(Master Protocol)

STUDY OBJECTIVE

1) To maintain an accurate, reliable, secure relational database so as to demonstrate and coordinate longitudinal prostate cancer data collection as part of a multi-center DOD prostate cancer repository at USUHS.
2) To use the database to analyze patterns of care, prognostic factors and intermediate and long-term outcomes for prostate cancer.
3) The CPDR database is suitable for analyzing epidemiological features of prostate cancer and treatment efficacy, and monitoring the quality of life of our patients. Our long-term goal is to have 20,000 patients followed for 20 years.

TECHNICAL APPROACH

Our goals and objectives will be achieved by:

1) Retrospectively collecting standardized data on all prostate cancer patients treated at specified military medical centers during the period 1960-1997 (under WU#2898)
2) Prospectively by colleting standardized date on all prostate cancer patients treated at specified military centers beginning in 1998. Prospective data collection will be with consent.

On 5 December 2001 the following modifications were approved:

1) Approval to mail consent forms to those patients in the database under WU# 2898 who are unable to travel to WRAMC to consent to 2857-98 due to medical reasons or distance.
2) Approval to mail consent forms to Medical Health Care Beneficiaries who read about our work and want to participate in our database but do not live near WRAMC or any of the other participating sites.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

**Main protocol:** As of 1/2002, the database has archived 355,629 clinical records on 15,305 men. The number of TRUS, biopsy, medical history, primary staging, radical prostatectomy, and necropsy records were 17617, 16623, 12739, 11859, 5569, 2883, respectively. The order of treatment modality was as follows: radical prostatectomy (47.0%), external beam radiation (38.1%), brachytherapy (4.2%) and cryotherapy (0.2%). Mean number of follow-up visits per patient is presently 10.2. Dead/alive ratio is 24.3%. The ratio of death due to prostate cancer vs. death due to other cause is 22.9%. In the radical prostatectomy patients, one-year disease free survival is significantly improved since 1995 ($p < 0.05$).

The number of subjects enrolled to the study since last APR at WRAMC is 573 and the total enrolled to date at WRAMC is 5001. The total number enrolled study-wide is 15,305.

CONCLUSIONS: Radical prostatectomy is currently the most common treatment modality for military men with prostate cancer. More than two-thirds of patient mortality is due to non-prostate causes. Disease free survival in patients who underwent radical prostatectomy is improved.

**2857-98 (01, 21, 24) Retrospective Review of the Changing Face of Prostate Cancer in the 1990's**

STUDY OBJECTIVE **STATUS: O**

To explore trends in the military health-care experience with prostate cancer in the 1990's.

TECHNICAL APPROACH

**(01)** Our objectives will be achieved by collecting the following data for the calendar years 1990 thru 1997:

1. The number of patients diagnosed with prostate cancer between
2. Taking the number of new stage D patients (D1 and D2) diagnosed and dividing that number by total number of cases to provide a percentage of stage D per year.
3. The percentage of cases stratified by Gleason score (Sum): 2-4, 5-6, 7, 8-10.
4. The percentage of patients who were diagnosed with clinical T1c disease.
5. The number of patients with: Clinical stage A + B (T1 and T2); Clinical stage C (T3); Clinical stage D (Tang N + and/or M +)
6. The median age at diagnosis of the patients diagnosed
7. The percentage of patients having primary treatment: radical prostatectomy alone; radiation therapy (external and brachytherapy) alone; primary hormonal therapy alone; watchful waiting (no treatment); combination treatment (ie NHT + RP and NHT + XRT)
8. The mean, median, and range of PSA values at the time of diagnosis for patients diagnosed
9. The racial composition of patients

**(21)** The following additions were made with this amendment:

1) Include data from 1988-1998
2) Patients most recent follow-up date
3) Patients date of consent
4) If patient died, date of death and cause of death
5) Pathologic stage of patients undergoing radical prostatectomy: a) seminal vesicle status b)margin status c) capsule status d) gleason sum in radical prostatectomy specimen e) tumor grade in radical prostatectomy specimen f) volume of tumor in radical prostatectomy specimen g) number of tumors in radical prostatectomy specimen
6) Date of recurrence of prostate cancer after primary treatment
7) Tumor grade, on biopsy, or all patients diagnosed between 1988 and 1998

**(22)** The following additions were made with this amendment: To broaden the epidemiological data from the PSA era, which started in 1988, data from 1988 through 2000 will be used.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE .

A literature search was performed and no new relevant articles were found. The most important finding of this study is the significantly increased 5-year disease-specific survival, and overall survival, when comparing early, mid, and later PSA era patients. This parallels the work of Gilliland et al. who showed improved survival during a period of PSA screening in New Mexico using the SEER (Surveillance, Epidemiology and End Results Program of the National Cancer Institute) data. The SEER 5-year relative cancer survival rates for patients diagnosed in the following year groups: 1974-1976, 1980-1982, and 1989-1995 were 67%, 73%, and 92%; each of these changes were statistically significant ($p<0.05$). The critics of PSA testing argue that the benefits of screening are merely a result of lead-time bias. However, Etzioni et al. have determined that the improved survival is not due simply to PSA testing, even if one considers a very short lead-time of three years. Other factors such as increased public awareness and the increased use of hormone therapy in patients with metastatic disease may also be affecting survival and mortality. The percentage of deaths due to prostate cancer has decreased in the more recent year groups . This effect emphasizes the improved survival of patients diagnosed in more recent year groups, and suggests that patients diagnosed in the PSA era are more likely to live longer and die of other causes, rather than dying of prostate cancer. Unfortunately, only after the results of ongoing screening trials become validated, will the survival benefits of PSA testing become truly evident. We have demonstrated a significant stage migration. Most strikingly, the percentage of patients presenting with metastatic disease decreasing from 14.1% and 19.8% in 1988 and 1989, respectively, to 3.3 % in 1998. Before a survival benefit, a decrease in metastatic disease should

be evident; which is clearly being shown on a national level by several studies. These findings are more impressive in light of the fact that no curative treatment exists for patients with metastatic disease. Similarly, there was a statistically significant decrease in the incidence of clinical T3 and T4 disease. PSA-testing is reclassifying many of these tumors as T1c, which is associated with decreased recurrence rates, and increased disease-specific survival, when compared to other clinical stages. The percentage of tumors that have a clinical stage of T1a and T1b has decreased. This is most likely a result of medical management of benign prostatic hyperplasia (BPH) and the use of PSA screening. Patients with BPH, and an elevated PSA, will undergo a transrectal ultrasound (TRUS) and biopsy of the prostate, prior to transurethral resection of the prostate (TURP). This often results in the discovery of T1c cancers, and subsequent stage reclassification. A recent comprehensive review of TURP shows that the chance of discovering cancer on TURP is 6%, down from over 20% prior to the PSA era.

CONCLUSIONS

Data from this study indicates that during the PSA era there has been a statistically significant improvement in survival which is most likely secondary to a clinical stage migration from metastatic disease to disease that is amenable to curative treatment. In addition the chance of a patient dying of prostate cancer had decreased dramatically over the 13 years of the study (1988-2000). Continued follow-up of these patients is mandatory to further delineate the improvements in patient outcomes that have been achieved during the PSA-era. Comparing 1988-89, with 1998-99: The percentage of African American (AA) men with extracapsular extension (ECE) decreased from 100%, to 34.8% ($p=0.007$), and for Caucasians from 56.9%, to 43.2% ($p=.269$). The percentage of AA men with positive margins decreased from 100%, to 26.1% ($p<0.001$), and for Caucasians from 41.2%, to 27.0% ($p=0.021$). Mean age at surgery decreased from 66.6 to 59.9 years for AA ($p<0.001$), and from 65.9 to 61.1 years for Caucasians ($p<0.001$). Mean PSA level (1990 to 1999) decreased from 16.5 to 6.5 ng/dl for AA men ($p<0.001$), and from 10.1 to 6.6 ng/dl for Caucasians ($p<0.001$). We believe that the striking decrease in ECE and positive margins in AA men is due to PSA testing, coupled with improved public awareness, and equal access to care. It appears reasonable to recommend PSA testing in AA men, who have historically experienced poor outcomes from prostate cancer. This amendment has broad objective and the intention is to continue to track changes in trends.

**2857-98 (04) CPDR Multi-Center Prostate Cancer Database Retrospective Chart Review Study of PSA Recurrence in Black and White Radical Prostatectomy Patients with Emphasis on PSA Velocity During Recurrence** **STATUS: C**

STUDY OBJECTIVE

This protocol is in support of a project at the University of Virginia Medical Center whose primary goal was to evaluate whether upon PSA falure after RP (defined as PSA >0.2), African Americans experienced a more rapid increase in PSA. Because the University of Virginia researchers had insufficient numbers of patients to address the research question of whether there is a racial difference in PSA velocity during the time of disease progression in those men who are recurring after radical prostatectomy, they contacted the DoD-CPDR to collaborate.

TECHNICAL APPROACH

This will be a CPDR Multicenter Database retrospective review of all radical prostatectomy patients treated between 1988 and 1996 who have had disease progression defined by rising PSA values in the post-operative period. The key data is a listing of all PSA values and dates. In addition to this key retrospective PSA data, the following will also be obtained:

1) Date of RP (Surgery Date)
2) Pre-Biopsy and/or Pre-Treatment PSA value and date
3) Race: African American or Caucasia
4) Worst Radical Prostatectomy Path Gleason Sum: 2-10
5) Radical Prostatectomy Pathologic T Stage Group: T1a,b,c; T2a,b,c: T3a,b,c; T4A,b
6) Radical Prostatectomy Pathologic N Stage Group: N0 or N1,2,3
7) Clinical T Stage: T1a,b,c; T3a,b,c
8) Start Date of XRT (If applicable given as treatment for PSA only recurrence)
9) Dose of Radiation Therapy given
10) Start date of hormonal therapy (if applicable given as treatment for PSA only recurrence)

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A literature search was performed and no new relevant articles were found. Current progress: Our data suggested that PSA velocity at tumor recurrence was related to preoperative PSA on a continuous scale (p=0.063). However in our analysis there was little evidence that race had any effect on PSA velocity at tumor recurrence in our patient cohort (p=0.58). Likewise, little difference in PSA velocity was seen in regard to Gleason score (p=0.89) or pathological stage (p=0.23) in these patients. With data on 37 black men available for analysis it was likely that only large or extreme trends could be detected. Results could be used to estimate required sample sizes for assessment of less extreme trends.

CONCLUSIONS
Our data on tumor growth rate at recurrence, as reflected by PSA velocity kinetics, do not support the hypothesis that prostate tumors in black men are necessarily more aggressive due to enhanced growth. Further studies comparing the molecular and biological differences between prostate cancers in black and white males are needed to clarify reasons for the apparent differences in initial presentation, as compared to that at tumor recurrence in those two groups.

**2857-98 (05) Erectile Dysfunction in Patients with Prostate Cancer** **STATUS: O**
STUDY OBJECTIVE
Research on the side effects of prostate cancer treatment has been largely focused upon the absolute number of side effects (incontinence, impotence or bladder neck contracture) of surgery or radiation therapy, but has not evaluated the effectiveness of the treatments rendered. The widespread availability of prostheses, infection therapy and oral medications create new dilemmas in the proper treatment of post-prostate cancer erectile dysfunction. All of these treatments incur additional costs for the care of prostate cancer patients. In most health care reimbursement systems, these costs are not covered by the health care plans. Collection data on the pre- and post-treatment rates of erectile dysfunction and comparing the effectiveness of various treatments may give clinicians valuable insight into the most effective treatment options. This information will assist clinicians and patients in making these very important decisions, and the cost-effectiveness created by avoiding treatments with low likelihood of success wil provide increased resources throughout the health care system.

TECHNICAL APPROACH
The following data points will be collected and analyzed: Unique patient identifier, age, date of birth, diagnosis date, pathology, primary treatment, pre-treatment potency, follow-up dates, follow-up potency. Erectile Dysfunction (ED) treatment used, and effectiveness of the ED treatment.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A literature search was performed and no new relevant articles were found. Current progress: no significant difference was noted in the post treatment erectile function between patients treated with radical prostatectomy of external beam radiation (10% vs. 15%). Patients selecting watchful waiting have the lowest risk of erectile dysfunction. Clinical stage and race were significant predictors of the development of erectile dysfunction in the watchful waiting and external beam radiation treatment groups

CONCLUSIONS
Erectile dysfunction develops in greater that 80% of patients treated for prostate cancer. External beam radiation has the same risk for erectile dysfunction as radical prostatectomy. We want to assess Viagra and other treatments for impotence outcomes next

**2857-98 (06) The Impact of SocioEconomic Status on Clinical Parameters of Radical Prostatectomy Patients in an Equal Access Health Care System** **STATUS: C**
STUDY OBJECTIVE
Socioeconomic status has an established association with cancers of the breast, lung, cervix, and stomach. Divergent data on the association of socioeconomic status with prostate cancer has previously been reported. The goal of this study is to determine the impact of socioeconomic status on the clinical parameters and outcome of radical prostatectomy patients using military rank as a measure of socioeconomic status.

TECHNICAL APPROACH
The preoperative clinical parameters, pathological stage, and clinical surveillance of patients who underwent radical prostatectomy between January 1988 and August 1997 for localized (T1b-T2c) prostate cancer will be analyzed. Various parameters of the retired enlisted patients will be compared to the retired officer patients using military rank as a surrogate for socioeconomic status. The following data will be collected and analyzed: 1) Rank; 2) Ethnicity; 3) Age; 4) Date of Surgery; 5) Pre-biopsy and/or Pre-treatment PSA value; 6) Pre-treatment clinical stage and clinical TNM; 7) Pathologic stage and pathologic TNM; 8) PSA recurrence; 9) Date of PSA recurrence; 10) Clinical Recurrence; 11) Date of Clinical Recurrence; 12) Patient follow-up PSA and date

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE .
A literature search was performed and no new relevant articles were found. The percentage of patients with pathologic Gleason grade 7 or greater prostate cancer was higher in enlisted (45%) than in officer (37%) patients (p=0.021). However, no difference was found between these groups with respect to pathologic stage or biochemical recurrence rates. African Americans presented at a younger age (p=0.003), with a higher pretreatment PSA level (p=0.001), and demonstrated higher biochemical recurrence rates than other ethnic groups ( p=0.037). The Cox proportional hazards analysis showed that a lower socioeconomic status (SES) (p=0.010) but not African American race (p=0.696) was an independent predictor of a higher grade ( Gleason Grade 7 or higher) cancer. However, biochemical progression was more common in African American men ( p=0.035)and was not related to SES (p=0.883).

CONCLUSIONS
In an equal access health care system, patients of lower SES presented with higher grade prostate cancer at the time of RP. However, only African American race predicted biochemical progression after radical prostatectomy.

**2857-98 (07) The Utility of Computed Tomography and Bone Scan to Identify Residual Disease in Patients with an Elevated Serum Prostate Antigen After Radical Prostatectomy** **STATUS: O**

STUDY OBJECTIVE
Radical prostatectomy is a common treatment for localized prostate cancer. Approximately 15% of patients with pathologically localized prostate cacner and 50% of patients with locally extensive disease will have a rising prostate specific antigen (PSA) with-in 10 years. A bone scan and abdominopelvic CT are commonly performed to attempt to classify patients as locally recurrent disease vs. metastatic disease. This study will attempt to define the usefulness of these radiographic studies in this clinical situation. It is suspected that the studies are of low utility, and many patients may be spared the cost and inconvenience of having them performed.

TECHNICAL APPROACH
A retrospective analysis of the CPDR database will be performed identifying all patients who underwent RP between 1988 and 1998 who have suffered a PSA recurrence. The patients will be entered into a database and CHCS will be queried to determine if they underwent a bone scan and/or a CT. The results of those studies will be obtained and entered into a database. The likelihood of the radiographic studies being positive and the nature of the abnormality will be analyzed. The following data will be collected: 1) Name, Initials or SSN; 2) Ethnicity; 3) Age at diagnosis; 4) PSA at diagnosis; 5) Grade at diagnosis; 6) Clinical stage; 7) Date of surgery; 8) Pathologic stage; 9) Pathologic Grade; 10) Date of PSA recurrence; 11) PSA values and dates – most recent three prior to hormonal therapy; 12) Clinical recurrence; 13) Bone scan results: Positive, negative, equivocal – if positive site of abnormality; 14) CT scan results: Positive, negative, equivocal for local or distant Cap recurrence – if positive site of recurrence 15) Type of adjuvant therapy: XRT, HT, observation, other.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A literature search was performed and no new relevant articles were found. The multicenter data query is pending while the data holes are identified and filled.

CONCLUSIONS None at this time.

**2857-98 (08) Review of the Prostatic Intraepithelial Neoplasia (PIN) in Prostatectomy Specimens Pre-Treated with Neoadjuvant Hormonal Therapy (NHT)** **STATUS: O**

STUDY OBJECTIVE

The goal of this study is to: a) Determine how often PIN is present and how extensive it is in patients treated with hormonal therapy prior to surgery versus those treated with surgery alone; b) Compare the histologic features of the PIN to that of the coexisting invasive carcinoma, particularly with respect to the extent of treatment effect; c) determine, by immunohistochemistry, if PIN is still capable of progression utilizing the standard monoclonal antibody MIB-1 which is a routine marker of used proliferative activity d) evaluate the presence of neuroendocrine cells in the detectable carcinomas and PIN by immunohistochemistry (chromogranin, a standard routine non-investigational stain).

TECHNICAL APPROACH

Retrospective data on all AFIP-referred RP patients who were treated at WRAMC and NMCSD between 1993 and 1998 will be studied. The following information will be gathered: 1) AFIP Accession Number; 2) Race; 3) Age at diagnosis; 4) Start and stop date for hormonal therapy (LHRH start and stop dates, Antiandrogen start and stop dates, Orchiectomy date); 5) Surgery date; 6) Clinical Stage and TNM clinical stage: A,B,C; T1, T2, T3; 7) Total number of tumors in radical prostatectomy specimen; 8) Total tumor volume in radical prostatectomy specimen (as performed in WU#2834); 9) Pre-treatment PSA value (ng/ml); 10) Surgical Margin status: Positive, Negative; 11) Benign Glands in Margin: Yes, No; 12) Path Gleason Score: 2-10 (worst gleason sum in radical prostatectomy); 13) WHO differentiation: Well, Moderate, Poor; 14) Nuclear Grade: I, I-II, II-III, III; 15) PSA Recurrence: Yes, No; 16) Date PSA Recurrence; 17) Clinical Recurrence: Yes, No; 18) Date Clinical Recurrence; 19) Last Follow-up Date; 20) Last PSA Value and Date.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

In 9 of 26 prostatectomy specimens, PIN was detectable. In 2 patients, both PIN and tumor exhibited no appreciable proliferative activity, in three both tumor and PIN had a high proliferation rate. In three patients the tumor had a higher proliferation index than the PIN. Of the nine prostate specimens with PIN, only one retained high proliferative activity of the PIN following treatment, In six of the nine patients, tumor and PIN showed the same proliferation rate following androgen ablation . PIN was recognizable in three of the four patients with high proliferative activity in the tumors. But in two of these, the proliferative activity was low or minimal in the PIN. These findings may indicate a greater sensitivity of PIN to androgen blockade.

CONCLUSIONS None at this time.

**2857-98 (09) Adenocarcinoma of the Prostate: An Expensive Way to Die** **STATUS: C**

STUDY OBJECTIVE

PSA screening has resulted in a decrease in the incidence of prostate cancer. Despite this, many in the primary care community feel that PSA screening does little to enhance survival of the individual patient, and indeed results in unnecessary health care expenditures. Additionally, urologists report that PSA testing is not covered by 29% of insurance and managed health care plans. Approximately 113 American men die each day of metastatic adencarcinoma of the prostate. Death from prostate cancer is a prolonged process, resulting in extreme morbidity with consequent expenditures of health care resources. Aus, reviewing a large population of men dying or prostate cancer, reported that at least 41% underwent at least one transurethral resection, 17% had procedures to relive upper tract obstruction, with as many as 4 separate hospitalizations with an average of 37 days in the hospital prior to death.

TECHNICAL APPROACH

Information on patients that have died of prostate cancer in the last 24 months (1997-1998) will be required. Age at diagnosis, age at death, marital status, days hospitalized, procedures (surgeries) required, need and number of transfusions, etc. will be collected. The information is to be collected pertaining to the last year of life for each patient. After collection the number of days hospitalized, procedures, etc. will be priced according to US Medicare reimbursement rates.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A literature search was performed and no new relevant articles were found. A retrospective chart review was conducted at five military medical centers concerning 32 patients that died from prostate cancer over a two-year period. Results: the mean duration of metastatic disease was 3.4 years. The mean duration of hospitalization in the last year of life was 19 days. Seven patients required Channel TURP. Three patients required either percutaneous nephrostomies or stinting. The mean number of transfusions was 5.4. 18 patients underwent orchiectomy. 14 used LHRH agonists and eleven used anti-androgens. The mean cost of hospitalization, studies, outpatient visits to urologists, palliative procedures and hormonal therapy was $24,600. Comparatively, the cost of radical prostatectomy is $12,250 and three-dimensional conformal radiation therapy is $13,823.

CONCLUSIONS Our estimation of costs due to metastatic disease is at best an underestimation. Costs from hospice, outpatient medications, equipment, skilled nursing, transportation, loss of work by the patient or spouse, etc. were not obtainable. Death due to prostate cancer costs one billion dollars a year in the US.

**2857-98 (10) A Multi-Institutional Pooled Analysis of Prostate Cancer Stage Migration and Race** **STATUS: C**

STUDY OBJECTIVE
Previous analysis of prostate cancer stage migration in a Chicago area study demonstrated a decline in serum PSA in African-American patients from 1988 through 1995, but not in white patients during the same period; however, in this study, a clinical stage migration was seen in all patients. This study demonstrated a difference in stage migrations for whites versus African-Americans; in particular, the results suggest that he higher tumor cell burden for African-American patients during the earlier years of the analysis was likely related to socioeconomic factors and is likely to be ameliorated by widespread screening. A multi-institutional pooled analysis is being undertaken to determine whether a similar phenomenon occurred nationwide.

TECHNICAL APPROACH
The charts of patients with prostate cancer diagnosed from 1988 through 1997 will be reviewed. The information to be collected is as follows: (1) patient identifier; (2) clinical stage; (3) Pathological biopsy grade, age, pre-treatment PSA value; (4) Date of pre-treatment PSA; (5) Race.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE A literature search was performed and no new relevant articles were found. A multi-institutional database representing 6790 patients (1,417 African American, 5,373 white, diagnosed with non metastatic prostate cancer between 1988 and 1997 was constructed. PSA, stage, and grade data was tabulated by calendar year and region, and time trend analyses based on race and region were performed. There was an overall decline of PSA of 0.8% / year, which was significant ($p=0.0001$), with a faster rate of decline in African Americans (1.9%/yr) than for whites (0.65/yr). The odds ratio (OR) for a stage shift was 1.09, which was significant ($p<0.0001$), and this shift was greater in whites. The OR for the overall grade shift was 1.15, which was significant ($p=0.0001$). Although grade and PSA trends were similar for the different regions, there were significant regional differences in stage trends.

CONCLUSIONS Conclusions: the face of prostate cancer had changed over the past decade; i.e., the distributions of stage, grade, and PSA ( the most important prognosticators) have changed. In addition, the countenances of that face are different for whites and African-Americans. For African-Americans, that is good news: the stage, grade and PSA distributions are more favorable now than before. For whites, the trends are more complex and more dependent on region. These finding should be used for future clinical and health-policy decision in the screening and treatment of prostate cancer.

**2857-98 (11, 19) The Role of Pre-Treatment Serum Albumin to Predict Pathological Stage and Recurrence in Radical Prostatectomy Cases** **STATUS: C**

STUDY OBJECTIVE
The goal of this retrospective review of the CPDR Multicenter Prostate cancer Database as well as CHCS review for serum pretreatment albumin level is to determine if albumin is an independent prognostic marker of disease recurrence in a large cohort of radical prostatectomy patients.

TECHNICAL APPROACH

**(11)** A retrospective review of all patients who underwent a radical prostatectomy at WRAMC from 1 July 1990 until 31 December 1996 who had a pretreatment serum albumin within 6 months prior to surgery. The following data fields from the CPDR database will be used: diagnosis date, surgery date, age, race, pretreatment PSA, PAP, Testosterone, creatinine and alkaline phosphatase, pathologic stage, tumor grade, and recurrence date (if applicable), last follow-up date and follow-up status regarding cancer recurrence or no recurrence. Pretreatment albumin levels (which are not a standard data field in the CPDR database) will be obtained using CHCS. Logistical regression will be used to analyze the clinical utility of serum albumin to predict extra prostatic or non-organ-confined prostatic cancer. Life table and Kaplan-Meier survival methodology will be used to analyze the predictive ability of serum albumin for first PSA-recurrence of prostatic cancer after radical prostatectomy.
**(19)** This amendment allowed for the collection of one additional data point – date of death.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A literature search was performed and no new relevant articles were found. A retrospective review was performed on 354 patients who underwent radical prostatectomy at a tertiary facility from April, 1990 until 3 December, 1996 who had a pretreatment serum albumin within 6 months prior to surgery. Albumin levels were analyzed and compared to the values of standard prognostic factors to assess the ability of albumin to predict pathological stage and serological recurrence by PSA level after radical prostatectomy.

CONCLUSIONS

Albumin level was not of value in predicting serological disease recurrence, but interestingly was an independent prognostic factor in predicting risk of non organ- confined disease (T3or T3). Our data also showed that, as expected, grade and pretreatment PSA levels were independent predictors of pathological state. However, it is not of value in predicting serological disease recurrence following radical prostatectomy. Further study in other cohorts and in using additional analysis such as neural networks is indicated.

**2857-98 (13) Can Seminal Vesicle Invasion of CaP Predict Disease Progression** **STATUS: O**

STUDY OBJECTIVE

It has been observed that patients who have Seminal Vesicle (SV) invasion have a worse prognosis. This study will look at the extent of SV invasion within the CPDR database to see if the magnitude has any bearing on recurrence of disease within the patient population.

TECHNICAL APPROACH

The surgical pathology reports and PSA post radical prostatectomy data will be reviewed to determine how many people have SV invasion. After defining who has SV invasion, the data will be analyzed to determine if prostate cancer disease progression can be predicted according to the amount of SV invasion that is present.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A literature search was performed and no new relevant articles were found. 505 prostatectomies obtained from 1993-1999 sectioned at 2.2mm intervals were processed as whole-mounts. All tumors with pathologic stage 3b and 4 were reviewed for the pattern of SVI as reported by Ohori et al. The pattern and extent of SVI were correlated with tumor grade, surgical margin status, vascular invasion and post-operative biochemical progression. Three of 53 patients showed SVI along the ejaculatory ducts (type I). In 34 cases SVI occurred through the capsule with or without ejaculatory duct involvement (type II or type I and type II). In 16 cases, SVI occurred with our direct connections to the main tumor (type III) . Vascular invasion was observed in 22 patients. Surgical margins were positive in 35 patients. In 41 patients, extraprostatic extension was present in other sites that SVI. All but 4 patients had poorly differentiated elements which exceeded 25% of the tumor in 21 patients. In 12 patients, SVI did reach the attachment site. None of the patients with type I SVI recurred. 17 of 34 patients with type II or I and II, SVI recurred. 6 of these showed vascular invasion . Of the 16 patients with type III SVI, 6 recurred. 33% of patients with SVI up to the attachment site recurred vs. 46.3% extending into the free part of the SV. We found no difference with respect to progression considering the presence of vascular invasion.

CONCLUSIONS When SV is invaded from the prostate, progression appears to be lower than when it is due to capsular penetration of "metastatic" spread. We did not observe any difference in progression rate when comparing type II or I and III. To type III invasion.

**2857-98 (14) Time to NADIR of Serum Prostate Specific Antigen (PSA) for Patients with Prostate Cancer Treated with Radiotherapy** **STATUS: O**

STUDY OBJECTIVE

Several surrogate endpoints have been proposed for patients with CaP after definitive therapy because of the long natural history of the disease in most cases. PSA nadir values have received most attention, but no time to nadir has been proposed as a surrogate that better incorporates kinetics of PSA half-life. Some studies have reported that patients who ultimately fail therapy reach higher nadir values earlier than patients who remain without evidence of disease (NED); other reports state that time to nadir is not related to outcome.

TECHNICAL APPROACH

The following data from all curative radiotherapy patients (excluding: post prostatectomy; if hormonal therapy was provided before radiation therapy) between 1 January 1992 and 31 December 1994 will be analyzed: Age; Stage; Grade; PSA date and value closest to XRT therapy start date; All PSA values and date post-XRT; XRT treatment date (Dose, # fractions, # days, technique, date therapy was completed); date of last follow-up; Date of hormonal treatment; Date of death.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE A literature search was performed and no new relevant articles were found. The multicenter data query is pending while the data holes are identified and filled.

CONCLUSIONS None at this time.

**2857-98 (15) Prostate Specific Antigen (PSA) Response After Combined Temporary Androgen Suppression and External Beam Radiotherapy** **STATUS: O**

STUDY OBJECTIVE The American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus Panel definition for biochemical failure following external beam radiation therapy for prostate cancer is three consecutive increases in PSA. In recent years, temporary androgen suppression has been combined with external beam radiotherapy as curative therapy for localized prostate cancer. There is almost always an excellent PSA response with this combination, but it is not uncommon for the PSA to rise to some degree once androgen suppression has been stopped. The purpose of this study is to test the validity of the ASTRO definition of biochemical failure in patients treated with combined androgen suppression and radiotherapy.

TECHNICAL APPROACH

The following data from all patients treated with curative intent for prostate cancer with temporary androgen suppression and external beam therapy (excluding: post prostatectomy; if the androgen suppression therapy was > 12 months which does not exclude patients who subsequently fail and were then placed on long term hormonal therapy) between 1 January 1986 and 31 December 1996 will be analyzed: Age at Diagnosis; Clinical stage (AJCC); Tumor grade (Gleason score); PSA date and value prior to any therapy (pretreatment PSA); All PSA dates values after radiotherapy; Radiation therapy treatment (Total dose, Technique, # fractions and # of days, date therapy was started and completed); Dates and type of hormonal therapy(dates and dose, 1 or 3 months, of LHRH agonist injections; start and end dates of antiandrogen (flutamide, Casodex)); Date and site of clinical failure (ie. bone scan, re-biopsy, etc.); date and type of subsequent therapy; Date of last follow-up; Date of death.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A literature search was performed and no new relevant articles were found. The multicenter data query is pending while the data holes are identified and filled.

CONCLUSIONS None at this time.

**2857-98 (17) Race as a Prognostic Factor in Carcinoma of the Prostate Treated with Radiotherapy**

STUDY OBJECTIVE **STATUS: C**

Socioeconomic status (SESO) has been invoked as a potential reason for the fact that African-American (black) men have a higher incidence of prostate cancer (CaP), and decreased survival once diagnosed. Prior research from our group has revealed that black men have higher prostate-specific antigen (PSA) levels at diagnosis when corrected for SES, stage, grade, and age, and that this may be due to an increased tumor burden (defined as tumor volume on whole-organ prostatectomy mounts after radical prostatectomy). It remains unproven that race is a significant prognostic factor after definitive radiotherapy for CaP when corrections are applied for stage, grade, and age, with some authors finding a correlation, and some not finding such. Most recently, CPDR examined a large military population of radical prostatectomy patients and found that black race remained a significant adverse prognostic factor on multivariate analysis. Conversely, Fowler and Terrill studied Veteran's Administration patients who had received radiation or surgery for localized CaP and found no racial difference in survival. Military healthcare is an example of an equal-access system. All eligible patients are provided for, and care is provided at no cost to the patient. With respect to radiation therapy specifically, Department of Defense managed care contracts require that therapy be performed at one of the 11 Military Treatment (MTF'S) facilities with radiation therapy services rather than in the civilian sector whenever possible. Absent other insurance plans to which military-eligible members might belong, MTF's act as gatekeepers for civilian radiotherapy care of this population. As such, the military healthcare system provides an infrastructure that largely removes access and socioeconomic status from confounding clinical outcomes. When data from several geographically disparate MTF's are rigorously collected and analyzed, the effect would be to further remove those two variables from the analysis.

TECHNICAL APPROACH

The following data will be analyzed: Date of Birth; Race; Biopsy Gleason; Clinical Stage; Pretretment PSA; Date of CRT; Field Size; Total Dose; Number of Days; Number of Fractions; Technique; All follow-up PSA data; Date of Death; Cause of Death; Disease Status at Death. If applicable, the following data will also be included: Date of local failure; Date of Distant failure; Date of Surgery; type of Surgery; Pathological Stage; Pathological Gleason; Nodel Status.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A literature search was performed and no new relevant articles were found. The records of 1806 patients treated with definitive RT between 1973 and 2000 were reviewed. Records of patients receiving adjuvant hormonal therapy, or of patients receiving adjuvant or salvage RT post-operatively were excluded. Biochemical failure was calculated in over 96% of cases by the ASTRO criteria; patients with few follow-ups were considered to have biochemical failure with a PSA value more than tenfold greater than the previous value, or for any value >50.0 ng/ml. Median RT doses were similar. Median follow-up was 58.4 months. Results: There was no statistically significant difference in biochemical disease-free survival by race when patients were stratified by T-stage. African-American ethnicity conferred a negative prognosis for patients with lesions of biopsy grade Gleason 7 ($p$=0.004), but not for patients with Gleason 2-4 ($p$=0.14), Gleason 5-6 ($p$=0.79), or Gleason 8-10 ($p$=0.86) sums. Similarly, African American ethnicity conferred a negative prognosis only in patients presenting with PSA values between 20 and 50 ng/ml ($p$=0.01), but not in patients with presenting PSA values <4.0 ng/ml ($p$=0.84), between 4.0 and 10.0 ng/ml ($p$=0.71), between 10 and 20 ng/ml ($p$=0.75), or above 50 ng/ml ($p$=0.15). On multivariate analysis, ethnicity was not a statistically significant predictor of outcome.

CONCLUSIONS

In the equal-access healthcare system of the Department of Defense, race does not confer a consistent negative prognosis for patients treated with definitive RT for CaP. Race appears to confer a negative prognosis only in the subset of patients presenting with advanced disease.

**2857-98 (18) Age as a Prognostic Factor in Carcinoma of the Prostate Treated with Radiotherapy** **STATUS: C**

STUDY OBJECTIVE

Surgery is often preferred therapy for young patients with early stage prostate cancer (CaP) because of relatively higher rate of biochemical disease-free survival than after radiotherapy. Unfortunately, the effect of young age on outcome after therapy for CaP has been infrequently reported on the surgical literature and even less frequently reported in the radiotherapy literature. This protocol will document outcomes after radiotherapy in young men; specifically defined as </= 59 years old at diagnosis. Subset analysis will be reported for men </= 55 years, and if sufficient data exists, </= 50 years. These will be compared with surgical outcomes once patients are matched by pretreatment Gleason score, pretreatment clinical stage, and pretreatment PSA.

TECHNICAL APPROACH

The following data will be analyzed for this study: Date of Birth; race; Biopsy Gleason; Clinical Stage; Pretreatment PSA; Date of CRT; Field Size; Total Dose; Number of Days; Number of Fractions; Technique; All follow-up PSA data; Date of Death; Cause of Death; Disease Status at Death. If applicable, the following data will also be analyzed: Date of Local Failure; Date of Distant Failure; Date of Surgery; Type of Surgery; Pathological Stage; Pathological Gleason; Nodel Status

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A literature search was performed and no new relevant articles were found. Records of 1048 patients with T1 - T3 CaP treated with definitive RT between 1988 and 2000 were reviewed. Records of patients receiving adjuvant hormonal therapy, or of patients receiving adjuvant or salvage RT post-operatively were excluded. Biochemical failure was calculated by the ASTRO criteria. Median potential follow-up was 85.4 months as of 12/31/2001. Age did not affect bNED survival significantly when considered as < 60 versus >= 60 years ($p = 0.629$), when considered by decades ($p = 0.295$), or as a continuous variable (correlation coefficient $r = 0.011$, regression slope = 0.005 with $p = 0.726$ and $R^2 < 0.001$). Figure 1 shows bNED survival plotted against age, with the almost horizontal regression line superposed. When bNED survival was considered in multiple regression in order to reduce the effect of other variables, age was still not significant ($p = 0.486$). Other variables assessed for predictive capability were pre-treatment PSA ($p < 0.001$: significant), Gleason score ($p = 0.035$: significant), stage ($p = 0.356$: not significant), and RT dose ($p = 0.054$: not significant but suggestive).

CONCLUSIONS Age and bNED survival after RT for CaP are not related.

**2857-98 (20) Comparison of Disease Free Survival and Overall Survival of Patients with Carcinoma of the Prostate Treated with Radical Prostatectomy of Radiation Therapy in the PSA Era** **STATUS: O**

STUDY OBJECTIVE

The CPDR database is unique, in that it contains longitudinal data on patients treated for CaP from 1988-1999 in the military health care system at 10 different medical facilities. The goal of this protocol is to retrospectively examine patients that were primarily and solely treated with RP or XRT between 1988-1994. The subjects will be stratified for tumor grade, Gleason sum, clinical stage, ethnicity, age, pre-biopsy and/or pre-treatment PSA to determine if there is a statistically significant difference in DFS, development of distant metastatsis, and/or death from CaP between these two groups (XRT and RP) with a minimum of a 5 year follow-up (1995-1999). The study will also determine if margin status, in those patients that underwent RP, is an independent predictor for PSA recurrence, DFS, distant metatasis, and mortality. The study will examine the dose of radiation given to see if that is an independent predictor of DFS, distant metastasis or mortality. The results of this study will help inform clinicians on how to counsel patients, with various pre-treatment criteria, on which from of treatment, XRT or RP, may be best suited to them.

TECHNICAL APPROACH

This study will use multivariate Cox regression analysis to determine significant pre-treatment variables for both XRT and RP for DFS, development of distant metastasis, and death from CaP. Also. Regression analysis will be used to determine if age, medical history, margin status, pathologic stage, and particularly primary treatment (XRT or RP) is an independent predictor of DFS, development of distant metastasis, and death.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A literature search was performed and no new relevant articles were found. The multicenter data query is pending while the data holes are identified and filled. Meanwhile, manuscript with WRAMC data is being drafted.

CONCLUSIONS The study is ongoing and there are no conclusions at this time.

**2857-98 (23) Retrospective Review of Prostate Needle Biopsy Site to Predict Radical Prostatectomy Margin Status** **STATUS: O**

STUDY OBJECTIVE
Surgery is often preferred therapy for young patients with early stage prostate cancer (CaP) because of relatively higher rate of biochemical disease-free survival than after radiotherapy. Unfortunately, the effect of young age on outcome after therapy for CaP has been infrequently reported on the surgical literature and even less frequently reported in the radiotherapy literature. This protocol will document outcomes after radiotherapy in young men; specifically defined as </= 59 years old at diagnosis. Subset analysis will be reported for men </= 55 years, and if sufficient data exists, </= 50 years. These will be compared with surgical outcomes once patients are matched by pretreatment Gleason score, pretreatment clinical stage, and pretreatment PSA.

TECHNICAL APPROACH
Data will be analyzed for relationship's: between location of positive biopsy and location of positive margin on RP specimens, impact of nerve sparring and its relationship to positive biopsy location, margin status and number of biopsies, margin status and size of prostate gland, margin status and Gleason score and margin status and pre-tx PSA. Data will then be analyzed by a statistician using a univariate and multivariate regression analysis.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A literature search was performed and no new relevant articles were found.
The multicenter data query is pending while the data holes are identified and filled.

CONCLUSIONS
The study is ongoing and there are no conclusions at this time.

Report Date: 02 April 2001 Work Unit # 2858-98

# DETAIL SUMMARY SHEET

TITLE: An Ultrasound-Based System for Examination and Diagnosis of Prostate and Urinary Conditions – A Phase I Clinical Study

KEYWORDS: ultrasound, prostate cancer, transrectal, transurethral

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Spevak, Marianne CCRC

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 26 May 1998

## STUDY OBJECTIVE

The objective of this study is to evaluate the safety and efficacy of a new device called UROTECH in the detection of prostate cancer. The objective of this phase I study will be to compare whole-amount histology obtained from radical prostatectomy specimens with images derived from this device obtained prior to the prostatectomy.

## TECHNICAL APPROACH

Approximately fifty patients will be enrolled in this protocol. Patient will have standard of care TRUS and biopsy performed. Prior to surgery, patients will be studied with the UROTECH device. The device will carefully map the prostate through the utilization of transrectal and transurethral transducers to develop a preoperative map of designated areas of the prostate. After surgery, the whole amount of specimens prepared at AFIP with 3-D reconstruction will be compared to the images obtained with the UROTECH device.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 4 and the total enrolled to date at WRAMC is 4. Enrollment is continuing at this time. There has been some difficulty with the sponsor to obtain the urethral catheter, but this is expected to resolve shortly. There have been no adverse events to date.

## CONCLUSIONS

None at this time.

Report Date: 03 August 2001

Work Unit # 2858-98

# DETAIL SUMMARY SHEET

TITLE: An Ultrasound-Based System for Examination and Diagnosis of Prostate and Urinary Conditions – A Phase I Clinical Study

KEYWORDS: ultrasound, prostate cancer, transrectal, transurethral

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Spevak, Marianne CCRC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 26 May 1998

## STUDY OBJECTIVE

The objective of this study is to evaluate the safety and efficacy of a new device called UROTECH in the detection of prostate cancer. The objective of this phase I study will be to compare whole-amount histology obtained from radical prostatectomy specimens with images derived from this device obtained prior to the prostatectomy.

## TECHNICAL APPROACH

Approximately fifty patients will be enrolled in this protocol. Patient will have standard of care TRUS and biopsy performed. Prior to surgery, patients will be studied with the UROTECH device. The device will carefully map the prostate through the utilization of transrectal and transurethral transducers to develop a preoperative map of designated areas of the prostate. After surgery, the whole amount of specimens prepared at AFIP with 3-D reconstruction will be compared to the images obtained with the UROTECH device.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. This study and the contract have been terminated at this time. Two adverse events have been reported to DCI and USAMRMC: anxiety and moderate to severe pain.

## CONCLUSIONS

The device was unable to produce images that could be compared to the AFIP specimens. There were multiple concerns and problems with the equipment for this protocol. The contract for this protocol expired on 30 June 2001 and was not renewed.

Report Date: 28 November 2001 Work Unit # 2859-98

# DETAIL SUMMARY SHEET

TITLE: SWOG 8894: A Comparison of Bilateral Orchiectomy With or Without Flutamide for the Treatment of Patients with Histologically Confirmed Stage D2 Prostate Cancer

KEYWORDS: cancer, prostate, orchiectomy

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 05 February 1998

STUDY OBJECTIVE
To test the hypothesis that total androgen blockade (orchiectomy plus flutamide) may be better than orchiectomy alone.

TECHNICAL APPROACH
This is a prospective, randomized, double blind, placebo controlled study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is zero, and the total enrolled to date at WRAMC is 35. The total number enrolled study-wide is 1387. Two patients are currently followed for survival data. One is alive and well; the other is living with metastatic prostate cancer. This is a SWOG protocol and was closed to enrollment 15 September 1994.

CONCLUSIONS
The Combined Androgen Blockade (CAB) benefit is clinically negligible.

Report Date: 27 November 2001 Work Unit # 2861-98

# DETAIL SUMMARY SHEET

TITLE: ECOG P-Z887: A Phase I Study of Intravesical Tumor Necrosis Factor in the Treatment of Superficial Bladder Cancer

KEYWORDS: intravesical, tumor necrosis factor (TNF), bladder cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 05 February 1998

## STUDY OBJECTIVE

To determine: 1) safety of TNF instilled into the bladder as an intravesical form of therapy for superficial bladder cancer; 2) the scope and severity of toxicity of the TNF in patients with bladder cancer; 3) the dose limiting toxicities and maximum tolerated dose of TNF; 4) any systematic effects of the TNF on other organ systems and to determine systemic pharmacokinetics.

## TECHNICAL APPROACH

Three patients will be treated at each dose level (200-250 mcg.) Each patient will receive all treatments of TNF in a single dose level. If DLT is seen in more than one patient, an additional three patients will be entered at this dose level. If a total of three of these six patients exhibit a DLT, then dose escalation will end all subsequent patient will be entered at this dose level.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is zero, and the total enrolled to date at WRAMC is three. The total number enrolled study-wide is unavailable, if multi-site study. This study was closed by ECOG in 1991 due to poor accrual. We are following two patients for survival. Both show no evidence of disease. One patient has died.

## CONCLUSIONS

None at this time.

Report Date: 28 November 2001 Work Unit # 2864-98

# DETAIL SUMMARY SHEET

TITLE: ECOG EST 9887: A Phase III Trial of Treatment of Pathologic Stage C Carcinoma of the Prostate with Adjuvant Radiotherapy

KEYWORDS: prostate, cancer, adjuvant radiotherapy

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: McLeod, David COL MC

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 05 February 1998

STUDY OBJECTIVE
To compare in a randomized study, the disease-free survival rates in completely resected patients with pathologic Stage C (T3N0M0) carcinoma of the prostate assigned to be treated with adjuvant external beam radiotherapy to that in patients assigned to receive no adjuvant therapy. To assess the qualitative and quantitative toxicities of patients with pathologic Stage C carcinoma of the prostate when treated with eternal beam radiotherapy.

TECHNICAL APPROACH
After prostatectomy with pelvic lymphadenectomy and no evidence of regional lymph node or metastatic disease, the patient is randomized to receive adjuvant radiation therapy or no adjuvant therapy. All patients are off treatment 1 year after randomized or at disease progression.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is zero, and the total enrolled to date at WRAMC is four. The total number enrolled study-wide is unavailable. We are following four patients for survival. One of those patients continues to receive his routine clinical care at WRAMC; the other has moved to New Mexico and is contacted by telephone for survival information. Two patients have died. This is an ECOG protocol, and has been closed to enrollment since 1996 due to poor accrual nationwide.

CONCLUSIONS
None available at this time.

Report Date: 01 May 2002

Work Unit # 2867-98

# DETAIL SUMMARY SHEET

TITLE: Advanced Computer Algorithms for Assessing Prognostic and Treatment Variables in Prostate Cancer

KEYWORDS: prostate cancer algorithms

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 22 June 1998

STUDY OBJECTIVE
To ascertain whether patterns exist in the CPDR database at WRAMC that permit accurate diagnosis of the disease in a retrospective and subsequently prospective manner.

TECHNICAL APPROACH
Using specific variables, a number of artificial neural networks and fuzzy logic systems of artificial intelligence will attempt to find underlying patterns. Examples of these patterns are predicting stage given biopsy and clinical information and predicting recurrence given surgical pathology information

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The PI has decided to close the protocol even though the work was never started or completed.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
None. Data was never assembled; therefore, it could not be analyzed.

Report Date: 31 May 2002 Work Unit # 2871-98

# DETAIL SUMMARY SHEET

TITLE: Creation of a Tissue Library for the Molecular Biologic Study of Patients with Prostate Cancer

KEYWORDS: prostate, cancer, tissue

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 21 July 1998
MASTER PROTOCOL

STUDY OBJECTIVE

1) To create a tissue library for the molecular biologic study of prostate cancer.
2) Develop a primary and immortalized cell cultures from prostate cancer specimens.
3) Define the role that oncogenes and tumor suppressor genes play in the progression of prostate cancer.
4) Analyze genetic susceptibility factors for prostate cancer such as androgen receptor CAG repeats and HPCI mutations.
5) Correlate RNA and DNA molecular biology assays to the ongoing clinical database (WU # 2898). Create a 3-dimensional reconstruction of the prostate gland to assess the volume of all individual tumors, their locations within the prostate gland, their molecular pedigree and any extracapsular extension of the neoplasm.

TECHNICAL APPROACH

Samples will be obtained from TURP and radical prostatectomy specimens that will include cancerous and normal tissue. Informed consent will allow interoperative collection of blood, bone marrow, and tissue biopsies of the excised organ. It will allow the use of these specimens as well as the retrieval and use of their original archival biopsy tissue. Blood samples will be used to measure specific molecular markers and will be compared to clinical features. All samples will be processed by AFIP using SOP, and sent to the CPDR lab as required.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

MASTER PROTOCOL: There have been no adverse events under this protocol. A literature search has been performed and there are no new results to report. Since the last APR COL Moul replaced COL McLeod as the PI. On 30 July 2001, Addendum 11, the addition of DeWitt Army Community Hospital as a site, was approved. On 24 January 2002 Addendum 12 was approved. The original protocol called for primary prostate cultures to be infected with LXSN16E6E7, which contains the genes for human papilloma virus 16 E6 and E7 and a neomycin resistance gene. This amendment allows the use of telomerase in addition to LXSN16E6E7. Telomerase is an enzyme responsible for replicating telomeres, and is composed of an RNA subunit containing an integral catalytic subunit hTERT. Recent findings have directly implicated telomerase in the escape from cellular senescence. Indeed, transfection of hTERT into certain human cell types can itself induce immortalization. Interestingly, telomerase expression in human somatic cells does not induce any change associated with a transformed phenotype or an altered genetic phenotype. Primary cells transduced with the gene that delays replicative senescence will show increased growth potential without converting transformation nor showing karyological artifacts, thus making them ideal in vitro models for the study of prostate carcinogenesis.

The number of subjects enrolled to the study since last APR at WRAMC is 99 and the total enrolled to date at WRAMC is 370. (There are also 187 consented under WU#2894, bringing the total to 557 consented in the tissue bank.) The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS

None at this time.

**2871-98 (01)** **STATUS: O**

**Involves Spectral Karyotyping and collaboration with Dr. Kenneth Carter - no subtitle given for this amendment**

STUDY OBJECTIVE

Perform Spectral Karyotyping (SKY) analysis and identification of genetic alterations in prostate samples.

TECHNICAL APPROACH

Cultured cells will be harvested and fixed on glass slides using standard techniques for chromosome preparation. The prepared slides will be transferred to the International Genetics Associates (IGA), Inc. for SKY analysis. (International Genetics Association ( IGA) has changed its name to Avolon.)

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The molecular mechanisms underlying the pathogenesis of prostate cancer have remained poorly understood despite all the advances in modern day genomic technologies. More compelling is the problem of assigning clinical relevance to information gleaned from the application of such technologies. Only recently, are some of these platform technologies facilitating the search for putative candidate genes and drug targets that are not only better defined but are also better annotated and validated functionally in the context of the phenotypic profile of the disease. Currently, large data sets of information are obtained by high-throughput gene expression profiling (GEP) approaches, and gene signatures are assigned to specific disease entities. However, extensive functional validations need to be performed to narrow down the search and focus attention on a few key gene players. In other words, judiciously separating the wheat from the chaff.

Since the complexity of cancer genomes are beginning to be better elucidated by the application of high-through-put cutting edge technologies, Avalon Pharmaceuticals has designed, implemented, and validated a platform that combines the relative merits of such genomic technologies to accelerate the search for putative candidate genes in prostate cancer. The search has been improved several fold by combining GEP with very high-content and high resolution/high definition molecular cytogenetic tools such as Comparative Genomic Hybridization (CGH), Spectral Karyotyping (SKY) and custom arrays of genomic elements on a chip (array-CGH). Proprietary computational biology and bioinformatics tools have been devised to analyze profiles of genomic imbalances in prostate cancer against global GEP of clinical prostate cancer samples. In this study, we have profiled 10 primary prostate cancer cell lines obtained from the Center for Prostate Disease Research, in Rockville MD, through a collaboration with the Center, and 3 commercially available metastatic prostate cancer cell lines LNCaP, DU 145, and PC3. A comprehensive molecular cytogenetic analysis of these lines was done applying SKY, CGH, and array-CGH.

GEP data for about 85 clinical prostate cancer samples, 35 normal prostate tissues, and the 3 commercially available metastatic prostate cancer cell lines LNCaP, DU 145 and PC3 was analyzed using Avalon's corporate subscription to Genelogic's gene expression database, Gene Express™ to compute prostate cancer specific gene signature sets.

Using the above resources, chromosomal regions of interest in prostate cancer have been identified that are referenced as candidate regions that harbor putative oncogenes and tumor suppressor genes. The functional relevance and differential gene expression of genes in these regions of interest that also show relevant differential gene expression in clinical samples to help identify novel prostate cancer specific genes. Further, using the tools developed in house, the functional validation of novel prostate cancer genes identified by this process is under-way.

The CPDR will complement this study by participating in the validation of candidate prostate genes by verifying the relevance in samples of interest. The successful completion of this collaboration would result in the identification of new candidate prostate cancer genes that can be identified as good diagnostic and prognostic markers and also as novel drug targets at Avalon.

CONCLUSIONS

None at the time of this APR.

**2871-98 (03)** **STATUS: O**

**Genetic Susceptibility to Prostate Cancer**

STUDY OBJECTIVE

To test the hypothesis that genes which regulate the levels of circulating testosterone and the bioactivation of heterocyclic amines predispose individuals to the development of prostate cancer.

TECHNICAL APPROACH

Samples will be tested by Dr. Reynolds at the Center for Disease Control - National Institute of Occupational Safety and Health.

200 prostate cancer patients and 200 age-matched controls will be evaluated for CYP17 and NAT2 genotypes by combination of PCR gene amplification (normal/3' mismatch) and restriction enzyme digestion. Individual genotypes (CYP17 or NAT2) and combination genotypes (CYP17 and NAT2) will be analyzed for association with susceptibility or resistance to prostate cancer.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

184 samples from prostate cancer patients and 110 samples from controls have been analyzed for both NAT2 and CYP17 genotype. All 184 have been identified by race (Caucasian or African-American). Of the prostate cancer samples, approximately 57% of the African-American samples were found to be fast acetylators by NAT2 genotype analysis (59% expected) whereas 42% of the Caucasian-American samples were found to be fast acetylators by NAT2 genotype ( 40-50% expected). Approximately 71% of the African-American prostate cancer samples and 57% of the Caucasian-American samples were found to exhibit a "high expression" genotype for the CYP17 gene (45% of the general population are expected to exhibit a "high expression" genotype for CYP17). These data suggest that a "high expression" genotype for the CYP17 gene may be a risk factor for prostate cancer development in African - American individuals. A manuscript is in preparation.

CONCLUSIONS

None at the time of the APR.

**2871-98 (04)** **STATUS: O**

**The Polygenic Model of Prostate Cancer Risk Focusing on Polymorphisms in Multiple Genes Involved in Androgen Signaling**

STUDY OBJECTIVE

To validate the hypothesis that polymorphisms in multiple genes confers higher risk for prostate cancer than do polymorphism in one gene alone.

TECHNICAL APPROACH

We have proposed to study the polygenic model of prostate cancer risk focusing on polymorphisms in multiple genes involved in the androgen signaling. Known polymorphisms in four genes involved in the androgen metabolism/ signaling pathways were proposed for analysis including 1) CYP3A4, involved in the deactivation of testosterone; 2) SRD5a2, involved in the conversion of testosterone to dihydrotestosterone; 3) androgen receptor (AR), involved in the regulation of growth of the prostate; and 4) prostate specific antigen (PSA), a prostate specific gene. We will isolate genomic DNA from peripheral blood lymphocytes of normal and prostate cancer subjects using Qiagen tip 100 and manufacturer's protocol (Quiagen Inc. Valencia, CA). We will use this DNA in PCR reactions for genotyping CYP3A4, SRD5A2, PSA and AR using published procedures.

CYP3A4: variant detection (AA, AG and GG variants) will be performed by the TaqMan assay, originally described by Paris PL et al (Cancer Epidemiology Biomarkers & Prevention 8, 901-905, 1999). Specific primers used for amplification of this gene are 5'-ATCTGTAGGTGTGGCTTGTTGG-3' (forward primer) and 5'-TATCAGAAACTCAAGTGGAGGCAT-3' (reverse primer). Labeled primers for detecting the polymorphisms in this gene will be 5'-TTAAATCGCCTCTCTCTTGTCTCTAT-3' (FAM-labeled) and 5'-AATCGCCTCTCTCCTGCCCTTGTCTCTAT-3' (TET-labeled). SRD5A2: A49T and V89L variants will be

detected following the protocol by Jaffe JM et al (Cancer Research 60, 1626-1630, 2000). The primers used for amplification of this gene are 5'-GCAGCGGCCACCGGCGAGG-3' (forward primer) and 5'-AGCAGGGCAGTGCGCTGCACT-3' (reverse primer). Upon completion of thermocycling, the PCR product will be subjected to restriction enzyme fragment analysis. The V89L variant will be identified with Rsal and the A49T variant will be identified with Mwol.

PSA: gene variants (AA, AG, GG genotypes) will be identified as described by Xue et al (Cancer Research 60, 839-841, 2000). The polymorphic site in the prostate specific antigen will be amplified with forward primer (5'-TTGTATGAAGAATCGGGGATCGT-3') and reverse primer (5'-TCCCCCAGGAGCCCTAAATAAAA-3'). The PCR product will be digested with Nhel restriction enzyme for identifying the three genotypes.

The CAG repeat length of the AR gene will be estimated by Giovannucci E et al (Proc. Natl. Acad. Sci. USA 94, 3320-3323, 1997). The primers used for amplification of this polymorphic site are 5'-TCCAGAATCTGTTCCAGAGCGTGC-3' (forward primer) and 5'-GCTGTGAAGGTTGCTGTTCCTCAT-3' (reverse primer). These primers will be fluorescently labeled and the PCR product will be run on 310 genetic analyzer (Perkin Elmer Inc. Emeryville, CA) for accurate assessment of fragment length by automated fluorescence detection. Fluorescently labeled DNA markers will be used to construct a standard curve of peak arrival time. This standard curve will be used to calculate the CAG repeat length of the unknown DNA. The work will be done by Dr. Chilukauri Nageswararao (C.N. Rao) a member of the Center for Prostate Disease Research Team.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Analysis on the SRD582 gene has been completed. CYP384 gene has been optimized and studies will be initiated this year. Manuscript on SRD582 is in process.

CONCLUSIONS None at this time.

**2871-98 (05)** **STATUS: O**

**Involves collaboration with Dr. Anil Jaiswal - no subtitle given for this amendment**

STUDY OBJECTIVE

A role of quinone oxidoreductases (NQ01 and NQ02) and transcription factor Nrf2 in prostate cancer is hypothesized because of the role these enzymes have in prevention of oxidative stress and neoplasia.

TECHNICAL APPROACH

Presently prostate cancer is defined as the prostate tissue biopsy positive for cancer cells as determined by the pathologist. Blood DNAs in cancer group come from patients who have undergone radical prostatectomy specimens and these individuals have clinically significant prostate cancers. A valid concern was raised that there may be prostate cancer predisposing genetic changes in some control individuals without clinical symptoms. At present we are faced with this limitation in prostate cancer field as no such genetic marker has been defined that has tight association with prostate cancer predisposition. In fact the goals of this specific study to evaluate certain gene polymorphisms e.g., NQ01, NQ02 and Nrf2 that may be associated with increased risk of prostate cancer. Future implications of such studies are to define gene alterations that may have predisposing effects.

Exposure of cells to chemically induced oxidative stress is known to cause DNA and membrane damage, apoptotic cell death, degeneration of tissues, premature aging, mutagenicity and carcinogenicity. Accumulation of mutations in susceptible target tissue(s) due to oxidative stress is also suspected to play roles in age related cancers such as prostate cancer. NQO1 and NQO2 are cellular proteins that catalyze metabolic detoxification of chemicals (e.g. quinones and their derivatives) and protect the cells against oxidative stress [reviewed in V. Radjendirane, P. Joseph and Anil K. Jaiswal, Gene expression of DT-diaphorase (NQO1) in cancer cells. In "Oxidative Stress and Signal Transduction". Edited by Henry J. Forman and Enrique Cadenas. Publisher Chapman & Hall, New York. pp 441-475 (1997)]. This protection is due to prevention of superoxide formation. Nrf2 is a nuclear transcription factor that regulates the expression and induction of NQO1, NQO2 and other chemical detoxification enzymes. Since there is some evidence that oxidative stress may play a role in prostate cancer (W.H. Lee, R.A. Morton, J.I. Epstein, J.D. Brooks, P.A. Campbell, G.S.

Bova, W.S. Hsieh, W.B. Isaacs and W.G. Nelson. Cytidine methylation of regulatory sequences near the pi-class glutathione S-transferase gene accompanies human prostatic carcinogenesis. Proc. Natl. Acad. Sci USA 91: 11733-11737, 1994), we plan to analyze NQO1, NQO2 and Nrf2 gene loci for germiline polymorphisms/ mutations leading to the loss of decreased activity/expression of respective proteins. In the past, Dr. Anil Jaiswal's laboratory has cloned the genes encoding NQO1, NQO2 and Nrf2. They have all the necessary techniques and primers to amplify the various exons of these genes by PCR. The PCR amplified products will be analyzed by SSCP to detect mutations. The DNA samples detected with the mutations will be cloned and sequenced.

Dr. Anil Jaiswal in conjunction with the Center for Prostate Disease Research (CPDR) will analyze the polymorphism/ mutation of the above mentioned genes in the constitutional DNAs (peripheral blood lymphocyte derived) of age matched individuals with or without prostate cancer. For this purpose we will use an aliquot of pre-existing DNA from 200 prostate cancer patients which we have utilized for our in house research projects. Additionally, we will need DNA from age matched 200 individuals without prostate cancer. These samples will come from the approved protocol WU# 2801 entitled "Establishment of a Serum Bank for Future Detection of New Prostate Cancer Markers in Serum of Patients with Prostate Cancer, Benign Prostate Conditions, and No Prostate Disease."

The polymorphisms/ mutations occurring at high frequency will be correlated with data on clinico-pathologic features of the cancer patients in a blinded fashion. In the related *in vitro* experiments, these mutations will be created in the respective proteins by site directed mutagenesis. The mutant NQO1 and NQO2 proteins will be analyzed for its capacity to detoxify chemicals. Similarly, the mutant Nrf2 proteins will be analyzed for its capacity to regulate the expression of genes encoding NQO1 and NQO2.

Human genes encoding NQO1, NQO2 and Nrf2 have been cloned and sequenced in Dr. Jaiswal's laboratory (Biochemistry 30: 10647-10653, 1991; JBC 269: 14502-14508, 1994; PNAS 91: 9926-9930, 1994). The primers have been synthesized to amplify the individual exons of these genes by PCR. PCR products will be analyzed by SSCP procedures established in Dr. Srivastava's laboratory (J. Urol 154:414,1995). Allelic variations will be detected by observation of difference in the mobility of DNA bands on the gels. The polymorphic variants will be subcloned in pcDNA3 vector (Invitrogen, California) and sequenced with T7 primer.

In Vitro Experiments: The specific allelic variants from PCR/SSCP/Sequencing results will be selected to determine if these polymorphisms/mutations result in the loss of the function of the respective proteins. We plan to use site directed mutagenesis kit from Invitrogen to incorporate specific mutations by procedures as described in the Manual from the manufacturer. The wild type and mutated cDNAs will be transfected in eukaryotic cells to overexpress the cDNA derived wild type and mutant proteins in separate experiments. The effect of site directed mutagenesis in NQO1 and NQO2 proteins will be determined by NQO1 and NQO2 enzyme assays by procedures as previously described (JBC 263: 13572-13578, 1988; ABB 347: 221-228, 1997). The effect of mutations in Nrf2 will be determined by DNA-band shift assays by procedures as described (Oncogene 17: 3145-3156, 1998). These experiments will demonstrate that which of the specific mutations result in the loss of protein function.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

NAD(P)H: quinone oxidoreductase1 (NQO1) and NRH: quinone oxidoreductase2 (NQO2) are flavoproteins that protect against chemically induced redox cycling and oxidative stress. The DNA samples from normal and prostate cancer patients were analyzed for mutations in NQO1 and NQO2 genes. Six exons of NQO1 and seven exons of NQO2 were amplified by PCR, analyzed for mutations by SSCP and sequenced. Mutations were not detected in NQO1 gene. Several mutations were detected in exon 5 of the NQO2 gene from normal and cancer patients. However, these mutations did not change the amino acid in NQO2 protein. Analysis also did not reveal any specific mutation in NQO2 gene associated with cancer patients. Future analysis will be focused on identification of mutations in Nrf2, a nuclear protein that regulates expression of NQO1 and NQO2 genes.

CONCLUSIONS

None at the time of this APR.

**2871-98 (06)** **STATUS: C**

**Involves collaboration with Dr. Joy Ware and Dr. Catherine Dumur - no subtitle given for this amendment**

STUDY OBJECTIVE

Specimens sent to Dr. Ware will be used to test the hypothesis that quantitative and/or qualitative differences in the expression of WT1 (as a full length transcript or as the shorter sh-WT1) is a prognostic or diagnostic indicator in human prostate cancer.

TECHNICAL APPROACH

We will be working in collaboration with Joy L. Ware, Ph.D. and Catherine Dumur, Ph.D. We will be sending approximately 300 tissue specimens over a 3-year interval. The specimens will be frozen sections of benign and malignant prostate glands from each patient. Frozen sections 8 microns thick, attached to a glass slide will be sent. A minimum of 2 sections of tumor and 2 sections of benign tissue per case will be sent. Additional sections may be provided in some cases for immunohistochemistry with anti-WT1 antibodies. An adjacent H+E stained slide will be provided with each for orientation.

The frozen sections containing slides will be shipped on dry ice. On receipt in Dr. Ware's laboratory, specimens will be entered into a log and stored at –80 degrees C until analysis. Sections will be quickly stained with H+E and subjected to laser capture microdissection using an Arcturus Pixel II microdissector in Dr. Ware's laboratory. RNA will be extracted and analyzed by RT-PCR for expression of both the full length and the novel, truncated WT1 transcripts (recently described in Dr. Ware's laboratory). All material will be used up completely in this analysis.

Specimens will be sent without personal identifiers, and the CPDR ID system will remain in place to correlate presence of the WT1 transcripts or proteins with recurrence serum PSA after prostatectomy. CPDR is one of two sites contributing specimens to Dr. Ware's lab for this study. The other site is the Richmond McGuire VA Medical Center. Statistical analysis will be done. Dr. Hans Carter, Chair of VCU Biostatistics, will conduct the multivariate analysis for the data for significance. Dr. Moul will provide clinical interpretation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This project did not receive funding and was not pursued.

CONCLUSIONS

N/A

**2871-98 (07)** **STATUS: O**

**Novel Role of Candidate Tumor Suppressor Gene, ANX7 in Prostate Cancer**

STUDY OBJECTIVE

Drs. Meera Srivastava's and Harvey Pollard's laboratory has discovered *ANX7* as a candidate tumor suppressor gene using *ANX7* gene knockout model (Srivastava et al., PNAS, 96, 13783-13788, 1999). Their studies hypothesize that *ANX7* gene alterations by loss of expression or mutations are important in human cancers. Therefore, *ANX7* expression will be analyzed in matched normal and tumor tissues of prostate cancer patients using laser capture dissection (LCM) and quantitative RT-PCR. *ANX7* expression will be correlated with clinico-pathologic features e.g.: pathologic stage of tumor, age, grade, size, androgen receptor status and disease free survival after treatment. We will also analyze *ANX7* gene mutations using LOH and DNA sequence analysis.

Drs. Srivastava/ Pollard's laboratory has shown that reduced expression of the *ANX7* protein by semi-quantitative immunohistochemistry on tissue micro-arrays is significantly associated with prostate cancer progression. To further dissect if *ANX7* alteration is reflected at the transcription level, Drs. Srivastava and Pollard are proposing to collaborate with us to do a complementary study of *ANX7* expression at RNA level in human prostate cancer specimens available at CPDR. It is also possible that *ANX7* locus may have undergone deletions in tumors showing reduced or loss of *ANX7* expression. Therefore, DNA from prostate cancer specimens will also be analyzed for the loss of heterozygosity LOH,

a common phenomenon associated tumor suppressor locus. Biologic activity of *ANX7* and *ANX7* knockout mice experiments strongly suggest that *ANX7* is a candidate tumor suppressor gene.

Microdissected normal and tumor specimens derived from radical prostatectomy of 50 prostate cancer patients will be utilized for expression of *ANX7* gene. We anticipate that about a third of specimens will show reduced or loss of *ANX7* expression. The experiments proposed here are complementary in nature to their previous immunohistochemistry studies and justify the sample size. These experiments may be extended to specific subset of cancer specimens depending on the preliminary data generated here.

TECHNICAL APPROACH

RNA from tumor and normal cells of individual patients will be isolated by laser capture micro-dissection (LCM) of the matched normal and tumor tissues. RNA will be prepared by the RNAzol method. cDNA fragment representing the nucleotides 400-500 in the coding region of *ANX7* protein will be analyzed by Taqman procedure using the Perkin Elmer-7700 machine. Analysis of the expression of GAPDH using similar procedure will be serve as a control for the input RNA. Levels of *ANX7* in tissue specimens will be normalized with respect to GAPDH expression. Ratios of the *ANX7* expression between matched normal and tumor will be the final data for grouping specimens into reduced/loss of expression, elevated expression or no change. These data will be correlated to clinico-pathologic features of the tissue.

LOH is a possible mechanism for reduction in *ANX7* expression in tumors. To test the hypothesis that loss of *ANX7* gene expression can result from loss of heterozygocity, we will use 4 pairs of microsatellite markers located on or near the *ANX7* locus. We have selected these on the basis of radiation hybrid screening of chromosome 10 (data not shown). PCR will be performed on the genomic DNA samples derived from normal and tumor specimens. PCR products will be analyzed on Perkin Elmer 300 DNA Analyzer. LOH will be scored using the built in software in 310 DNA analyzer.

The data on *ANX7* expression or *ANX7* deletions will be correlated with various clinico-pathologic features and their statistical significance will be determined using univariate and multivariate analyses. Mr. Roger Connelly, the statistician with CPDR will perform these analyses.

The proposed experiments will be done in collaboration with Dr. Shiv Srivastava group at CPDR. PCRs will be performed by Drs. Meera Srivastava and Harvey Pollard group in the Department of Anatomy and Cell Biology at USUHS. Taqman and LOH assays will be performed at CPDR laboratory by a postdoctoral fellow from Drs. Meera Srivastava/Harvey Pollard group. To assist CPDR in this project we also want to add Dr. Meera Srivastava, Ph.D. and Dr. Harvey Pollard as collaborating personnel.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

LOH and ANX7 have been analyzed and we report that human tumor cell proliferation and colony formation are markedly reduced when the wild type ANX7 gene is transfected into two prostate call lines, LNCaP and DU145. Consistently, analysis of ANX7 protein expression in human prostate microarrays reveals a significantly higher rate of loss of ANX7 expression in metastatic and local recurrences of hormone refractory prostate cancer as compared with primary tumor ($p=0.0001$). Using four microsatellite markers at or near the ANX7 locus, and laser capture microdissected tumor cells, 35% of the twenty primary prostate tumors show LOH. The microsatellite marker closest to the ANX7 locus showed the highest rate of LOH, including one homozygous delegation.

CONCLUSIONS

We conclude that the ANX7 gene exhibits many biological and genetic properties expected of a TSG and may play a role in prostate cancer progression.

**2871-98 (08)** **STATUS: C**

**Profiling of Expressed Sequence Tags (ESTs) in Prostate Cancer**

STUDY OBJECTIVE

Dr. Zoltan Szallasi's laboratory has identified a set of putative oncogenes and tumor suppressor genes that are consistently misregulated in breast cancer. They would like to study the expression of these genes in other cancers including prostate cancer. Specifically, they will analyze expression of KIAA 193, S1002A, Cadherin E, Cadherin 5, and five more novel genes identified as expressed sequence tags (ESTs). An expressed sequence

tag (EST) is a small part (300-500 sequences) of a known or novel gene, made from cDNA, which can be used to fish the rest of the gene out. The lack of homology of an EST to DNA sequences in the DNA sequence database suggests a novel gene. ESTs in the context of this proposal are defined as novel cDNA sequences that were differentially expressed in breast cancer specimens. These novel cDNAs were initially identified by differential gene expression analysis of normal breast epithelial cells and breast cancer cells. Dr. Szallasi proposes to use preexisting RNA from prostate cancer tissues available in the CPDR laboratory.

TECHNICAL APPROACH
Dr. Zoltan Szallasi's laboratory will perform quantitative real time RT-PCR assays using Taqman procedure in their laboratory. They will analyze RNA from a total of 30 prostate cancer specimens: 15 representing organ confined (pathologic stage T2) and 15 representing non-organ confined (pathologic stage T3). They will compare the prostate cancer-gene expression data to other cancers such as breast cancer. On the basis of these preliminary data future proposal will be made. The exploratory nature of this project justifies the sample size. To assist CPDR in this project we also want to add Dr. Zoltan Szallasi, MD as collaborating personnel.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Funding was not granted and this project was not pursued.

CONCLUSIONS N/A

**2871-98 (09)** **STATUS: O**

**Evaluation of Glutamine Repeat Protein-1 (GRP-1) Expression in Prostate Cancer**

STUDY OBJECTIVE Glutamine repeat Protein-1 (GRP-1) is expressed most abundantly in mouse testis, expressed differentially in rat prostate tissues, and expressed in several human prostate cancer cell lines. As part of a project aimed at examining the role of GRP-1 in the regulation of androgen receptor activity and prostate cancer, we propose (1) to examine the expression of GRP-1 in benign and malignant human prostate tissues and (2) to analyze benign and malignant human prostate tissues for mutated GRP-1. Our working hypotheses are that GRP-1 expression is regulated by androgen and that there is an alteration of GRP-1 expression and/or function in the prostate that coincides with progression from benign to malignant tissue. Overall, we suggest that decreased expression or function of GRP-1 (or GRP-1-interacting proteins) plays a role in the progression of prostate cancer to androgen-independence. The major rationales for doing the work proposed are that (1) GRP-1 is expressed predominantly in androgen-responsive tissues and may be regulated by the androgen signaling pathway and (2) GRP-1 represses androgen receptor activity and alteration of GRP-1's expression and/or function (including that due to polymorphism of the polyglutamine/glutamine-rich region) may be associated causally with the progression of prostate cancer.

TECHNICAL APPROACH
Briefly, RNA from normal and tumor tissues (40 total RNA specimens; 20 each of normal and malignant prostate) will be analyzed for GRP-1 gene expression by quantitative reverse transcriptase-polymerase chain reaction analyses using the TaqMan procedure and ABI Prizm 7700 sequence detection system (PE Biosystems, Inc. documentation and protocols). The housekeeping genes GAPDH and epithelial cell-specific cytokeratin 18 will be analyzed simultaneously as controls. We will also examine DNA from the same benign and malignant human prostate tissues for expansion or deletion polymorphism within the polyglutamine/glutamine-rich domain of GRP-1. Genomic DNAs will be subjected to PCR amplification using GRP-1-specific primers that flank the histidine-glutamine-glutamine- and polyglutamine-rich domain (i.e., bp 280-624). Labeled PCR products will be resolved by electrophoresis in 3.5% native polyacrylamide gels and analyzed by automated DNA sequencing.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Funding was not granted, this project was never pursued.

CONCLUSIONS N/A

**2871-98 (10)** **STATUS: O**

**Expression of 1D10 Antigen in Prostate Cancer**

STUDY OBJECTIVE

We propose to do an initial screening of 1D10 antigen in prostate cancer. The Walter Reed group has demonstrated that patients with more aggressive CLL (i.e. those requiring significant numbers of treatment cycles for their disease or being refractory to fludarabine) have a higher frequency of being negative for this antigen, we will examine expression in three different grades of prostate cancer (well differentiated, moderately differentiated, and poorly differentiated). We will examine a total of 12-15 patients in each group as an initial pilot study. The primary objective of this pilot study is to prove the null hypothesis, that being that 1D10 positively occurs at a frequency below 26% in each of these subsets. Such a low frequency of expression would make further exploration of this antibody in prostate cancer of little interest. The 95% confidence interval is 0-26% if zero of ten evaluable patients are positive for this antigen. It may be anticipated that 2-5 samples may not be adequate for staining. Therefore, we will examine 12-15 samples from each group and effectively prove the null hypothesis if no patients in this group are positive for 1D10 antigen expression.

TECHNICAL APPROACH

The expression of 1D10 antigen on tumor tissues will be tested using the immunohistochemistry assay using standard methodology. This requires frozen sections from prostate tumors bearing the histology documented above. If any additional extra samples are not used they will be discarded at PDL. PDL will perform this immunohistochemical staining. The assay employed by PDL has been validated as part of the ongoing NHL phase I trial for which Walter Reed Army Medical Center is participating. To assist CPDR in this project, we also want to add Dr. Joseph M. Flynn as collaborating personnel.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Prostate tissue immunochemistry assay of ID10 has been performed. Initial data promises further characterization in additional specimens.

CONCLUSIONS

None at this time.

Report Date: 15 October 2002

Work Unit # 2873-98

# DETAIL SUMMARY SHEET

TITLE: Macroscopic and Microscopic Anatomy of the Arterial Supply to the Human Vas Deferens

KEYWORDS: arterial supply, vas deferens, cadaver

PRINCIPAL INVESTIGATOR: Dean, Robert LTC MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 11 August 1998

STUDY OBJECTIVE

The objective is to describe the gross and microscopic blood supply to the vas deferens. Additional objectives are to assess the variability of the arterial and venous structures, assess collateral blood supply to the vas deferens, and to utilize the new understanding of the vascular supply to improve operations on the spermatic cord, scrotal adnexa and vas deferens.

TECHNICAL APPROACH

The gross dissection of the deferential blood supply will be to perform gross dissection of cadaveric and autopsy specimens, dissection of en bloc spermatic cord specimens from formalin preserved and frozen cadavers, and microdissections on cadaveric specimens and autopsy specimens and recording of findings using photos and drawings. The microscopic description of deferential blood supply will include injection studies and will be performed using methylene blue injections of the deferential artery, internal iliac artery and internal spermatic artery. Specimens will also be injected with resin, and the surrounding soft tissue treated with acidifying agent to create casts of the deferential artery and its branches. Histologic sections will be performed using a dissecting microscope in the straight and convoluted portions of the vas deferens sagittally and transversely. These sections will be recorded using photomicrographs and drawings from medical illustrators. The donated cadavers/autopsy specimens will be provided by USUHS. The dissection will be conducted in the Anatomical Teaching Laboratory at USUHS.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There are no new literature findings to report. No amendments or modifications to the research study have been made since the last review. No adverse events have occurred and no patients have withdrawn from the study.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study.

CONCLUSIONS

None at this time.

Report Date: 12 August 2002 Work Unit # 2877-98

# DETAIL SUMMARY SHEET

TITLE: Study of the Safety and Effectiveness of the Mentor Saline-Filled Testicular Prosthesis

KEYWORDS: prosthesis, testicular, implant

PRINCIPAL INVESTIGATOR: McLeod, David G. COL MC
ASSOCIATES: Peppas, Dennis S. LTC MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 01 September 1998

## STUDY OBJECTIVE

The objectives of the study are to assess the safety and effectiveness of the Mentor saline-filled testicular prosthesis. We will also look at the rates of and time to explanation, revision and other re-surgery of the prosthesis.

## TECHNICAL APPROACH

This is a multi-center open label study. Patients are stratified into four groups: adult males who are missing their testicle at baseline; adult males who are not missing their testicle at baseline; pediatric males who are missing their testicles at baseline and pediatric males who are not missing their testicle at baseline. Patients will be followed for five years. Patients complete quality of life questionnaires and satisfaction questionnaires throughout the length of the study

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This is a multi-center study with 18 sites involved. To date 10 patients have been enrolled in this study at WRAMC. Since the last APR, 0 patients have been enrolled at WRAMC. The total number of subjects enrolled study-wide is 149. Enrollment has now ended (August 31, 1999). A total of 9 patients have received the testicular prosthesis at WRAMC. Patient 007 was sent TDY out of the country prior to surgery and dropped from the study. Patient 002 had his prosthesis explanted due to its displacement and migration and is withdrawn from the study. Patient 004 transferred to Korea and is lost to follow-up. Patient 008 has moved without a forwarding address and is not able to be located. He is lost to follow-up. All adverse events occurring at WRAMC have been reported. No serious adverse events have been reported from other sites.

## CONCLUSIONS:

None to date.

Report Date: 6 August 2001

Work Unit # 2879-99

# DETAIL SUMMARY SHEET

TITLE: A Randomized, Double-Blind Comparative Trial of Bicalutamide (CASODEX™) 150mg Monotherapy Versus Placebo in Patients with a Rising PSA After Radical Prostatectomy for Prostate Cancer

KEYWORDS: prostate, monotherapy, radical prostatectomy

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Moul, Judd COL MC, Spevak Marianne

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 06 October 1998

## STUDY OBJECTIVE

The primary objective is to compare Bicalutamide 150mg with placebo for time to treatment failure. Time to treatment failure is defined as the time from randomization to the time of any of the following: AE leading to withdrawal of randomized therapy, objective disease progression, imitation of systemic treatment or radiotherapy, or withdraw from the study for any reason. The secondary objective includes QOL questionnaire including a PSA anxiety questionnaire (MAX-PC) and the FACT-P instrument, time to objective disease progression, PSA response and time to PSA progression.

## TECHNICAL APPROACH

This is a multi-center, randomized, double-blind, parallel-group trial. The patients must be at least one year out from radical prostatectomy and have a rising PSA of greater than or equal to 0.4ng/ml confirmed on two occasions at least one week apart. Patients must have a negative CT scan and bone scan to be eligible for the study. Patients are then randomized to receive placebo or Bicalutamide 150mg. Patient visits are every twelve weeks. They may continue on the study for up to 2 years if they respond to treatment.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 118, if multi-site study. Enrollment ended from the sponsor. The two patients enrolled at out site are now off study. Since enrollment has ended and our patients have completed the study, we are now closing this study. There have been no new AEs reported.

## CONCLUSIONS

There are no conclusions at this time. Since this is a multi-center study, there are still patients receiving treatment and follow-up at other sites. The sponsor has not analyzed the data as yet. Results are pending.

Report Date: 6 September 2002 Work Unit # 2881-99

# DETAIL SUMMARY SHEET

TITLE: Retrospective Study of the CPDR Prostate Cancer Database to Perform Statistical Modeling Using Pre-Treatment Prognostic Variables in Predicting Disease Progression After Radiotherapy for Clinically Localized Prostate Cancer

KEYWORDS: statistical modeling, disease progression, prostate cancer

PRINCIPAL INVESTIGATOR: Moul, Judd W. COL MC
ASSOCIATES: Petroski, Raymond CPT MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 29 October 1998

## STUDY OBJECTIVE

1) To use pre-treatment prognostic variables to predict disease progression in men who have received primary external beam radiotherapy (XRT) using regression analysis. 2) To validate a regression equation to predict disease recurrence in men who have received primary external beam radiotherapy in localized prostate cancer.

## TECHNICAL APPROACH

Retrospective chart review using the CPDR database WU # 2857-98 of all men treated with XRT at WRAMC between 01 January 1989 and 30 June 1996. The Cox proportional hazards model will be used to assess the simultaneous influence of possible predictor variables on time to disease recurrence after treatment with XRT. Patients will be placed into age, race and stage matched cohorts, with 70% of the patients being used to create the model and the remaining 30% used to validate the model. A backward stepwise elimination procedure will be used to remove the covariates from the model if they are not correlated to the risk of recurrence.

## PRIOR AND CURRENT PROGRESS

No new literature findings to report. No adverse events. Study still in progress and has not been completed because of resident graduation and lack of Radiation Oncology support due to multiple Radiation Oncologists leaving active duty at WRAMC. We have now identified a Navy Radiation Oncologist (Dr. Robert Douglas) who will collaborate, and we plan to complete this protocol in the coming year. The number of subjects enrolled to the study since last APR at WRAMC is zero, and the total enrolled to date at WRAMC is zero.

## CONCLUSIONS

None at this time.

Report Date: 24 September 2001

Work Unit # 2883-99

# DETAIL SUMMARY SHEET

TITLE: Cyclosporine Treatment and the Effect on Post Vasovasostomy Semen Parameters in the Lewis Rat

KEYWORDS: vasectomy, anti-sperm antibodies,

PRINCIPAL INVESTIGATOR: Petroski, Rayford CPT MC
ASSOCIATES: Zubal, Irenna

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 3 November 1998

## STUDY OBJECTIVE

The study objective is to study the effect of cyclosporine therapy on semen parameters after vasovasotomy and the correlation between semen parameters and levels of antisperm antibodies. The hypothesis is that the use of cyclosporine in conjunction with vasovasostomy will improve semen parameters in previously vasectomized rat. This will be directly correlated with decrease in antisperm antibodies in cyclosporine treated rats.

## TECHNICAL APPROACH

Using Lewis rats, we will create individual groups to include treated and untreated rats with cyclosporine. These groups will initially undergo vasectomy and then vasovasotomy with pre and post semen analysis to determine improved semen parameters in the treated groups. These parameters will be correlated with pre and post antisperm serologic and semen antibodies. A control group of nonvasectomized rats will be used to determine baseline antisperm antibodies and normal semen parameters. These groups will consist of approximately ten animals. Cyclosporine will be dose at 10mg/kg in the treated groups.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Data acquisition is complete. Statistical analysis is complete. Scientific paper is being written and completion pending.

## CONCLUSIONS

Pending.

Report Date: 30 April 2002 Work Unit # 2887-99

# DETAIL SUMMARY SHEET

TITLE: ALZA Overactive Bladder Registry Design Document

KEYWORDS: overactive bladder, incontinence

PRINCIPAL INVESTIGATOR: Dean, Robert C. LTC MC
ASSOCIATES: Michael J. Danier CAPT MC USN

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 08 June 1999

## STUDY OBJECTIVE

The principle objective of this study is to provide comparative outcome information on the effectiveness, tolerability, and quality of life associated with different types of treatments, both pharmacological and behavioral for overactive bladder. The secondary objectives of this study are to: estimate resource utilization of health care services attributable to overactive bladder, provide physician-specific information to enhance patient care, and identify areas for possible further study.

## TECHNICAL APPROACH

Patients were enrolled from the urology clinic. Patients with a newly diagnosed overactive bladder or patients with overactive bladder that have been off medication for at least 12 months were asked to participate. Patients completed the required diaries and questionnaires and will be followed up via telephone calls from the Overactive Bladder Registry at 3 months, 6 months and then every 6 months until up to 3 years. Patients may withdraw at any time.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A literature review has been done and there are no new findings to report.
No adverse events have occurred.
Enrollment for the pilot portion of the program was completed and the patients are finishing up the follow-up portion of the data collection.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 15. The total number enrolled study-wide is 217, if multi-site study.

## CONCLUSIONS:

Pending at this time.

Report Date: 28 June 2002

Work Unit # 2888-99

# DETAIL SUMMARY SHEET

TITLE: An Open-Label, Randomized, Parallel Group Study Comparing the Perioperative Administration of Procrit (Epoetin Alfa) Plus Iron Versus Iron Alone in Patients Undergoing Radical Retropubic Prostatectomy for the Treatment of Prostate Cancer

KEYWORDS: prostate, cancer, procrit

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 22 June 1999

STUDY OBJECTIVE

1) To study the efficacy and safety of a 2-dose PROCIT regimen [on days –7(+ or – 2), and the day of surgery] in patients with prostate cancer undergoing radical prostatectomy, 2) to examine the number of patients who require allogenic blood transfusion, and 3) to examine the changes in hematological parameters.

TECHNICAL APPROACH

This is a pilot study being conducted only at WRAMC. It is a randomized, open-label, parallel group study. Following informed consent and evaluation for eligibility, patients will be randomized to receive either procrit plus iron or iron alone. The initial dose of procrit will be given subcutaneously seven days (+ or -2 days) prior to scheduled radical prostatectomy. They will receive a second dose of procrit following surgery in the recovery room. All patients will start an iron supplement after screening laboratory evaluations are obtained. Study laboratory evaluations will be performed on post-op day 1, on day of discharge from the hospital, and post-op week l and week 2. There have not been any addenda to the original protocol

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A literature search was performed and no new articles were found. The protocol is being closed by mutual consent of the PI and the sponsor.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 18. There have been no adverse events since the last APR was submitted.

CONCLUSIONS:

A paper is being written and will be submitted for approval when completed.

Report Date: May 21 2002

Work Unit # 2889-99

# DETAIL SUMMARY SHEET

TITLE: Radical Prostatectomy of Prostate Cancer Patients and Circulating Cancer Cell Test (CCCT)

KEYWORDS: Circulating, Cancer cell, Prostate

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 27 July 1999

STUDY OBJECTIVE
To use the CCCT to determine the incidence of circulating prostate cancer cells: 1) before, during and after radical prostatectomy (RRP) and correlate the positive detection of circulating cancer cells to disease recurrence after surgery 2) to correlate the relationship of CCCT and RRP surgical path findings.

TECHNICAL APPROACH
CCCT is drawn within ten days of RRP, within ten minutes after the prostate is removed, on discharge from WRAMC and 3-4 weeks after the surgery. These patients are followed every six months for two years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is 12 and the total enrolled to date at WRAMC is 23. The total number enrolled study-wide is N/A, if multi-site study.
No serious or adverse events have occurred at WRAMC or been reported by the sponsor. Nineteen (19) subjects are actively participating in the study. Three (3) subjects have voluntarily withdrawn from the study and one (1) subject has left the area, not able to be contacted, and is lost to follow-up.

CONCLUSIONS
None at this time.

Report Date: 15 October 2002

Work Unit # 2890-99

# DETAIL SUMMARY SHEET

TITLE: Creation of a Prospective and Retrospective Database of Patients Evaluated and Treated for Urinary Incontinence

KEYWORDS: database, incontinence, therapy

PRINCIPAL INVESTIGATOR: Dean, Robert LTC MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 11 August 1998

## STUDY OBJECTIVE

To collect retrospective and prospective data beginning 1 May, 1994 on all patients age 18 years or older, who present to the Urology and Urogynecology Clinics at Walter Reed Army Medical Center (WRAMC) with the complaint of urinary incontinence. To use this database to analyze treatment outcomes for patients undergoing therapy for urinary incontinence. Analysis will include, but not be limited to: risk of development of urinary incontinence; risk of recurrent incontinence; therapy failure; therapy durability; complications of therapy; efficacy of therapy based on type of incontinence; and comparison of therapy modalities.

## TECHNICAL APPROACH

To prospectively and retrospectively collect data on patients seen in the Urology and Urogynecology Clinics at WRAMC complaining of urinary incontinence. Information collected will be those data points included on Database Forms. The procedures and tests in this protocol are standard of care for urinary incontinence. Separate consent forms will be obtained for the standard of care testing and procedures. The only thing that is not standard of care is the questionnaires. Patients participating in the study will be given additional questionnaires to complete. The history, physical examination, and testing will be the same for the patients that participate on this study as it would for patients that do not participate on this study. All patients will undergo complete history and physical based on gender, American Urologic Association symptom score questionnaire, urodynamics study, quality of life questionnaire, three day voiding diary, one hour pad test, and sexual function questionnaire. Patients will then be offered therapy based on current practice. Patients will undergo repeat evaluation (the same type of an evaluation as the initial evaluation), 6 month, 1 year following onset of any therapy received. In addition to the initial and the 6 months to one-year evaluations any additional follow ups, examinations or tests, pertaining to incontinence, required throughout patient's treatment would be recorded.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There are no new literature findings to report. No amendments or modifications to the research study have been made since the last review. No adverse events have occurred and no patients have withdrawn from the study. The project has encountered computer problems; therefore no patients have been enrolled since the last review.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

None at this time.

Report Date: 6 September 2002 Work Unit # 2891-99

# DETAIL SUMMARY SHEET

TITLE: Ureteral Stenting After Distal Ureteroscopy and Stone Retrieval: A Prospective Randomized Study

KEYWORDS: kidney stone, stent, ureteral

PRINCIPAL INVESTIGATOR: Schenkman, Noah, LTC MC
ASSOCIATES: Spevak, Marianne

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 11 August 1998

STUDY OBJECTIVE Use a prospective, randomized, un-blinded protocol to determine if a difference can be demonstrated in postoperative pain, stone free rates, and complications between stented and unstented ureters after distal ureteroscopic removal of calculi.

TECHNICAL APPROACH Patients with distal ureteral calculi as demonstrated by intravenous pyeloureterogram (IVP) or non-contrast CT of the abdomen and pelvis, amenable to ureteroscopic removal, will be eligible to be enrolled in this study. Patients will be randomized to either the stented or unstented group. Preoperative lab evaluation will include UA, urine culture, and serum creatinine. Preoperatively the patient will fill out the pain questionnaire, which will serve as an internal control. The calculus will be removed using standard ureteroscopic techniques. An operative data sheet will be filled out at the time of surgery by the surgeon. Patients will complete the pain questionnaire and narcotic count sheet at 48 hours post-op, 7-10 days post-op and 4 weeks post-op. Those patients with ureteral stents in place will have them removed cystoscopically or via urethral string in the clinic on the 7-10 day post-op visit. The patient will return again at 4 weeks after the day of surgery. Post-op UA, urine culture, and serum creatinine will be checked at this time. An IVP will be checked to assess stone-free status and ureteral patency.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE A total of 113 patients with distal ureteral calculi amenable to ureteroscopic treatment were prospectively randomized into stented (53) and unstented (60) groups. Stones were managed with semi-rigid ureteroscopes with or without distal ureteral dilation and/or intracorporeal lithotripsy. Preoperative and postoperative pain questionnaires were obtained from each patient. Patients with stents had them removed 3 to 10 days postoperatively. Radiographic follow-up was performed postoperatively to assess stone-free rates and evidence of obstruction. Six patients randomized to the unstented group were withdrawn from the study after significant intraoperative ureteral trauma was recognized, including 3 ureteral perforations that required ureteral stent placement leaving 53 with stents and 54 without for analysis. Patients with stents had statistically significantly more postoperative flank pain ($p = 0.005$), bladder pain ($p < 0.001$), urinary symptoms ($p = 0.002$), overall pain ($p < 0.001$) and total narcotic use ($p < 0.001$) compared to the unstented group. Intraoperative ureteral dilation or intracorporeal lithotripsy did not statistically significantly affect postoperative pain or narcotic use in either group ($p > 0.05$ in all cases). Overall mean stone size in our study was 6.6 mm. There were 4 (7.4%) patients without stents who required postoperative readmission to the hospital secondary to flank pain. All patients (85%) who underwent imaging postoperatively were without evidence of obstruction or ureteral stricture on follow-up imaging (mean follow-up plus or minus standard deviation 1.8 +/- 1.5 months), and the stone-free rate was 99.1%. The number of subjects enrolled to the study since last APR at WRAMC is 21 and the total enrolled to date at WRAMC is 21. The total number enrolled study-wide is 113, if multi-site study.

CONCLUSIONS Uncomplicated ureteroscopy for distal ureteral calculi with or without intraoperative ureteral dilation can safely be performed without placement of a ureteral stent. Patients without stents had significantly less pain, fewer urinary symptoms and decreased narcotic use postoperatively. This study has been closed and the paper with the results has been published in the Journal of Urology.

Report Date: 2 January 2002

Work Unit # 2892-99

# DETAIL SUMMARY SHEET

TITLE: #VCL 1102-202: Phase II Study Evaluating the Safety and Efficacy of Neoadjuvant Leuvectin Immunotherapy for the Treatment of Prostate Cancer (and Amendment 1)

KEYWORDS: prostate, cancer, immunotherapy

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: McLeod, David COL MC; Esther, Thomas PA

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 31 August 1999
(Six-Month Review)

STUDY OBJECTIVE

Further investigate the toxicity and tolerability of Leuvectin in patients scheduled for retropubic prostatectomy. Evaluate the efficacy of Leuvectin in preventing or delaying manifestation of prostate cancer progression as demonstrated by biochemical failure or clinical recurrence.

TECHNICAL APPROACH

This is an open label multicenter study of patients with clinically organ confined prostate cancer. Patients will receive two injections of the IL-2 plasmid DNA-Lipid complex, followed by a prostatectomy. Patients will receive follow-up visits for 5 years with no additional treatment. An amendment (#2.02) was submitted and reviewed at the 6/21/ 00 HUC Meeting which changed the inclusion criteria to allow patients with a minimum PSA of > 5.0ng/ml to enroll in the study to adhere more closely to the standard of care.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Zero patients have been enrolled in this study at WRAMC. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 13, if multi-site study. No new adverse events have occurred at WRAMC or any other sites. This study has been closed for enrollment.

CONCLUSIONS:

None to date. No patients have been enrolled in this study.

Report Date: 24 June 2002 Work Unit # 2892-99

# DETAIL SUMMARY SHEET

TITLE: #VCL 1102-202: Phase II Study Evaluating the Safety and Efficacy of Neoadjuvant Leuvectin Immunotherapy for the Treatment of Prostate Cancer (and Amendment 1)

KEYWORDS: prostate, cancer, immunotherapy

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: McLeod, David COL MC; Esther, Thomas PA

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 31 August 1999
(Six-Month Review)

STUDY OBJECTIVE
Further investigate the toxicity and tolerability of Leuvectin in patients scheduled for retropubic prostatectomy. Evaluate the efficacy of Leuvectin in preventing or delaying manifestation of prostate cancer progression as demonstrated by biochemical failure or clinical recurrence.

TECHNICAL APPROACH
This is an open label multicenter study of patients with clinically organ confined prostate cancer. Patients will receive two injections of the IL-2 plasmid DNA-Lipid complex, followed by a prostatectomy. Patients will receive follow-up visits for 5 years with no additional treatment. An amendment (#2.02) was submitted and reviewed at the 6/21/ 00 HUC Meeting which changed the inclusion criteria to allow patients with a minimum PSA of > 5.0ng/ml to enroll in the study to adhere more closely to the standard of care.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Zero patients have been enrolled in this study at WRAMC. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 13, if multi-site study. No adverse events have occurred at WRAMC or any other site. This study is closed for enrollment.

CONCLUSIONS:
None to date. No patients have been enrolled in this study. The sponsor has suspended enrollment in this study. Based on these factors, the PI has decided to close this protocol.

Report Date: 2 January 2002

Work Unit # 2893-99

# DETAIL SUMMARY SHEET

TITLE: #VCL 1102-203: Phase II Study Evaluating the Safety and Efficacy of Neoadjuvant Leuvectin Immunotherapy for the Treatment of Prostate Cancer (and Amendment 1)

KEYWORDS: prostate, cancer, immunotherapy

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: McLeod, David COL MC; Esther, Thomas PA; Gallagher, Jane RN BSN

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 31 August 1999
(Six-month review)

## STUDY OBJECTIVE

Further investigate the toxicity and tolerability of Leuvectin in this patient population. Collect a database of PSA values, slope over time, and clinical assessment to estimate the effect of Leuvectin in preventing or delaying manifestations of prostate cancer progression.

## TECHNICAL APPROACH

This is an open label, multicenter study of patients with evidence of locally recurring prostate cancer following radiation therapy. Patients will receive up to three series of 2 intraprostatic injections of Leuvectin followed by one year of follow-up visits every three months with no additional treatment. An amendment (#1.02) was submitted and reviewed at the 6/21/00 HUC Meeting which changed the inclusion criteria to lower the PSA value from l0ng/ml over a 6 month period to > 1.0ng/ml over a 3 month period to adhere more closely with the standard of care. An amendment (#1.03) was submitted and reviewed at the 6/21/00 HUC Meeting that changed the exclusion criteria to include patients who have had neoadjuvant hormonal therapy prior to radiation therapy.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Four patients have been enrolled in this study at WRAMC. The number of subjects enrolled to the study since last APR at WRAMC is 4 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 23, if multi-site study. No new adverse events have occurred at WRAMC or any other site. This study is closed for enrollment.

## CONCLUSIONS

None to date.

Report Date: 24 June 2002 Work Unit # 2893-99

# DETAIL SUMMARY SHEET

TITLE: #VCL 1102-203: Phase II Study Evaluating the Safety and Efficacy of Neoadjuvant Leuvectin Immunotherapy for the Treatment of Prostate Cancer (and Amendment 1)

KEYWORDS: prostate, cancer, immunotherapy

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: McLeod, David COL MC; Esther, Thomas PA; Gallagher, Jane RN BSN

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 31 August 1999
(Six-month review)

STUDY OBJECTIVE
Further investigate the toxicity and tolerability of Leuvectin in this patient population. Collect a database of PSA values, slope over time, and clinical assessment to estimate the effect of Leuvectin in preventing or delaying manifestations of prostate cancer progression.

TECHNICAL APPROACH
This is an open label, multicenter study of patients with evidence of locally recurring prostate cancer following radiation therapy. Patients will receive up to three series of 2 intraprostatic injections of Leuvectin followed by one year of follow-up visits every three months with no additional treatment. An amendment (#1.02) was submitted and reviewed at the 6/21/00 HUC Meeting which changed the inclusion criteria to lower the PSA value from l0ng/ml over a 6 month period to > 1.0ng/ml over a 3 month period to adhere more closely with the standard of care. An amendment (#1.03) was submitted and reviewed at the 6/21/00 HUC Meeting that changed the exclusion criteria to include patients who have had neoadjuvant hormonal therapy prior to radiation therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Four patients have been enrolled in this study at WRAMC. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 23, if multi-site study. No new adverse events have occurred at WRAMC or any other site. This study is closed for enrollment.

CONCLUSIONS
None to date.

Report Date: 26 August 2002

Work Unit # 2894-99

# DETAIL SUMMARY SHEET

TITLE: Database of Urinary Stone Patients

KEYWORDS: database, kidney stone, outcomes

PRINCIPAL INVESTIGATOR: Schenkman, Noah LTC MC
ASSOCIATES: Spevak, Marianne CCRC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 07 September 1999

## STUDY OBJECTIVE

The goals of this study are to accumulate long-term data on all kidney stone formers in our clinic. This information will be used to provide needed epidemiologic information on urolithiasis. The information provided will answer questions such as the impact of kidney stones on military readiness, effectiveness of medical treatment regimens and the true recurrence rate of kidney stones in the modern era. With the exception of the completion of patient questionnaires, all other testing, procedures, and patient history are standard of care.

## TECHNICAL APPROACH

Male and female patients with confirmed urinary stone disease by either radiographic imagining or passage of calculi will be included in this study. Patients that do not have confirmed stone disease by either of those two methods will be excluded. A clinical suspicion of stone disease does not warrant inclusion - it must be confirmed urinary stone disease. After the diagnosis of urolithiasis is made, the patients will be given information about the database. The patients will then be asked to sign an informed consent if they wish to participate. An initial evaluation will include a complete history and focused physical examination. The patient will be asked to fill out the stone database questionnaire. The following results will be recorded, if available: initial laboratory work including serum electrolytes, uric acid, calcium, phosphorus and parathyroid hormone; stone analysis; and radiographic and imaging exams; twenty-four hour urine analysis. The patient's clinical course and condition will dictate follow up. Data of each follow-up, including surgical procedures, will be recorded.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 84 and the total enrolled to date at WRAMC is 136. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

None at this time.

Report Date: 5 August 2002

Work Unit # 00-3002

# DETAIL SUMMARY SHEET

TITLE: Noninvasive Screening for Coronary Artery Disease Using A Digital Electronic Stethoscope

PRINCIPAL INVESTIGATOR: Popa, Christian MAJ MC
ASSOCIATES: Taylor, Allen LTC MC; Gorman, Patrick LTC MC

DEPARTMENT: Surgery
SERVICE: Critical Care Medicine

STATUS: O
INITIAL APPROVAL DATE: 1 August 2000

STUDY OBJECTIVE Primary objective: To define the relationship between digital electronic stethoscope signals and the presence of angiographic coronary artery disease. Secondary objective: To numerically evaluate the presence of angiographically proven CAD stenosis with the output from the DES.

TECHNICAL APPROACH: Methodology: sonographers blinded to all clinical data will perform heart sound recordings. Immediately prior to cardiac catheterization (in either the cardiac catheterization lab or in the Cardiology Short Stay Observation Center) a foam acoustic chamber will be placed on the subject's chest using the xyphoid process as a reference mark. The purpose of this device is to standardize sound acquisition with the DES and dampen extraneous sounds. The acoustic chamber contains *nine* recording positions that correspond to the following anatomic locations: $RSB_1$, $RSB_2$, $RSB_3$, $LSB_1$, $LSB_2$, $LSB_3$, $S_1$, $S_2$, $S_3$. Once the acoustic chamber has been correctly placed on the subject, the digital electronic stethoscope will be placed at each listening position, the acoustic chamber lid closed, and 20 seconds of sound data collected. Recordings will be made with the subject in a semi-recumbent position at 30 degrees. A simultaneous EKG will be taken for integration into the sonospectrographic recording. It is anticipated that the entire data set acquisition will take approximately 15 minutes per patient. Following data collection, elective coronary angiography will proceed as planned. Data Collection: Following informed consent, a cardiac history will be collected for the purpose of descriptive reporting. Supine blood pressure will be measured using an automated blood pressure cuff. Sonographic data will be collected as described above using the nine designated listening positions of the acoustic chamber with 20-second recordings at each position. Left and right coronary cineangiograms will be obtained at the discretion of the angiographer. Sample Size/Data Analysis: Endpoints: Coronary angiographic data will be analyzed by Dr. Gorman without knowledge of the DES data. The primary variable of interest is the worst angiographic stenosis in a major epicardial coronary artery measured with an automated edge detection system for quantitative coronary angiographic analysis. Signal data from DES will be forwarded to Randy Ford, PhD at SonoMedica for analysis. Signal data are stored as electronic files on Write Once Read Many (WORM) un-re-writable CDROMs that will provide a permanent record of the acoustic data. Copies of these unalterable CDROMs will be coded and provided to WRAMC as a record of the acoustic tests to assure that there is no bias in the correlation of the data comparison between angio and acoustic records. Patient confidentiality will be preserved by labeling each study with an anonymous identifier (study enrollment number). The optimal measurement from DES for correlation with coronary angiography is unknown. Two values will be used: 1) The threshold presenting signal, and 2) The maximal observed acoustic frequency. Signal data results will be provided to the PI for further analysis as described below. Secondary analysis: Agreement between the two methods (angiography and DES) will be further described using ROC curve analysis. An ROC curve will be constructed for the sensitivity and specificity of the diagnosis of angiographic stenosis by DES.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE There has been no new published literature concerning this technology that would impact this study. We applied for and received a CRDA July 2001. We have currently studied 56 patients and are conducting an interim analysis of our results to assess the accuracy of the digital stethoscope and the quality of our data collection prior to enrolling additional patients. We hope to have that completed early in the fall. The number of subjects enrolled to the study since last APR at WRAMC is 56 and the total enrolled to date at WRAMC is 56.

CONCLUSIONS No conclusions to report at present.

Report Date: 2 May 2002

Work Unit # 01-30001

# DETAIL SUMMARY SHEET

TITLE: Remote Management of the Critically Ill Patient Via Telecommunication

PRINCIPAL INVESTIGATOR: Popa, Christian MAJ, MC
ASSOCIATES: Thomas Fitzpatrick, COL, MC, and Thomas T Carmody, MAJ, MC

DEPARTMENT: Surgery
SERVICE: Critical Care Medicine

STATUS: O
INITIAL APPROVAL DATE: 14 June 2001

STUDY OBJECTIVE
1. Primary Objective: To demonstrate the feasibility of providing consultative services on critically ill patients from a remote site by specialty trained intensivists using telecommunication equipment. While the greatest potential application of providing consultative services via telecommunication will be at smaller community hospitals which do not employ critical care medicine physicians, we will test the system at an academic medical center (Walter Reed AMC Thoracic Intensive Care Unit) utilizing a critically ill patient population which does not receive routine consultative critical care services.
2. Secondary Objectives: a) To describe the clinical outcomes in critically ill patients who have received consultative services from a remote site by specialty trained intensivists using telecommunication equipment. b) To describe provider (nurse and physician) ratings of various aspects of remote monitoring using telemedicine, e.g., perceived value, level of comfort, satisfaction, and perceived quality of care.

TECHNICAL APPROACH This is a prospective trial that investigates the feasibility of providing critical care consultation using the Visicu system at some distance from the intensive care unit. The cohort consists of 300 post-operative patients convalescing in the Cardiothoracic ICU. The remote consultative service will be operational from 7 AM to 7 PM during the workweek. On a daily basis, an intensivist will make remote "morning rounds" on the patients from the monitoring station in conjunction with Cardiothoracic Surgery service morning rounds and offer management suggestions. He will then periodically reevaluate the patients as their medical condition dictates and be available by pager for additional management questions or issues from the surgeons. Intensivist, bedside nurse, surgical house staff, and attending surgeon satisfaction with and other responses to the remote monitoring system will be assessed using questionnaires. Technical data such as ease of establishing videoconferencing with the patient rooms, ability to visualize the patient, the infusion pumps and the ventilator and ability to contact the bedside nurse will also be tracked on a daily basis. Given the novelty of the equipment, the primary focus of this investigation will be to determine the feasibility and potential usefulness of remote intensive care management

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE Since receiving approval from DCI, the protocol underwent review and approval at HSSRB, Fort Detrick. It then received final approval 12 Feb 2002. Since then, a retrospective chart review of the previous 200 Cardiothoracic ICU admissions has been completed to establish a control group for clinical outcome measurements. This has been completed and we are currently installing the last required piece of equipment in the electronic ICU, a CIS terminal for access to the electronic medical record. We expect to begin enrolling patients next week. Additionally, a related protocol involving remote consultation on ICU patients at Fort Belvoir has been submitted and is currently undergoing CIC review. A similar project to establish a telemedicine ICU link to Guam utilizing Visicu equipment is underway at Tripler Army Medical Center. There have been no recent literature developments which impact on either study design or patient safety. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

CONCLUSIONS Ongoing study; no conclusions to date regarding feasibility of implementation in military facilities.

Report Date: 8 May 2002 Work Unit # 3000

# DETAIL SUMMARY SHEET

TITLE: Characterization of the Cytokines Mediating Different Phases of Inflammation Following Controlled Abdominal Trauma

KEYWORDS: cytokine, tumor necrosis factor, interleukins, abdominal trauma, inflammation, hemicolectomy and inguinal hernia

PRINCIPAL INVESTIGATOR: Blanchard, Jeremy MAJ MC
ASSOCIATES: Armstrong, John, LTC, MC, Ling, Geoffrey, LTC, MC, Hadro, Neal, MAJ, MC, Maniscalco-Theberge, Mary, COL, MC, Otchi, Daniel, COL (ret), MC, Calkins, M. MD

DEPARTMENT: Surgery
SERVICE: Critical Care Medicine

STATUS: C
INITIAL APPROVAL DATE: 29 July 1997

## STUDY OBJECTIVE

The objective of this study is to characterize the serum levels of several inflammatory cytokines at serial time points after controlled abdominal trauma. Our hypotheses are:
1. Following traumatic injury to bowel, proinflammatory cytokines (TNF-a, interleukin-1B, and interleukin-6) are released at specific times after injury.
2. Subsequent to the initial inflammatory response, anti-inflammatory cytokines (interleukin-10 and interleukin-1 receptor antagonist) are released.
3. A percentage of elective preoperative patients have elevated cytokine levels at baseline (as per our addendum, approved 8 April 1999).

## TECHNICAL APPROACH

We are conducting a prospective controlled observational study. Thirty consenting adult patients will receive an elective hemicolectomy and thirty consenting adults will receive a laparoscopic inguinal hernia repair. 3 ml blood samples will be collected in heparinized blood collection tubes: preoperatively, 15, 30 minutes, and 1, 1.5, 2, 4, 6, 8, 12, 24, 96 (only hemicolectomy have a 96 hour time point) hours after hernia incision and hemicolectomy. The samples are centrifuged and the supernatant drawn off and frozen at -70°C. Serum levels of the proinflammatory cytokines, a-TNF, IL-1B, and IL-6, and anti-inflammatory cytokines, IL-10 and IL-1 receptor antagonist are quantified using electrochemiluminescence (ECM) assays. All excess blood collected from study a participant is discarded. An addendum was approved to allow the 96-hour blood sample in the hemicolectomy patients and CBCs in both groups of patients.

We also are working on the addendum study (approved 8 April 1999) looking at preoperative cytokine levels. One hundred consecutive APPC pre-operative patients, already having their blood drawn, were enrolled to evaluate their a-TNF, IL-I beta, IL-6, IL-10 and IL-1 receptor antagonist levels prior to their surgery. We collected a 3 ml sample of blood and processed it as above.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Unfortunately, review of the data shows too small of numbers to make significant conclusions. As well, the assay to ascertain cytokine levels was adapted during the study and the values are varied between the assays and thus limit the conclusions that can be made from this study. Lastly, the challenge in successful recruiting of patients to this study has made further enrollment unreasonable. Review of the literature shows no new studies that would have bearing on the results or methodology of this study.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 20 (one was dropped from the study because of the missing consent form.)

CONCLUSIONS

In conclusion, the cytokine comparison of the pro-inflammatory cytokines (TNF, IL-1B, and IL-6) shows a heightened response of IL-6 to hemicolectomies. However, the significance of this by itself is minimal and is already represented in the literature. The inability to evaluate the anti-inflammatory cytokines secondary to assay change, and the lack of response, makes the original hypothesis unlikely and the value of this study is minimized. The TNF is physiologically zero in both group and the IL-1 beta is mildly elevated in both groups.

In the addendum study, although 100 patients were enrolled, only 30 had their samples partially processed prior to a freezer breaking and the remaining samples thawing and being lost for analysis. Thus, the results have been presented in the past for these preliminary results, but the study was not continued because of this set back. No new publications have been submitted over the last year.

Report Date: 21 August 2002 Work Unit # 3002-99

# DETAIL SUMMARY SHEET

TITLE: Characterization of the Cytokines Mediating Different Phases of Inflammation Following Controlled Head Trauma

KEYWORDS: cytokines, transphenoidal hypophysectormy, temporal lobectomy

PRINCIPAL INVESTIGATOR: Popa, Christian MAJ MC
ASSOCIATES: Calkins, Mark MAJ MC; Ling, Geoffrey LTC MC; Blanchard, Jeremy, MAJ MC; Fitzpatrick, Thomas COL MC

DEPARTMENT: Surgery
SERVICE: Critical Care Medicine

STATUS: O
INITIAL APPROVAL DATE: 27 October 1998

## STUDY OBJECTIVE

To characterize the serum and cerebrospinal fluid level of several inflammatory Cytokines at serial time points following controlled head trauma. We hypothesize that both pro-inflammatory and anti-inflammatory cytokines are released.

## TECHNICAL APPROACH

Transphenoidal hypophysectomy patients, acoustic neuroma surgery patients, and patients undergoing temporal lobectomy for refractory seizures will serve as controls and surgical models of head trauma, respectively. There have been no addenda to this protocol.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

We have previously enrolled and collected data on a total of four subjects, all of who underwent transphenoidal hypophysectomy with lumbar drain placement. These four patients did well and there were no study related adverse effects. We have analyzed this data for TNF-a, IL-1, and Il-6 by chemiluminescence and noted a rise in CSF TNF-a as well as a bimodal elevation of CSF IL-6 that was mirrored by a smaller rise in blood IL-6. A dural tear complicated one of the cases. The others were not. The greater elevation in CSF-cytokine levels suggests that the brain is not a protected site as previously thought. Though these procedures were extradural and did not violate brain parenchyma (minus the one dural tear), the brain did mount an inflammatory response. We feel this is an important finding and plan to recruit several additional patients before publishing. We have not been able to recruit patients for the temporal lobectomy arm of the study. We plan to concentrate on transphenoidal hypophysectomy and acoustic neuroma patients. We have not recruited additional patients within the last year, but are continuing our efforts and would like to recruit several additional patients in order to be able to publish a case series. There have not been any significant developments, findings, or publications that would warrant modification of this protocol.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

We would like to extend this protocol for an additional year in order to recruit additional patients.

Report Date: 4 January 2002

Work Unit # 01-32003

# DETAIL SUMMARY SHEET

TITLE: Palatal Sclerotherapy with Sotradecol as a Treatment for Obstructive Sleep Apnea Syndrome

KEYWORDS: Sclerotherapy, sleep apnea, Sodium Tetradecyl Sulfate, Palatal injection

PRINCIPAL INVESTIGATOR: Scott E. Brietzke, CPT MC
ASSOCIATES: Eric A. Mair, LtCol, MC, USAF

DEPARTMENT: Surgery
SERVICE: Otolaryngology – Head & Neck

STATUS: O
INITIAL APPROVAL DATE: 27 February 2001

## STUDY OBJECTIVE

The objective of this prospective, non-randomized study is to investigate the efficacy of palatal Sotradecol injection as a primary treatment of Obstructive Sleep Apnea Syndrome (OSAS).

## TECHNICAL APPROACH

This study is designed to be a prospective, non-randomized cohort study to investigate the use of palatal Sotradecol injection as the primary treatment for OSAS. A single cohort of patients (goal = 50 patients) will be prospectively followed after treatment. Each patient will serve as his/her own control with the primary data being the pre-treatment versus post-treatment polysomnogram parameters (RDI) measured with a standardized polysomnogram device.

## PRIOR AND CURRENT PROGRESS

Thirty-three patients have been enrolled to date with all patients having completed the study. The remaining patients are being followed with the post-treatment sleep study pending. Enrollment is ongoing with a goal of fifty to sixty patients. Four of the seven patients who have completed the study have had significant improvements in their OSA measurements. There have been no complications.

The number of subjects enrolled to the study since last APR at WRAMC is 33 and the total enrolled to date at WRAMC is 33. The total number enrolled study-wide is 33, if multi-site study.

## CONCLUSIONS

Injection Snoreplasty continues to be a safe, effective, well-tolerated procedure. Approximately half of the patients who have completed the study have had their OSA successfully treated with this technique. More study is needed and patient enrollment is ongoing.

Report Date: 12 June 2002

Work Unit # 01-32003

# DETAIL SUMMARY SHEET

TITLE: Palatal Sclerotherapy with Sotradecol as a Treatment for Obstructive Sleep Apnea Syndrome

KEYWORDS: Sclerotherapy, sleep apnea, Sodium Tetradecyl Sulfate, Palatal injection

PRINCIPAL INVESTIGATOR: Scott E. Brietzke, CPT MC
ASSOCIATES: Eric A. Mair, LtCol, MC, USAF

DEPARTMENT: Surgery
SERVICE: Otolaryngology – Head & Neck

STATUS: C
INITIAL APPROVAL DATE: 27 February 2001

## STUDY OBJECTIVE

The objective of this prospective, non-randomized study is to investigate the efficacy of palatal Sotradecol injection as a primary treatment of Obstructive Sleep Apnea Syndrome (OSAS).

## TECHNICAL APPROACH

This study is designed to be a prospective, non-randomized cohort study to investigate the use of palatal Sotradecol injection as the primary treatment for OSAS. A single cohort of patients (goal = 50 patients) will be prospectively followed after treatment. Each patient will serve as his/her own control with the primary data being the pre-treatment versus post-treatment polysomnogram parameters (RDI) measured with a standardized polysomnogram device.

## PRIOR AND CURRENT PROGRESS

Thirty-five patients have been enrolled to date with all patients having completed the study. Enrollment is closed. Data analysis is ongoing, but early analysis shows no improvement in OSA measurements following treatment. There have been no complications.

The number of subjects enrolled to the study since last APR at WRAMC is 35 and the total enrolled to date at WRAMC is 35. The total number enrolled study-wide is 35, if multi-site study.

## CONCLUSIONS

Injection Snoreplasty continues to be a safe, effective, well-tolerated procedure, but appears to be ineffective in the treatment of OSA.

Report Date: 4 January 2002

Work Unit # 01-32004

# DETAIL SUMMARY SHEET

TITLE: Treatment of Snoring with Palatal Stiffening Injection Sclerotherapy Using Ethanol

KEYWORDS: Sclerotherapy, snoring, Ethanol, Palatal injection

PRINCIPAL INVESTIGATOR: Scott E. Brietzke, CPT MC
ASSOCIATES: Eric A. Mair, LtCol, MC, USAF

DEPARTMENT: Surgery
SERVICE: Otolaryngology – Head & Neck

STATUS: O
INITIAL APPROVAL DATE: 27 February 2001
(6-month review)

## STUDY OBJECTIVE

The objective of this prospective, non-randomized study is to investigate the efficacy of palatal ethanol (Dehydrated Alcohol) injection as a primary treatment for palatal flutter snoring.

## TECHNICAL APPROACH

This study is designed to be a prospective, non-protocol to investigate the use palatal Ethanol injection as the primary treatment for palatal flutter snoring. A single cohort of patients (goal = 30 patients) will be prospectively followed after treatment each patient will serve as his/her own control with the primary data being the pre-treatment versus post-treatment polysomnogram parameters measured with a standardized polysomnogram device, called the SNAP test.

## PRIOR AND CURRENT PROGRESS

Twenty-seven patients have been enrolled in the study with 6 patients having completed the study. Enrollment has been closed in this study. Three patients have developed a transient palatal fistula after inject with ethanol. This is considered a minor complication as it has resolved without treatment in all cases and has had no lasting consequences, apart from a significant reduction in snoring. For the patients who have completed the study, all have reported subjective benefit. Post-treatment objective testing has confirmed a stiffened palate in these patients.

The number of subjects enrolled to the study since last APR at WRAMC is 27and the total enrolled to date at WRAMC is 27. The total number enrolled study-wide is 27, if multi-site study.

## CONCLUSIONS

Injection Snoreplasty (IS) with ethanol appears to have a higher palatal fistula rate than IS with Sodium tetradecyl sulfate. Subjective pain reports seem to indicate noticeably more pain with Ethanol, although still far less than with other snoring treatments. However, IS with Ethanol is very effective in reducing snoring based on subjective report and objective testing (SNAP Test).

Report Date: 12 June 2002

Work Unit # 01-32004

# DETAIL SUMMARY SHEET

TITLE: Treatment of Snoring with Palatal Stiffening Injection Sclerotherapy Using Ethanol

KEYWORDS: Sclerotherapy, snoring, Ethanol, Palatal injection

PRINCIPAL INVESTIGATOR: Scott E. Brietzke, CPT MC
ASSOCIATES: Eric A. Mair, LtCol, MC, USAF

DEPARTMENT: Surgery
SERVICE: Otolaryngology – Head & Neck

STATUS: C
INITIAL APPROVAL DATE: 27 February 2001
(6-month review)

## STUDY OBJECTIVE

The objective of this prospective, non-randomized study is to investigate the efficacy of palatal ethanol (Dehydrated Alcohol) injection as a primary treatment for palatal flutter snoring.

## TECHNICAL APPROACH

This study is designed to be a prospective, non-protocol to investigate the use palatal Ethanol injection as the primary treatment for palatal flutter snoring. A single cohort of patients (goal = 30 patients) will be prospectively followed after treatment each patient will serve as his/her own control with the primary data being the pre-treatment versus post-treatment polysomnogram parameters measured with a standardized polysomnogram device, called the SNAP test.

## PRIOR AND CURRENT PROGRESS

Twenty-nine patients have been enrolled in the study with all patients having completed the study. Enrollment has been closed in this study. Three patients have developed a transient palatal fistula after injection with ethanol. This is considered a minor complication as it has resolved without treatment in all cases and has had no lasting consequences, apart from a significant reduction in snoring. For the patients who have completed the study, all have reported subjective benefit. Post-treatment objective testing has confirmed a stiffened palate in these patients. Manuscript preparation is underway.

The number of subjects enrolled to the study since last APR at WRAMC is 29 and the total enrolled to date at WRAMC is 29. The total number enrolled study-wide is 29, if multi-site study.

## CONCLUSIONS

Injection Snoreplasty (IS) with ethanol appears to have a higher palatal fistula rate than IS with Sodium tetradecyl sulfate. Subjective pain reports seem to indicate noticeably more pain with Ethanol, although still far less than with other snoring treatments. However, IS with Ethanol is very effective in reducing snoring based on subjective report and objective testing (SNAP Test).

Report Date: 24 July 2002

Work Unit # 01-32005

# DETAIL SUMMARY SHEET

TITLE: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Cevimeline in the Treatment of Xerostomia Secondary to Radiation Therapy for Cancer in the Head and Neck Region (Protocol 2011A-PRT003)

KEYWORDS:

PRINCIPAL INVESTIGATOR: COL John Casler MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Otolaryngology Head and Neck

STATUS: O
INITIAL APPROVAL DATE: 24 July 2001

STUDY OBJECTIVE
To determine the possible efficacy of Cevimeline in reducing the effects of radiation-induced xerostomia in patients who have been previously treated for head and neck cancer.

TECHNICAL APPROACH
Prospective double-blinded randomization of active medication versus placebo. Patients are examined for improvement of xerostomia and salivary output is recorded.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Four patients enrolled to date. No serious adverse events in enrolled patients. Some reports at other centers of cholangitis and other biliary problems have led to revised informed consent form. While not all of the adverse events appear to be related to the study drug, there is some good evidence to suggest that patients with biliary or liver problems are at increased risk for cholangitis from the study medication. No patients have withdrawn from the study. The study is still ongoing, and is still blinded. Some patients have noted a slight improvement in their xerostomia, but it is not known whether they have received the active medication. The number of subjects enrolled to the study since last APR at WRAMC is 4 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is unknown, if multi-site study.

CONCLUSIONS
There may be some benefit to patients suffering from radiation-induced xerostomia, but it is too early to tell.

Report Date: 6 June 2002 Work Unit # 01-3201

# DETAIL SUMMARY SHEET

TITLE: Endoscopic Transection of the Corrugator and Procerus Muscles Through an Open Rhinoplasty Approach

KEYWORDS: Corrugator, Procerus, Endoscopic

PRINCIPAL INVESTIGATOR: McClellan, James CPT MC
ASSOCIATES: Winslow, Catherine P. MAJ MC

DEPARTMENT: Surgery
SERVICE: Otolaryngology – Head and Neck

STATUS: C
INITIAL APPROVAL DATE: 14 November 2000

## STUDY OBJECTIVE

Assess the feasibility of corrugator and procerus resection through an open rhinoplasty approach. This is to be done in an endoscopic fashion, in keeping with minimally invasive standards.

## TECHNICAL APPROACH

Ten fresh cadaver heads underwent open septorhinoplasty in a supraperiosteal plane. A zero degree endoscope was advanced to the glabella, and the procerus and corrugator muscles were identified. Both muscles were then transected using bipolar dissection under direct visualization. Care was taken during the dissection to preserve the supratrochlear nerve.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Nothing new to report from previous correspondence. The number of subjects enrolled to the study since last APR at WRAMC is n/a and the total enrolled to date at WRAMC is n/a.

## CONCLUSIONS

Our study achieved near complete resection of the procerus and corrugator muscles through a minimally invasive approach. We believe that this new approach will decrease the surgical morbidity seen with the endoscopic brow lift approach and is suitable for patients undergoing rhinoplasty and not desiring a brow lift.

Report Date: 18 September 2001 Work Unit # 01-3202

# DETAIL SUMMARY SHEET

TITLE: Does Oral Steroid Therapy After Tonsillectomy Decrease Postoperative Pain and Morbidity? A Prospective, Double-Blinded and Placebo Controlled Analysis

KEYWORDS:

PRINCIPAL INVESTIGATOR: Battiata, Andrew CPT MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Otolaryngology – Head and Neck INITIAL APPROVAL DATE: 30 November 2000

STUDY OBJECTIVE:
To determine if postoperative steroids following tonsillectomy will result in decreased morbidity and pain.

TECHNICAL APPROACH
Prospective, double blinded placebo controlled trial.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is N/A if multi-site study. There has been no additional literature affecting this protocol, to date.

CONCLUSIONS
There have been no conclusions drawn from the work done on this protocol.

Report Date: 4 January 2002 Work Unit # 01-33001

# DETAIL SUMMARY SHEET

TITLE: In Vitro Gamma-Interferon Response to MTB Antigens in BCG-Vaccinated Individuals and Those with Equivocal PPD Skin Test Compared to Negative and Positive Control Subjects

KEYWORDS:

PRINCIPAL INVESTIGATOR: Katial, Rohit MAJ MC
ASSOCIATES:

DEPARTMENT: Allergy and Immunology STATUS: O
SERVICE: INITIAL APPROVAL DATE: 13 February 2001

STUDY OBJECTIVE:
1) To see if subjects with equivocal PPD skin tests (>0 mm <10) will test positive or negative in an in vitro γ-interferon whole blood assay. 2) To see if positive levels of γ-interferon in negative PPD SKT subjects can predict PPD SKT conversion at a 6 month retest; 3) To compare the release of γ-interferon in an in vitro whole blood assay in subjects with equivocal PPD skin tests with those having positive PPD skin tests, with those having negative PPD skin tests, and with those having a history of BCG vaccination, using as stimulating antigens human PPD, avian PPD, Mycobacterium tuberculosis (MTB) culture filtrate fractions, or recombinant MTB antigens, singly and in combination; 4) to look at cell-mediated immune responses to the various MTB antigens in an in-vitro cytokine flow cytometry assay.

TECHNICAL APPROACH:
A PPD skin test is repeated on all subjects whose previous PPD test results are more than 2 months old. Blood samples obtained from each subject are incubated at 37°C for 20 hours with no antigen (phosphate buffered saline or PBS), the mitogen phytohemagglutinin (PHA), Human PPD, avian PPD, and a panel of specific MTB antigens, singly and in combination. These antigens include Antigen 85 complex and Mpt 32, Mpt 64, GrosES, GroEL, and ESAT 6. For the flow cytometry intracellular cytokine assay, whole blood is cultured with brefeldin A in addition to stimulating antigens in order to retain any cytokine produced in the intracellular space. Fluorescent-conjugated antibodies to Th1 type cytokines and cell-surface markers are used to measure the immune response to the antigens. These antibodies measure T-cell CD 69 activation and intracellular cytokine γ-IFN. The EIA immunoassay measures secretion of γ-IFN in whole blood culture in response to culture with the TB antigens. Plasma supernatants from the whole blood culture are harvested and frozen at –70°C until ready for the cytokine assay using the enzyme-linked immunoassay provided with the QuantiFERON kit. Results will be compared among the different groups.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The optimal concentrations of the specific antigens were determined in preliminary dose/response experiments using the first 5 subjects in the positive and the negative groups. Although a detailed analysis of the raw data has not been conducted, the response of the antigens GrosES and GroEL appears to be higher than that of the other antigens in the PPD skin test positive subjects. Including the preliminary dose/response subjects, a total of 37 patients have been enrolled in the study to date. The number of subjects enrolled in the study since last APR at WRAMC is 37. Thus far, there have not been any adverse events. Also, no patients have withdrawn from the study.

CONCLUSIONS
There are no conclusions to be made at this time.

Report Date: 15 January 2002

Work Unit # 01-33002

# DETAIL SUMMARY SHEET

TITLE: Suppression of Ragweed Wheal Response by Montelukast: A Double-blind Study

KEYWORDS: ragweed, montelukast, skin testing

PRINCIPAL INVESTIGATOR: Waibel, Kirk H. CPT MC
ASSOCIATES: Martin, Bryan L. LTC(P)

DEPARTMENT: Allergy-Immunology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 20 March 2001

## STUDY OBJECTIVE

To demonstrate that the proportion of wheal reduction >50% during skin prick testing with ragweed in montelukast treated subjects (Group 1) will be different from the proportion of subjects in the placebo group (Group 2).

## TECHNICAL APPROACH

The design is a prospective randomized double-blind study. Group 1 will receive 10 mg of Montelukast by mouth once a day for seven days. Group 2 will receive placebo for seven days. Below is a general study outline.

| | Outline: | Time Allotment | Day# |
|---|---|---|---|
| 1. | Patient enrollment | 1 hour | 1 |
| 2. | Initial skin testing | 30 minutes | 1 |
| 3. | Study arm randomization | 30 minutes | 1 |
| 4. | Repeat SPT 3hrs after first tablet | 3 hours | 1 |
| 5. | Repeat SPT at one week | 30 minutes | 7 |
| 6. | Patient finished with study | N/A | 7 |

Detailed outline: see protocol

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

1. There are no study amendments to date.
2. Number of study participants enrolled since 3-20-01: Two
   This patient was consented, enrolled, and skin tested initially. His skin test was too small to meet the inclusion criteria for the study and the patient was not continued in the study.
   The second patient is currently enrolled and finished steps 1-4 above.
3. No adverse events.

The number of subjects enrolled to the study since last APR at WRAMC is two and the total enrolled to date at WRAMC is two. Patients are continuing to be contacted who may meet the criteria for this study. To date, twelve subjects have expressed interest in this study and are awaiting time to come in to the clinic to enroll.

## CONCLUSIONS

No conclusions to date.

Report Date: 1 April 2002 Work Unit # 3369

# DETAIL SUMMARY SHEET

TITLE: Survey of Prevalent Pollen and Fungal Aeroallergens in the Washington DC Area

KEYWORDS: pollen, aeroallergen, fungal

PRINCIPAL INVESTIGATOR: Kosisky, Susan
ASSOCIATES:

DEPARTMENT: Allergy-Immunology STATUS: O
SERVICE: INITIAL APPROVAL DATE: 11 May 1993

## STUDY OBJECTIVE

To identify the predominant aeroallergens in the Washington, DC area. Identification of prevalent trees, weeds, and grasses are essential to the effective treatment and diagnosis of the allergic patient. Daily volumetric samples will reveal peak concentrations and pollination periods for area allergenic aeroallergens. Seasonal definition of pollination periods for trees, weeds, grasses, and molds will allow for the development of a better patient treatment regimen.

## TECHNICAL APPROACH

Daily volumetric sampling using a Rotorod Sampler is conducted. Two polyurethane "I" rods are exposed to the atmosphere for collection of aeroallergens. The rods are microscopically examined for pollen grains and mold spores. Counts are converted to a volumetric grains/cubic meter assessment. The Rotorod Sampler is on the roof of the hospital, Building 2. Counts are conducted daily, weather permitting.

## PRIOR AND CURRENT PROGRESS

The pollen and spore counts are submitted to the National Allergy Bureau, local and national media networks and various websites for data dissemination. CNN and our local Channel 9 news in the DC area report our counts to the public. A public information group for the daily pollen and mold spore report continues to serve the Walter Reed community and DOD Region 1 through CHCS and Outlook. Data and pictures of area allergenic plants are published through the Academy of Allergy, Asthma and Immunology's Pollen and Spore Report and other informative pamphlets and handouts. The analysis of pollen and spore data continues as well as the correlation with meteorological variables. Our aerobiological center for the Washington, DC area continues to support area allergists by providing data used for various study protocols. There has been no modification to the research study since the last review.

## CONCLUSIONS

The study is ongoing. Data collected over a greater period of time allows for us to see trends in the prevalence and seasonal distribution of predominant area allergens. Year to year variations occur with respect to aeroallergen concentrations. Data analysis will allow for correlations with meteorological variables to provide for a predictive model. The data has been utilized in devising a regional skin-testing panel to be used in DOD Region 1 as well as nationwide. Consistent with the new skin-testing panel our inventory of allergen extract biological continues to be refined and reduced saving money and time. Many predominant area pollens and molds which reach significant atmospheric concentrations are not available for skin testing making it difficult to assess the atopic patient. Various allergen extract manufacturers have utilized our Washington DC data to supply extracts of predominant molds and pollens for the testing and treatment of the atopic patient.

Report Date: 07 November 2001

Work Unit # 3372

# DETAIL SUMMARY SHEET

TITLE: Mosquito Hypersensitivity: Immunology and Value of Skin Testing with Whole Body Mosquito Extracts

KEYWORDS: skin testing, mosquito, hypersensitivity

PRINCIPAL INVESTIGATOR: Engler, Renata COL MC
ASSOCIATES:

DEPARTMENT: Allergy-Immunology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 21 December 1993

## STUDY OBJECTIVE

To: 1) determine the sensitivity, specificity and predicative value of prick and intradermal skin tests at different dilutions to mosquito whole body extracts; 2) measure the total mosquito-specific IgE and IgG and IgG subclasses in patients with no reactions, minor reactions, large local reactions, and systemic anaphylaxis to mosquito bites.

## TECHNICAL APPROACH

A total of 60 clinically negative subjects (with no adverse reactions to mosquito bites) and 60 clinically positive subjects will be enrolled. Prick and intradermal skin tests with Aedes egypti and Culex pipiens mosquito extracts in five dilutions will be administered. A permanent imprint of the wheal and flare will be measured. Blood will be drawn before and 3 weeks after skin testing to evaluate mosquito-specific IgG, IgG subclasses, and IgE.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is zero and the number enrolled and consented to date at WRAMC is twenty-eight. An audit in 2000 resulted in the removal of the two index cases and six other subjects from the database and serum bank. The remaining 28 subjects are validly consented. Of these, two had a history of systemic reactions, three had a history of large local reactions, and 23 had negative reactions. The adverse reactions were neither serious nor unexpected. No cases of mosquito bite anaphylaxis were seen this year. One hundred percent of the subjects with a history of large local or anaphylactic reactions responded positively to mosquito whole body extract skin tests. Of those subjects with a history of minimal to no reaction, 64% responded positively.

## CONCLUSIONS

To date, no strong correlation has been shown between dilution strength of whole body extracts and reaction history of the subjects enrolled in this study. We would like to keep this protocol open so that subjects can be enrolled as they present.

Report Date: 09 November 2001 Work Unit # 3385

# DETAIL SUMMARY SHEET

TITLE: Adverse Reactions with Intravenous Immunoglobulin Therapy

KEYWORDS: adverse reactions, intravenous immunoglobulin

PRINCIPAL INVESTIGATOR: Engler, Renata COL MC
ASSOCIATES:

DEPARTMENT: Allergy-Immunology STATUS: O
SERVICE: INITIAL APPROVAL DATE: 10 December1996

STUDY OBJECTIVE
To review, retrospectively and prospectively the quality assurance monitor data collected for the IVIG subcommittee of the WRAMC Pharmacy and Therapeutics Committee. To determine the incidence and demographics of adverse reactions to IVIG between 1991 and 1995 using the CHCS pharmacy register of administrations, laboratory clinical results and individual patient chart reviews. To monitor, prospectively the adverse reactions associated with both intra muscular and IVIG therapy at WRAMC and to develop a database registry. To establish a serum bank and to determine if proteinuria is a "normal" side effect of IVIG therapy.

TECHNICAL APPROACH
The Department of Allergy and Immunology provides all adult immunizations including IVIG therapy. A database of immunizations exists back to 1992 so that subjects have received IVIG therapy can be identified. The actual work of this protocol includes: monthly monitoring of patients receiving IVIG, entering adverse reactions into database, tabulating QA questionnaires from IVIG patients, monthly reviews of IVIG doses and volumes given establishment of a serum bank of patients receiving IVIG and gammaglobulin used at WRAMC, quantifying the level of proteinuria and microhematuria associated with the administration of IVIG by urine dipstick test before and after IVIG. A patient questionnaire filled out at the time of IVIG administration will be kept on file at the Allergy Clinic.

PRIOR AND CURRENT PROGRESS
The number of subjects enrolled in the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 16. Previous APRs recording 25 enrollees had mistakenly included subjects from retrospective records review in the count. Monthly reporting on immunoglobulin prescriptions established with WRAMC pharmacy tracking of IVIG use has provided additional subjects for prospective enrollment and a means of retrospectively identifying prior adverse effects. No patients have been withdrawn from the study. No adverse reactions have occurred as a result of study enrollment. The study is designed to observe adverse reactions during clinically indicated immunoglobulin administration independent of study participation. Recent proposals of mechanisms responsible for adverse reaction such as renal disease caused by excessive sucrose exposure illustrate the continued need for adverse monitoring.

CONCLUSIONS
Adverse reactions are infrequent, but when present, range widely in severity and type. There is a need for continued prospective enrollment of patients to provide additional unbiased prospective data.

Report Date: 29 March 2002

Work Unit # 3390-99

# DETAIL SUMMARY SHEET

TITLE: A Phase 3 Study to Determine the Efficacy and Safety of C1-Inhibitor (HUMAN) Vapor Heated, Immuno in Subjects of Hereditary Angioedema (HAE)

KEYWORDS: Hereditary Angioedema, C1-Inhibitor

PRINCIPAL INVESTIGATOR: Nelson, Michael LTC MC
ASSOCIATES:

DEPARTMENT: Allergy-Immunology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 25 May 1999

## STUDY OBJECTIVE

The purpose of this study is to provide effective documentation to support an application to the Food and Drug Administration for the C1-Inhibitor (HUMAN) drug to be licensed in the United States to treat Hereditary Angioedema (HAE). This drug is in the final stage of testing. This drug will be given to a large number of patients (adults, children and pregnant adults) to find out its safety and effectiveness.

HAE is caused by a lack of an adequate amount of a blood substance called C 1-Inhibitor. C1 concentrates can be made from human blood to replace this missing substance. This kind of therapy may reduce the swelling associated with attacks of HAE, as well as the associated pain and discomfort.

## TECHNICAL APPROACH

This study is divided into 4 parts:
In part 1, the-patients will receive two treatments for an acute attack of HAE. They will be randomly assigned to treatment with either C1-Inhibitor or placebo. At one hour from the beginning of their first treatment, they will receive the other product (i.e., if the patient receives C1-Inhibitor first, the placebo will be received second; if the patient receives the placebo first, the C 1-Inhibitor will be received second). The doctor will not know whether the patients will be receiving C1-Inhibitor or the placebo. However, if needed, the doctor can find out from the pharmacy which treatment the patients will be receiving.
In part 2, the patients will receive open label active C1-Inhibitor (HUMAN) for acute attacks of HAE.
In part 3, the patients will receive active CI-Inhibitor (HUMAN) to prevent an attack should they require surgery.
In part 4, females who are pregnant will be able to receive active C1 -Inhibitor (HUMAN) under a separate consent form.

Part 1 of the study was completed and the results reported to investigators on 23 March 2002. Enrolled subjects will enter part 2 or 3 without the need to complete part 1.
Parts 2, 3, and 4 will continue until licensure of the product or close of the study. An addendum to the protocol dated 4 January 2001 increased the number of enrollees allowed nationwide to 200.

## PRIOR AND CURRENT PROGRESS

The intermediate results discussed with investigators on 23 March 2002, and summarized in 26-27 March 2002 communications, are summarized as follows:

60 patients treated under part 1 (randomized)

- 15/60 reported relief within one hour (8 treated with experimental drug, 7 with placebo).
- Study failed to show a difference between the C1-Inhibitor group and the placebo group (p=0.766)
- 350 HAE attacks under part 2 (open label).
- 260/350 abated within one hour (81%).

- The Food and Drug Administration has been made aware of these results and Baxter will not receive licensure for the plasma-derived C1 Inhibitor (HUMAN) in the United States.
- No safety concerns elaborated.
- The protocol will continue through 30 September 2002, and restricted to enrolled patients under parts 2, 3, & 4.
- Another manufacturer is attempting to initiate a related protocol in the fall of 2002.
- Manufacturer will not permit compassionate use of product upon request.
- Enrollment remains closed.

WRAMC update

- Three enrolled subjects reduced to two due to relocation of one subject – two currently enrolled.
- One interval infusion under part 2.
- No adverse events in interval or since protocol initiation.
- Two enrolled subjects with continued risk for future events.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 3 (2 remain actively enrolled). The total number enrolled study-wide is 200.

CONCLUSIONS

Renewal of this study through planned completion date of 30 September 2002 is requested in light of:

1. Supporting efficacy data from open label component of study
2. Improvement with all open label treatments by WRAMC enrolled subjects
3. Historical European data supporting safety and efficacy
4. Lack of new safety concerns with current study
5. Lack of alternative treatment above standard of care (often insufficient in this life-threatening disease)
6. Lack of compassionate-use availability

We will review a related Dyax protocol (tentative fall initiation) for study design and applicability for our patient population.

Report Date: 17 October 2001

Work Unit # 01-36001

# DETAIL SUMMARY SHEET

TITLE: Perceptions of Pain Control: Oncology Patients and Their Physicians

PRINCIPAL INVESTIGATOR: Rutledge, Matthew MAJ MS
ASSOCIATES: COL Ricke J. Weickum, Mr. Dominic Solimando Jr., and Dr. Gregory Fant.

DEPARTMENT: Pharmacy
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 29 May 2001

## STUDY OBJECTIVE

To describe the difference between a patient's perception of pain control and their respective physician's perception of pain management using an established tool for assessing the severity and impact of cancer pain. We anticipate current documentation of physician pain assessment will be minimal and that a discrepancy exists between the perceptions of patients and their physicians leading to inadequate pain management in this population.

## TECHNICAL APPROACH

This project involved two simultaneous studies, each using a cross-sectional study design. Patients were identified according to inclusion criteria and asked to complete a modified-Brief Pain Inventory survey. The modified patient-Brief Pain Inventory assesses the patient's history of pain and its relationship to their disease. Patients were asked to rate their pain at its worst, least, usual pain, and pain now. On the pain scales, patients were asked to circle a number from 0-10 to indicate the intensity of their pain. Zero is labeled 'no pain' and 10 is labeled 'pain as bad as you can imagine.' Following the pain ratings, patients were asked to rate how much pain interferes with their mood, relations with other people, walking ability, sleep, normal work, and enjoyment of life. We included a final question regarding the patient's perception of their physician's performance at controlling their pain to the original BPI, using the same 0-10 scale. On the last page, patients were asked for demographic information including age, sex, ethnicity, marital status, education and employment status.

Once a patient had completed his/her survey, their respective physician was asked to complete a similar survey instrument. The modified physician-Brief Pain Inventory asked the same questions as the 'patient' version utilizing the same 0-10 scale. The intent was for the physician to answer each question as they "perceived" the patient to experience. The final question on this version asked the physician to rate themselves as to how they were managing the specific patient's pain. Physicians were also asked to provide information regarding the patient's disease, disease-stage and time since diagnosis.
This study will evaluate any differences between the patient's and physician's perspectives.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

At this time 31 patients have completed a modified Brief Pain Inventory survey. One patient's survey was excluded because they answered the survey incorrectly, noting one score for one type of pain and a second score for the same question for a second type of pain they were experiencing. A corresponding survey has been received from the linked physician for each patient accrued. Therefore, the original goal of 30 patients with their linked physician has been achieved and the study is closed to additional patient accrual. The total number of subjects enrolled in the study to date at WRAMC is 31. The total number of evaluable patients is 30. No additional study sites were utilized. No adverse events occurred.

## CONCLUSIONS

No conclusions can be drawn at this time as data has yet to be analyzed.

Report Date: 28 November 2001 Work Unit # 00-3701

# DETAIL SUMMARY SHEET

TITLE: Early Signaling Events in Lupus B Cells

KEYWORDS: B Lymphocytes, systemic lupus erythematosus, signaling events

PRINCIPAL INVESTIGATOR: Jeanne P. Mitchell CPT (P) MC
ASSOCIATES: George Tsokos COL MC

DEPARTMENT: Medicine
SERVICE: Rheumatology

STATUS: C
INITIAL APPROVAL DATE: 15 February 2000

## STUDY OBJECTIVE

To study early signaling events in B lymphocytes of patients with systemic lupus erythematosus (SLE). More specifically, to quantify the B cell receptor mediated free intracytoplasmic calcium response after cross-linking the Fc-gamma and CR2 receptors with various ligands in B cells from patients with SLE and from patients with other systemic connective tissue diseases, and to quantify the degree of protein tyrosine residue phosphorylation after cross-linking these B-cell receptors with the same ligands. Lastly, to correlate the obtained free intracytoplasmic calcium responses with the degree of protein tyrosine residue phosphorylation for each receptor-ligand interaction.

## TECHNICAL APPROACH

Patients with a diagnosis of systemic lupus erythematosus, in accordance with the ACR classification criteria, will be asked to participate and will have blood drawn, consisting of a 25 cc sample, at the hospital laboratory. B cells will be separated from the peripheral blood sample using the standard Ficoll-Hypaque gradient centrifugation method and then will be negatively selected by staining the samples with sell surface marker labeled antibodies. Intracellular calcium measurements will be performed using the flow cytometry and will be obtained at each sample's baseline and after simulation with anti-sIg mAb's and Fc-gamma and CR2 ligands. Lysates of the B cell enriched populations will be separated by gel electrophoresis and the resolved proteins will be immunoblotted with anti-phosphotyrosine Ab. Densitometric readings will be obtained for the molecular regions of 30-70kD. An age and sex-matched control sample will run in each experiment. Addenda: (1) The surface expression of the CR2 and FcγRIIB receptors on the B cells was determined by flow cytometry.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is zero, and the total enrolled to date at WRAMC is sixty.

## CONCLUSIONS

One result indicated that both deficient FcγRIIB mediated suppression and increased CR2 mediated enhancement are involved in the augmented intracellular cytoplasmic calcium responses of B cells from patients with systemic lupus erythematosus. The detection of abnormal regulatory events that are initiated by B cell surface membrane molecules will contribute to our understanding of basic defects contributing to the pathogenesis of this prototype autoimmune disease. Therapeutic interventions designed to target specific biologic processes may be developed as a result of having more specific information in this regard.

Report Date: 26 February 2002

Work Unit # 00-3702

# DETAIL SUMMARY SHEET

TITLE: Aberrant T Cell Receptors in Systemic Lupus Erythematosus

KEYWORDS:

PRINCIPAL INVESTIGATOR: Gregory J. Dennis, COL, MC
ASSOCIATES: William N. Fishbein, MD, PhD

DEPARTMENT: Medicine
SERVICE: Rheumatology

STATUS: O
INITIAL APPROVAL DATE: 7 March 2000

## STUDY OBJECTIVE

Compare the percentage of aberrant T cell receptors in patients with systemic lupus erythematosus to that of rheumatoid arthritis.

## TECHNICAL APPROACH

Using the chromosome 7 inversion assay blood samples of patients with these diseases will be analyzed for the presence of Vγ-Jβ1 hybrid T-cell receptors and quantified as the number of inversions per ug DNA. Samples have been further analyzed using a non-radioactive PCR and Southern blot followed by chemiluminescent detection. The latter probe will allow an important comparison of the technique in this patient population.

## PRIOR AND CURRENT PROGRESS

In accordance with the instructions delineated at the time of approval 54 patients were enrolled in the protocol. Two samples were found not be suitable for analysis; consequently, laboratory testing was performed on a total of 52 samples. No additional study subjects have been entered into the protocol since the last APR as the maximum enrollment was achieved. There remain no studies to date analyzing patients with autoimmune disease in this manner. The additional analysis of the samples using non-radioactive PCR and Southern blot followed by chemiluminescent detection will provide confirmation of the findings. The change in access to the Composite Health Care System of WRAMC hampered our ability to collect clinical information on individual subjects for input into the clinical database.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 54.

## CONCLUSIONS

1. We are presently in the process of reviewing the data to ensure that our stated approach to analysis of the data is appropriate.
2. Efforts are underway to complete the collection of data for clinical comparisons.

Report Date: 10 December 2001 Work Unit # 01-37001

# DETAIL SUMMARY SHEET

TITLE: Visconsupplementation in the Treatment of Chondromalacia Patellae

PRINCIPAL INVESTIGATOR: Roebuck, Jonathan D. CPT MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Rheumatology INITIAL APPROVAL DATE: 20 February 2001

STUDY OBJECTIVE: 1. To compare the mean difference in the degree of knee pain between two groups of subjects that receive either viscosupplementation or placebo for the treatment of chondromalacia patella. 2. To compare the mean difference in the functional status between two groups of subjects that receives either viscosupplementation or placebo in the treatment of chondromalacia patella.

TECHNICAL APPROACH:

1. Initial evaluation for clinical signs/symptoms of chondromalacia patella (CMP): patellar apprehension, pain, disability (standard of care)
2. Rule out exclusionary criteria, rule in, inclusionary (research)
3. Consent patients to the study (research)
4. Randomize patients to aforementioned treatment arms (research): Control (standard therapy plus placebo); Treatment (standard therapy plus viscosupplementation)
5. See subjects once a week for 3 weeks to inject either SYNVISC or placebo into the affected knee (as described in detail in the background section above)
6. Follow up evaluation with physical exam, data collection questionnaires at 3 month intervals for 6 months (research)
7. Questionnaires will be filled out on 3 separate occasions for each patient in the treatment and control groups, first at enrollment, then at each of the 3 month follow up visits. The questionnaire includes pain inquiries with visual analog scale for many measures according to the WOMAC (Western Ontario McMaster University osteoarthritis index) score as well as determinants of functional status by Lequesne's index and WOMAC scores (10, 11, 12).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
Since this protocol was actually approved just this past August and I have been involved with OCONUS TDY and preparing for licensing boards, the project is still in its infancy. Since the approval, another member of WRAMC Rheumatology has become involved in this study, Dr Brian McKinley. We are currently in the active recruiting phase for patients. Our target referral population includes Rheumatology, PMR, and Orthopaedic clinics and we are establishing points of contact within those clinics for timely referrals. We have blocked off time in January and February for patient evaluation and anticipate starting injections on patients in late January of 2002. I reviewed PUBMED and MD Consult medical search engines and find no new studies relating directly to the study objectives outlined in this protocol. I believe this to be a unique application for the mechanical device SYNVISC. There is renewed interest in the manufacturers of SYNVISC and they may be supplying us with product and placebo injection material. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is __, if multi-site study.

CONCLUSIONS:
Due to other commitments, this study is really just getting going. There have been no significant updates since the protocols final approval. We are very excited to get this study moving and anticipate completion within the next 9-12 months.

Report Date: 25 August 2002

Work Unit # 3724

# DETAIL SUMMARY SHEET

TITLE: Immunogenetic Factors During the Clinical Evolution of Systemic Lupus Erythematosus

KEYWORDS: Systemic lupus erythematosus, lupus, SLE, connective tissue disease, autoimmunity

PRINCIPAL INVESTIGATOR: Gregory Dennis MD
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Rheumatology

STATUS: C
INITIAL APPROVAL DATE: 30 July 1997

## STUDY OBJECTIVE

Identify a cohort of military service members who meet the American College of Rheumatology Criteria for a diagnosis of systemic lupus erythematosus (SLE) to be followed longitudinally. Compare the frequency of Epstein Barr Virus seroconversion of patients with systemic lupus erythematosus in the military to a group of patients without autoimmunity. Characterize the maturation of the humoral autoimmune response before clinical presentation and diagnosis and relate these findings to the later clinical and serologic expression of disease.

## TECHNICAL APPROACH

Retrieve sera from the Army/Navy serum repository on active duty or previously active duty military that have a confirmed diagnosis of systemic lupus erythematosus and from age and sex matched controls. Each serum sample received is evaluated for the presence of defined autoantibodies and antibodies to EBV.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Controversy regarding the potential role of EBV in the immunopathogenesis of SLE remains. The view that serological profiles present in patients with lupus is a consequence of immune dysregulation secondary to SLE or its therapy rather than rampant infection with EBV has not altered our view. We plan to continue retrieving serum samples to test our hypothesis. To date, we have not collected a sufficient of cases to allow us to draw a statistically significant conclusion at this time.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 66. The total number enrolled study-wide is 205, if multi-site study.

## CONCLUSIONS

The prevalence of positive EBV serologies was only low enough in the target population of Caucasian and Hispanic males to have tested the hypothesis that EBV exposure precedes the development of SLE. A new protocol has been created in which we will continue to identify cases to increase our total number of subjects, which will allow statistical comparisons to be made. In the absence of being able to enroll new individuals into the study in the past year, no additional conclusions can be made.

Report Date: 13 February 2002 Work Unit # 3726-98

# DETAIL SUMMARY SHEET

TITLE: Prevalence and Impact of Cyclical Mastalgia in Rheumatology Clinic Patients

KEYWORDS: Mastalgia, Fibromyalgia Syndrome

PRINCIPAL INVESTIGATOR: Jeanne P. Mitchell MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Rheumatology INITIAL APPROVAL DATE: 10 March 1998

STUDY OBJECTIVE
(1) Identify the prevalence and impact of cyclical mastalgia in military and DEERS-eligible women with fibromyalgia and rheumatoid arthritis, and (2) compare the prevalence of mastalgia in these groups with existing data from women without rheumatologic disorders. In addition, we propose to examine the relationship between functional status of patients with these rheumatologic disorders and their reports of cyclical mastalgia.

TECHNICAL APPROACH
Addendum to original protocol: We wish to implement the following in regard to obtaining information from the above selected patients: (1) Identification of patients with either fibromyalgia or rheumatoid arthritis by chart review, (2) Verbal consent for participation in this study via telephonic contact, and (3) Participant receipt and completion of study questionnaire via mail.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been no amendments or changes to the research protocol since the last APR in June 2001. Additionally, there have been no additional enrollments. The total enrollment to date is unchanged since the last APR, i.e. 54 total subjects (31 Rheumatoid arthritis patients, 23 fibromyalgia patients). No patients were withdrawn from the study. As noted in the audit for this protocol, the original research files were lost and the protocol was transferred to a second PI at the time that the original PI left WRAMC.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 54. The total number enrolled study-wide is NA, if multi-site study.

CONCLUSIONS
We would like to terminate this study for the following reasons. One, the original research files have not been located. The original PI was contacted and he did not know the location of the research files. The information that he had for me (which included a copy of the original protocol) had been shared with the study auditor at the time of audit and did not include consent forms or research files. Secondly, The NIH affiliate researcher was contacted regarding the study. The resulting discussion concluded that the original research protocol was asking a question that did not retain its original clinical significance and that the protocol would have to be re-written in order to ask a more interesting, in-depth question about fibromyalgia patients. For these reasons, we have elected to terminate this study.

Report Date: 15 May 2002

Work Unit # 3727-98

# DETAIL SUMMARY SHEET

TITLE: Lymphocyte Signaling Defects in Patients with Lupus

KEYWORDS: autoimmunity, cell signaling, immune cells, humans

PRINCIPAL INVESTIGATOR: Tsokos, Gregory COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Rheumatology

STATUS: O
INITIAL APPROVAL DATE: 21 July 1998

## STUDY OBJECTIVE

Characterize signaling abnormalities in human autoimmune cells. Specifically, study the antigen-mediated signaling events including activation of kinases, phosphatases, calcium mobilization and transcription factor activation in lymphocytes from patients with systemic autoimmune diseases (lupus).

## TECHNICAL APPROACH

Isolate lymphocytes from peripheral blood; perform calcium mobilization studies; measure kinase and phosphatase activity using biochemical assays, measure transcription factor activity using shift assays.

## PRIOR AND CURRENT PROGRESS

This project has established that the ζ chain of the T cell receptor is decreased or absent in SLE T cells. Lack of this chain has been associated with aberrant cell signaling in these cells. During the last year, we found that the missing ζ chain is replaced by another chain of the same group of proteins...the γ chain. We found novel forms (alternatively spliced products) of the ζ chain to be expressed in SLE T cells, and we started experiments to understand why the transcription of the ζ chain is decreased.

The number of subjects enrolled to the study since last APR at WRAMC is 28 and the total enrolled to date at WRAMC is 110. The total number enrolled study-wide is n/a, if multi-site study.

## CONCLUSIONS

Decreased TCR ζ chain is responsible for aberrant cell signaling in SLE T cells. The absent ζ chain is replaced by γ chain and alternatively spliced forms of the ζ chain.

Report Date: 29 May 2002 Work Unit # 3729-99

# DETAIL SUMMARY SHEET

TITLE: The Clinical Efficacy and Tolerability of Moderate-Dose Oral Compared to Subcutaneous Methotrexate in Rheumatoid Arthritis: A Prospective Crossover Trial

KEYWORDS:

PRINCIPAL INVESTIGATOR: Downs, Walter LCDR, MC
ASSOCIATES: Christopher Parker CPT, MC; LTC William Gilliland, MC; Elizabeth Mcshaw RN, MSN; COL Gregory J. Dennis, MC

DEPARTMENT: Medicine
SERVICE: Rheumatology

STATUS: C
INITIAL APPROVAL DATE: 16 February 1999

## STUDY OBJECTIVE

To evaluate the effectiveness of switching from oral to subcutaneous methotrexate at the upper limit of the recommended oral dose range

## TECHNICAL APPROACH

A prospective, open label, examiner blinded, randomized cross over trial

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Nine patients have met the inclusion criteria and have been enrolled. All the patients have completed the trial. No patients have withdrawn or suffered adverse reactions. Both the oral and subcutaneous methotrexate administrations were well tolerated. Two of nine patients significantly responded by American College Rheumatology (ACR) criteria while on the subcutaneous route of administration. One patient achieved an ACR 20 response. The other patient achieved an ACR 50 response. The average percent improvement in the pain scores of these two was 68%. One of the nine patients had significant improvement by ACR criteria with oral administration. This patient achieved an ACR 50 response with a 50% improvement in pain scores. The subcutaneous route of administration resulted in some improvement but it did not reach ACR 20 significance.

A single subject finished the study but no new subjects were enrolled since the last annual progress report (Jan 2002). Approximately thirty patients were identified as having an appropriate dose of methotrexate for entry into the study. Only one patient met the inclusion criteria and enrolled.

The difficulty with enrollment is multifactorial. Since the inception of the study, several new disease modifying anti-rheumatic agents (infliximab, etanercept, leflunomide and Anakira or IL-1 receptor antagonist) have been introduced. They have been shown to be very effective in slowing disease progress. In addition, the current trend is towards aggressive early treatment. This often entails using multiple drugs that target different inflammatory mediators or pathways with escalation of therapy every 6 to 8 weeks.

## CONCLUSIONS

The study design and subcutaneous route of methotrexate administration was well tolerated by this patient population. With the development of new disease modifying anti-rheumatic drugs and the trend for more aggressive therapy, there are few eligible subjects. It is unlikely that an adequate number of subjects to gain statistical significance can be enrolled from the current Rheumatology pool of patients. This protocol is closed. The small total number of subjects prevents meaningful statistical analysis (the study was designed to quantitate response). It appears that augmentation of methotrexate from 20 mg to 25 mg per week and possible changing the route of administration to subcutaneous injections may improve active rheumatoid arthritis in some patients.

Report Date: 7 May 2002 Work Unit # 00-4301

# DETAIL SUMMARY SHEET

TITLE: GOG 178 Phase III Randomized Trial of 12 Months vs. 3 Months of Paclitaxel in Patients with Advanced Ovarian, Fallopian Tube or Primary Peritoneal Cancer Who Attain a Clinically Defined Complete Response (CR) Following Platinum/Paclitaxel-Based Chemotherapy

KEYWORDS:

PRINCIPAL INVESTIGATOR: G. Scott Rose, LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 25 July 2000

STUDY OBJECTIVE:
To assess whether the continuation of paclitaxel, a cycle specific antineoplastic agent, for 12 months following the attainment of a clinically-defined complete response (CR) to initial platinum (carboplatinum or cisplatin)/paclitaxel-based chemotherapy can significantly increase progression-free survival and overall survival when compared to a 3-month continuation in women with advanced ovarian, fallopian tube or primary peritoneal cancer. To assess the toxicities associated with prolonged paclitaxel.

TECHNICAL APPROACH
This is a Phase III study. Patients on this study will be receiving paclitaxel either for a 12-month cycle (12 courses) or over a 3-month cycle (3 courses). Patients are followed for progression-free survival and overall survival and toxicities.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since the protocol's review one year ago, there have been no new publications reporting data involving this study.

The number of subjects enrolled to the study since last APR at WRAMC is 1 and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is 150, if multi-site study. Grade 4 toxicities include 7 hematologic, and 1 lung. Of the 49 patients evaluated for toxicity on the 12-course arm, one had Grade 4 dyspnea and two had Grade 4 neutropenia/granulocytopenia. Four of 52 patients evaluated for toxicity on the 3-course arm had Grade 4 neutropenia/granulocytopenia. This protocol was closed to patient entry on 12/1/01.

Ref: January 2002, GOG Statistical Manual

CONCLUSIONS
Too early.

Report Date: 13 June 2002 Work Unit # 00-4302

# DETAIL SUMMARY SHEET

TITLE: GOG 9901 Comparison of Quality of Life for Ovarian Germ Cell Cancer Survivors

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES: .

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 15 August 2000

STUDY OBJECTIVE
To compare germ cell tumor survivors with a matched control group of well females on the quality of life variables of health status and sexual functioning. Psychological well-being, emotional well-being, and social functioning will be compared as secondary end points.

TECHNICAL APPROACH
Enrollment will consist of patients with early and advanced ovarian germ cell tumors who have previously been enrolled on GOG protocols 45, 78, 90, and 116. Patients and control individuals will complete a self-administered questionnaire. They will also be administered a variety of instruments that will assess physical and sexual functioning, social networks, and psychological functioning. A detailed statistical analysis will be done to compare patients and controls for these variables.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been a few publications reported since the last APR review.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 108, if multi-site study.

Ref: Jan 02 GOG Statistical Report.

CONCLUSIONS:
Too early.

Report Date: 13 June 2002

Work Unit # 00-4303

# DETAIL SUMMARY SHEET

TITLE: GOG 175: A Randomized Phase III Trial of IV Carboplatin (AUC 6) and Paclitaxel 175 mg/m$^2$ Q 21 Days x 3 Courses Plus Low Dose Paclitaxel 40 mg/m$^2$/wk vs. IV Carboplatin (AUC 6) and Paclitaxel 175 mg/m$^2$ q 21 Days x 3 Courses Plus Observation in Patients with Early Stage Ovarian Carcinoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 15 August 2000

STUDY OBJECTIVE
To compare the progression-free interval and overall survival in the two treatment arms. To assess the frequency and severity of toxicities due to the continued low dose paclitaxel regimen. To investigate markers of angiogenesis and metastasis as prognostic indicators for early stage epithelial ovarian cancer.

TECHNICAL APPROACH
All patients must have a histopathologic diagnosis of epithelial ovarian cancer. Patients with sufficient tumor tissue must have tissue specimen(s) sent to the GOG Tissue Bank.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 280, if multi-site study. Grade 4 toxicities include 2 WBC, 2 platelets, 104 granulocytes, 1 allergy, 1 cardiovascular, 3 gastrointestinal, and 2 neurologic.

Ref: Jan 02 GOG Statistical Report

CONCLUSIONS:
Too early.

Report Date: 23 July 2002 Work Unit # 00-4305

# DETAIL SUMMARY SHEET

TITLE: GOG 171 Expression of the MN Protein in Atypical Glandular Cells of Undetermined Significance (AGUS or AGCUS) as Potential Diagnostic Biomarker of Cervical Dysplasia/Neoplasia

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 26 September 2000

STUDY OBJECTIVE
To evaluate the utility of a novel tumor-associated antigen termed "MN" as a potential diagnostic biomarker for cervical glandular and/or squamous neoplasia in patients with cytologic diagnosis of atypical glandular cells of undetermined significance (AGUS). To measure the frequency and type of cervical pathology associated with AGUS diagnosis.

TECHNICAL APPROACH
Patients with cytologic diagnosis of AGUS in whom complete histological examination of cervix (cone or LEEP biopsy) is planned will be eligible for this protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's last review there have been no publications reporting data from studies with similar study design in the literature. The number of subjects enrolled to the study since last APR at WRAMC is 12 and the total enrolled to date at WRAMC is 24. The total number enrolled study-wide is 269, if multi-site study. No toxicities reported.

Ref: Jan 02 GOG Statistical Report

CONCLUSIONS:
Too early.

Report Date: 22 February 2002

Work Unit # 00-4403

# DETAIL SUMMARY SHEET

TITLE: A Trial of Vitamin B Complex for the Treatment of Chemotherapy Induced Peripheral Neuropathy

KEYWORDS: Vitamin B Complex, Neuropathy

PRINCIPAL INVESTIGATOR: Parker, Mary F. LTC MC
ASSOCIATES: Rogers, Stacey J. LCDR MC; Aylesworth, Cheryl, MD; Giroux, Donna, RN, BSN; Petrov, Jean, RN, MS

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology

STATUS: O
INITIAL APPROVAL DATE: 18 April 2000

STUDY OBJECTIVES:
To determine if vitamin B complex is effective in the treatment of chemotherapy induced neuropathy and to determine the side-effects of such treatment.

TECHNICAL APPROACH
There have been no modifications since the protocol was approved. Subjects receiving chemotherapy with a Taxol-containing regimen who develop peripheral neuropathy are given vitamin B complex twice a day for 6 weeks. Subjects are queried at baseline (prior to starting the vitamin B complex), weekly during the study, and at the conclusion of the study regarding their neurologic symptoms and any changes that occur during the course of the vitamin treatment. A brief neurologic examination is performed at baseline and at the completion of the six weeks of treatment. Based on the questionnaires and neurologic examinations, grades of peripheral neuropathy are assigned. Response is defined as an improvement in peripheral neuropathy by at least one grade. After 25 subjects who can be evaluated have been accrued, statistical analysis will be performed to determine if further study is warranted.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been no modifications since the protocol was approved. This was the second APR for this study. There have been fifteen subjects enrolled to date. There has been one subject withdrawn from the study due to facial flushing associated with the vitamin B complex. The flushing resolved upon discontinuation of the vitamin B complex. This adverse event was not serious. As noted in the consent form, facial flushing is usually seen at higher dosages than given in this study. Two additional patients have reported facial flushing -- not requiring withdrawal from the protocol -- possibly related to the vitamin B complex instead of their chemotherapy. All subjects have reported the expected color change and/or odor in their urine.

Summary of findings to date: Of the 15 subjects enrolled, one subject was withdrawn from the study as noted above. Of the remaining 14 subjects, there were nine subjects reporting a response, and five non-responders. Among the five non-responders, there were three subjects reporting no change in symptoms, and two subjects reporting a worsening of symptoms.

CONCLUSIONS
Due to the high response rate, interim analysis is underway to determine the need for further accrual. Quality of Life for responders has been enhanced. Further study via randomized trial may be warranted to compare the effect of vitamin B complex to placebo, as well as to ensure the vitamin treatment does not adversely affect patient survival (currently unknown).

Report Date: 11 June 2002 Work Unit # 00-4404

# DETAIL SUMMARY SHEET

TITLE: The Creation of a Blood and Tissue Bank and the Collection of Clinical Data From Patients Undergoing In Vitro Fertilization

KEYWORDS: in vitro fertilization, tissue bank

PRINCIPAL INVESTIGATOR: Mark P. Leondires, MD
ASSOCIATES: Lynette Scott, PhD

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Reproductive Endocrinology

STATUS: C
INITIAL APPROVAL DATE: 27 June 2000

## STUDY OBJECTIVE

To collect prospective clinical data on patients aged 18 years and over being treated for infertility using in vitro fertilization at WRAMC.
To accomplish the collection and storage of human blood, granulosa cells, and follicular fluid from *in vitro fertilization* patients which would otherwise be discarded.
To make available normally discarded human blood, granulosa cells, and follicular fluid for proposed projects in the Pediatric and Reproductive Endocrinology Branch and the Endocrinology and Reproduction Branch of the National Institute of Child Health and Human Development.

## TECHNICAL APPROACH

This is an observational study with no active intervention. The technical approach is to prospectively collect clinical data using a computerized database.

Secondary to failure of a working –70° freezer no bloods, fluids or cells have been saved or stored. In addition no laboratory at the NIH/NICHD desired to utilize or store any specimens. Therefore nothing has been sent to the NIH.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There is no recent literature with particularly applied to this data collection protocol.

The number of subjects enrolled to the study since last APR at WRAMC is 153 and the total enrolled to date at WRAMC is 339. The total number enrolled study-wide is NA, if multi-site study.
There have been no adverse events associated with this study.

## CONCLUSIONS

Please be aware that secondary to the issues stated above, the federal requirements associated with data collection for IVF programs, the necessity of a database to manage a successful *in vitro* fertilization program, the lack of involvement or benefit from the NIH the consenting of patients fell off distinctly during the last year. Patients within the IVF program already have to sign four consents, and secondary to issues associated with tissue samples many patients did not want to do this protocol. That led to them not wanting to even sign the data collection part. I admit that myself and my staff bear some responsibility, but since this protocol did not benefit the program at all it fell out of favor. Especially since we were not storing any specimens or blood.

Report Date: 25 April 2002

Work Unit # 00-4405

# DETAIL SUMMARY SHEET

TITLE: A Prospective, Randomized, Double-Blind, Placebo Controlled Study of Oral Misoprostol Prior to Operative Hysteroscopy

KEYWORD

PRINCIPAL INVESTIGATOR: McKeeby, Jeffery CDR
ASSOCIATES: Preen, Amy CPT MC

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Reproductive Endocrinology

STATUS: O
INITIAL APPROVAL DATE: 27 June 2000

STUDY OBJECTIVE:

Null hypothesis: Oral misoprostol prior to hysteroscopy, will not enhance cervical dilation or decrease operating time. We will investigate the time needed for cervical dilation, time needed for hysteroscopy and the ease at which hysterscopy is performed with preoperative administration of misoprostol. If oral misoprostol is effective in softening the uterine cervix, we expect that operative time; complication rate and patient post-operative discomfort will all be reduced. Primarily, we plan to measure length of dilation, length of surgery, and the first noted cervical dilator with resistance. Secondarily, we plan to subjectively assess ease of procedure and the patient's symptoms prior to surgery and post-operative pain. We will assess the incidence of complication such as uterine perforation.

TECHNICAL APPROACH

1. Patients will have been already been scheduled for an indicated operative hysteroscopy at Walter Reed Army Medical Center will be advised of the study. All patients undergoing operative hysteroscopy have urine HCG the day of surgery to assure the patient is not pregnant.
2. At their routine scheduled pre-operative visit patients will be counseled as to the risks, benefits, and alternatives and then sign the consent to participate in the study. Once they have signed the consent they will be given an opaque coded sealed envelope that will contain a misoprostol 400 microgram capsule (an orally approved drug, provided by the Walter Reed Army Medical Center pharmacy) or placebo. Factors (menopausal status, parity, and use of estrogen replacement therapy) that may affect the outcome measure (i.e. time needed for cervical dilation) will be determined for stratification. Patients within each stratum will be randomized to either misoprostol or placebo with equal number. Randomization will be by assignment of a random number generated by the DCI random number generator for each stratified group. The pharmacy will have a copy of the randomization scheme. However, the pharmacist will not have access to it. Patients will be given a pre-questionnaire to fill out the time and date the capsule was taken and any side effect experienced.
3. They will take the capsule the night prior to surgery, approximately 12 hours prior to the procedure. Twelve hours will be determined from the planned operation scheduled time. Patients will be asked to record the time the capsule was taken.
4. When they arrive for surgery approximately 12 hours later they will finish the pre-questionnaire regarding any noted discomforts or symptoms they experienced after taking the capsule. The time the capsule was taken should have already been recorded. This questionnaire will be completely filled out prior to the procedure and collected by the operating surgeon.

5. The surgeon will fill out a questionnaire to include basic information about the surgery (secondary outcomes): the procedure performed (for example: myomectomy, polypectomy, septum resection; adhesiolysis), media used (sorbitol, saline, hyskon, mannitol or CO2), and the total media deficit. The questionnaire will also include primary endpoints: time at start of dilation, time at finish of dilation (largest dilator needed to place operative hysteroscope), first cervical dilator with noted resistance, start time and finish time of hysteroscopy. Secondary end-points will also be recorded: ease of procedure (visual analogue scale) and any complications that occurred.
6. The day after the procedure the patient will be called by a department secretary to remind them to fill out the post-procedure questionnaire. The patient will be asked to rate post-operative discomfort on a visual analogue scale along with any side-effects they have felt regarding the medicine and the procedure. They will record these on a post-questionnaire given to them prior to discharge from the hospital. A stamped/addressed envelope will be supplied for patients to mail it back to the department.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
Since this protocol's review a year ago, there has been one publication reporting data from studies with similar study design in the literature. (Ref: Nagi SW: Hum Reprod., 01 Jul 2001; 16(7): 486-8.)

The number of subjects enrolled to the study since last APR at WRAMC is 28 and the total enrolled to date at WRAMC is 46. The total number enrolled study-wide is NA, if multi-site study. There were no reportable adverse events or patient withdrawn from this study.

CONCLUSIONS:
Although limited by sample size, this pilot study failed to demonstrate any clinical benefit for oral administration of misoprostol with regard to time needed for dilation, time needed for hysteroscopy, dilator with first resistance, ease of procedure, and post-operative pain. Further research is needed with a larger sample size for verification.

Report Date: 16 May 2002

Work Unit # 00-4406

# DETAIL SUMMARY SHEET

TITLE: Characterization of Peritoneal Fluid in Differentiating Benign from Malignant Adnexal Masses

KEYWORDS:

PRINCIPAL INVESTIGATOR: McBroom, John MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology

STATUS: O
INITIAL APPROVAL DATE: 05 July 2000

STUDY OBJECTIVE

If peritoneal fluid LDH, cholesterol, or interleukin-6 levels can discriminate between benign and malignant adnexal masses. We will also compare the serum:peritoneal fluid ratios to determine if this augments the ability to discriminate.
To determine if these chemistry values are significantly different between women with an adnexal mass and those without an adnexal mass.

TECHNICAL APPROACH

This research study involves patients who are scheduled to undergo surgery in the gynecology department. They will evaluate the fluid in the patient's peritoneal cavity and their blood for chemical markers. These markers may have the ability to determine if a patient with a mass has cancer or not. If they are undergoing gynecologic surgery and do not have a mass the patients participation is needed in order to compare their values to those women with a mass.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's review a year ago, there have been no publications reported.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 15. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS

Too early.

Report Date: 25 February 2002 Work Unit #01-43002

# DETAIL SUMMARY SHEET

TITLE: GOG 0179: A Randomized Phase III Study of Cisplatin vs. Cisplatin Plus Topotecan vs. MVAC in Stage IVB, Recurrent or Persistent Carcinoma of the Cervix

KEYWORDS:

PRINCIPAL INVESTIGATOR: LTC G. Scott Rose MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 17 April 2001

STUDY OBJECTIVE
The first purpose is to determine if combination of cisplatin and topotecan or MVAC are better than cisplatin alone in the treatment of advanced or recurrent cervical cancer. The second purpose is to compare side effects and health-related quality of life between the three treatments.

TECHNICAL APPROACH
For patients with advanced, persistent or recurrent squamous cell carcinoma of the cervix no longer amenable to surgical resection or radiation therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this is the first review for this study, there have been no publications reporting data from studies with similar study design in the literature. The objectives of this investigation have not been fulfilled by prior studies.

The number of subjects enrolled to the study since last APR at WRAMC is N/A_and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 239, if multi-site study. Regimen III (MVAC arm) closed to patient entry 7/23/01. Review of adverse event reports by the committee revealed a 5% Treatment-Related Mortality rate on the MVAC arm. Grade 4 toxicities for Regimen III (MVAC arm) are 19 WBC, 3 hemoglobin, 6 platelets, 31 granulocytes, 2 other hematologic, 2 other cardiovascular, 1 coagulation, 3 constitutional, 2 nausea, 2 vomiting, 2 stomatitis/pharyngitis, 5 other GI, 2 genitourinary, 1 hemorrhage, 1 hepatic, 1 infection/febrile neut., 4 metabolic, 1 musculoskeletal, 1 other neurologic, 1 other pain. Grade 5 toxicities include 2 other cardiovascular, 4 infection/febrile neutr., 1 pulmonary.

Ref: Jan 02 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 25 February 2002

Work Unit #01-43003

# DETAIL SUMMARY SHEET

TITLE: GOG 0184: A Randomized Phase III Study of Tumor Volume Directed Pelvic Plus or Minus Para-Aortic Irradiation Followed by Cisplatin and Doxorubicin or Cisplatin, Doxorubicin and Paclitaxel for Advanced Endometrial Carcinoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: LTC G. Scott Rose MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 24 April 2001

STUDY OBJECTIVE
To compare treatment outcomes (survival and progression-free survival) in patients with Stage III-IV endometrial carcinoma ($\leq$ 2 cm residual disease) treated with tumor volume directed pelvic plus or minus para-aortic irradiation followed by cisplatin and doxorubicin or cisplatin, doxorubicin and paclitaxel chemotherapy. Compared short and long-term toxicities between the chemotherapy regimens.

TECHNICAL APPROACH
All patients with advanced endometrial carcinoma, of any histology including clear cell and serous papillary carcinomas.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This is the first review for this study. There have been no publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 164, if multi-site study. Grade 4 toxicities include 24 WBC, 25 ANC/AGC, 1 other hematologic, 2 cardiovascular, 1 nausea, 1 gastrointestinal-other, 1 neurologic-other.

Ref: Jan 02 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 2 April 2002 Work Unit # 01-43004

# DETAIL SUMMARY SHEET

TITLE: GOG 0182: A Phase III Randomized Trial of Paclitaxel and Carboplatin Versus Triplet of Sequential Doublet Combinations in Patients with Epithelial Ovarian or Primary Peritoneal Carcinoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: LTC G. Scott Rose, MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 15 May 2001

STUDY OBJECTIVE
To compare the efficacy of each experimental arm with the control arm (paclitaxel and carboplatin). Efficacy will be determined through analysis of overall survival (OS) and progression-free survival (PFS). A single interim analysis based on PFS will be performed to select promising arms for full accrual.

TECHNICAL APPROACH
This is a Phase III randomized trial of paclitaxel and carboplatin versus three drugs given at the same time or two drugs given at the same time in patients with epithelial ovarian or primary peritoneal cancer.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This is the first APR for this study. There have been no publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is 7. The total number enrolled study-wide is 667, if multi-site study. Grade 4 toxicities for Arms A, B, C, D, and E include: 2A/8B/8C/2D/7E-WBC, 2B/3E/-HGB, 1A/4B/1C/5D/3E-Platelets, 39A/48B/52C/34D/23E-Granulocytes, 2B/1D/1E-Other Hematologic, 1D-Allergy, 2A/1B/2E-Cardiovascular, 1B-Coagulation, 1C/2D-Constitution, 1B-Dermatologic, 1B/1E-Gastrointestinal, 1B-GU/Renal, 1A/1B/1E-Hemorrhage, 1A/1D/1E-Infection/Fever, 1B/2E-Metabolic, 1D-Musculoskeletal, 1B-Central Neurologic, 1A/1D-Pulmonary.
Grade 5 toxicities include: 1B/2E-Cardiovascular, 2B-Constitution, 1D/1E-Infection/Fever, 1E-Central Neurologic.

Ref: Jan 02 GOG Statistical Report

CONCLUSIONS
A preliminary review of dose-limiting toxicity, adverse event reports, and treatment delivery confirms the feasibility of each regimen as written. Accrual on all five arms continues pending planned interim analysis.

Report Date: 2 April 2002

Work Unit # 01-43005

# DETAIL SUMMARY SHEET

TITLE: GOG 0189: Randomized Phase III Crossover Trial of Chemotherapy (Doxorubicin/Cisplatin /Paclitaxel and G-CSF) vs. Hormonal Therapy (Tamoxifen/Megestrol Acetate) in Patients with Stage III & IV or Recurrent Endometrial Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: LTC G. Scott Rose, MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 15 May 2001

STUDY OBJECTIVE

To determine if combination doxorubicin, cisplatin (TAP) and paclitaxel chemotherapy improved progression-free survival and response when compared to hormonal therapy. To determine if the sequence of treatments, alternating megestrol acetate and tamoxifen (MAT) hormone therapy or TAP chemotherapy, affects survival. To determine if progesterone receptor status provides information on whether a patient is more likely to benefit from TAP chemotherapy.

TECHNICAL APPROACH

The patient has been diagnosed with endometrial cancer that cannot be cured with surgery or radiation therapy. The patient will be randomized to receive one of two treatments which will also include a crossover design to assess the effect of therapy sequence on overall survival.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This is the first APR for this study. There have been no publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 17, if multi-site study. There are no Grade 4 toxicities reported.

Ref: Jan 02 GOG Statistical Report

CONCLUSIONS

Too early.

Report Date: 19 September 2001 Work Unit # 01-4301

# DETAIL SUMMARY SHEET

TITLE: ACRIN 6651: Role of Radiology in the Pretreatment Evaluation of Invasive Cervical Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 21 November 2000

STUDY OBJECTIVE
This study is to determine the usefulness of modern imaging in diagnosing and evaluating cervical cancer. Specifically, to see how accurate imaging is when it is compared to surgical findings, and if in the future modern imaging can represent a "one-stop shop" before making treatment decisions in patients with newly diagnosed cancer of the cervix.

TECHNICAL APPROACH
Patients with documented cervical cancer and clinical FIGO Stage IB1 and tumor size >2cm, Stage IB2, and greater, who are scheduled for surgery, will be imaged preoperatively with CT and MRI.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This is the first APR for this study at our institute. There have been no publications reporting data from this study.

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 110, if multi-site study.

CONCLUSIONS
Too early.

Report Date: 13 November 2001

Work Unit # 01-44002

# DETAIL SUMMARY SHEET

TITLE: The Comparison of the Effectiveness of Burch Colposuspension Versus Suburethral Sling in the Management of Primary Genuine Stress Urinary Incontinence

KEYWORDS:

PRINCIPAL INVESTIGATOR: Lockrow, Ernest G. LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecology

STATUS: O
INITIAL APPROVAL DATE: 9 January 2001

STUDY OBJECTIVE:
Comparison of effectiveness of primary sling versus primary burch.

TECHNICAL APPROACH:
Chart review and patient questionnaires.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Charts have been reviewed and data sheets completed. Patient questionnaires have been mailed. This is the first APR for this study and there has been no literature to report. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 74. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
Too early since final approval was in August 2001.

Report Date: 14 November 2001 Work Unit # 01-44003

# DETAIL SUMMARY SHEET

TITLE: Fragile Histidine Triad (FHIT) Expression in Advanced Cervical Carcinoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES: Krivak, Thomas MAJ MC

DEPARTMENT: Obstetrics and Gynecology STATUS: C
SERVICE: Gynecologic Oncology Service INITIAL APPROVAL DATE: 9 January 2001

## STUDY OBJECTIVE

We propose to use the DoD tumor registry database to identify patients with advanced cervical carcinoma and evaluate for FHIT expression in tumor cells in patients with recurrent disease after therapy.

## TECHNICAL APPROACH

The FHIT assessment of tissue is performed by histochemical techniques. These techniques are applied to tissue samples that have been paraffin embedded and 5-micron selections cut onto slides. FHIT assessment will be performed at the National Cancer Institute Rockville lab. No paraffin embedded tissue will be sent out. Pathology at WRAMC will pull the available tissue and will perform the 5-micron sectioning and only the slides will be sent out. The slides will be picked up and stained by the principal or associate investigator. The slides will have indirect identifiers placed on them. The slides will be cataloged in a blinded fashion so that the investigators will not know the outcome prior to the study. This will also serve to blind the interpreted information.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No literature to report on this study. This is the first APR for the study. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 13. The total number enrolled study-wide is N/A, if multi-site study. No adverse events to report. This study closed June 2001 per Dr. Krivak. This study can be closed here at Walter Reed.

## CONCLUSIONS

Too early.

Report Date: 12 December 2001

Work Unit # 01-44004

# DETAIL SUMMARY SHEET

TITLE: Creation of a Tissue Library for the Study of Molecular Alterations Characteristic of Uterine Leiomyomata

KEYWORDS:

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES: Rose, G. Scott LTC MC

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecology Service

STATUS: O
INITIAL APPROVAL DATE: 20 February 2001

STUDY OBJECTIVE

1) Create a tissue bank of uterine fibroids to facilitate the investigation of characteristic molecular alterations.
2) Collect normal DNA from myometrium and blood cells in addition to uterine fibroids to facilitate genetic analysis.
3) Develop primary and immortalized cell cultures from uterine leiomyomata specimens.

TECHNICAL APPROACH

Following completion of the hysterectomy the surgeon will accompany the specimen to the anatomic pathology unit in order to obtain tissue samples for the bank.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this is the first APR for this study there have been no publications reporting data from studies with similar study design in the literature. The objectives of this investigation have not been fulfilled by prior studies.

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is 16. The total number enrolled study-wide is N/A, if multi-site study.
No adverse events have been reported.

CONCLUSIONS

Too early.

Report Date: 18 April 2002 Work Unit # 01-44005

# DETAIL SUMMARY SHEET

TITLE: An Observational Trial To Evaluate Tissue and Peripheral Immune Response to HPV 16-Induced Cervical Intraepithelial Neoplasia

KEYWORDS:

PRINCIPAL INVESTIGATOR: Parker, Mary F., LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: INITIAL APPROVAL DATE: 20 February 2001

STUDY OBJECTIVE
This is an observational study evaluating tissue and peripheral blood assays of endogenous immune response to cervical infection with human papilloma virus (HPV) 16, in correlation with clinical, histological, and virologic evaluation. No investigation therapy will be involved. All patients will receive state-of-the-art diagnostic and therapeutic care. This information will lay the groundwork for the responses, which will be evaluated in subsequent vaccine trials. The overall goal of this initial study is to characterize the immune response to cervical precursor lesions.

1. To characterize local tissue response to high-grade cervical intraepithelial lesions.
2. To characterize peripheral measures of immune response in patients with high-grade cervical intraepithelial lesions.
3. To correlate these assays of immune response with known clinical, histopathologic, and virologic prognostic features of HPV-induced disease.

The secondary objectives of this study are:

1. To estimate person-to-person variations in clinical endpoints including change in lesion size and change in viral load.
2. To characterize the magnitude of change attributable to standard of care, in these endpoints.
3. To estimate the within person variability of these measures over the course of the observation period.

TECHNICAL APPROACH
The technical approach involves understanding how the immune system reacts to the pre-cancerous changes and to a virus call HPV 16 (human papilloma virus) that may be causing the pre-cancerous changes. Swabs of the cervix and blood tests will be performed to see how many HPV 16 viruses are present in the cervix and to look at special blood cells that are part of the immune system. Cervical tissue removed for biopsies or treatment of the pre-cancerous changes will also be analyzed to look for special cells that are part of the immune system. The results of his study will be used to decide which immune responses will be looked at in the future.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this is the first APR for this study there have been no publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is 0. Of the 80 patients consented for participation at Johns Hopkins University, there are 16 evaluable patients to dated. No adverse events have been reported.

CONCLUSIONS
Too early.

Report Date: 19 September 2001

Work Unit # 01-4401

# DETAIL SUMMARY SHEET

TITLE: Creation of a Tissue Library for the Study of Molecular Carcinogenesis in Gynecologic Malignancies

KEYWORDS:

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecology Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 21 November 2000

STUDY OBJECTIVE:
Create a tissue bank of uterine fibroids to facilitate the investigation of characteristic molecular alterations. Collect normal DNA from myometrium and blood cells in addition to uterine fibroids to facilitate genetic analysis. Develop primary and immortalized cell cultures from uterine leiomyomata specimens.

TECHNICAL APPROACH
Patients who present to the WRAMC GYN Oncology division and are found to require surgery for uterine leiomyomas will be considered eligible for participation in this protocol during the first year of activation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This is the first APR for this study and there have been no publications reporting data from this study and other with similar study design.

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
Too early.

Report Date: 14 November 2001 Work Unit # 4113

# DETAIL SUMMARY SHEET

TITLE: Cooperative Gynecologic Oncology Group

KEYWORDS: gynecologic, oncology, group

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 31 January 1974

STUDY OBJECTIVE
Walter Reed section of Gynecologic Oncology is involved with the nationally organized Gynecologic Oncology Group, consisting of 40 major medical centers in the country interested in the area of gynecologic tumors and the treatment of gynecologic cancer. The GOG is recognized and funded through the National Cancer Institute.

TECHNICAL APPROACH
Walter Reed is active in approximately 48 GOG protocols. Presently, there are approximately 60 protocols that are either active or continue to provide significant data. These protocols involve treatment of ovarian carcinoma, cervical carcinoma, adenocarcinoma of the endometrium, uterine sarcoma, vulvar carcinoma, and gestational trophoblastic disease.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Approximately 1152 patients have been entered into GOG protocols from WR; 36 during this year. The number of subjects enrolled to the study since last APR at WRAMC is 36 and the total enrolled to date at WRAMC is 1152. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
Detailed in individual reports.

Report Date: 26 February 2002

Work Unit # 4229

# DETAIL SUMMARY SHEET

TITLE: GOG 86A: Master Protocol for Phase II Drug Studies in Treatment of Advanced or Recurrent Carcinoma of the Endometrium

KEYWORDS: advanced, carcinoma, endometrium

PRINCIPAL INVESTIGATOR: LTC G. Scott Rose MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 29 April 1986

## STUDY OBJECTIVE

To identify additional active agents for treating advanced or recurrent endometrial adenocarcinoma by studying single new drugs in patients with this disease who have not been previously exposed to chemotherapy.

## TECHNICAL APPROACH

Patients must have histologically confirmed advanced, persistent, or recurrent endometrial carcinoma with documented disease progression after local therapy. All patients must have measurable disease. Patients must have failed local therapeutic measures or must be considered incurable with local therapy.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This is a master protocol. Please see individual protocols for further information.

## CONCLUSIONS

See individual protocols for further information.

Report Date: 4 April 2002 Work Unit # 4231

# DETAIL SUMMARY SHEET

TITLE: GOG 87A: Master Protocol for Phase II Drug Studies in the Treatment of Recurrent or Advanced Uterine Sarcomas

KEYWORDS: advanced, uterus, sarcoma

PRINCIPAL INVESTIGATOR: LTC G. Scott Rose MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 27 May 1986

STUDY OBJECTIVE
To allow the best possible chance for a new cytotoxic agent to demonstrate activity, this study constitutes a Phase II design in a population of patients who have had no prior drug therapy.

TECHNICAL APPROACH
To treat an average sample size of 30 patients per drug studied for each of the following cell categories: mixed mesodermal tumor, leiomyosarcoma, and other sarcomas. Patients will have histological confirmed advanced, persistent, or recurrent uterine sarcoma with documented disease progression after appropriate local therapy. Each patient will receive a chemotherapeutic regimen as outlined in each segment of the protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This is a master protocol. Please see individual protocols for further information.

CONCLUSIONS
See individual protocols for further information.

Report Date: 29 January 2002 Work Unit # 4244

# DETAIL SUMMARY SHEET

TITLE: GOG 90: Evaluation of Cisplatin, Etoposide, and Bleomycin (BEP) Induction Followed by Vincristine, Dactinomycin, and Cyclophosphamide (VAC) Consolidation in Advanced Ovarian Germ Cell Tumors, Phase II

KEYWORDS: ovarian, germ cell, tumors

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 31 March 1987

## STUDY OBJECTIVE

To evaluate the effect of induction chemotherapy with cisplatin plus etoposide plus bleomycin (BEP), followed by consolidation with vincristine plus dactinomycin plus cyclophosphamide (VAC) in previously untreated patients with advanced ovarian germ cell tumors.

## TECHNICAL APPROACH

Eligible patients include those with histologically confirmed malignant germ cell tumors of the ovary who have incompletely resected Stage II, III, or IV disease. Patients who have previously received pelvic radiation therapy will be eligible, but the initial dose of etoposide will be reduced 20%.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's review one year ago, there have been no new publications reporting data involving this study. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 131, if multi-site study. Grade 4 toxicities include 45 leukopenia, 15 thrombocytopenia, 76 granulocytopenia, 5 GI, 2 fever, 4 anemia, 1 pulmonary, 1 allergic reaction, 1 hepatic, 1 metabolic, 1 sepsis, 1 leukemia/death. This protocol was closed to patient entry effective 27 July 1998.

Ref: Jan 02 GOG Statistical Report

## CONCLUSIONS

Data from this and other studies have identified patients that should and should not undergo second look laparotomy. Patients with advanced dysgerminoma have very high response rate to chemotherapy.

Report Date: 4 April 2002 Work Unit # 4247

# DETAIL SUMMARY SHEET

TITLE: GOG 95: Randomized Clinical Trial for the Treatment of Women with Selected Stage IC and II (A, B, C) and Selected Stage IAi and IBi and IAii and IBii Ovarian Cancer, Phase III

KEYWORDS: randomized, ovarian, cancer

PRINCIPAL INVESTIGATOR: LTC G. Scott Rose, MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 26 May 1987

STUDY OBJECTIVE
This study seeks to compare the progression-free interval and overall survival between p32 and a combination of cyclophosphamide and cisplatin for patients with early ovarian cancer and to determine the patterns of relapse for each form of therapy.

TECHNICAL APPROACH
All patients must have a histopathologic diagnosis of epithelial ovarian cancer of each histologic cell type: serous mucinous; others include endometrioid, transitional mesonephroid (clear cell), adenocarcinoma (endometrioid with squamous metaplasia), mixed epithelial, and unclassifiable (undifferentiated).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review last year, there have been no additional publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 6. The total number enrolled study-wide is 251, if multi-site study. Grade 4 toxicities include 86 neutropenic episodes, 4 thrombocytopenias, and 1GI. Two patients experienced small bowel perforation during p32 administration. There have been two treatment related deaths. This protocol was closed to patient entry 14 March 1994.

Ref: Jan 02 GOG Statistical Report

CONCLUSIONS
After adjusting for stage and histologic grade, the recurrence rate on the cisplatin regimen is 34% lower than the p32 regimen. Estimated relative risk of 0.665 (90% confidence interval: 0.440-1.006).

Report Date: 3 May 2002 Work Unit # 4254

# DETAIL SUMMARY SHEET

TITLE: GOG 93: Evaluation of Intraperitoneal Chromic Phosphate Suspension Therapy Following Negative Second-Look Laparotomy for Epithelial Ovarian Carcinoma, Stage III, Phase III

KEYWORDS: chromic phosphate, ovarian, carcinoma

PRINCIPAL INVESTIGATOR: G. Scott Rose, LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 28 July 1987

STUDY OBJECTIVE
To evaluate the role of intraperitoneal chromic phosphate suspension therapy in patients with Stage III epithelial ovarian carcinoma who have no detectable evidence of disease at the second-look laparotomy.

TECHNICAL APPROACH
Patients will be given Topotecan *.5 mg/m$^2$ IV over 24 hours every three weeks until progression of disease or adverse effects prohibit further therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since the protocol's review one year ago, there have been no new publications reporting data involving this study.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 267, if multi-site study. Grade 4 toxicities are 1 hematologic and 3 GI. This protocol was closed to patient entry on 28 October 1996.

Ref: Jan 2002, GOG Statistical Report

CONCLUSIONS
No significant differences were noted in the progression-free and overall survival between the intraperitoneal chromic phosphate treatment group and the observation group.

Report Date: 24 July 2002 Work Unit # 4255

# DETAIL SUMMARY SHEET

TITLE: GOG 78: Evaluation of Adjuvant Vinblastine, Bleomycin and Cisplatin Therapy in Totally Reducing Choriocarcinoma, Endodermal Sinus Tumor or Embryonal Carcinoma of the Ovary, Pure and Mixed with Other Elements, Phase II

KEYWORDS: VP-16, bleomycin, cisplatin

PRINCIPAL INVESTIGATOR: Rose G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 29 September 1987

STUDY OBJECTIVE
To evaluate the effect of adjuvant VP-16, bleomycin, and cisplatin chemotherapy in patients with endodermal sinus tumor, choriocarcinoma, embryonal carcinoma, and grades 2 and 3 immature teratoma of the ovary after removal of all gross tumors.

TECHNICAL APPROACH
Eligible patients include those with histologically confirmed Stage I choriocarcinoma, endodermal sinus tumor, embryonal carcinoma, and grades 2 and 3 immature teratoma. Patients with Stage II and III disease are also eligible if all gross tumor is removed. Serum AFP and beta-HCG levels should be normal.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 117, if multi-site study. Grade 4 toxicities reported on the last APR include 8 leukopenia, 3 thrombocytopenia, 39 granulocytopenia, 2 GI, 1 dermatologic, and 2 anemia. This study was closed to patient accrual 10 February 1992.

Ref: Jan 02 GOG Statistical Report

CONCLUSIONS:
This trial has confirmed the effectiveness of BEP in patients with ovarian germ cell tumors who have been initially completely resected. Nearly all patients treated this way will survive free of cancer. Short and long-term morbidity is acceptable.

Report Date: 6 September 2002 Work Unit # 4257

# DETAIL SUMMARY SHEET

TITLE: GOG 99: A Phase III Randomized Study of Adjunctive Radiation Therapy in Intermediate Risk Endometrial Adenocarcinoma

KEYWORDS: radiation, endometrial, adenocarcinoma

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 27 October 1987

## STUDY OBJECTIVE

1) To determine if patients with intermediate-risk endometrial adenocarcinoma who have no spread of disease to their lymph nodes benefit from postoperative pelvic radiotherapy, and 2) evaluate how the addition of pelvic radiotherapy will alter the site and rate of cancer recurrence in these intermediate-risk patients.

## TECHNICAL APPROACH

Patients with primary histologically confirmed grades 2 and 3 endometrial adenocarcinoma are eligible. Patients must have had a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling, pelvic washings, and found to be surgical Stage I. Patients must have myometrial invasion.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's last review there have been no publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 9 (1 now deceased). The total number enrolled study-wide is 448, if multi-site study. Grade IV toxicities include 4 GI, 5 GI obstruction, 1 cutaneous, 1 pulmonary. This study was closed to patient entry effective 3 July 1995.

## CONCLUSIONS

The use of adjuvant RT in women with intermediate risk endometrial cancer decreases the risk of recurrences, but has an inappreciable effect on overall survival.

Report Date: 3 May 2002 Work Unit # 4266

# DETAIL SUMMARY SHEET

TITLE: GOG 76A: Master Protocol for Phase II Drug Studies in the Treatment of Advanced or Recurrent Squamous Cell Carcinoma of the Cervix

KEYWORDS: advanced, squamous cell carcinoma, cervix

PRINCIPAL INVESTIGATOR: G. Scott Rose, LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 26 July 1988

STUDY OBJECTIVE
To continue identification of new active drugs in the treatment of advanced or recurrent squamous cell carcinoma of the cervix so that combinations of cytotoxic drugs can be formed which might lead to an improved complete remission rate.

TECHNICAL APPROACH
Patients enrolled in individual protocols under this Master Protocol will have histologically confirmed, advanced, persistent, or recurrent squamous cell carcinoma of the cervix with documented disease progression after local therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
This is a master protocol. Please see individual protocols for further information.

Ref: January 2002, GOG Statistical Report

CONCLUSIONS:
See individual protocols.

Report Date: 15 November 2001 Work Unit # 4274

# DETAIL SUMMARY SHEET

TITLE: GOG 104: Intraperitoneal Cisplatin/Intravenous Cyclophosphamide Vs. Intravenous Cisplatin/Intravenous Cyclophosphamide in Patients with Nonmeasureable Disease Stage III Ovarian Cancer, Phase III

KEYWORDS: cisplatin, cyclophosphamide, ovary

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 31 January 1989

STUDY OBJECTIVE
To carry out a Phase III randomized trial of intermediate dose intraperitoneal cisplatin plus intravenous cyclophosphamide versus intermediate dose intravenous cisplatin plus intravenous cyclophosphamide for optimal Stage III ovarian cancer.

TECHNICAL APPROACH
Patients will be randomized to receive one of the two regimens listed above. Eligible patients must have a histologically confirmed pure epithelial ovarian carcinoma. Those with a borderline tumor will be excluded.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, there have been a couple of publications in the works for this study. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 649, if multi-site study. Grade 4 toxicities include 1 abdominal pain, 20 anemia, 5 anorexia, 1 anxiety/depression, 1 clinical hearing loss, 3 creatinine, 1 dehydration, 2 infection, 1 edema, 189 granulocytopenia, 5 hepatic-bilirubin, 1 hypotension, 53 leukopenia, 2 nausea/vomiting, 2 pulmonary, 1 renal cr. clearance, 1 renal-other, 1 sepsis, 1 stomatitis, 15 thrombocytopenia, and 1 vision. Protocol was closed to patient enrollment effective 15 July 1992.

Ref: Jul 01 GOG Statistical Report

CONCLUSIONS
The ovarian cancer patients with optimally debulked (less than 2cm residual tumor mass) Stage III disease, IP administration of cisplatin is associated with statistically significant prolongation of survival and fewer incidences of clinical hearing loss, tinnitus, granulocytopenia, leukopenia, and thrombocytopenia. The IV administration has fewer incidences of abdominal pain and cramping. The IP administration is recommended for cisplatin treatment of this patient population.

Report Date: 4 April 2002

Work Unit # 4277

# DETAIL SUMMARY SHEET

TITLE: GOG 108: Ifosfamide and the Uroprotector, Mesna, with or without Cisplatin in Patients with Advanced or Recurrent Mixed Mesodermal Tumors of the Uterus, Phase III

KEYWORDS: ifosfamide, uterine, sarcoma

PRINCIPAL INVESTIGATOR: LTC G. Scott Rose, MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: C
INITIAL APPROVAL DATE: 23 May 1989

## STUDY OBJECTIVE

To confirm reported high response rates of advanced or recurrent mixed mesodermal tumors of the uterus to ifosfamide/Mesna. To determine whether the addition of cisplatin to ifosfamide/Mesna improves response rates or survival in patients with these tumors.

## TECHNICAL APPROACH

Eligible patients include those with primary, histologically confirmed, heterologous or homologous (carcinosarcoma) mixed mesodermal tumors of the uterus. All patients must have measurable disease. Patients who have received prior chemotherapy are not eligible.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been no new publications this year since the last APR for studies with similar study design.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is 224, if multi-site study. Two are now deceased and 1 surviving. Within Walter Reed, one patient experienced disease progression and died from disease. Grade 4 toxicities include 1 hematologic toxicity, 68 neutropenic episodes, 36 thrombocytopenias, and 4 GI. This protocol was closed to patient entry 29 July 1996. Although one patient at WRAMC has survived, this patient will not be followed up as part of this research project. This protocol is now terminated effective 4 May 2001. This study can now be closed here at Walter Reed Army Medical Center.

Ref: Jan 02 GOG Statistical Report

## CONCLUSIONS

Combination therapy results in a higher response rate, greater toxicity, and no improvement in survival when compared with ifosfamide alone. The study comparing Ifosfamide versus Ifosfamidel/Taxol is currently ongoing.

Report Date: 15 November 2001 Work Unit # 4281

# DETAIL SUMMARY SHEET

TITLE: GOG 8801: A Phase I Evaluation of Multiple Daily Fraction Radiation and Hydroxurea in Patients with Stage IIB, III, and IVA Carcinoma of the Cervix with Negative Para-aortic Nodes

KEYWORDS: radiation, hydroxyurea, cervix

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: C
INITIAL APPROVAL DATE: 30 January 1990

STUDY OBJECTIVE
To determine the toxicity of accelerated hyperfractionated radiation plus hydroxyurea in patients with cancer of the cervix. To determine the optimal tolerated dose of hyperfractionated radiation when combined with hydroxyurea and intracavitary radiation.

TECHNICAL APPROACH
Patients must have primary previously untreated histologically confirmed carcinoma of the cervix; squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma are eligible. Patients must have FIGO Stage IIB, IIIA, IIIB, or IV disease with negative para-aortic nodes. Patients must have a para-aortic lymphadenectomy and intraperitoneal exploration with cytologic washings as outlined in the protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since the last review the manuscript in press was published. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is 39, if multi-site study. Grade 3 toxicities include 4 GI toxicities, otherwise minimal toxicity. This protocol was closed to patient entry effective 14 February 1994. The protocol was terminated effective 11 August 1997. This protocol can be closed here at WR since the GOG will not collect any more data on these patients.

Ref: Jul 01 GOG Statistical Report

CONCLUSIONS
Dose level 3 appears to be intolerable in terms of chronic reactions. A fourth dose level is not planned.

Report Date: 15 November 2001 Work Unit # 4282

# DETAIL SUMMARY SHEET

TITLE: GOG 8901: A Phase I Evaluation of Multiple Daily Fraction Radiation and 5FU Plus Cisplatin in Stage IIB, III, IVA Carcinoma of the Cervix with Negative Para-aortic Nodes

KEYWORDS: radiation, 5FU, cisplatin

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: C
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 30 January 1990

STUDY OBJECTIVE
To determine the toxicity of accelerated hyperfractionated radiation plus 5-fluorouracil (5-FU) and cisplatin in patients with cancer of the cervix. To determine the optimal tolerated dose of hyperfractionated radiation when combined with 5-FU, cisplatin, and intracavitary radiation.

TECHNICAL APPROACH
Patients must have primary previously untreated histologically confirmed carcinoma of the cervix. Squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma are eligible. Patients must have FIGO Stage IIB, IIIB, or IVA disease with negative para-aortic nodes. Patients must have a para-aortic lymphadenectomy and intraperitoneal exploration with cytologic washings as outlined in the protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since last reported the manuscript in print has been published. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 34, if multi-site study. There have been three Grade 3-4 toxicities at dose level 3, one vault necrosis, and one rectovaginal fistula. Dose levels 1 and 2 had no treatment related complications. This protocol was closed to patient entry effective 8 November 1993. This protocol was terminated 11 August 1997. This protocol can be closed because the GOG will not be collecting any more data from these patients.

CONCLUSIONS
This chemotherapy regimen appears less toxic than hydroxyurea as given on GOG 8801. Dose level 3 appears to be tolerable both in terms of acute and chronic reactions. Data are maturing for acute/chronic reactions.

Report Date: 15 April 2002 Work Unit # 4309

# DETAIL SUMMARY SHEET

TITLE: GOG 120: A Randomized Comparison of Hydroxyurea vs. Hydroxyurea, 5-FU Infusion and Cisplatin vs. Weekly Cisplatin as Adjunct to Radiation Therapy in Patients with Stages II-B, III, or IV-A Carcinoma of the Cervix and Negative Para-Aortic Nodes

KEYWORDS: cervix, carcinoma, Phase III

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology INITIAL APPROVAL DATE: 30 June 1992

STUDY OBJECTIVE
To determine whether hydroxyurea; hydroxyurea, 5-FU infusion plus bolus cisplatin; or weekly cisplatin is superior as a potentiator of radiation therapy in locally advanced cervical carcinoma

TECHNICAL APPROACH
Patients with cervical carcinoma (Stages II-B, III-A, III-B, or IV-A) will undergo extraperitoneal staging surgery. Those patients with negative para-aortic nodes will then be randomized to receive radiotherapy plus either: 1) cisplatin; 2) cisplatin, 5FU, and hydroxyurea; or 3) hydroxyurea. Following the completion of therapy, the patients will be followed clinically.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review a year ago, there have been no publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 5. Two of the five patients enrolled at WRAMC are deceased. The total number enrolled study-wide is 575, if multi-site study. Grade IV toxicities reported in the last APR were 36 hematologic, 30 GI, 8 GU, 1 neurologic, 6 cutaneous, 1 fever, 2 hypomagnesemia. The protocol was closed to patient entry 21 April 1997.

Ref: January 2002 GOG Statistical Report

CONCLUSIONS
Cisplatin based chemotherapy and radiation is more effective than chemotherapy and radiation with hydroxyurea. The weekly cisplatin regimen is less toxic than the three-drug cisplatin-containing regimen.

Report Date: 13 June 2002 Work Unit # 4310

# DETAIL SUMMARY SHEET

TITLE: GOG 136: Acquisition of Human Ovarian and Other Tissue Specimens and Serum to be Used in Studying the Causes, Diagnosis, Prevention and Treatment of Cancer

KEYWORDS: ovarian, tissue, collection

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 25 August 1992

STUDY OBJECTIVE
To: 1) accomplish the collection of human ovarian tissue specimens and serum within GOG participating institutions; and 2) provide a long-term storage repository for ovarian tumors and serum. The material will be used in studies to better understand the molecular biology of ovarian tumors.

TECHNICAL APPROACH
All patients who have had ovarian tumor tissue or extra-ovarian peritoneal serous carcinoma tissue removed are eligible. All patients who have had ovaries removed because of a family history of ovarian cancer are eligible. The tissue, when removed, is shipped along with serum specimens to the GOG repository facility.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
According to GOG Statistical Report there have been at least 96 papers and 29 abstracts that have been generated using tissue bank materials. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 82. The total number enrolled study-wide is 4030, if multi-site study.

Ref: Jan 02 GOG Statistical Report.

CONCLUSIONS:
None.

Report Date: 24 July 2002

Work Unit # 4311

# DETAIL SUMMARY SHEET

TITLE: GOG 134: A Phase III Trial of Taxol at Three Dose Levels and G-CSF at Two Dose Levels in Platinum-Resistant Ovarian Carcinoma

KEYWORDS: taxol, ovarian, G-CSF

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 29 September 1992

## STUDY OBJECTIVE

To: 1) determine if taxol at different dose levels affects response rate, progression-free interval, or survival in patients with platinum-resistant ovarian cancer; 2) compare toxicities of the regimens; and 3) compare the efficacy and toxicity of G-CSF in patients receiving high-dose taxol.

## TECHNICAL APPROACH

Patients with platinum-resistant ovarian epithelial cancer with clinically measurable disease will be randomized to receive taxol at three different dose levels. Patients at the highest dose level will also receive G-CSF at one of two dose levels. Patients are then followed clinically to assess response.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's last review there have been no new publications reporting data. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 6. The total number enrolled study-wide is 449, if multi-site study. Grade 4 toxicities include 1 pulmonary, 1 renal, and 3 infections. This study was closed to patient accrual 6 February 1995.

Ref: Jan 02 GOG Statistical Report

## CONCLUSIONS

Prognostic factors associated with survival and PFS include prior platinum resistance, measurable disease, mucinous or clear cell histology and poor performance score.

Doubling the dose of G-CSF did not reduce the frequency of neutropenic fever following the first course of treatment.

Report Date: 23 August 2001 Work Unit # 4312

# DETAIL SUMMARY SHEET

TITLE: GOG 122: Whole Abdominal Radiotherapy vs. Combination Doxorubicin-Cisplatin Chemotherapy in Advanced Endometrial Carcinoma

KEYWORDS: radiation, endometrial, chemotherapy

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 27 October 1992

STUDY OBJECTIVE
1) To assess treatment outcomes (survival and progression-free interval) and failure patterns for advanced Stages III and IV endometrial adenocarcinoma patients using adjuvant, whole, abdominal radiation therapy vs. combination intravenous chemotherapy, and 2) treatment toxicities of either therapy.

TECHNICAL APPROACH
All patients with endometrial carcinoma undergo surgical staging (TAH, BSO, LNS) and in advanced stage disease are randomized to adjuvant whole abdominal radiation (tele-therapy) vs. combination intravenous doxorubicin-cisplatin chemotherapy every 3 weeks for eight courses.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Nothing has changed from last year's review; there have been no publications reporting data from this study.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4 (1 now deceased). There was a typo of 3 on last report. The total number enrolled study-wide is 422, if multi-site study. Grade IV toxicities include 34 WBC, 124 ANC, 21 platelets, 6 other hematological, 130 max. hematological, 14 gastrointestinal, 2 hepatic, 2 genitourinary, 5 cardiac, 2 vascular, 1 pulmonary, 2 neurological, 1 fatigue, 6 sepsis/infection, 3 fever, and 1 dermatological. This protocol was closed to patient entry effective 25 February 2000.

Ref: Jul 01 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 1 October 2001 Work Unit # 4319

# DETAIL SUMMARY SHEET

TITLE: GOG 118: Evaluation of the Predicted Value of Antineoplastic Drug Resistance Determined by In-Vitro Assay

KEYWORDS: carcinoma, ovarian, drug

PRINCIPAL INVESTIGATOR: Rose, G. Scott MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: C
INITIAL APPROVAL DATE: 30 November 1993

## STUDY OBJECTIVE

To evaluate the correlation between response to chemotherapy and in vitro drug resistance assays. To correlate lab results with clinical responses, both complete (CR) and partial (PR).

## TECHNICAL APPROACH

Patients with Stage III/IV ovarian epithelial carcinoma treated with taxol/CDDP will be eligible for entry into this study.

## PRIOR AND CURRENT PROGRESS

Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature.

Ref: Jul 01 GOG Statistical Report

## CONCLUSIONS

Too early.

Report Date: 21 September 2001 Work Unit # 4320

# DETAIL SUMMARY SHEET

TITLE: GOG 140: An Assessment of Age and Other Factors Influencing Protocol vs. Alternative Treatments for Patients with Epithelial Ovarian Cancer Referred to Gynecologic Oncology Group Institutions

KEYWORDS: familial, carcinoma, genetics

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 30 November 1993

STUDY OBJECTIVE
To assess the frequency at which patients with ovarian cancer enroll in prospective clinical studies. To assess whether age effects enrollment vs. other demographic or clinicopathological factors.

TECHNICAL APPROACH
All patients with primary ovarian carcinoma, including low malignant potential tumors, will fill out a patient questionnaire.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 24 (4 have died). The total number enrolled study-wide is 982, if multi-site study. This protocol was closed to patient entry 5 February 1996.

Ref: Jul 01 GOG Statistical Report

CONCLUSIONS
Among patients entered on this protocol there is a significant relationship between age at diagnosis and stage of disease at diagnosis. In fact older patients tend to present with more advanced disease than younger patients.

This preliminary analysis suggests that among early stage patients, few are enrolled on GOG studies and this does not vary by age. However, among advanced stage patients entered on this survey study, 36% of younger patients compared to 26% of older patients were enrolled on GOG clinical studies. Further analysis is underway to investigate whether the relationship of age to planned treatment among advanced stage patients can be explained by other coexisting medical conditions related to the aging process. The validity of this study depends upon the extent to which patients were "captured" for this study at each participating institution. Information is being collected from tumor registries to assess the number of patients missed and the reasons for failing to capture these patients.

Report Date: 19 October 2001

Work Unit # 4323

# DETAIL SUMMARY SHEET

TITLE: GOG 26LL: A Phase II Trial of Prolonged Oral Etoposide (VP-16) in Patients with Advanced Pelvic Malignancies

KEYWORDS: carcinoma, chemotherapy, pelvic

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 21 December 1993

## STUDY OBJECTIVE

To determine the efficacy of oral etoposide in patients with advanced pelvic malignancies.

## TECHNICAL APPROACH

Patients with histologically-confirmed recurrent or metastatic gynecologic cancer refractory to standard therapy with measurable disease receive oral VP-16 on days 1-21 monthly. Treatment continues until response or toxicity occurs.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 6 (5 now dead). The total number enrolled study-wide is 151, if multi-site study. Grade 4 toxicities include: 10 leukopenia, 4 thrombocytopenia, 14 neutropenia, 1 GI, 4 anemia, 1 pulmonary, and 1 infection. Study met accrual goal and closed to patient entry effective 5 September 2000.

Ref: Jan 01 GOG Statistical Report

## CONCLUSIONS

There is evidence of activity with this regimen in patients with recurrent epithelial ovarian carcinoma. Phase I studies of dose escalating oral Etoposide in combination are being conducted in untreated and previously treated ovarian carcinoma.

Report Date: 19 October 2001 Work Unit # 4324

# DETAIL SUMMARY SHEET

TITLE: GOG 109: A Randomized Comparison of 5-FU Infusion and Bolus Cisplatin as an Adjunct to Radiation Therapy Alone in Selected Patients with Stages I-A2, I-B, and II-A Carcinoma of the Cervix Following Radical Hysterectomy and Node Dissection Phase III Intergroup

KEYWORDS: cisplatin, radiation, cervix

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 21 December 1993

STUDY OBJECTIVE
To determine whether the combination of 5-fluorouracil (5FU) and cisplatin used as an adjunct to radiation therapy will improve survival rate or progression-free survival and decrease extra pelvic failure compared to radiation therapy alone in patients with positive parametrical involvement or positive surgical margins following radical hysterectomy and lymph node dissection for Stages I-A2, IB, and IIA carcinoma of the cervix.

TECHNICAL APPROACH
Patients with Stage IA2, IB, and IIA invasive squamous, adeno or adenosquamous carcinoma of the cervix, status post radical hysterectomy with histologically-positive lymph nodes, parametric, or surgical margins will be enrolled. Patients will receive standard whole pelvic radiation with or without chemosensitization.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since the last review, there have been no new publications reported. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 226, if multi-site study. Grade 4 toxicities include 1 anemia, 1 cardiac, 5 diarrhea, 2 dyspnea, 12 granulocytopenia, 1 infection, 3 leukopenia, 1 skin ulceration (non-local), 2 small bowel obstruction, 1 stomatitis, and 3 vomiting. The protocol was closed to patient entry effective 12 December 1996.

Ref: Jan 01 GOG Statistical Report

CONCLUSIONS
It was concluded that the addition of chemotherapy to radiation therapy significantly improves progression-free and overall survival for high-risk, Stage I-A2 through II-A patients who undergo radical hysterectomy and pelvic lymphadenectomy for carcinoma of the cervix.

Report Date: 19 October 2001

Work Unit # 4325

# DETAIL SUMMARY SHEET

TITLE: GOG 123: A Randomized Comparison of Radiation Therapy and Adjuvant Hysterectomy vs. Radiation Therapy and Weekly Cisplatin and Adjuvant Hysterectomy in Patients with Bulky Stage IB Carcinoma of the Cervix (Phase III)

KEYWORDS: carcinoma, cervix, radiation

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 21December 1993

## STUDY OBJECTIVE

To determine if weekly cisplatin infusion improves local-regional control and survival when added to radiation therapy and extrafascial hysterectomy. Also, to determine the toxicities of these two treatments.

## TECHNICAL APPROACH

Patients with bulky IB and barrel-shaped cervical invasive squamous, adeno, or adenosquamous carcinomas who have surgically-negative pelvic/para-aortic nodes receive either whole pelvic radiation with or without cisplatin chemosensitization followed by extrafascial hysterectomy

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been no new publications reported since the last APR. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 374, if multi-site study. Grade 4 toxicities include 6 hematologic, 14 GI, 3 GU, 1 cardiovascular, and 1 cutaneous. This study was closed 7 April 1997 to patient accrual.

Ref: Jan 01 GOG Statistical Report

## CONCLUSIONS

The addition of weekly cisplatin during irradiation was associated with a reduction in risk of recurrence of 49% and a risk of death 46%. Both statistics were highly significant.

Report Date: 15 November 2001 Work Unit # 4329

# DETAIL SUMMARY SHEET

TITLE: GOG 149: A Randomized Study of Cisplatin Plus Ifosfamide and Mesna Versus Cisplatin, Bleomycin, Ifosfamide, and Mesna in Stage IV-B, Recurrent or Persistent Squamous Cell Carcinoma of the Cervix

KEYWORDS: cervix, carcinoma, chemotherapy

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: C
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 25 January 1994

STUDY OBJECTIVE
To determine if bleomycin plus ifosfamide/mesna plus cisplatin (BIP) improves response rate, response duration, and survival in advanced squamous cervical cancer compared to treatment with cisplatin plus ifosfamide/mesna. Also, to compare toxicities of these regimens.

TECHNICAL APPROACH
Patients with histologically proven Stage IVB, recurrent or persistent squamous cell cervical carcinoma with measurable disease are treated with either chemotherapy regimen.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review a year ago, there has been one additional publication. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2 (now deceased). The total number enrolled study-wide is 303, if multi-site study. Grade 4 toxicities include 136 leukopenia, 22 thrombocytopenia, 167 neutropenia, 7 anemia, 18 nausea/vomiting, 6 GI, 2 renal, 1 cardiac, 1 peripheral neurotoxicity, 3 central neurotoxicity, 2 hematuria, 1 pulmonary, 1 hepatic, 4 sepsis, 1 allergy reaction, and 1 infection. This protocol was closed to patient entry 28 April 1997. This protocol can be closed here at WRAMC because both patients enrolled are now deceased.

Ref: Jul 01 GOG Statistical Report

CONCLUSIONS
Response rate, progression free survival, and survival were essentially identical between the two arms.

Report Date: 15 November 2001

Work Unit # 4333

# DETAIL SUMMARY SHEET

TITLE: GOG #150 A Phase III Randomized Study of Whole Abdominal Radiotherapy (WAR) versus Combination Ifosfamide-Mensa with Cisplatin in Optimally Debulked Stage I, II, III or IV Carcinosarcoma (CS) of the Uterus

KEYWORDS: uterine, sarcoma, therapy

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 25 January 1994

STUDY OBJECTIVE

To compare outcomes and failure patterns in patients with Stage I-IV uterine carcinosarcoma treated with whole abdominal radiotherapy vs. combination chemotherapy with cisplatin/ifosfamide/mesna. Also, to compare toxicities of two regimens.

TECHNICAL APPROACH

All eligible patients will be enrolled who have had surgical Stage I-IV disease, s/o TAH, BSO, and maximal resection of macroscopic abdomino-pelvic lesions (including lymph nodes) to greater than 1 cm disease. All patients less than 8 weeks post-op will be randomized to either program.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 153, if multi-site study. Grade 4 toxicities include 1 anemia, 4 GI, 1 hepatic, 2 cardiovascular. Grade 4 late effects (adverse events which occurred or persisted after completing study treatment) 1 GI, 2 hepatic, and 1 other.

Ref: Jul 01 GOG Statistical Report

CONCLUSIONS

Too early.

Report Date: 5 April 2002 Work Unit # 4339

# DETAIL SUMMARY SHEET

TITLE: GOG 152: A Phase II Randomized Study of Cisplatin (NSC #119875) and Taxol (Paclitaxel) (NSC #125973) with Interval Secondary Cytoreduction Versus Cisplatin and Paclitaxel in Patients with Suboptimal Stage III Epithelial Ovarian Carcinoma

KEYWORDS: ovary, cancer, chemotherapy

PRINCIPAL INVESTIGATOR: LTC G. Scott Rose, MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 31 May 1994

STUDY OBJECTIVE
To determine if secondary cytoreduction contributes to progression-free interval and survival in patients with suboptimally debulked Stage III and IV epithelial ovarian cancer. Also, to determine the morbidity of the cytoreduction surgery.

TECHNICAL APPROACH
Suboptimal debulked Stage III and IV ovarian epithelial cancer patients receive three courses of taxol/cisplatinum intravenously. Patients who respond are randomized to an interim cytoreduction followed by three additional courses of taxol/cisplatinum versus no surgery but three courses of taxol/cisplatinum.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's last review there has been one publication reporting data for this study.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 7. The total number enrolled study-wide is 550, if multi-site study. Grade 4 toxicities include 23 leukopenia, 303 granulocytopenia, 1 thrombocytopenia, 23 GI, 2 pulmonary, 4 cardiac, 1 neurologic, 2 infection, and 4 metabolic. This study was closed to patient entry effective 29 January 2001.

Ref: Jan 02 GOG Statistical Report

CONCLUSIONS
Data is now mature and the results are being analyzed.

Report Date: 29 January 2002

Work Unit # 4365

# DETAIL SUMMARY SHEET

TITLE: GOG 157: A Randomized Phase II Trial of Carboplatin (AUC 7.5) and Paclitaxel 175 mg/m2 q 21 Days X Three Courses vs. the Same Regimen X Six Courses, in Patients with Selected Stage IC and II (A, B, C) and Selected IA and IB Ovarian Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 28 March 1995

STUDY OBJECTIVE
To evaluate any chemotherapy schedule dependence in the treatment of early-stage ovarian cancer.

TECHNICAL APPROACH
This is a Phase III protocol studying the difference between three vs. six cycles of taxol carboplatin in patients having early-stage ovarian cancer.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, there have been no publications reported, but a first draft is pending.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 8. The total number enrolled study-wide is 457, if multi-site study. Grade 4 toxicities include 9 leukopenia, 191 granulocytopenia, 41 thrombocytopenia, 1 anemia, 9 GI, 2 neurologic, 1 infection, and 4 allergy. This study was closed to patient accrual effective 25 May 1998.

Ref: Jan 02 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 26 February 2002 Work Unit # 4366

# DETAIL SUMMARY SHEET

TITLE: GOG 9404: p53 Mutation and c-erB-2 Expression in Advanced Stage Epithelial Ovarian Carcinoma and Correlation with Prognostic Factors and Treatment Outcomes

KEYWORDS: ovary, p53, c-erB-2

PRINCIPAL INVESTIGATOR: LTC G. Scott Rose MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: C
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 18 April 1995

STUDY OBJECTIVE
To determine the incidence of p53 and c-erB-2 mutations in advanced epithelial ovarian carcinoma.

TECHNICAL APPROACH
Molecular analysis is performed on archived tissue blocks from patients previously enrolled on GOG 111. DNA is extracted from slices of these blocks and probed for oncogene mutations.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been no additional publications reporting data from this study or similar study designs in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 145, if multi-site study. This protocol was closed to patient enrollment effective 18 May 1998. This protocol can be closed here at Walter Reed.

Ref: Jan 02 GOG Statistical Reports

CONCLUSIONS
Too early.

Report Date: 13 June 2002

Work Unit # 4370

# DETAIL SUMMARY SHEET

TITLE: GOG 158: A Phase III Randomized Study of Cisplatin and Paclitaxel (24-Hour Infusion) vs. Carboplatin and Paclitaxel (3-Hour Infusion) in Optimal Stage III Epithelial Ovarian Carcinoma

KEYWORDS: cisplatin, paclitaxel, ovarian

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 25 August 1992

STUDY OBJECTIVE
To compare recurrence-free interval and survival in patients with less than or equal to 1 cm residual Stage III epithelial ovarian cancer receiving cisplatin and paclitaxel administered by a 24-hour infusion vs. carboplatin plus paclitaxel administered by a 3-hour infusion.

TECHNICAL APPROACH
This is a Phase III study. Patients must have histologic diagnosis of epithelial ovarian cancer Stage III with less than or equal to 1 cm residual disease. All patients must have appropriate surgery for ovarian carcinoma.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, there has been one additional abstract awaiting first draft of secondary manuscript.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 3 (1 now deceased). The total number enrolled study-wide is 850, if multi-site study. Grade 4 toxicities include 72 leukopenia, 89 thrombocytopenia, 596 other hematologic, 54 GI, 1GU, 2 pulmonary, 6 cardiovascular, 2 neurologic, 3 fever, 9 allergic, 3 fatigue, 8 infection, 10 metabolic, 2 pain, 1 hepatic and 1 lymphatic.

Ref: Jan 02 GOG Statistical Report

CONCLUSIONS:
Too early.

Report Date: 22 October 2001

Work Unit # 4372

# DETAIL SUMMARY SHEET

TITLE: GOG # LAP1: Orientation and Evaluation Study in Performing a GOG Standardized Procedure for Laparoscopic FIGO Staging in Adenocarcinoma of the Endometrium

KEYWORDS: endometrium, cancer, laparoscopy

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: C
INITIAL APPROVAL DATE: 19 December 1995

STUDY OBJECTIVE
To determine the feasibility of laparoscopic surgery in managing patients with clinical Stage I endometrial cancer.

TECHNICAL APPROACH
Laparoscopic-assisted transvaginal hysterectomy with pelvic and para-aortic lymph node sampling. This procedure is videotaped to document safety and adequacy of the surgery.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The protocol has had no new publications since it's last review. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 62, if multi-site study. No grade 4 toxicities have been reported. This protocol was closed to patient entry effective Jan 26, 1998. This protocol has been terminated effective 20 April 2001. This protocol can be closed here at WRAMC.

Ref: Jan 01 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 5 April 2002

Work Unit # 4378

# DETAIL SUMMARY SHEET

TITLE: GOG 162: A Phase III Randomized Trial of Cisplatin (NSC #119875) with Paclitaxel (NSC #125973) Administered by Either 24-Hour Infusion or 96-Hour Infusion in Patients with Selected Stage III and Stage IV Epithelial Ovarian Cancer

KEYWORDS: ovary, neoplasm, taxol

PRINCIPAL INVESTIGATOR: LTC G. Scott Rose, MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 28 May 1996

## STUDY OBJECTIVE

To compare progression-free survival, overall survival and frequency of response of 24-hour vs. 96-hour paclitaxel (Taxol) infusions, each combined with cisplatin, in the treatments of selected stage III and stage IV epithelial ovarian cancer. To determine the incidence and severity of adverse events, including catheter complications and chemotherapy toxicity, for 96-hour infusions of paclitaxel. To examine the relationship between plasma paclitaxel concentrations and measures of drug toxicity and response in both 24-hour and 96- hour infusion schedules.

## TECHNICAL APPROACH

This is a Phase III trial randomizing between 24-hour and 96-hour taxol infusions in patients with advanced ovarian carcinoma.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been no publications reporting data from this study or from studies with similar study design in the literature.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 7. The total number enrolled study-wide is 293, if multi-site study. Grade 4 toxicities 50 leukopenia, 189 granulocytopenia, 11 thrombocytopenia, 1 anemia, 31 GI, 1 GU, 2 renal, 1 hepatic, 4 pulmonary, 5 cardiac, 10 infection, 1 pain, 2 central neuropathy, 2 allergy, and 8 metabolic. This study was closed to patient accrual effective 2 August 2000.

Ref: Jan 02 GOG Statistical Report

## CONCLUSIONS

Prolonged infusion of paclitaxel for 96 hours followed by cisplatin does not significantly increase progression-free survival overall survival when compared to 24-hour infusion of paclitaxel followed by cisplatin. However, granulocytopenia occurs with greater severity on the 24-hour infusion regimen.

Report Date: 3 May 2002 Work Unit # 4380

# DETAIL SUMMARY SHEET

TITLE: GOG # LAP2: A Phase III Randomized Clinical Trial of Laparoscopic Pelvic and Para-Aortic Node Sampling with Vaginal Hysterectomy and BSO vs. Open Laparotomy with Pelvic and Para-Aortic Node Sampling and Abdominal Hysterectomy and BSO in Endometrial Adenocarcinoma, Clinical Stages I, IIA, Grades I, II, and III

KEYWORDS: laparoscopy, lymphadenectomy, endometrium

PRINCIPAL INVESTIGATOR: G. Scott Rose, LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 30 July 1996

STUDY OBJECTIVE
To measure surgical outcomes in patients with early-stage endometrial cancer to open laparotomy vs. laparoscopic procedures.

TECHNICAL APPROACH
This is a Phase III study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been no publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is 15 and the total enrolled to date at WRAMC is 28. The total number enrolled study-wide is 1028, if multi-site study. Grade 4 toxicities include 2 urinary tract infection, 2 fever, 1 pelvic cellulitis, 2 abscess, 10 pulmonary embolus, 2 bowel obstruction, 2 ileus, 2 pneumonia, 1 urinary fistula, and 1 bowel fistula.

Ref: January 2002, GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 22 October 2001 Work Unit # 4382

# DETAIL SUMMARY SHEET

TITLE: GOG # 9302 – Laparoscopic Staging in Patients with Incompletely Staged Cancer of the Ovary, Primary Fallopian Tube Carcinoma and Primary Peritoneal Carcinoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 17 December 1996

STUDY OBJECTIVE
To determine the feasibility of performing laparoscopic staging in those patients incompletely staged by laparotomy. To evaluate the adverse effects related to laparoscopic staging.

TECHNICAL APPROACH
Laparoscopy will replace a second laparotomy in those patients incompletely staged with ovarian, fallopian tube, or peritoneal cancers.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's last review there is a manuscript in preparation. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 7 (1 disqualified). The total number enrolled study-wide is 73, if multi-site study. No grade 4 toxicities reported. Study met its accrual goal; and closed to patient entry effective 28 August 2000.

Ref: Jan 01 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 26 February 2002

Work Unit # 4389

# DETAIL SUMMARY SHEET

TITLE: GOG #164 Randomized, Controlled Trial of Salvage TX w/Paclitaxel & Carboplatin vs. Salvage TX w/Stem Cell Supported High-Dose Carboplatin, Mitoxantrone & Cyclophosphamide in Patients w/Persistent Low Volume Ovarian CA

KEYWORDS: ovarian, chemotherapy, bone marrow

PRINCIPAL INVESTIGATOR: LTC G. Scott Rose MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 24 April 1997

STUDY OBJECTIVE
1) To compare outcomes of salvage therapy with either standard dose chemo or bone marrow reconstitution following high dose chemo in patients with drug sensitive, low volume persistent ovarian cancer after standard therapy; 2) to compare the toxicities of these two salvage regimens; 3) to compare selected health related dimensions of quality of life in these two patient populations.

TECHNICAL APPROACH
This is a phase III trial design of the above. Parameters to be measured include overall survival, progressive free survival, toxicities, and selected quality of life issues.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 24, if multi-site study. This study was closed to patient entry 10 May 1999. This protocol was terminated effective 7 February 2000 due to insufficient accrual rate. No Grade 4 toxicities have been reported to date.

Ref: Jan 02 GOG Statistical Report

CONCLUSIONS
Study closed due to insufficient accrual rate.

Report Date: 23 July 2002 Work Unit # 4400

# DETAIL SUMMARY SHEET

TITLE: GOG 137: A Randomized Double-Blinded Trial of Estrogen Replacement Therapy Versus Placebo in Women with Stage I or II Endometrial Adenocarcinoma.

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 30 September 1997

## STUDY OBJECTIVE

To determine the effect of estrogen replacement therapy on recurrence free and overall survival in women with a history of stage I and II endometrial adenocarcinoma.

## TECHNICAL APPROACH

Patients are randomized to either receive ERT for 3 years, or a placebo for three years. Both groups are followed for five years.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is 2, and the total enrolled to date at WRAMC is 11. The total number enrolled study-wide is 1077, if multi-site study. No toxicities reported.

Ref: Jan 02 GOG Statistical Report

## CONCLUSIONS

Too early.

Report Date: 12 December 2001 Work Unit # 4403-98

# DETAIL SUMMARY SHEET

TITLE: GOG 141: Treatment of Patients with Suboptimal ("Bulky") Stage IB Carcinoma of the Cervix: A Randomized Comparison of Radical Hysterectomy and Pelvic and Para-Aortic Lymphadenectomy With or Without Neoadjuvant Vincristine and Cisplatin Chemotherapy

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: C
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 05 February 1998

STUDY OBJECTIVE
Determine neoadjuvant cisplatin and vincristine chemotherapy prior to radical hysterectomy and bilateral pelvic and para-aortic lymphadenectomy for patients with suboptimal stage IB carcinoma of the cervix improves progression-free survival.

TECHNICAL APPROACH
This is a Phase III trial for patients with suboptimal (bulky) stage IB carcinoma of the cervix.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's last review there have been no publications reporting data for this study.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 290, if multi-site study. Grade 4 toxicities include 4 hematologic, 7 GI, 1 GU, 1 hepatic, and 2 metabolic. This protocol was closed to patient accrual effective 23 July 2001. This protocol can be closed here at WRAMC.

Ref: Jul 01 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 13 December 2001

Work Unit # 4404-98

# DETAIL SUMMARY SHEET

TITLE: GOG 165: A Randomized Comparison of Radiation Plus Weekly Cisplatin vs. Radiation Plus PVI (Protracted Venous Infusion) 5FU in Patients with Stage IIB, IIIB, and IVA Carcinoma of the Cervix

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 05 February 1998

STUDY OBJECTIVE

To compare the progression-free survival of patients with advanced cervical cancer limited to the pelvis receiving radiation only to radiation plus weekly cisplatin. To compare the progression free survival of patients with advanced cervical cancer limited to the pelvis receiving radiation plus prolonged venous infusion (PVI) 5-fluorouracil to radiation plus weekly cisplatin. To determine the relative toxicities of radiation plus chemotherapy (either weekly cisplatin or PVI 5 fluorouracil) compared to radiation alone. To compare the progression-free survival and survival of patients with advanced cervical cancer limited to the pelvis whom; (a) smoke at the time of diagnosis and (b) smoke during radiation therapy vs. those who quit.

TECHNICAL APPROACH

This study deals with patients with stage II-B, III-B and IV-A carcinoma of the cervix.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 352, if multi-site study. Grade 4 toxicities include 11 hematologic, 25 GI, 5 GU, 2 pulmonary, 3 metabolic, 2 fatigue, 3 cutaneous, 2 cardiovascular. This protocol was closed to patient entry effective August 2, 2000.

Ref: Jul 01 GOG Statistical Report

CONCLUSIONS

Too early.

Report Date: 13 December 2001 Work Unit # 4406-98

# DETAIL SUMMARY SHEET

TITLE: GOG 161: A Phase III Trial of Ifosfamide (NSC #109724) vs. Ifosfamide plus Paclitaxel (NSC #125973) in Patients with Advanced, Persistent or Recurrent Carcinosarcoma (Mixed Mesodermal Tumors) of the Uterus

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 24 February 1998

STUDY OBJECTIVE
To determine whether the addition of paclitaxel improves length of survival, progression-free interval and response rate when compared to ifosfamide alone in previously untreated patients with advanced, persistent or recurrent carcinosarcoma (mixed mesodermal tumors) of the uterus.

TECHNICAL APPROACH
This is a Phase III trial for patients with advanced, persistent or recurrent carcinosarcomas (mixed mesodermal tumors) of the uterus.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's last review there have been no publications reported.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 116, if multi-site study. Grade 4 toxicities include 6 leukopenia, 21 granulocytopenia, 1 GI, 1 cardiac, 1 neurologic, 1 fever, 1 pulmonary, 1 methemoglobinemia.

Ref: Jul 01 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 29 January 2002

Work Unit # 4413-99

# DETAIL SUMMARY SHEET

TITLE: The Effect of Environmental C02 on Thermotolerance-Associated Heat Shock Protein Synthesis

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 02 March 1999

STUDY OBJECTIVE
To determine if heat shock protein synthesis associated with the development of thermotolerance can be influenced by increasing environmental C02 concentration in-vitro.

TECHNICAL APPROACH
This is a basic service project involving no human subjects. All experiments are derived from established cell line.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There are no publications reporting data on this study.

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is N/A. The total number enrolled study-wide is N/A, if multi-site study. This is a Walter Reed study that does not involve human subjects. Work is being done on this study at this time, but there are no results to report.

CONCLUSIONS
Too early.

Report Date: 10 June 2002 Work Unit # 4417-99

# DETAIL SUMMARY SHEET

TITLE: Evaluation of Metabolic Products of Embryo Culture and Their Correlation with Morphologic Appearance and Pregnancy Outcome

PRINCIPAL INVESTIGATOR: Scott, Lynnette, Ph.D., DAC

DEPARTMENT: Obstetrics & Gynecology STATUS: C
SERVICE: Reproductive Endocrine INITIAL APPROVAL DATE: 06 July 1999

STUDY OBJECTIVE: Development of a non-invasive methodology for assessing embryos would complement and perhaps supplant current morphologic criteria in the selection of viable embryos for transfer. The objectives of this study are: a) to characterize metabolic changes occurring in developing embryos as reflected in cellular products deposited into the culture media, (these metabolic characteristics can be correlated with the current 'gold standard' of embryo grading) and b) to assess whether metabolic parameters are better predictors of implantation and pregnancy outcome than cellular morphology.

TECHNICAL APPROACH:
a) Subjects: Patients undergoing in-vitro fertilization (IVF) cycles at the Reproductive Science at Walter Reed Army Medical Center (RSC-WRAMC). All subjects involved in these cycles are eligible to participate. After 1200 cycles, over 3 years; patients mean age is 34.4, with a standard deviation of 4.8 and a range of 22-43.
b) Inclusion and Exclusion Criteria: All patients involved in IVF cycles at RSC-WRAMC are eligible for inclusion. Patients not going to oocyte retrieval are excluded from the protocol.
c) Study Design: Prospective observational and laboratory assay study.
d) Methodology: Oocyte retrieval, embryo culture and embryo transfer will proceed as normal and as outlined in the standard operating procedures of the NT laboratory. All inseminations; embryo scoring and transfer to fresh media will be done at set times which will be as follows:

Insemination: 40h post-human Chorionic Gonadotrópin (hCG injection)
Pro-nuclear check:
Day 1: 18 post-insemination: 58 h post-hCG
Day 2: Scored and moved at 82 h post-hCG
Day 3: Scored at 106 h post-hCG; embryos for day 3 embryo transfer (ET) moved to ET dish; embryos far extended culture (Day 5 ET or cryo) moved to extended culture (EC) dishes
Day 4: Scored and moved to new EC drops at 130 h post-hCG
Day 5: Scored at 154 post-hCG; embryos for ET moved to ET dish; embryos for Day 5 cryopreservation moved to cryo dish; embryos for Day 6 culture moved to fresh drops.
Day 6: Scored at 178 post-hCG; any appropriated blastocysts are cryopreserved and the remainder discarded.
EMBRYO GRADING
Pro-nuclear Staging
Group 1: Aligned nucleoli, equal sizes and numbers
Group 2: Scattered nucleoli, equal sized and numbers
Group 3: Unequal alignment, unequal sizes, unequal numbers
Day 3
Grade I: >8 cell; no fragmentation
Grade II: >8 cell; <10% fragmentation
Grade III: 6-8 cell; no fragmentation OR >8 cell with 10-20% fragmentation
Grade IV: >20% fragmentation
Grade V: Arrested embryo OR >30% fragmentation
Day 5 (Blastocyst):
Baby-grade blastocyst: Achievement of blastocoel cavity and good cellular integrity
Non-baby grade blastocyst: Absence of blastocoel cavity and/or poor cellular integrity

On day 2, 3, 4 and 5 after embryos are moved from their culture drops, the media will be aspirated from the dish using a fine pulled pipette and placed in Eppendorf tubes. A drop of media from the same dish containing no embryo will be collected and used as a control. Cycle number and unique patient identifier known only to the laboratory director will code all media samples. There will be no departure from normal operating procedures. The media will be collected would normally be discarded. Embryos will not be comprised in any way by the collection of this media.

e) Data Collection: As has been outlines in the Methodology section; embryos will be cultured in defined media, as is the standard for the Reproductive Science Center. At the conclusion of each 24-hour period of embryo culture, embryos will be moved from one culture dish and placed in the next fresh drop of media. The used media, which is normally discarded, will be used for metabolic assessment. The study will have two objectives. The first objective will be to characterize metabolic products elaborated during the culture period. Changes in the composition of media over a 24-hour time period will be evaluated as appropriate by High Performance Liquid Chromatography (HPLC) or by Enzyme-linked immunoassay (ELISA). There will be a systemic approach of analysis in utilizing HPLC and ELISA. HPLC will be used for pyruvate, glucose and amino acid analysis and ELISA for determination of hCG levels. At present, the single most significant discriminator for predicting pregnancy in IVT is maternal age, with embryo morphology second. The aim of this study to is to look at embryonic metabolic factors as they relate to age and embryo morphology as well as implantation. All age groups qualifying for Assisted Reproductive Technologies (ART) at WRAMC are eligible to participate. Media will be stored on all embryos at all time points. A drop of media from the same dish containing no embryo will be collected and used as control. Analysis of media will be on select embryos determined after embryo transfer. Initially, pro-nuclear embryos will be scored according to the criteria system already in place in the laboratory. Embryos from groups 1 and 2 have been shown to give highest implantation rates and the greatest conversion to blastocyst and therefore transfer. Embryos will be followed through to day 4 and from day 4 to 5. On day 5, one to three embryos, according to morphology and patient age, will be transferred. The pyruvate, glucose and amino acid metabolism and hCG production of embryos transferred on day 5 and one to three non-transferred controls will be measured. Pyruvate metabolism at the pro-nuclear stage on day one will be measured on this same group of embryos. The implantation of embryos will be correlated with pro-nuclear, day 3 and blastocyst morphology, pyruvate and glucose metabolism and hCG production. It must be emphasized that, given the variable nature of embryology with regard to number and qualify of embryo products for each patient, it will be up to the Laboratory-Director to select the embryos used for evaluation. Specific pregnancy outcomes would include: a) chemical pregnancy (P hCG elevation without detection of clinical pregnancy by ultrasound), b) ectopic gestation (pregnancy outside of the uterine cavity), c) clinical pregnancy with spontaneous abortion (detection of an intrauterine gestational sac with subsequent demise), d) ongoing or delivered pregnancy. Statistical procedures used would include unpaired Student's t-test for comparison of individual metabolic products. For evaluation of morphology and pregnancy outcomes once metabolic products are characterized, Fisher's exact test and/or chi-square contingency tables would be used. Other statistical procedures, including non-parametric assessment would be used as indicated. No addenda have been made to the original protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE: The number of subjects enrolled to the study since last APR at WRAMC is 48 and the total enrolled to date at WRAMC is 395. The total number enrolled study-wide is NA, if multi-site study.

CONCLUSIONS: No data was generated, there were no findings. This study can be terminated. It was never really initiated due to lack of personnel to collect samples and analyze them. No consent forms were signed in the year 2002, and the consents signed early in 2001 are located at WRAMC.

Report Date: 24 July 2002 Work Unit # 4418-99

# DETAIL SUMMARY SHEET

TITLE: GOG #9902: Quality of Life of Gynecologic Cancer Survivors (NCI 1 RO1 CA 79039-01)

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 21 September 1999

STUDY OBJECTIVE
To describe the significant quality of life (QOL) concerns and long-term survivorship issues of women who were diagnosed and treated for early-stage ovarian and endometrial cancer five or more years ago.
To identify mechanisms which contribute to a gynecologic cancer survivorship model through comparison and prediction of high versus low QOL associated with long-term adjustment and survivorship.

TECHNICAL APPROACH
This is a QOL phone interview for survivors who completed GOG clinical trial #95 (ovarian), or GOG clinical trial #99 (endometrial) at least 5 years and are without recurrent disease.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been no publications reporting data from studies with similar study design in the literature.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 6. The total number enrolled study-wide is 162, if multi-site study.

Ref: GOG Statistical Report

CONCLUSIONS:
Too early.

Report Date: 23 July 2002

Work Unit # 4419-99

# DETAIL SUMMARY SHEET

TITLE: GOG 167: A Two Part Study of the Treatment of Atypical Endometrial Hyperplasia
Part A: A Prospective Study of Immediate Hysterectomy
Part B: A Randomized Phase II Study of Medoroxyprogesterone Acetate Versus Depo-Provera

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 21 September 1999

## STUDY OBJECTIVE

Part A: To estimate and compare the frequency of adenocarcinoma in patients diagnosed with atypical hyperplasia (AEH) at initial biopsy in groups defined by the Study Co-Chairs and those not considered AEH by central review. Given favorable results, Part B will be opened to pt accrual.

Part B: To conduct a randomized phase II trial to determine the frequency of complete remission of atypical endometrial hyperplasia (AEH) in patients treated for three months with oral medroxyprogesterone acetate or Depo-Provera IM.

## TECHNICAL APPROACH

Part A: Patients diagnosed with atypical endometrial hyperplasia and entry onto the study, patients will receive immediate hysterectomy.

Part B: Patients with confirmed diagnosed of endometrial hyperplasia will be randomized to:

Regimen 1: Medroxyprogesterone acetate (MPA) 10mg/po/day continuously for three months.
Regimen 2: Depo-Provera 150mg IM (gluteal or deltoid muscle) Q months for three months.

After three months patients will undergo total hysterectomy.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's last review there have been no reported publications for this particular study. The number of subjects enrolled to the study since last APR at WRAMC is 6 and the total enrolled to date at WRAMC is 11. The total number enrolled study-wide is 171, if multi-site study. Grade 4 toxicities include 2 hemoglobin, 2 other hematologic, 1 cardiovascular, 1 coagulation, 1 metabolic, and 1 pulmonary.

## CONCLUSIONS

Too early.

Report Date: 10 July 2002 Work Unit # 4420-99

# DETAIL SUMMARY SHEET

TITLE: Hyperspectral Diagnostic Imaging of the Cervix

KEYWORDS: hyperspectral, imaging

PRINCIPAL INVESTIGATOR: Parker, Mary F. LTC MC
ASSOCIATES: McBroom, John MAJ MC

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology

STATUS: C
INITIAL APPROVAL DATE: 29 September 1999

## STUDY OBJECTIVES

To continue the development of hyperspectral diagnostic imaging (HSDI) for the detection and localization of cervical dysplasia.

## TECHNICAL APPROACH

There have been no addenda to the original protocol.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 54. Tripler Army Medical Center (TAMC) is currently enrolling subjects (15 to date) to a related hyperspectral imaging protocol. This data will be analyzed separately from the WRAMC data.

There have been no adverse events or subjects withdrawn from the study at either site. Since the last APR, data analysis was performed, data registration procedures were reviewed, and design modifications for future spectrometer construction were discussed. Data analysis was performed using a spectral match filter approach. This approach proved to be less cumbersome than the techniques we used previously for establishing the neural nets, while providing a comparable level of accuracy for spectral discrimination. Analysis of high-grade dysplasia suggests that fluorescence alone may be inadequate for attaining the sensitivity and specificity required for clinical implementation of the technology. A problem with data registration was identified, limiting the utility of some of the spectral data. This problem was attributed to the method used to obtain the video tiff matched with each fluorescence scan. The current design of the spectrometer was felt to be too bulky and not as user-friendly as would be needed for widespread acceptance of the device.

Two peer-reviewed publications related to this work are currently in press for FY02. An additional peer-reviewed publication is undergoing review.

## CONCLUSIONS

Analysis of the spectral data suggests fluorescence is useful for discriminating among different types of cervical tissue and different levels of dysplasia, but does not appear to be sufficient as a stand-alone method of detection and diagnosis when analyzed by the spectral match filter approach. Other optical imaging modalities, such as reflectance and light scattering, should be considered for study in combination with fluorescence. From the experience with this device at WRAMC, modification of the data registration technique used is recommended. Future spectrometers will also need to be smaller and more user-friendly.

Report Date: 9 August 2001

Work Unit # 00-4501

# DETAIL SUMMARY SHEET

TITLE: Feasibility, Accuracy and Efficiency of an Internet Based Tele-Nuclear Consultation System for the Military. Phase I: Phantom Studies

KEYWORDS:

PRINCIPAL INVESTIGATOR: MAJ Aaron Stack MC
ASSOCIATES: Barry Cannon, RN; Eiping Quang, PhD; LTC Poropatich; COL Lenoard Nagorski; MAJ Carlos Jimenez

DEPARTMENT: Radiology
SERVICE: Nuclear Medicine

STATUS: O
INITIAL APPROVAL DATE: 12 October 1999

## STUDY OBJECTIVE

1. To determine the feasibility of an Internet based Tele-Nuclear consultation system between Walter Reed Army Medical Center and Fort Knox Department of Radiology. Feasibility is defined as the technical ability to perform this transmission and review using existing technology. Efficiency is defined as the speed of transmission and time of evaluation using the system.
2. To examine the concordance in the image quality between native phantom studies vs. those reviewed using the Internet based Tele-Nuclear system.
3. To examine the concordance in the diagnosis between native phantom studies vs. those reviewed using the Internet based Tele-Nuclear system.

## TECHNICAL APPROACH

This is a prospective, concordance trial using similar data from two separate locations. The image phantoms will be filled with appropriate radiopharmaceutical agents, and images will be acquired at Fort Knox Radiology Department using the protocols sent out by the ACNP. Two board certified nuclear medicine physicians at Walter Reed using criteria from the ACNP data collection sheet will score these studies independently. Rater 1 will review the six phantoms at Fort Knox, while rater 2 will review the data acquired from the six phantoms via the Internet based system at Walter Reed. After a one-month delay to insure reader blinding, Rater 2 will then review the phantoms at Fort Knox while Rater 1 reviews the phantoms at Walter Reed. A third board certified nuclear medicine physician at Rodrigues Army Health Clinic, Puerto Rico will provide an independent reading of only the transmitted images from Fort Knox for comparison. By having a third reader, we can evaluate the concordance between two readers blinded to the transmitted study. These sets of data will be evaluated for concordance. The phantom images collected will be evaluated using an ACNP data collection sheet.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There has been no interval activity with this protocol over the past year. The PI was changed recently, and the Telemedicine contacts have changed due to PCS of the previously involved persons. There were some technical problems, I am told, with the telemedicine transmission equipment at Ft. Knox that are being worked on. Hopefully they will be resolved in the very near future. It is anticipated that Phase I will be actively in progress by December 2001. This will necessitate a site visit by the PI to Ft. Knox for coordination and as part of the protocol.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

CONCLUSIONS: None at this time.

Report Date: 3 March 2002 Work Unit # 01-45002

# DETAIL SUMMARY SHEET

TITLE: Preoperative Evaluation of Breast Carcinoma Utilizing Tc99m-Depreotide

KEYWORDS:

PRINCIPAL INVESTIGATOR: MAJ Jaime L. Montilla-Soler, MC
ASSOCIATES:

DEPARTMENT: Radiology STATUS: O
SERVICE: Nuclear Medicine INITIAL APPROVAL DATE: 15 May 2001

## STUDY OBJECTIVE

To evaluate the preoperative diagnostic utility of a new, FDA approved polypeptide, Tc99m-depreotide (NeoTect), which targets somatostatin receptors 2, 3 and 5 for the detection of breast carcinoma.

## TECHNICAL APPROACH

Nuclear Medicine:
Injection and imaging of Technetium 99m-depreotide:
Technetium 99m-depreotide is a commercially available, FDA approved radiopharmaceutical for the evaluation of solitary pulmonary nodules at risk for primary lung carcinoma. The radiopharmaceutical is available in kit form and is formulated on site in our nuclear pharmacy. Each vial will be made per approved standard operating procedures and assayed for radiochemical purity using saturated sodium chloride solution prior to injection into the subject. The radiopharmaceutical, after being prepared and passing quality assurance testing, will be injected into the subject using an intravenous route of administration. The intravenous injection will be administered in the contralateral arm with respect to the affected breast. Twenty millicuries (20 mCi) of Technetium 99m-depreotide will be used for each subject. Two hours after injection the subject will be imaged utilizing a standard gamma camera. Two cameras approved for nuclear imaging will be utilized for this study: the BIAD (Trionix Corporation, Twinsburg, Ohio) and the XLI SMV (SMV corporation, Twinsburg, Ohio). Imaging will be performed using planar and SPECT (single photon emission tomography) techniques with the patient placed in the prone position using the scintimammography table adapter.

Planar images of the chest will be obtained in the anterior and lateral projections with the patient placed in a prone position using the mammography table insert with breast cutouts and the arms raised with the hands positioned on the head. SPECT images of the head, neck and chest to include the breasts will be performed in the same position. The SPECT acquisition images will be acquired using a step and shoot protocol (45 steps, 4 degrees per step, 30 seconds per stop), 128 X 128 matrix, and a low energy high-resolution collimator. The energy window will be centered at 140 keV. Regions of interest (ROI) will be drawn around the areas of abnormal accumulation of the radiotracer within the breast as well as around a comparable area size in the unaffected breast. If no clearly defined abnormal uptake is seen, an ROI of the upper outer quadrants will be used to calculate an uptake ratio, with the 'abnormal' side determined after review of the patient's history. The region of interest data will be tabulated for statistical evaluation, to determine a normal vs. abnormal uptake ratio value within a breast abnormality when compared to the anatomical pathology results. Images will be reviewed by at least two board certified nuclear medicine physicians. The initial exam interpretation will consist of a blinded interpretation, without the benefit of any clinical history, physical examination or clinical stage of the patient as determined by the oncologic surgeon. This exam interpretation will be rendered as a positive/negative examination for abnormal breast radiotracer accumulation. Subsequently, the interpreting physician will be provided with the clinical information as well any anatomical/radiological information available and a second exam interpretation will be performed. The purpose of this second interpretation with the benefit of clinical data is to provide

the interpreting physician with the benefit of comparing the normal vs. the suspected abnormal breast as well as for accurate selection and determination of ROI's in the suspicious breast quadrant to compare with the normal breast. This information will be recorded on the nuclear medicine data collection forms (Appendix 1A & 1B). If there is disagreement between the two physicians a third board certified nuclear medicine physician will be employed and a consensus achieved. Recording of the abnormalities will be performed on a data collection sheet and printed for review.

Surgery:
Surgical procedures will be performed as per standard of care. The surgery will take place more than 24 hours after the injection of Technetium 99m-depreotide. A 24-hour window is desired, since the target population is also eligible for gamma probe assisted sentinel node biopsy at the time of surgery. The 24-hour window is required to preserve the eligibility of these patients for the gamma probe assisted sentinel node biopsy procedure. After initial survey the surgeon will fill out a form identifying suspicious sites on a data collection form (Appendix 2). Identification of the primary cancer location will be obtained. Sampling of tissue will be performed per standard of care and directed by conventional imaging and clinical criteria. The surgeon on a data collection form (Appendix 3) will identify sampled tissue. The attending surgeon will not have knowledge of the Tc99m-depreotide scintimammography results prior to the surgery. Results obtained from the Tc99m-depreotide scintimammography will not alter patient care.

Specimen treatment:
Samples will undergo routine pathologic evaluation. This includes histological evaluation of the breast tissue as well as tissue marker evaluation, specifically determination of HER and NEU marker positive/negative status, which is part of our standard pathological evaluation at our institution. No additional histological evaluation or different tissue handling from the standard pathology department's SOP will be required in this study. The nuclear medicine imaging results will be compared to the standard pathological evaluation results rendered as a pathology report on this hospital's medical information system; CHCS. The pathology results that the protocol will be looking at include the presence or absence of breast cancer (positive or negative histology) as well as the histology type of the breast tissue obtained for pathological evaluation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is 4 and the total enrolled to date at WRAMC is 4. This is not a multi-site study. No new recent articles have been published regarding this subject. No adverse effects have been reported by the patients to date. We experienced a decrease in patient referrals from the breast care clinic at WRAMC following the events of 11 September 2001, with the early deployment of one of the investigators involved in the protocol. Slowly we have been able to get the cooperation of the nursing staff of the breast clinic to help us enroll patients in the protocol.

CONCLUSIONS
So far, it is too early to draw any conclusions from the data gathered. The patients have tolerated the required studies well and the preliminary results are promising. We plan to continue recruitment of patients for this protocol.

Report Date: 30 July 2002 Work Unit # 01-45003

# DETAIL SUMMARY SHEET

TITLE: An Open Label, Multicenter, Phase 3 Trial Evaluating Ventricular Function as Assessed by Left-Ventricular Ejection Fraction and Wall Motion Using Technetium-99m Tetrofosmin Gated SPECT Imaging

KEYWORDS:

PRINCIPAL INVESTIGATOR: Bridwell, Robert S. MD MBA
ASSOCIATES:

DEPARTMENT: Radiology STATUS: C
SERVICE: Nuclear Medicine INITIAL APPROVAL DATE: 19 June 2001

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This protocol review was not finished prior to the completion of the multicenter trial. This protocol was never initiated at this institution and no patients were enrolled. No publications were prepared.

CONCLUSIONS
None.

Report Date: 6 November 2001

Work Unit # 01-4501

# DETAIL SUMMARY SHEET

TITLE: Intraoperative Staging of Lung Cancer Using the Gamma Probe and Tc-99m Depreotide

KEYWORDS:

PRINCIPAL INVESTIGATOR: Bridwell, R.S. MAJ MC
ASSOCIATES: Mulligan, C.; Montilla, J.

DEPARTMENT: Radiology
SERVICE: Nuclear Medicine

STATUS: O
INITIAL APPROVAL DATE: 12 December 2000

## STUDY OBJECTIVE

To evaluate the use of Tc-99m depreotide with the intraoperative gamma probe in patients undergoing thoracotomy for the staging of lung cancer. Objectives that will be realized within the scope of staging using Tc-99m depreotide are:

1. Correlate the imaging findings with anatomical pathology.
2. Correlate findings on conventional imaging to Tc-99m depreotide.
3. Develop quantitative imaging region of interest and correlate with anatomical pathology.
4. Correlate the quantitative ROI system, visual study interpretation to the intraoperative gamma probe reading from sampled tissue that have been removed from the subject at time of surgery.
5. Correlate the gamma probe findings to nodal anatomical pathology examination.
6. Correlate the stage found by quantitative imaging techniques to anatomical pathology stage.

## TECHNICAL APPROACH

This is a prospective observational study comparing the gamma probe counts of lymph node tissue removed from the body after injection with Technetium 99m depreotide with anatomical pathology in patients undergoing staging operative procedures for lung cancer. There has been no modification since the study started.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

To date there have been six patients enrolled. Three of the six patients did not complete the study due to terrorist attack and power outage, respectively. There have been no adverse events in the six patients that have been enrolled in the study.

The number of subjects enrolled to the study since last APR at WRAMC is 6 and the total enrolled to date at WRAMC is 6.

## CONCLUSIONS

This study is ongoing and there have been too few patients to report any results. Only three of the six subjects enrolled have completed the study due to events beyond the control of the investigators.

Report Date: 07 February 2002 Work Unit # 4546

# DETAIL SUMMARY SHEET

TITLE: Intravenous Administration of 1311-6-B Iodomethylnorcholesterol (NP-59) for Adrenal Evaluation and Imaging

KEYWORDS:

PRINCIPAL INVESTIGATOR: Allen, Thomas W. LTC MC
ASSOCIATES:

DEPARTMENT: Radiology STATUS: O
SERVICE: Nuclear Medicine INITIAL APPROVAL DATE: 24 April 1997

## STUDY OBJECTIVE

Clinical evaluation of NP-59 as a diagnostic agent for the detection of adrenal-cortical disorders.

## TECHNICAL APPROACH

This study will be performed in humans of either sex. NP-59 will be administered by slow intravenous injection with a dose of 2mCi in adults, 15 uC8/kg in children. Lugol's solution, 5 drops twice daily starting one day before injection and continuing for two weeks, will be used to block thyroid uptake of radionuclide. Planar and SPECT images will be obtained on the 3rd, 4th and 5th days after injection using the scintillation camera and the on-line microcomputer. The drug to be used in this study, NP-59 is investigational and will be used under IND number 12605, which is held by the University of Michigan.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 4. There have been no adverse events (AE) for the four patients enrolled to date in the protocol. This is not a multi-center study. No patient enrolled in the study has withdrawn from it. Both patients enrolled since last APR had studies that were diagnostic for unilateral functioning adrenal cortical adenomas. Both patients underwent follow-on surgery and had pathologically confirmed adrenal adenomas.

## CONCLUSIONS

Since receiving final approval to begin work on this protocol 08 May 1998, a total of four patients have been studied at WRAMC to date. In each case, the NP-59 study has provided valuable information that altered patient management. Three of the four NP-59 patients have undergone surgical resection of the affected adrenal gland, guided by the results of their NP-59 study. All three surgical patients had pathologically confirmed functioning adrenal adenomas. The radiopharmaceutical being studied in this protocol, 131I-6-B Iodomethylnorcholesterol (NP-59) has been used and validated in over 200 patients throughout the US for diagnosing both functional and structural abnormalities of the adrenal gland. Multi-center phase III clinical trials of NP-59 have previously been completed. However, the drug has not been submitted for approval to the FDA, and it is currently classified as an orphan drug. The FDA has issued an IND (# 46,355) to WRAMC for this agent, and LTC Thomas W. Allen is its current sponsor. NP-59 is produced solely by the University of Michigan. NP-59 remains a useful, but infrequently used, imaging modality in the evaluation of patients with suspected functioning adrenocortical disorders, especially in patients with equivocal clinical presentations and laboratory data. WRAMC Endocrinology Service is the primary source of patient referral and screening for this protocol. WRAMC's Nuclear Medicine and Endocrinology Services conduct weekly joint conferences. During these conferences, the management of interesting endocrinology patients is discussed. Both endocrinology and nuclear medicine physicians are aware of this protocol and remain vigilantly seeking new patients to enroll in the protocol.

Report Date: 26 November 2001

Work Unit # 01-46001

# DETAIL SUMMARY SHEET

TITLE: Evaluation of Intra-prostatic Radio-opaque Markers for Prostate Localization and Refinement of External Beam Treatment Techniques

KEYWORDS:

PRINCIPAL INVESTIGATOR: MAJ William B. Warlick MC
ASSOCIATES: MAJ Micheal Dullea; COL Judd Moul MC

DEPARTMENT: Radiology
SERVICE: Radiation Therapy

STATUS: O
INITIAL APPROVAL DATE: 18 January 2001

STUDY OBJECTIVE:
The objectives of the study are: 1) to quantify the movement of marker seeds within the prostate during a course of radiation therapy and 2) to measure any movement of the prostate in reference to the initial planning CT scan over a course of radiation therapy.

TECHNICAL APPROACH:
We are still following the same approach as described in the original protocol. We place the marker seeds as an outpatient procedure in the Urology clinic. This procedure has been well tolerated. We then proceed with standard radiation planning followed by standard radiation treatments. We also take additional weekly diagnostic quality x-rays for seed location and measurements as well as a repeat CT scan in week 4 and week 7 of the radiation treatments for prostate position.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT
The participation by patients has been good. The patients have tolerated the placement of the seeds well. There have been no side effects other than minor bleeding at the time of the procedure. During the course of radiation treatments, there have been no unexpected side effects. Currently, three patients have experienced Grade 1 acute urinary toxicity (increased urinary frequency and urgency). One patient experienced Grade 2 acute urinary toxicity (hematuria) and two patients experienced Grade 2 acute urinary toxicity (frequency/urgency requiring medications). Three patients experienced Grade 1 acute GI toxicity (change in bowel habits not requiring medications). These side effects are similar to our patients undergoing standard radiation treatments.

There have been no new advancements that would impact upon the treatment of these patients.

The number of subjects enrolled to the study since last APR at WRAMC is 9 and the total enrolled to date at WRAMC is 9. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
We will continue to accrue patients. We plan on enrolling thirty patients. We are on schedule to complete the study by July 2002.

Report Date: 22 August 2002 Work Unit # 4601

# DETAIL SUMMARY SHEET

TITLE: RTOG 94-08: A Phase III Trial of the Study of Endocrine Therapy Used as a Cytoreductive and Cytostatic Agent Prior to Radiation Therapy in Good Prognosis Locally-Confined Adenocarcinoma of the Prostate

KEYWORDS: Zoladex, Flutamide

PRINCIPAL INVESTIGATOR: Scott Roberts, MD, Michael Dullea, MAJ MC

ASSOCIATES:

DEPARTMENT: Radiology STATUS: O
SERVICE: Radiation Therapy INITIAL APPROVAL DATE: 23 May 1995

## STUDY OBJECTIVE

To evaluate the potential impact of a combination of Zoladex and Flutamide used as cytoreductive agents prior to undergoing definitive radiation therapy in locally confined carcinomas of the prostate.

## TECHNICAL APPROACH

There are two arms to this randomized study for patients with clinical stages T1b-T2b adenocarcinoma of the prostate. The control arm (Arm 2) is radiation therapy only to the prostate and regional lymphatics. The experimental arm (Arm 1) involves the use of total androgen suppression (Zoladex and Flutamide) for 2 months prior and 2 months during radiation therapy to the prostate and regional lymphatics.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The multi-institutional trial opened on October 31, 1994. The study was finished accruing on April 30, 2001, when meeting its accrual goal of 1980 cases. At Walter Reed, eighteen patients were enrolled. The number enrolled at each year are as follows: 1995 – 3, 1996 – 6, 1997 – 4, 1998 – 2, and 1999 – 3. We have not enrolled any further patients. Two deaths have occurred (July 1997 and February 2000) from causes unrelated to prostate cancer. One patient has terminated participation in the study. One patient has been lost to follow-up.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 18. The total number enrolled study-wide is 1980, if multi-site study.

## CONCLUSIONS

We are awaiting the preliminary results from this trial. The companion study with more locally advanced disease (RTOG 94-13) did show a benefit with the addition of hormonal therapy in regards to disease free survival. This trial was closed earlier and the results were presented last year at our annual ASTRO meeting. Initial analysis of the patients enrolled in RTOG 94-08 is expected early next year. It is still uncertain if hormonal therapy will add to the earlier staged patients that were studied in this trial.

Report Date: 01 April 2002

Work Unit # 4602

# DETAIL SUMMARY SHEET

TITLE: RTOG 94-13: A Phase III Trial Comparing Whole Pelvic Irradiation Followed by a Conedown Boost to Boost Irradiation Only and Comparing Neoadjuvant Total Androgen Suppression

KEYWORDS: radiotherapy, prostate cancer

PRINCIPAL INVESTIGATOR: Warlick, William B. MAJ MC
ASSOCIATES: Dullea, Michael D. MAJ MC

DEPARTMENT: Radiology
SERVICE: Radiation Therapy

STATUS: O
INITIAL APPROVAL DATE: 27 February 1996

## STUDY OBJECTIVE

To determine optimal method of delivery of hormonal therapy with radiotherapy in the treatment of localized prostate cancer. A secondary objective is determination of optimal field size in the delivery of radiotherapy.

## TECHNICAL APPROACH

There are four arms to the study: Army 1 delivers neoadjuvant and concurrent hormonal therapy with pelvis radiation. Army 2 delivers neoadjuvant and concurrent hormonal therapy with prostate-only radiation. Arm 3 delivers concurrent and adjuvant hormonal therapy with pelvis radiation. Arm 4 delivers concurrent and adjuvant hormonal therapy with prostate-only radiation.

## PRIOR AND CURRENT PROGRESS

The study was opening nationally on April 1, 1995 and closed on June 1, 1999 with a total enrollment of 1323 cases. The median age for all patients was 70 years and nearly 25% were of African-American origin. The results of the study were presented at a plenary session at the annual meeting of ASTRO in Oct 2001. Patients treated with the whole pelvis radiotherapy (WPRT) experienced a 4 year Progression Free Survival (PFS) of 56% compared to 46% when treated with prostate only radiotherapy (PO RT) p=0.014), but no difference is yet seen in OS (85 bs83%, p-0, 53). Patients treated with neoadjuvant hormonal therapy (NHT) experienced a 4 yr progression free survival of 53 vs. 48% for adjuvant hormonal therapy (SH) (p=0.005). However, no OS advantage is yet seen (88% vs. 83,81,82%, respectively, p=0,15). Grade 3 or higher GU and GI toxicities were not clinically significantly different between treated patients on any of the four arms (3% vs. 1%).

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is sixteen (16). Two patients have died of unrelated causes, which have been reported. This leaves 14 (fourteen) patients actively being followed per protocol. Three (3) adverse events (any Grade 2 or Grade 3) have occurred at WRAMC and were reported as per protocol. The total number enrolled study-wide is 1323 patients.

## CONCLUSIONS

The preliminary analysis demonstrated that WP RT is associated with and improvement in PFS compared to PO RT in patients.

Report Date: 16 April 2002 Work Unit: #01-47002

# DETAIL SUMMARY SHEET

TITLE: Postmenopausal Coronary Artery Disease and Osteoporosis: A Pilot Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Feuerstein, Irwin MD
ASSOCIATES:

DEPARTMENT: Radiology STATUS: O
SERVICE: Diagnostic Radiology INITIAL APPROVAL DATE: 17 April 2001

STUDY OBJECTIVE:
There has been no change in the study objectives, which remain as follows. The overall goal of this protocol is to evaluate combined radiologic evaluation for coronary artery disease (CAD) and osteoporosis in postmenopausal women. Subgoals include evaluating the relationship between CAD and osteoporosis, and comparing osteoporosis evaluation in the thoracic and lumbar spines. This information will be used to develop and evaluate a high-quality, one-step technique for the evaluation of coronary artery calcium (CAC) and bone mineral density (BMD) using electron beam computed tomography (EBCT). A further subgoal is to validate the measurement of thoracic spine bone density with Dual Energy X-ray Absorptiometry (DEXA).

TECHNICAL APPROACH:
There has been no change in the technical approach.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
We have reviewed the literature, and there were a few articles addressing the use of CT bone mineral densitometry. Similar to the prior literature, they all find the technique safe and effective. A few references are given below.

1. High-resolution three-dimensional micro-computed tomography detects bone loss and changes in trabecular architecture early: comparison with DEXA and bone histomorphometry in a rat model of disuse osteoporosis. Invest Radiol. 2002 Jan;37(1):40-6.
2. A comparison of quantitative computed tomography and dual X-ray absorptiometry for evaluation of bone mineral density in patients on chronic hemodialysis. Am J Kidney Dis. 2001 Jun;37(6):1247-52.
3. A comparison of spinal quantitative computed tomography with dual energy X-ray absorptiometry in European women with vertebral and nonvertebral fractures. Calcif Tissue Int. 2001 Feb;68(2):74-82.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 39.

CONCLUSIONS:
The results are still being collected, and conclusions have not yet been drawn. These will be rendered after statistical analysis. There have been no complications or ill events, and the protocol seems to be safe and well tolerated.

Report Date: 4 June 2002

Work Unit # 01-47003

# DETAIL SUMMARY SHEET

TITLE: Field Trial of Mobile Digital Telemammography- Phase I (Installation and Testing)

KEYWORDS: digital, mammography

PRINCIPAL INVESTIGATOR: COL Michael Brazaitis, MC
ASSOCIATES:

DEPARTMENT: Radiology
SERVICE: Diagnostic Radiology

STATUS: C
INITIAL APPROVAL DATE: 22 May 2001

## STUDY OBJECTIVE

Determine efficacy and patient satisfaction of a digitally acquired mammogram with remote interpretation.

## TECHNICAL APPROACH

Up to thirty women will be recruited for mammographic examinations from the Department of Radiology at WRAMC. These women will be of screening mammogram age. In addition, up to thirty women will be recruited from the Indian Health Service (IHS) offices, and will be participating under an IHS-approved consent form. The Primary Investigator will function as a consultant for the IHS participants in this study.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 12 and the total enrolled to date at WRAMC is 12. The total number enrolled study-wide is 12, if multi-site study.

## CONCLUSIONS

Study terminated at inception without actual performance of the study protocol due to failure of the applied physics laboratory of the Johns Hopkins University to establish the transmission (satellite and hard line) capabilities required to perform the study. Twelve (12) patients had digitally acquired mammograms performed (FDA- approved technology) in the mobile (MBCC) setting with hard copy film generated and interpreted in the usual manner (MQSA standards) at WRAMC Dept of Radiology. Reports and films provided to the patients- study participants to be included in their medical record and reports provided to appropriate health care provider for each participant without incident or complication.

Report Date: 30 October 2001 Work Unit # 01-4701

# DETAIL SUMMARY SHEET

TITLE: Creation of a Retrospective and Prospective Database of Patients Examined with Electron beam Computed Tomography of the Coronary Arteries

KEYWORDS: Coronary, calcinosis, EBCT, calcium, tomography

PRINCIPAL INVESTIGATOR: Feuerstein, Irwin MD DAC
ASSOCIATES: COL M. Brazaitis, Dr. S. Greberman, Dr. M. Greberman, COL J. Zoltick

DEPARTMENT: Radiology STATUS: O
SERVICE: Diagnostic Radiology INITIAL APPROVAL DATE: 21 November 2000

STUDY OBJECTIVE:
To collect clinical data on patients examined with electron beam computed tomography (EBCT) of the coronary arteries. To collect follow-up information of medical history subsequent to the EBCT. To analyze patient demographics, calcium score distributions, and treatment outcomes.

TECHNICAL APPROACH
This is a database and survey protocol. Anonymous clinical data and laboratory results will be entered into a research database. Patients will be sent outcome questionnaires yearly for five years, and the data analyzed. This is considered a minimal risk protocol. The only changes in the protocol have been the separation of prospective and retrospective portions, and the questionnaire changed in format and was submitted as part of the review process. An advertisement letter was submitted yesterday for review.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Given the survey nature of the protocol, there has been no major impact of the literature on the handling of the protocol. The only changes would reflect available medications, and the development of new laboratory tests that the patients might report. The prospective part of the protocol was just approved last week, and just started in the clinic two days ago, so there are no significant data to report. There are no adverse events to report.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 9 by COB 29 October 2001. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
The protocol was separated into distinct prospective and retrospective protocols. The prospective protocol received final DCI approval just last week, and we started enrollment two days ago. An advertisement letter was submitted this week. Thus, there is nothing significant to report in terms of results. The retrospective protocol is still under review.

Report Date: 5 March 2002

Work Unit # 4705

# DETAIL SUMMARY SHEET

TITLE: Proton Magnetic Resonance Spectroscopic Imaging in Patients with Partial Epilepsy

KEYWORDS: spectroscopy, proton, epilepsy

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC
ASSOCIATES:

DEPARTMENT: Radiology
SERVICE: Diagnostic Radiology

STATUS: C
INITIAL APPROVAL DATE: 25 April 1995

## STUDY OBJECTIVE

To investigate the yield and clinical utility of Magnetic Resonance Spectroscopy (MRS) in patients with partial epilepsy.

## TECHNICAL APPROACH

Fifty subjects with partial epilepsy will undergo MRS -- a noninvasive technique that allows focused study of biochemistry within normal and diseased brains. Conventional MRI with additional special equipment and software is utilized to allow spectral analysis.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is none and the total enrolled to date at WRAMC remains at twenty-four. No side effects were noted.

## CONCLUSIONS

This study shows focal abnormalities of MRS (changes of NNA, choline, creatinine) on the side of epileptic EEG abnormality, the finding that can be helpful in surgical management of these patients. Pathology groups are still too small for performing statistical analysis of MRS/pathology correlation.

Report Date: 31 January 2002 Work Unit # 4710-99

# DETAIL SUMMARY SHEET

TITLE: Comparison of Electron Beam Computed Virtual Colonoscopy (EBCT-VC) with Visual Colonoscopy, Using Each Patient as Their Own Control

KEYWORDS: Colonoscopy; X-ray computed tomography; Electron beam computed tomography; Colon, Cancer, colon; Polyp; Imaging; Three-dimensional imaging

PRINCIPAL INVESTIGATOR: Irwin M. Feuerstein, MD
ASSOCIATES: COL Michael P. Brazaitis, MC; CPT Roger Polish, MC; CPT Eric Osgard, MC; COL Roy Wong, MC; Corinne Maydonovitch, BS; Audrey Chang, PhD; Gregory N. Bender, MD

DEPARTMENT: Radiology
SERVICE: Diagnostic Radiology

STATUS: O
INITIAL APPROVAL DATE: 23 March 1999

## STUDY OBJECTIVE

To determine whether computed tomography (CT) colography, using electron beam computed tomographic virtual colonoscopy (EBCT-VC) methodology, could identify the normal colon with a high degree of predictability. Secondary information of benefit will be to identify the length of CT colography (CTC) examination time relative to the examination time of colonoscopy, to identify the success rate of CTC in visualizing the entire colon relative to the success rate of colonoscopy to do the same, to identify which examination is more preferable to the patient, and to identify if CTC can be relied upon to such a degree that repeat colonoscopy might be necessary if initially negative in the face of a positive CTC examination.

## TECHNICAL APPROACH

There have been no changes to the technique since the prior APR, and the new technique appears to working quite acceptably. There have been no patient issues, and no scanner failures. Patients will receive virtual and fiberoptic colonoscopy on the same day, with the information conveyed via the patient guardian. Fiberoptic colonoscopy will be done in the standard manner, while virtual colonoscopy will be done on the electron beam scanner with Colyte preparation and air insufflation using a standard tip. Images will be reviewed in both 2- and 3-dimensions with fly-through. The current scans are done without glucagons, and without oral contrast, using air contrast only. The 2-D images continue to be viewed on the Scribe workstation before the fiberoptic study, and fly-through images still viewed on the AccuImage workstation after the fiberoptic study.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT

The literature continues to evolve, adding some new information while solidifying prior concepts and conclusions. These involve scanner and computer developments, changes in technique, and performance of the examination.

There continue to be rapid, dramatic developments in the area of scanner technology. Multi-section fast helical scanners are available. Four- and eight-slice machines are the norm, with 16- and 32-slice machines on the horizon. Several studies have described the use of the newer machines, though none have compared them with CT-colography on EBCT. There is some early data that thinner-section, multi-slice helical scans may be more sensitive for polyps less than 10 mm, but at the expense of false positive results. All studies perform well for polyps greater than 10 mm, which are the polyps of greatest interest. Controversy continues to rage about the need or desire to detect polyps less than 10 mm, which are very likely to be benign, often hyperplastic, polyps. There have also been concerns about the study designs and the radiation dosage delivered by multi-slice helical CT. It is not clear that the possible small incremental benefit justifies the increase in radiation or potential false positive results.

Stool tagging is an active area of investigation. The first iteration of this protocol used one type of stool tagging, and was found to cause problems when virtual and fiberoptic studies were done on the same day. It remains to be seen if different types of stool tagging cause less problems for the gastroenterologists. Our study appears to be doing fine without the oral contrast, so we shall continue without it. MR-colography remains an investigational procedure. Attempts have been made to use intravenous contrast to the examination. The incremental benefit has not been great, and PI resists any additions to the protocol that increase the risk, time, or difficulty for the patient.

Like most things computed, the advances in computer hardware and software occur very quickly. New packages come out all the time, with new ways of looking at things. Computer aided diagnosis and virtual pathology are of great interest, and may add speed and performance in the future. The performance of the new techniques are all of interest, but there is no compelling data to suggest that any of those new or novel techniques offer solidly better results or better patient outcomes than what is being done now. In addition, virtually all of the new techniques involve either more radiation, the possibility of more false positives, more needles and intravenous drugs, and/or more oral contrast which could interfere with the fiberoptic studies done the same day. PI stands by the techniques, and feels they are reasonable, safe, and effective.

Since the last APR and with the new modifications, there have been no minor or major adverse events. There have been no withdrawals. All patients and studies have been satisfactory. The number of subjects enrolled to the study since last APR at WRAMC is 6 and the total enrolled to date at WRAMC is 6. Note that PI decided at the last HUC to start over from scratch, so the five patients prior to last APR are not counted in the above numbers.

CONCLUSIONS

The study, in its new form, amended at the same time at the last APR, has been going well. There have no adverse events, and all studies have been satisfactory. Though PI has not analyzed the data yet, the feeling is that the results will be right in line with known literature. Basically, CT-colography sees the larger polyps well, misses the tiny ones, and the in-between ones are in-between. PI feels comfortable that the techniques being used are safe, effective, and well tolerated by the patients. The future should be interesting. The only issue is patient enrollment, which is proceeding slowly. PI is working on ways to streamline the procedure and make it more attractive to the patients.

Report Date: 23 January 2002 Work Unit # 01-48001

# DETAIL SUMMARY SHEET

TITLE: Use of Robotic Telepathology as an Adjunct to Frozen Section Consultation

KEYWORDS: Telepathology, frozen section, diagnosis, AFIP

PRINCIPAL INVESTIGATOR: Kaplan, Keith CPT MC
ASSOCIATES: Myers, Cris P COL MC

DEPARTMENT: Pathology and Area Laboratories STATUS: O
SERVICE: INITIAL APPROVAL DATE: 13 March 2001

STUDY OBJECTIVE
To assess the validity and feasibility of remote, real-time telepathology consultation for frozen section (intraoperative consultation) in the AMEDD.

TECHNICAL APPROACH
Method and study design as proposed.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
No adverse events or effects because this is a retrospective study using glass slides. There is no impact on patient care. Previous literature and complete bibliography previously submitted at the time of protocol submission.

The number of subjects enrolled to the study since last APR at WRAMC is 10 and the total enrolled to date at WRAMC is 10. The total number enrolled study-wide is 10.

CONCLUSIONS
I have formally rescinded the protocol for further review at Womack Army Medical Center, Fort Bragg, NC. A host of problems were encountered with submission of above entitled protocol to WAMC IRB office upon review. A local PI was appointed to coordinate efforts on-site and facilitate approval process. Documents requested were provided in a timely fashion by myself or local site PI including requests to me for such items as *their* office symbols on documents, original signatures submitted via mail and re-requests for documents and forms unique to their requirements for final approval despite submission to the IRB months prior to their ongoing request. Despite numerous attempts, I could not make contact with the WAMC IRB "Clinical Investigation Clerk" by phone. E-mails to the clerk were deleted without being read on two occasions. I have since withdrawn the protocol for further review after eight months of failure to gain final approval prior to WAMC submitting the protocol separately to CIRO (despite review by CIRO previously of WRAMC protocol). I think this was excessive turn around time for an IRB office that reviews on average two protocols quarterly. The local PI attended one of these quarterly meetings in September. Because of a lengthy 1½ hour discussion on the protocol slated before this one, this protocol was not formally reviewed in presence of the local PI and discussed at the time of that meeting. I forwarded these comments to USAMRMC/TATRC, which approved the protocol for the other sites upon notification of this delay. The microscope previously scheduled for installation at Dewitt Army Community Hospital, Fort Belvoir, VA, was installed at Landstuhl Regional Medical Center in Germany as the pathologist at Dewitt refused installation, implementation, and participation in this research protocol. The site change was submitted as an amendment to the protocol. The protocol, methods, and materials are otherwise unchanged. No cases will be or have been reviewed from WAMC.

Report Date: 23 January 2002

Work Unit # 01-48002

# DETAIL SUMMARY SHEET

TITLE: Oxidative and Nitrosative Stress in Carcinogenesis of CTCL (MF)

KEYWORDS:

PRINCIPAL INVESTIGATOR: Myers, Cris P. COL MC
ASSOCIATES:

DEPARTMENT: Pathology and Area Laboratories
SERVICE:

STATUS: W
INITIAL APPROVAL DATE: 3 April 2001

STUDY OBJECTIVE
Study withdrawn by Principal Investigator.

TECHNICAL APPROACH
Study withdrawn by Principal Investigator.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Study withdrawn by Principal Investigator.

CONCLUSIONS
Study withdrawn by Principal Investigator.

Report Date: 30 July 2002 Work Unit # 01-48003

# DETAIL SUMMARY SHEET

TITLE: Oxidative and Nitrosative Stress in Carcinogenesis of Colitis-Associated Malignancies

KEYWORDS:

PRINCIPAL INVESTIGATOR: Marrogi, Aizen J. LTC MC
ASSOCIATES:

DEPARTMENT: Pathology and Area Laboratories STATUS: T
SERVICE: INITIAL APPROVAL DATE: 8 May 2001

STUDY OBJECTIVE

TECHNICAL APPROACH

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

CONCLUSIONS
Study was terminated due to lack of Annual Progress Report submission.

Report Date: 5 January 2002

Work Unit #: 01-48004

# DETAIL SUMMARY SHEET

TITLE: Extending the Expiration Date of Thawed Frozen Plasma

PRINCIPAL INVESITGATOR: William L. Turcan, MT (ASCP) SBB
ASSOCIATES: Angela M. Hudson, BS, MS, MT (ASCP) SBB, Capt, USAF

DEPARTMENT: Pathology and Area Laboratories
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 12 June 2001

## STUDY OBJECTIVE

The purpose of this study was to compare the coagulation factor activities of fresh frozen plasma and plasma frozen within 24 hours to determine if: 1) the two types of frozen plasma are similar and 2) if the current expiration date of 24 hours after thawing can be extended.

## TECHNICAL APPROACH

This was a two-group prospective study on units of plasma that had already been drawn, processed and frozen according to regulatory requirements. Our study began with thawing the units and sampling at baseline, 24, 36, 48, 60, 72, 96 and 120 hours after thawing and storage at 1-6$^0$C. Due to a loss of time point samples from one donor, the final number of units used for the statistical analysis was 41 units. In addition, one unit only had data on the time intervals baseline to 60 hours. All other units had data for all eight time points: baseline, 24, 36, 48, 60, 72, 96, and 120 hours.

Twenty-two units of FFP and twenty units of PF24 were selected from the WRAMC blood bank inventory that is maintained in a temperature controlled –30$^0$C freezer. Each unit of FFP was thawed using a temperature controlled circulating water bath consistent with the way frozen plasma is prepared. After thawing, approximately 3-5 mL were drawn from each unit using a sterile docking device and a satellite collection bag to maintain the sterility of the unit. The plasma sample collected was frozen in a 5 mL (12X75 mm) polypropylene tube at –18$^0$C to be tested at the end of the timed trial period. The plasma units were then placed in a monitored 1-6$^0$C refrigerator until the next sampling. Once all samples were collected, they were thawed and aliquoted into 3 - 1 mL aliquots to avoid continuous thawing and refreezing of the initial sample. The samples were then tested in batches, which were subdivided into: the screening tests, the common and extrinsic factors (II, V, VII, X) and the intrinsic factors (VIII, IX, XI, XII).

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

All testing and data gathering has been completed. Review of recent literature does not provide any further findings than was originally given in the original protocol submission. The literature review does not show this study has been recently investigated.

## CONCLUSIONS

This study compared the effects of extended storage at 1-6$^0$C of thawed plasma for FFP and PF24. The screening tests PT, APTT, TT and fibrinogen as well as the coagulation factors II, V, VII, X, VIII, IX, XI, and XII were assayed. For all factors measured, with the exception of factor VIII, there were no significant changes over the 120 hour storage period. As expected, factor VIII had the greatest decline in activity, but the mean remained above the 50% normal range.

Thawed frozen plasma that has been stored up to five days can safely be used to treat a number of other disease states, such as thrombotic thrombocytopenia purpura and reversing the effect of Coumadin. In these and other clinical situations, such as therapeutic plasma exchange, the need to ensure high levels of the labile coagulation factors is not as high a priority as it is for a patient who has a specific factor VIII deficiency.

Our data also indicate that PF24 can be used for transfusions in treatment protocols where FFP would be selected. Our results demonstrate that there is no significant difference between the two types of frozen plasmas. Therefore, extending the expiration date of FFP can also be applied to PF24.

This research study supports the use of thawed plasma after prolonged refrigerated storage for up to 120 hours. The results of this study will be presented to the Blood Utilization and Transfusion Committee and our hope is to gain approval for implementation of extended storage of thawed frozen plasma beyond 24 hours at Walter Reed Army Medical Center.

Future research should be directed toward a better understanding of the balance between the coagulation and fibrinolytic systems. Concentrating on the activators, inhibitors, and their roles in the coagulopathies associated with liver disease and massive transfusion will complete the coagulation workup we were unable to finish due to time constraints.

Report Date: 22 July 2002

Work Unit # 4833-98

# DETAIL SUMMARY SHEET

TITLE: Determination of Reference Values for Percent Free PSA in Patients for Prostatic Evaluation

KEYWORDS: free PSA, prostate, cancer

PRINCIPAL INVESTIGATOR: Moul, Judd W. COL MC
ASSOCIATES: Ali, Amina MT

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 1 September 1998

## STUDY OBJECTIVE

To determine Hybritech Tandem-MP free and total PSA ration values on WRAMC patient population related to age and race. In the men who are diagnosed with prostate cancer: to evaluate the free PSA and correlate it to the pathological stage and tumor stage.

## TECHNICAL APPROACH

This is a prospective study- previously frozen, stored serum samples under WU#2801 from patients who have had prostate biopsies will be used for this study. Clinical data will be provided from the CPDR database at WRAMC (Work Unit # 2857-98). For the patients who have a positive biopsy, we will correlate the percent free PSA to stage, grade and number of prostate biopsy cores involved with cancer and see if the percent free PSA is a marker of stage/grade. Specimens with total PSA values in the 2.0-10.0 ng/ml range will be used.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There are no new literature findings to report. There are no adverse events to report.
There were 232 previously frozen stored specimens from patients who have had prostate biopsies and out of the 232 specimens, 223 were used. The specimens were tested for free PSA and total PSA. The percent of free PSA was also calculated.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 223. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

A paper is currently being written and will be submitted to DCI for approval when it is finished.

Report Date: 25 August 2002 Work Unit # 00-6501

# DETAIL SUMMARY SHEET

TITLE: The Role of Ki-67 Antigen in Differentiated Thyroid Cancers

KEYWORDS: Ki-67, Thyroid, Cancer

PRINCIPAL INVESTIGATOR: Gary L. Francis COL MC
ASSOCIATES: Yvonne Lukes, DAC

DEPARTMENT: Clinical Investigation
SERVICE: Research Operations

STATUS: C
INITIAL APPROVAL DATE: 5 October 1999

## STUDY OBJECTIVE

This study was designed to determine the expression of Ki-67 positive (proliferating) cells in archived formalin fixed thyroid tissues.

## TECHNICAL APPROACH

Tissues were sliced and immunostained for Ki-67. Many Ki-67 positive cells were identified and proven to be lymphocytes.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 68 and the total enrolled to date at WRAMC is 68. The total number enrolled study-wide is 68. A total of 68 samples have been stained. There is correlation with the number of lymphocytes and the number of proliferation lymphocytes and the risk of recurrence.

## CONCLUSIONS

This study has shown that Ki-67 is frequently found in thyroid cancers and confined to the lymphocytes. No further study is planned for these stains or samples.

Report Date: 4 September 2001

Work Unit # 00-6502

# DETAIL SUMMARY SHEET

TITLE: Comparative Genomic Hybridization of Differentiated Thyroid Cancer

KEYWORDS: CGH, Thyroid Cancer

PRINCIPAL INVESTIGATOR: Andrew J. Bauer MAJ MC USA
ASSOCIATES: Cydney Fenton MAJ MC USA, Gary L. Francis COL MC USA, Aneeta Patel MSc, Diatmuid Nicholson, PhD, Henry Burch LTC MC USA, Bassem R. Haddad MD, Constantine A. Stratakis MD, R. Michael Turtle MD

DEPARTMENT: Pediatrics
SERVICE: Pediatric Endocrinology

STATUS: C
INITIAL APPROVAL DATE: 12 October 1999

## STUDY OBJECTIVE

To determine if different patterns of gene loss and/or gain exist in childhood and adult thyroid cancers and that those differences explain the heterogeneity of clinical behavior.

## TECHNICAL APPROACH

To test this hypothesis, we have been using the powerful technique of comparative genomic hybridization (CGH) to examine the entire genome of papillary thyroid carcinoma from children and adults, and to correlate specific genomic aberrations with the clinical course of the individual.
CGH is a molecular cytogenetic technique which uses quantitative two color fluorescent in situ hybridization (FISH) to simultaneously compare the entire genome from multiple test samples. In a single experiment, CGH can detect genetic imbalance in solid tumors and map the region of chromosomal gain or loss compared to normal reference metaphase chromosomes.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 10. The total number enrolled study-wide is 15, if multi-site study.

## CONCLUSIONS

Four samples (4/15, 27%) had aberrations detected by CGH. All four had a partial or complete gain of chromosome 20 and ¾ had a partial loss of chromosome 13. PTC with abnormal CGH were more likely to be invasive ($p=0.05$). We conclude that chromosomal instability is uncommon in PTC, but more likely to be associated with aggressive histologic and clinical features.

Report Date: 6 January 2002 Work Unit # 00-6503

# DETAIL SUMMARY SHEET

TITLE: Role of Thyroid Transcription Factor-1 Differentiated Thyroid Cancer

KEYWORDS: thyroid, transcription factors, cancer

PRINCIPAL INVESTIGATOR: MAJ Andrew J. Bauer, MC
ASSOCIATES: COL Gary L. Francis, MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Endocrinology

STATUS: C
INITIAL APPROVAL DATE: 2 November 1999

STUDY OBJECTIVE:
This study was designed to determine the expression of thyroid transcription factor-1 (TTF-1) in a group of benign and malignant thyroid lesions and to determine if the intensity of expression is related to the risk of metastasis or recurrence.

TECHNICAL APPROACH:
A group of archived, previously existing thyroid tumors were stained for the expression of TTF-1 using immunohistochemical techniques and antisera specific for TTF-1. The sub-cellular location and intensity of staining were graded by two independent examiners and scored for nuclear or cytoplasmic staining of intensity grade 1-3.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
53 papillary (PTC) and 9 follicular (FTC) carcinomas, 15 benign lesions and 2 normals have been stained for TTF-1 expression. Nuclear TTF-1 was present in benign (77%) and malignant lesions (69%) and of similar intensity. Nuclear TTF-1 staining correlated with the effective serum TSH level ($r = 0.434$, $p = 0.024$) and patient age ($r = 0.29$, $p = 0.035$) and was detected in 35 PTC, of which, 8 developed recurrent or persistent disease (22.9%, 10.4-40.1 %, 95% CI).

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 79.

CONCLUSIONS:
Nuclear TTF-1 correlates with serum TSH activity, increases with age, and may be increased in patients who develop recurrent or persistent PTC.

Report Date: 28 September 2001

Work Unit # 00-6504

# DETAIL SUMMARY SHEET

TITLE: Role of Focal Matrix Metalloproteinases in Differentiated Thyroid Cancer

KEYWORDS: metalloproteinase, thyroid, cancer

PRINCIPAL INVESTIGATOR: Fenton, Cydney MAJ MC
ASSOCIATES:

DEPARTMENT: Pediatrics
SERVICE: Pediatric Endocrinology

STATUS: O
INTIAL APPROVAL DATE: 30 November 1999

STUDY OBJECTIVE:
This study is designed to determine if the expression of matrix metalloproteinases is increased in a group of archived paraffin-embedded thyroid tissue blocks when compared to a similar group of archived benign thyroid lesions. If so, this would provide evidence that metalloproteinases are important in thyroid cancer and would offer a novel therapeutic window of inhibitors of metalloproteinases for this disease.

TECHNICAL APPROACH:
Archived thyroid tissues are deparaffinized and stained by immunohistochemistry for matrix metalloproteinase expression. The intensity of staining is graded by two independent examiners and then compared to the rate of recurrence, tumor size, and presence of metastasis.

PRIOR AND CURRENT PROGRESS:
The number of subjects enrolled to the study since last APR at WRAMC is zero, and the total enrolled to date at WRAMC is zero.

CONCLUSIONS:
This is a study of archived samples for which the patient identity is unknown. These were obtained under DCI supervision from Protocol Work Unit # 6414. No patients have been contacted, and no patient has been examined.

Report Date: 19 June 2002 Work Unit # 00-6601

# DETAIL SUMMARY SHEET

TITLE: POG 9900: ALinC 17 Classification Protocol – A Pediatric Oncology Group Non-Therapeutic Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol MC; Merino, Margret MAJ MC

DEPARTMENT: Pediatrics STATUS: O
SERVICE: Pediatric Hematology-Oncology INITIAL APPROVAL DATE: 15 August 2000

## STUDY OBJECTIVE

(1) To provide the clinical and laboratory data necessary for placing each patient with Acute Lymphoblastic Leukemia (ALL) onto the proper therapeutic trial. (2) To provide an administrative base to capture classification data for correlative studies in ALL treatment protocols and series of historical protocols.

## TECHNICAL APPROACH

This is a non-therapeutic laboratory classification study for subjects with newly diagnosed ALL $\leq 21$ years of age at the time of diagnosis. Through local and reference laboratories each subject will have there leukemic cells biologically subclassified at the time of diagnosis using a variety of laboratory methods. This information will be used to place each subject onto the proper therapeutic trial.

## PRIOR AND CURRENT PROGRESS

Group-wide accrual stands at 1,688; 900 since the last APR. There have been six WRAMC registrations on this protocol; five since the last APR. Since this is a non-therapeutic study, there have been no toxicity data to report. Benefit to subjects is proper identification of leukemia subtype to determine appropriate therapy. Detailed laboratory reports can be found in the reference cited.

{Ref: COG Study Reports, Spring 2002}

## CONCLUSIONS

Study should remain open.

Report Date: 19 June 2002

Work Unit # 00-6602

# DETAIL SUMMARY SHEET

TITLE: POG 9907: ALinC 17 Cytogenetics Protocol – A Pediatric Oncology Group Non-Therapeutic Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol MC; Merino, Margret MAJ MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 15 August 2000

## STUDY OBJECTIVE

Assess the feasibility of obtaining high quality decentralized cytogenetic karyotyping in POG. To continue the POG tradition of having well cytogenetically characterized patients for use in correlative and descriptive cross-protocol studies in POG and in international collaborative analyses.

## TECHNICAL APPROACH

Children $\leq$ 21 years of age with newly diagnose acute lymphoblastic leukemia (ALL) will have their leukemia cells karyotyped at a POG approved cytogenetics laboratory. This information will be compiled and stored in a secure database for use in correlative and descriptive studies of this patient population. In addition, the cytogenetics data, if informative, will be taken into account by the UNM Molecular Reference Laboratory in reporting the DI (including hypodiploidy), FISH 4&10, and molecular detection results for the E2A/PBX-1, t (1;19); the BCR/ABL, (9;22); and MLL(11q23) rearrangements. The cytogenetics data will be considered in any case in which the DNA index, FISH 4&10, or molecular detection results are not straightforward.

## PRIOR AND CURRENT PROGRESS

Group-wide accrual stands at 1,235; 662 since the last APR. There have been four WRAMC registrations on this protocol to date, all since the last APR. Data evaluation continues to show excellent correlation between the routine karyotype results and results obtained from molecular studies (POG 9900) performed at the UNM Molecular Reference Laboratory.

{Ref: COG Study Reports, Spring 2002}

## CONCLUSIONS

Study should remain open.

Report Date: 18 April 2002 Work Unit # 01-65001

# DETAIL SUMMARY SHEET

TITLE: An Archival Fixed Tissue Thyroid Tissue Bank

KEYWORDS: Thyroid, Tissue

PRINCIPAL INVESTIGATOR: Gary Francis COL MC
ASSOCIATES:

DEPARTMENT: Pediatrics STATUS: O
SERVICE: Pediatric Endocrinology INITIAL APPROVAL DATE: 3 April 2001

STUDY OBJECTIVE
To consolidate all tissues and case histories created under previous WRAMC approved pediatric thyroid cancer studies into a single protocol. No new tissues are collected, no new case histories are collected, and no patients are contacted. All material for this protocol are previously existing samples.

TECHNICAL APPROACH
All samples were collected together into one protocol. All studies to be performed are submitted as individual protocols for review.

PRIOR AND CURRENT PROGRESS
Since initiation, four sub-study protocols have been submitted for review and approval under this master protocol. These include a study of caveolin expression by Patricia Powers COL MC; a study on the potential use of Xeloda by Andrew Bauer MAJ MC; a study on lymphocyte characterization by Jitu Modi CPT MC and a study on erythropoeitin receptos by Tom Eccles CPT MC.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study.

CONCLUSIONS:
This study is on going for submission of sub-studies. To date, four sub studies have been approved and another submitted (IGSs by Gary Francis COL MC).

The details of each sub-study will be provided under individual sub-study APR.

Report Date: 4 March 2002

Work Unit #01-65001a

# DETAIL SUMMARY SHEET

TITLE: The Role Of Caveolin-1 in Thyroid Carcinoma

KEYWORDS: Thyroid cancer, caveolin-1, benign thyroid tumors

PRINCIPAL INVESTIGATOR: Powers, Patricia COL MC
ASSOCIATES: Gary L. Francis, Catherine Dinauer, Andrew Bauer, Henry Burch, Yvonne Lukes, Diarmuid Nicholson, Maged Abdelrahim

DEPARTMENT: Pediatrics
SERVICE: Pediatric Endocrinology

STATUS: O
INITIAL APPROVAL DATE: 10 April 2001

STUDY OBJECTIVE: To improve our understanding of the molecular biology of thyroid cancer and how individual mutations or expressed protein products determine the clinical course of individual tumors. In the first part of this sub-study, we plan to determine if thyroid cancers which express caveolin-1 behave differently from thyroid cancers which do not express caveoin-1, and if benign lesions express caveolin-1 differently from malignant tumors. In the second part of the study, we plan to investigate the effect of angiogenesis stimulators and inhibitors on caveolin-1 expression in cell cultures.

TECHNICAL APPROACH

PART 1: The Expression of Caveolin-1 in Archived Thyroid Cancer Tissue Blocks

Subjects:

This protocol will use only previously existing, archived thyroid tissues / slides and the corresponding clinical data-domains outlined in the "master protocol" WU# 01-65001, entitled "An Archival Fixed-Thyroid Tissue Bank. The final number of materials available for this sub-study will vary slightly but will not exceed 200 adult tumors, 70 pediatric tumors, 50 benign thyroid lesions, and 75 radiation induced tumors.

Study Design:

Part 1 of this proposal is an observational, retrospective analysis of caveolin-1 expression among a group of diverse thyroid tumors. Caveolin-1 expression will be determined by immunohistochemistry and correlated with the clinical data domains outlined above. The results of caveolin-1 expression will be entered into a computerized database that includes the patient age and gender; tumor histology, size, and extent of disease at diagnosis; as well as the treatment and outcome for each individual patient. The tissue block and the database domains are identified by a corresponding random, unique number so that the result of the caveolin-1 testing can be correlated with the clinical history. However, neither the database nor the tissue blocks contain any patient name, number, or pathology number. By this means, no patient can be identified from either the tissue or the database. No patient will be contacted for this study, and no new patients will be recruited. Only the previously existing, archived materials already in the laboratory will be used.

Thyroid tissue sections will be stained for the expression of caveolin-1 by immunohistochemistry. In brief, tissue slices will be deparaffinized and rehydrated through a series of graded alcohol solutions. Endogenous peroxidase will be blocked (3% hydrogen peroxide), and antigen will be retrieved (0.25 M sodium citrate buffer, pH 6.0, 1 hr). Non-specific binding will be blocked with universal tissue blocker, and the slides will be incubated with primary anti-caveolin-1 antibody (Santa Cruz Biotechnology, Santa Cruz, CA) followed by biotinylated secondary antibody, horse radish peroxidase and diaminobenzidine chromogen. The intensity of staining will be semi-quantitatively graded by two blinded, independent examiners using a scale based on absent - intense staining. The intensity of staining will then entered into the database and compared between benign and malignant lesions as well

as correlated with the data domains outlined above.

PART 2: The Effect of Angiogenesis Stimuli and Inhibitors on the Expression of Caveolin-1 by Thyroid Cell Cultures.

We will use cell cultures to directly examine the effect of angiogenesis stimulators and inhibitors on in vitro caveolin-1 expression. The cell cultures to be used include ARO, WRO and NPA thyroid cancer cells. They were commercially obtained and the identity of the original patients from which they were obtained cannot be traced. Caveolin-1 expression will be determined by two methods, Western blot analysis of protein expression and RT-PCR determination of caveolin-1 mRNA production. Both methods will be used to determine if there is an effect at the transcription level (mRNA) or protein level (Western blot).

By studying the role of caveolin-1 in all three cell types, we will be able to determine if caveolin-1 expression is lost from anaplastic thyroid cancer (ARO), but retained by differentiated thyroid cancer (NPA). If so, this will allow caveolin-1 immunostaining to be used to help distinguish the level of tumor differentiation. We will then examine the direct effect of several of the more common angiogenic stimuli [vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), epidermal growth factor (EGF), and basic fibroblast growth factor (bFGF)] on the expression of caveolin-1 by each of these cell lines. The results of these experiments will directly determine if caveolin-1 expression is modulated by angiogenic stimuli in thyroid cancers. We will also examine the effect of angiogenesis inhibitors on caveolin-1 expression. We plan to study the effect of anti-VEGF antibody and thalidomide using all three cell cultures.

The intensity of caveolin-1 expression for each treatment will be compared to the control cultures. The intensity of caveolin-1 expression will be determined by scanning and densitometric analysis of the appropriate bands (NIH Image). Each experiment will be repeated three times to ensure any observed effect is replicable.

There have been no modifications to the original methodology.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
We have purchased materials and stained 30 archived tissue blocks as described in Part 1, but because of some personal medical issues resulting in my prolonged absence last fall, we have not completed analysis of these. We have not yet begun Part 2.

No recent literature to summarize. No amendments or modifications to the study since its approval. The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is N/A. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
None yet.

Report Date: 27 August 2002

Work Unit # 01-65001b

# DETAIL SUMMARY SHEET

TITLE: Pre-clinical Pilot Study to Determine if the Novel Tumor-Activated Fluoropyrimidine Carbamate Capecitabine (Xeloda®, Hoffman-Laroche, Inc.) Could be Used to Treat Thyroid Carcinoma: Are Cytidine Deaminase, Thymidine Phosphorylase, Dihydropyrimidine Dehydrogenase, and Thymidylate Synthase Present in Thyroid Carcinoma?

KEYWORDS: Xeloda, Pilot Study

PRINCIPAL INVESTIGATOR: Andrew J. Bauer, MAJ, MC
ASSOCIATES: Henry Burch COL MC USA; Patricia Powers COL MC USA; Gary Francis COL MC USA

DEPARTMENT: Pediatrics
SERVICE: Pediatric Endocrinology

STATUS: O
INITIAL APPROVAL DATE: 14 September 2001

STUDY OBJECTIVE:
Pilot study to determine if various forms of thyroid cancer express enzymes that would predict if the novel-tumor activated 5-FU analog, Xeloda, would be an effective therapy. Positive results from this pilot study would be used to extend the study to include a greater number of samples prior to consideration of a clinical therapeutic trial. A total of 40 samples will be examined in this pilot study.

TECHNICAL APPROACH
Immunohistochemical analysis of archived tissue.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The protocol was approved in August 2002 after revisions were completed and accepted. With the consent of DCI initiation of this project, and its budget, will be moved to FY 2003.

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is N/A.

CONCLUSIONS
Approved and pending initiation of the project until FY 2003.

Report Date: 29 May 2002 Work Unit # 01-65002

# DETAIL SUMMARY SHEET

TITLE: In Situ Expression of *cagA* in *H.Pylori* Infected Children: A Case Series with Endoscopic and Histologic Correlation

KEYWORDS: *Helicobacter pylori, cagA*, gastroduodenal disease, children, *in situ* hybridization

PRINCIPAL INVESTIGATOR: MAJ James R. Rick MC
ASSOCIATES: Dr. Andre Dubois, Dr. Cristina Semino-Mora, Dr. Eugenia Rueda-Pedraza, and Dr. Carolyn Sullivan

DEPARTMENT: Pediatrics
SERVICE: Gastroenterology and Nutrition

STATUS: O
INITIAL APPROVAL DATE: 10 July 2001

## STUDY OBJECTIVE

1. Describe the expression of *cagA* among *H.pylori* infected children using fluorescent *in situ* hybridization (FISH).
2. Describe the relation between *cagA* expression and gastroduodenal disease (endoscopic and histologic) in *H.pylori* infected children.
3. Describe the expression of MUC2 and MUC5AC among normal and *H.pylori* infected children using FISH and describe its relation to gastroduodenal disease.

## TECHNICAL APPROACH

Chart review and use of recuts made from archival gastric biopsies. These were subjected to Genta staining, immunocytochemistry, and FISH as described in the protocol. Data analysis is described in the protocol.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

An addendum was submitted and approved. This addendum detailed further studies to be done (FISH for mucins) and allowed for the inclusion of adults with normal gastric biopsies to serve as tissue controls for the additional mucin FISH. Lastly, it detailed a protocol deviation and included provisions to allow for that deviation. Namely, that in the initial fifty-one patients, there were some with *H.pylori* negative peptic ulcer disease. Review of literature pertaining to the role of mucins in *H.pylori* disease is included in the addendum. This addendum has been approved and letter of approval is pending. The number of subjects enrolled to the study since last APR at WRAMC is 51 and the total enrolled to date at WRAMC is 51.

## CONCLUSIONS

FISH is a useful tool to evaluate *H.pylori* virulence gene expression.
*CagA* expression impacts the severity of endoscopic and histologic disease in *H.pylori* infected children.
Prospective, long term studies are needed to investigate this impact.

Report Date: 28 May 2002

Work Unit # 01-65003

# DETAIL SUMMARY SHEET

TITLE: Open Label Administration of Human Botulism Immune Globulin

KEYWORDS: Infant Botulism

PRINCIPAL INVESTIGATOR: COL Harlan S. Patterson MC
ASSOCIATES: COL David I. Goldberg MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Critical Care

STATUS: O
INITIAL APPROVAL DATE: 24 July 2001

STUDY OBJECTIVE
Provide botulism immune globulin for victims of infant botulism.

TECHNICAL APPROACH
Multi-center open label administration of botulism immune globulin. (Pending final FDA approval of product.)

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is (unavailable at time of submission) if multi-site study.

CONCLUSIONS
Not available.

Report Date: 6 February 2002 Work Unit #01-66001

# DETAIL SUMMARY SHEET

TITLE: POG A LinC 17 – Induction Therapy for POG 9904, POG 9905 and POG 9906 (Consent Form Only)

KEYWORDS:

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES:

DEPARTMENT: Pediatrics STATUS: O
SERVICE: Pediatric Hematology-Oncology INITIAL APPROVAL DATE: 27 February 2001

STUDY OBJECTIVE
This is the common induction regimen for the three POG ALinC 17 ALL studies. (Please see individual studies for objectives).

TECHNICAL APPROACH
Patients age 1-21 years with newly diagnosed precursor B-cell ALL will receive this common induction therapy in an attempt to establish a remission prior to treatment on the appropriate low, standard, or high risk phase III therapeutic trial within the ALinC 17 protocols.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This is only the common induction regimen for the ALinC 17 ALL protocols. Please see individual protocols (POG9904, POG9905, POG9906) for study results.

CONCLUSIONS
This work unit should stay open to support the ALinC 17 therapeutic trials.

Report Date: 6 February 2002

Work Unit #01-66001a

# DETAIL SUMMARY SHEET

TITLE: POG 9904: ALinC 17 Treatment for Patients with Low Risk Acute Lymphoblastic Leukemia: A Pediatric Oncology Group Phase III Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES:

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 17 April 2001

## STUDY OBJECTIVE

In patients with low risk precursor B-cell ALL: To compare short MTX infusion (regimens A and C) with a longer infusion (regimens B and D) with respect to efficacy and toxicity. To determine in a randomized trial, if a delayed multi-drug intensification (regimens C and D), administered in the context of intensive anti-metabolite therapy, will improve outcome for children with ALL. To determine the correlation between peripheral blood and CSF concentrations of homocysteine and its metabolites and acute (seizures) and chronic neurotoxicity (neurocognitive dysfunction). To determine the relationship between a membrane bound glucocorticoid receptor and EFS via quantitation of the glucocorticoid receptor concentrations in marrow samples at diagnosis.

## TECHNICAL APPROACH

Patients ages 1 through 21 years with newly diagnosed low risk precursor B-cell ALL, after achieving remission with a standardized induction, are randomized to one of four regimens (A-D as above) with the following exceptions: (a) patients with trisomy 4/10 receive only A or B (regimens with no delayed intensification), while patients with the 1-19 translocation receive only C or D (regimens with delayed intensification).

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Toxicity, aside from early infection toxicity in the four drug induction (see below), has been within expectations and is detailed in the reference cited below. There have been no post induction deaths on this study. Since all three ALinC 17 studies use the same induction regimen, the induction data are common to all 3 studies. There have been two induction deaths during the 3 drug induction (0.4%), 2 deaths during the 4 drug induction with Prednisone (1.4%), and 2 deaths during the 4 drug induction with dexamethasone (11%). Two additional patients failed to achieve remission by day 29 and died one month later following the 3 drug induction. In June 2000 the induction was amended to replace dexamethasone with prednisone in the 4 drug regimen because of toxicity.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 268, if multi-site study.

[Ref: Children's Oncology Group Fall 2001 Meeting Report]

## CONCLUSIONS

Study should remain open to accrual.

Report Date: 6 February 2002 Work Unit #01-66001b

# DETAIL SUMMARY SHEET

TITLE: POG 9905: ALinC 17 Protocol for Patients with Standard Risk Acute Lymphoblastic Leukemia (ALL) – A Pediatric Oncology Group Phase III Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES:

DEPARTMENT: Pediatrics STATUS: O
SERVICE: Pediatric Hematology-Oncology INITIAL APPROVAL DATE: 27 February 2001

STUDY OBJECTIVE
In patients with standard risk precursor B-cell ALL: To compare short MTX infusion (regimens A and C) with a longer infusion (regimens B and D) with respect to efficacy and toxicity. To determine in a randomized trial, if a delayed multi-drug intensification (regimens C and D), administered in the context of intensive anti-metabolite therapy, will improve outcome for children with ALL. To determine the correlation between event-free survival (EFS) and minimal residual disease (MRD)/early response. To analyze samples obtained at relapse to ascertain whether markers of MRD remain constant. To determine the correlation between peripheral blood and CSF concentrations of homocysteine and its metabolites and acute (seizures) and chronic neurotoxicity (neurocognitive dysfunction). To determine the relationship between a membrane bound glucocorticoid receptor and EFS via quantitation of the glucocorticoid receptor concentrations in marrow samples at diagnosis.

TECHNICAL APPROACH
Patients ages 1 through 21 years with newly diagnosed standard risk precursor B-cell ALL, after achieving remission with a standardized induction, are randomized to one of four regimens (A-D as above).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
It is too early to report response or survival data. Toxicity, aside from early infection toxicity in the four drug induction (see below), has been within expectations and is detailed in the reference cited below. There have been no post induction deaths on this study. Since all three ALinC 17 studies use the same induction regimen, the induction data are common to all 3 studies. There have been two induction deaths during the 3 drug induction (0.4%), 2 deaths during the 4 drug induction with Prednisone (1.4%), and 2 deaths during the 4 drug induction with dexamethasone (11%). Two additional patients failed to achieve remission by day 29 and died one month later following the 3 drug induction. In June 2000 the induction was amended to replace dexamethasone with prednisone in the 4 drug regimen because of toxicity.
The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 303, if multi-site study.
[Ref: Children's Oncology Group Fall 2001 Meeting Report]

CONCLUSIONS
Study should remain open to accrual.

Report Date: 6 February 2002

Work Unit #01-66001c

# DETAIL SUMMARY SHEET

TITLE: POG 9906: ALinC 17 Protocol for Patients with Newly Diagnosed High Risk Acute Lymphoblastic Leukemia (ALL) – Evaluation of the Augmented BFM Regimen: A Phase III Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES:

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 17 April 2001

## STUDY OBJECTIVE

To determine for patients at high risk for treatment failure if the augmented Berlin-Frankfurt-Muenster (BFM) therapy is superior to ALinC 14/15 therapy, on the basis of historical controls. To determine if minimal residual disease at the end of induction is predictive of an inferior prognosis. To determine the correlation between event-free survival (EFS) and minimal residual disease (MRD)/early response (ER). To determine the correlation between peripheral blood and CSF concentrations of homocysteine and its metabolites and acute (seizures) and chronic neurotoxicity (neurocognitive dysfunction). To determine the relationship between a membrane bound glucocorticoid receptor and EFS via quantitation of the glucocorticoid receptor concentrations in marrow samples at diagnosis. To give POG investigators experience with BFM-type regimens as these will likely play a major role in COG protocols of the future.

## TECHNICAL APPROACH

Patients age 1 through 21 years are treated in a single arm study of the augmented BFM regimen in high risk acute lymphoblastic leukemia. The outcome for this regimen will be compared against historical POG regimens from ALinC14 and ALinC15. Historically, the four year event-free survival was 44% (S.E.=2.5%). This study is designed to have over 80% power to detect an improvement of 10% or more, at $P<.05$, one-sided, by Kaplan-Meier analysis.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

It is too early to report response or survival data. Toxicity, aside from early infection toxicity in the four drug induction (see below), has been within expectations and is detailed in the reference cited below. There have been no post induction deaths on this study. Since all three ALinC 17 studies use the same induction regimen, the induction data are common to all 3 studies. There have been two induction deaths during the 3 drug induction (0.4%), 2 deaths during the 4 drug induction with Prednisone (1.4%), and 2 deaths during the 4 drug induction with dexamethasone (11%). Two additional patients failed to achieve remission by day 29 and died one month later following the 3 drug induction. In June 2000 the induction was amended to replace dexamethasone with prednisone in the 4 drug regimen because of toxicity.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 79, if multi-site study.
[Ref: Children's Oncology Group Fall 2001 Meeting Report]

## CONCLUSIONS

Study should remain open to accrual.

Report Date: 1 April 2002 Work Unit #01-66002

# DETAIL SUMMARY SHEET

TITLE: ANBL00B1: Neuroblastoma Biology Studies

KEYWORDS:

PRINCIPAL INVESTIGATOR: Edwards, E. Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Reddoch, Shirley COL MC; Crouch, Gary LtCol MC; Merino, Margret MAJ MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 24 April 2001

## STUDY OBJECTIVE

1. To prospectively analyze the factors that are currently used for risk-group assignment in neuroblastoma tumors at the time of diagnosis. 2. To maintain a reference bank containing clinically and genetically characterized tumor tissue and paired normal DNA obtained at the time of diagnosis (all patients), at the time of second-look surgery (high-risk patients), and relapse (all patients) for future research studies. 3. To prospectively analyze the prevalence of 1p, 11q, 14q LOH and gain of 17q; the expression of nerve growth factor and its high affinity (Trk-A) and low affinity (p75 NTR ) receptors; and telomerase activity in neuroblastoma tumors compared to MYCN amplification, INSS stage, age, and histologic variables in predicting either response to treatment or outcome. 4. To build a database of the known biologic prognostic factors for patients on therapeutic studies.

## TECHNICAL APPROACH

Tumor tissue and blood from newly diagnosed neuroblastoma patients obtained at diagnosis and subsequent surgeries (relapse and second-look) are analyzed at reference laboratories for the factors listed above which are correlated with treatment response and outcome on COG neuroblastoma therapeutic studies. If available, neuroblastoma tissues, slides and nucleic acids are also stored for use in future studies. Enrollment on ANBL00B1 is a requirement for all neuroblastoma clinical trials open for patients at diagnosis. Banking of tissue is not a requirement for study registration.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study was opened for patient registration on January 5, 2001; this is the first WRAMC APR for this study. The total number of subjects enrolled study-wide is 436. There were two subjects enrolled at WRAMC since this study was approved here. The anticipated accrual rate was 470 patients per year. Enrollment is slightly behind schedule, likely secondary to there being no open high-risk protocol until recently. Unique to this protocol is rapid assessment of tumor specific variables (MYCN, DNA index and Shimada pathology) necessary for risk group assignment. Only 3.4% of patients could not have a risk group assigned, typically due to an inadequate specimen submitted for analysis. Since this is a non-therapeutic study there have been no adverse events. Possible benefit to subjects is proper determination of risk factors to determine best treatment.
The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 2.

## CONCLUSIONS

Study should remain open.

Report Date: 10 December 2001 Work Unit # 6121

# DETAIL SUMMARY SHEET

TITLE: POG 7799 Rare Tumor Registry

KEYWORDS: rare tumors, tumors, pediatric tumors

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 22 January 1980

## STUDY OBJECTIVE

To accumulate natural history data on malignancies that occur so rarely that larger series of cases cannot be accumulated at any single institution.

## TECHNICAL APPROACH

To build a registry which contains pathology review of patients with rare tumors and annual reporting of status of patients.

## PRIOR AND CURRENT PROGRESS

This study was closed on 20 September 2001. Data were being reported for the preceding five year interval, but the most recent COG agenda reported only the total cumulative enrollment and average annual accrual: 1189 total accrual with an average annual accrual of fifty (data through 7 September 2001). There were no WRAMC registrations on this protocol since the last APR. WRAMC total registrations are ten. Benefits to patients include participation in the national database, which expedites enrollment in newly developed rare tumor studies.

## CONCLUSIONS

Study is complete.

Report Date: 14 August 2001 Work Unit # 6188

# DETAIL SUMMARY SHEET

TITLE: POG 8650: National Wilm's Tumor Study -- A POG Phase III Study

KEYWORDS: Wilms' tumor, renal tumor, nephroblastoma

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, A. COL MC; Crouch, G. LtCol MC; Hartman, K. LTC MC

DEPARTMENT: Pediatrics STATUS: O
SERVICE: Pediatric Hematology-Oncology INITIAL APPROVAL DATE: 28 October 1986

STUDY OBJECTIVE
1) To gather data on morphology and correlate it with treatment and clinical outcome, and 2) refine clinical trials to reduce therapy to simpler and shorter regimens.

TECHNICAL APPROACH
To attempt to give the usual five-day course one day (has been done with other tumors), and to examine in randomized trial with current therapies.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This study closed to accrual effective 1 September 1994. Final accrual as of last reporting to POG (31 January 1996) is 3335. There were a total of 14 patients registered at WRAMC; the last WRAMC registration was in July 1993. There were no unexpected toxicities reported. Of the 14 WRAMC registrants 9 are followed at WRAMC and are in remission, 4 transferred to other POG institutions, and 1 died of relapse and progressive disease. Results showed no statistically significant difference in relapse-free survival or survival for patients treated with short versus long treatment regimens. No new outcome analyses have been reported as of the most recent COG report.

[Reference Study Reports from the Spring 2001 COG Meeting]

CONCLUSIONS
Study is closed to accrual but should remain open to complete ten-year follow-up period for patients followed at WRAMC.

Report Date: 6 August 2002

Work Unit # 6221

# DETAIL SUMMARY SHEET

TITLE: POG 8821: Intensive Multi-agent Therapy vs. Autologous Bone Marrow Transplant Early in First CR for Children with Acute Myelocytic Leukemia -- A Phase III Study

KEYWORDS: autologous bone marrow, transplant, acute myelocytic leukemia

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 September 1988

## STUDY OBJECTIVE

To: 1) determine DFS with intensive chemotherapy using non-cross resistant drug pairs; 2) determine if short-term intensive therapy with autologous bone marrow transplant (with 4-Hydroperoxycyclophosphamide purge) is effective therapy; and 3) compare the two regimens' results and to correlate outcome with clinical and laboratory features.

## TECHNICAL APPROACH

Registrants are 21 years of age and younger with previously untreated acute myelocytic leukemia (AML). Induction for both arms uses intrathecal Ara-C, daunomycin, Ara-C, 6-TG, followed by high-dose Ara-C. Patients are then randomized to receive IT Ara-C, VP-16/5-AZA plus ABMT with 4-HC purge, or to receive IT Ara-C, HDAC/daunomycin, Ara-C/6-TG, and VP-16/5-AZA.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study has been closed since11 March 1993. The 666 group wide accrual figure remains unchanged. Of the seven patients registered on study at WRAMC, four have relapsed (three of the relapsed patients died of their disease and one is in second remission after ABMT), one transferred to another COG institution, and two are alive (one in first CR and the other in CR2), off therapy. There have been no late reports of adverse reactions. Benefits to patients included the possibility of remission of disease. There were no further reports from COG in the last year.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 7. The total number enrolled study-wide is 666 (multi-site study).

## CONCLUSIONS

Study should remain open to follow WRAMC registrants.

Report Date: 15 May 2002 Work Unit # 6242

# DETAIL SUMMARY SHEET

TITLE: POG 8828: Late Effects of Treatment of Hodgkin's Disease: A POG Non-therapeutic Study

KEYWORDS: childhood, Hodgkin's disease, long-term effects

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Hartman, Kip COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics STATUS: O
SERVICE: Pediatric Hematology-Oncology INITIAL APPROVAL DATE: 23 May 1989

STUDY OBJECTIVE
To estimate incidence of late effects following treatment for Hodgkin's disease on current frontline POG studies and to attempt to identify pre-treatment and/or on-treatment factors which predict high risk of specific late effects.

TECHNICAL APPROACH
Registrants are patients on POG frontline Hodgkin's protocols and are followed through completion of late effects study forms every three years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This protocol will close to patient accrual as of 15 May 2002. Group wide, 604 patients have accrued to this study. For some reason this is twenty-seven fewer registrations than reported in 2001 (COG reports attached). There were no accruals at WRAMC in the past year; WRAMC total is nine. There have been no adverse effects from participation in this non-therapeutic study. Benefits to patients may result from greater awareness of late effects with subsequent earlier treatment intervention as a result of completing the late-effects study forms every three years.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 9. The total number enrolled study-wide is 604, if multi-site study.

[Ref: The Children's Oncology Group Current Reports, Spring 2001; The Children's Oncology Group Current Reports, Spring 2002]

CONCLUSIONS
Study should remain open to follow WRAMC registrants.

Report Date: 6 August 2002

Work Unit # 6261

# DETAIL SUMMARY SHEET

TITLE: POG 9047: Neuroblastoma Biology Protocol

KEYWORDS: cytogenetics, neuroblastoma

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 February 1990

## STUDY OBJECTIVE

To analyze cytogenetics of neuroblastoma cells and determine the clinical significance of genetic variations found, compared to conventional clinical, histologic, and biologic variables in predicting response to treatment or outcome. To develop a neuroblastoma serum and tissue bank for future studies, and to collect natural history and lab data on patients with untreated disease (stages A and DS).

## TECHNICAL APPROACH

All newly diagnosed patients 21 years old or less who are registered on POG neuroblastoma treatment protocols, or stage A or DS (favorable risk) will submit discarded biopsy material and serum for cytogenetic studies and banking.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study closed to accrual on 5 April 2001 and was subsequently replaced by biology study ANBL00B1 (which was opened at WRAMC on 24 April 2001; WU #01-66002). As of the most recent study report, 2429 patients have been enrolled in this biological study [Ref: Fall 2001 COG Current Reports of Studies]. There have been no reports of adverse events resulting from participation in this study. Benefits to patients include the possibility that the clinical significance of the genetic rearrangements will more accurately predict treatment outcome.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 15. The total number enrolled study-wide is 2429 (multi-site study).

## CONCLUSIONS

Study is closed to accrual. This study was marked as 'Complete/Closed' during the last APR, which was approved on 27 March 2001; this study should be re-opened at WRAMC in order that follow up data may be collected and forwarded to COG.

Report Date: 15 October 2001 Work Unit # 6302

# DETAIL SUMMARY SHEET

TITLE: POG: 9151 Intergroup Rhabdomyosarcoma Study IV Treatment for Stage 2 and 3 Diseases -- A Phase III Trial

KEYWORDS: rhabdomyosarcoma, children, chemotherapy

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics STATUS: C
SERVICE: Pediatric Hematology-Oncology INITIAL APPROVAL DATE: 26 November 1991

STUDY OBJECTIVE
To compare progression-free survival of children with rhabdomyosarcoma treated with chemotherapy, radiation, and surgery per protocol; to collect data on the toxicity of these treatments; to correlate disease features (cell biology, tumor size and location, and cytogenetic fractures) with treatment outcome and survival. Study will also collect material for a tumor tissue to use in future tumor biology studies.

TECHNICAL APPROACH
Subjects ages 21 years and less with rhabdomyosarcoma or undifferentiated soft tissue sarcoma will be randomized to receive one of three chemotherapy regimens: vincristine, actinomycim-D, cyclophosphamide; vincristine, actinomycim-D, etoposide; or vincristine, etoposide, ifosfamide. Registrants will also be randomized to receive radiation on a once daily or twice daily schedule. Supportive care with G-CSF will be given. Tumor cytogenetics will be evaluated at a central POG laboratory for future correlations with response data. Patients will be followed for relapse.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This protocol was closed to accrual in January 1998. There has been no new data reported since the last APR. The last IRSG report was reported in POG Fall 1998 Report and fails to break down the registrants (stages 1-3) by stage and combines data from the POG 9150/9151 protocols in IRS IV. Total of registrants on these intergroup studies was 988. There was one WRAMC registrant due to IRB closure of a required companion study (POG 9153). This patient developed recurrent disease at the primary site and died of her disease.

[Data from POG Meeting Agenda and Current Report of Studies, October 1998]

CONCLUSIONS
Study is complete.

Report Date: 26 March 2002

Work Unit # 6314

# DETAIL SUMMARY SHEET

TITLE: Barrier to Enrollment on POG Frontline Therapeutic Clinical Trials and development of Intervention Strategies; A POG Therapeutic Study

KEYWORDS: accrual, oncology treatment

PRINCIPAL INVESTIGATOR: Edward, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 31 March 1992

## STUDY OBJECTIVE

To 1) prospectively identify factors leading to non-accrual of eligible patients on POG frontline therapeutic studies; and 2) develop intervention strategies designed to decrease barriers to patient enrollment on POG studies, thus increasing future accrual rates in the POG.

## TECHNICAL APPROACH

Patients diagnosed with cancer at POG institutions and their physicians are surveyed within 7 days of their decision whether to participate on POG treatment studies. Survey results from those who decide not to participate (not register on frontline POG study) will be analyzed and compared to the results of those who do register.

## PRIOR AND CURRENT PROGRESS

As of the last COG report (Spring 2001), 259 patients were registered on POG 9284 and 104 patients were registered on POG 9285. For the data available for analysis on 223 cases, 124 (56%) representing 61 POG institutions and protocols were eligible for POG protocols that had not been submitted for IRB approval. The most frequently reported reason for not obtaining IRB approval was the limitation in the availability of support personnel at the institution to meet the needs of the protocol. Few institutions indicated a preference for a non-POG institutional protocol or non-protocol therapy.

For the 99(44%) cases that were eligible for an IRB approved POG protocol, physicians refused to approach patients with the protocol 73% of the time (72/99) and patients refused entry 27% of the time (27/99). The reasons given by physicians for not approaching patients/families seemed equally distributed among concerns that focus on potential treatment/protocol compliance. Patient refusals seem polarized to concerns regarding randomization and concerns about receiving experimental therapy.

It is still too early (too few patients) in the control groups to do a matched case control analysis comparing patient refusals to those who accept protocol therapy. There have been no adverse reactions reported from participation in the study. This is a non-therapeutic study. Benefits to patients include the possibility that participation in this study may lead to enrollment in an appropriate study. [Ref: Spring 2001 COG Current Report of Studies]

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date to WRAMC is 7. The total number enrolled study-wide is 363, if multi-site study.

## CONCLUSIONS

Study is complete. Since there is no follow-up on this study it should be closed at WRAMC.

Report Date: 15 May 2002 Work Unit # 6323

# DETAIL SUMMARY SHEET

TITLE: POG 9233/34: A Phase III Randomized Trial of Standard vs. Dose-Intensified Chemotherapy <3 years of Age with a CNS Malignancy Treated With or Without Radiation Therapy

KEYWORDS: brain tumor, child, pre-school, chemotherapy

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Hartman, Kip COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 26 May 1992

## STUDY OBJECTIVE

To study efficacy and toxicity of dose intensified chemotherapy in children less than three years old with selected types of brain tumors by means of a randomized comparison. To relate response to DNA index of tumor. To attempt to observe for disease progression over 1 year, with the option of giving irradiation if tumor relapses during this year.

## TECHNICAL APPROACH

Children less than three years of age with selected types of brain tumors will be randomized to receive either intensive or standard chemotherapy (POG 9233). If response is adequate, there will be one year of close observation, during which time radiation therapy on POG 9234 will be available if the tumor relapses. Patients who have less than adequate response on POG 9233 will receive irradiation on POG 9234 as soon as possible. The DNA index of diagnostic tumor tissue will be related to the treatment outcome.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

All strata of POG 9233 achieved accrual goals and were closed as of 8 May 1998. POG 9234 was closed to accrual on 14 December 2000. The last reported data are from the Children's Oncology Group Current Report of Studies, Spring 2000. Group wide total accrual for both 9233 and 9234 is 391 (338 on POG 9233 and 53 on POG 9234); zero since the previous APR. WRAMC has four registrations with none in the last year. A fifth patient is being followed at WRAMC after being transferred here from MAMC. Of the five patients followed at WRAMC, three remain in CR, and two have died of disease. Toxicity has been as expected with this therapy with the most common being myelosuppression (detailed toxicity data reported in Children's Oncology Group Current Report of Studies, Vol. II, Spring 2000). Early results from POG 9233 shows five-year EFS and survival of 21% and 34%, respectively. Data for POG 9234 are masked. Benefits to patients include the possibility of remission of disease.

## CONCLUSIONS

Study should remain open to follow study registrants at WRAMC.

Report Date: 26 March 2002

Work Unit # 6351

# DETAIL SUMMARY SHEET

TITLE: POG 9317: Chemotherapy for children with Advanced-Stage (III/IV) Diffuse Undifferentiated Burkitt's Lymphoma and B-Cell ALL -- A phase III Study

KEYWORDS: Burkitt's lymphoma, Cyotoxan, Ara-C

PRINCIPAL INVESTIGATOR: Edward, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 30 March 1993

## STUDY OBJECTIVE

To 1) evaluate the efficacy of adding VP-16/ifosfamide (VP/IFOS) intensification to the treatment of patients with advanced-stage B-cell malignancies (Stages III and IV DU NHL and B cell ALL will receive randomized induction therapy to compare the toxicity of high-dose Ara-C given by intermittent bolus (q 12 hours x 4) vs. bolus/continuous infusion.

## TECHNICAL APPROACH

Registrants must be 21 years old or younger and have had no previous chemotherapy. Concomitant registration on POG 9000 (biology study) is required. Children with diagnosed advanced-stage (III-IV) diffuse undifferentiated Burkitt's lymphoma and B-cell ALL will receive randomized induction therapy to compare the toxicity of high-dose Ara-C given by intermittent bolus (q 12 hours x 4) vs. bolus/continuous infusion over 48 hours, followed by randomization to receive or not receive VP/IFOS for intensification.

## PRIOR AND CURRENT PROGRESS

This study the number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 343, if multi-site study. Of the two patients enrolled at WRAMC, one died of progressive disease after relapse and 1 is alive and remains in CR. Current results show no significant difference in event-free survival between ARA-C vs ARA-C+VP/IFOS or continuous infusion vs bolus ARA-C. The following is of note: For the combined group of B-ALL CNS- patients and Stage IV CNS + patients, 2-year EFS has plateaued around 79% and few CNS relapses have been reported in any of the disease strata. These last two observations suggest that the 9317 treatments are excellent for both CNS prophylaxis and for the treatment of CNS disease (at diagnosis). Group wide reported ADRs and all toxicities are listed in the report cited below. There has been significant absolute neutrophil count, platelet and hemoglobin toxicity as expected for this therapy. Benefits to patients include the possibility of remission of disease. [Ref: Spring 2001 COG Current reports Studies]

## CONCLUSIONS

Study should remain open to follow WRAMC registrant.

Report Date: 6 February 2002 Work Unit # 6364

# DETAIL SUMMARY SHEET

TITLE: POG 9351/CCG 7921: Trial of Doxorubicin, Cisplatin and Methotrexate with and without Ifosfamide, with and without Muramyl Tripeptide Phosphatidyl Ethanolamine (MTP-PE) for Treatment of Osteogenic Sarcoma

KEYWORDS: doxorubicin, osteogenic, sarcoma

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol MC

DEPARTMENT: Pediatrics STATUS: O
SERVICE: Pediatric Hematology-Oncology INITIAL APPROVAL DATE: 22 February 1994

STUDY OBJECTIVE
To: 1) improve survival and compare results of two chemotherapeutic regimens; 2) determine whether histologic response assessed after prolonged therapy with more drugs predicts disease-free survival (DFS) with the same power seen in CCG-782, which used fewer drugs over a shorter time; 3) determine whether liposomal muramyl tripeptide-phosphatidyl ethanolamine can improve DFS; and 4) determine whether MDR expression is useful to determine prognosis or assign therapy.

TECHNICAL APPROACH
Patients </= 30 years old will be treated in a Phase III randomized trial of two chemotherapy regimens for the treatment of newly diagnosed, previously untreated osteogenic sarcoma. One regimen calls for the administration of high-dose methotrexate, doxorubicin, and cisplatin. The other regimen calls for the administration of these agents plus ifosfamide. Chemotherapy is administered for 10 weeks prior to surgical resection of primary tumor and any metastatic disease. Patients also are randomly assigned either to receive MTP-PE with maintenance chemotherapy or to receive maintenance chemotherapy alone.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This protocol was closed to accrual on 25 November 1997. There were eight toxic deaths on this study: five due to infections during neutropenia, one an intraoperative mortality, and there is insufficient data to characterize the other two. Results to date show no difference in outcome due to MTP in the CDDP/DOX/HDMTX regimen (4yr EFS=65% w/o MTP vs. 62% w/ MTP). There does appear to be a difference in outcome with the four-drug regimen (above combination plus ifosfamide) when MTP was added (4yr EFS= 57% without MTP vs. 70% with MTP). A detailed discussion of results and toxicity appears in the reference cited below. There have been no toxic deaths at WRAMC. Three of the four WRAMC registrants have died of recurrent or progressive disease. The other WRAMC registrant is alive with no evidence of disease. Benefits to patients include the possibility of remission of their disease. [Data is from Spring 2001 COG Current Report of Studies]

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 679 (POG 321), if multi-site study.

CONCLUSIONS
Study is closed to accrual. Study should remain open to follow WRAMC registrant.

Report Date: 31 October 2002

Work Unit # 6374

# DETAIL SUMMARY SHEET

TITLE: The Role of Nitric Oxide in Cerebrovascular Autoregulation in the Newborn Piglet

KEYWORDS: cerebrovascular, autoregulation, nitric oxide

PRINCIPAL INVESTIGATOR: Mark Thompson, MAJ, MC, USA
ASSOCIATES: J. Timothy O'Neill, Ph.D.

DEPARTMENT: Pediatrics
SERVICE: Neonatology

STATUS: C
INITIAL APPROVAL DATE: August 1994

## STUDY OBJECTIVE

To determine 1) the relationship between cerebral perfusion pressure and blood flow during induced hypertension in the newborn piglet and 2) the role on nitric oxide in the relationship between cerebral perfusion pressure and blood flow.

## TECHNICAL APPROACH

Chloralose and urethane anesthetized piglets were catheterized and instrumented for the measurement of regional blood flows with radioactive microspheres. Blood gases and pH were maintained in the normal range throughout the experiment. Blood flows were measured before and 30 minutes after 7-NI (25mg/kg i.p.) or peanut oil (the vehicle for the 7-NI,3 cc/kg i.p.). Mean arterial pressure (MAP) was then raised to 100-110 mmHg and 110-125 mmHg with aortic occlusion and/or norepinephrine infusion and blood flow measured in each pressure range.

## PRIOR AND CURRENT PROGRESS

We have previously shown that blockade of nitric oxide synthase (NOS) alters the newborn piglet's ability to maintain r CBF during acute hypertension (Soc Neurosci Abstr 1996, 22:1103). When NOS was inhibited by Nω-nitro-L-arginine methyl ester (L-NAME), blood flow to the cerebrum, particularly the cortical gray matter and occipital lobes, did not change when MAP was raised 36%. This elevation of MAP resulted in a 60-80% increase in blood flow in these structures of untreated animals. The lower brain rCBFs including medulla/pons midbrain/diencephalon and cerebrum were not altered by the blood pressures studied. Since L-NAME inhibits both neuronal and endothelial isoforms of NOS, we sought to determine the role of the neuronal isoform of NOS (nNOS) in the observed response by selectively inhibiting nNOS with 7-Nitroindazole (7-NI) in piglets. 7-NI did not change MAP, as did L-NAME. Baseline rCBFs were also not altered after 7-NI. After 7-NI, we elevated MAP from 83±3 to 103±2 and 117±1 sequentially. It appeared that no brain structure was capable of autoregulation after 7-NI. However, statistical analysis did not confirm this conclusion. Oxygen consumption to the cerebrum was monitored and was not elevated by 7-NI nor the elevated MAP. No animals were enrolled in the past year.

## CONCLUSIONS

Blockade of nNOS with 7-NI does not alter the newborn piglet brain's capability to maintain blood flow when blood pressure is acutely elevated. In light of our previous data, it seems possible that NO of endothelial origin is solely responsible for the upper limit of autoregulation during acute episodes of hypertension.

Report Date: 1 November 2002 Work Unit # 6383

# DETAIL SUMMARY SHEET

TITLE: POG 9405: ALinC16 Protocol for Patients with Newly Diagnosed Standard-Risk Acute Lymphoblastic Leukemia -- POG Phase III Study

KEYWORDS: leukemia, lymphoblastic, children

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 20 December 1994

## STUDY OBJECTIVE

To: 1) determine the efficacy of a higher vs. standard dose MTX infusion during consolidation; 2) describe the incidence of adverse reactions occurring with administration of higher dose MTX; 3) determine the efficacy of delivering oral 6 MP on a once vs. twice daily schedule during continuation.

## TECHNICAL APPROACH

Newly diagnosed B-Precursor ALL patients (including B-ALL that is not L3 morphology) will be enrolled prior to registration on POG 9400. Patients will be randomized to compare the efficacy of a higher vs. standard dose MTX infusion during consolidation.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study was closed to accrual in December 1995 due to excessive acute neurotoxicity. A total of 299 patients were registered on the protocol group-wide, with 285 non-Down patients achieving remission. One patient has been registered at WRAMC and continues to do well in complete remission without evidence of neurotoxicity. Reported toxicity was similar to that seen historically with methotrexate, including slurred speech, staring, ataxia and other gross motor findings, behavioral disorders, seizures, somnolence, and loss of milestones. Of concern was that, if actuarial projections continued, the incidence of neurotoxicity would approach 30%, compared with 3-12% historically. The protocol therapy was amended in January 1996 to minimize the risk of CNS toxicity in patients already enrolled and was closed early due to predicted neurotoxicity in the protocol. The last report from POG (Joint POG/CCG Fall 1999 Meeting Agenda and Current Report of Studies) was restricted to reporting of CNS toxicity. Of the 285 patients, 70 (25%) had a reportable CNS adverse event; 29 (10%) were seizures. Benefits to patients included the possibility of remission of disease.

## CONCLUSIONS

Study should remain open to follow the one WRAMC registrant.

Report Date: 1 November 2002

Work Unit # 6384

# DETAIL SUMMARY SHEET

TITLE: POG 9406: ALinC16 Protocol for Patients with Newly Diagnosed High-Risk Acute Lymphoblastic Leukemia -- A POG Phase III Study

KEYWORDS: newly-diagnosed, high-risk, lymphoblastic leukemia

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 20 December 1994

## STUDY OBJECTIVE

To: 1) compare, in a randomized trial, the efficacy and toxicity of 12 intensive courses of IV MTX/6-MP vs. 12 intensive courses of alternating chemotherapy pairs; and 2) assess short-term toxicity of modified regimen B (Treatment C) where higher-dose MTX is substituted in first cycle of consolidation.

## TECHNICAL APPROACH

Newly diagnosed non-T, non-B ALL patients who fit the following criteria will be enrolled: 1-21 years old, poor prognostic features based on age, ploidy, translocations, and immunophenotypes, and with no history of prior treatment. Two treatments will be compared: twelve intensive courses of IV MTX/6MP vs. twelve intensive courses of alternating chemotherapy pairs (MTX/6-MP, VM-26/Ara-C, daunomycin/Ara-C).

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study was closed to accrual on 15 November 1999, having met its accrual goals. Final accrual is 910 group-wide. Total registration at WRAMC remains three. All three WRAMC patients are in CR. The most significant toxicity has been neurotoxicity, which resulted in an amendment to the protocol adding additional leukovorin and changing triple intrathecal chemotherapy to methotrexate alone. No adverse reactions at WRAMC since the last report. Four-year event-free survival of randomized subjects is 74% (SE 2%).

The number of subjects enrolled to the study since last APR at WRAMC is zero, and the total enrolled to date at WRAMC is three. The total number enrolled study-wide is 910 as of 29 October 2002.

[COG Study Progress Reports Fall 2002.]

## CONCLUSIONS

Study should remain open to follow WRAMC registrants.

Report Date: 26 March 2002 Work Unit # 6386

# DETAIL SUMMARY SHEET

TITLE: POG 9362: A Phase II Study of Alpha Interferon in HIV-Related Malignancies; A Pediatric Oncology Group Wide Study

KEYWORDS: interferon, HIV, malignancies

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics STATUS: O
SERVICE: Pediatric Hematology-Oncology INITIAL APPROVAL DATE: 28 March 1995

STUDY OBJECTIVE
(1) Estimate the complete response rate for HIV-related malignancies treated with alpha interferon; 2) estimate the 1-year disease-free survival; and 3) evaluate the toxicity of alpha interferon alone or in combination with anti-retroviral therapy.

TECHNICAL APPROACH
All patients are required to be enrolled in POG 9182, and in compliance with all specimen submission requirements of that protocol. Additional tissue sampling will be minimized, including CSF or blood sampling except as required for monitoring for toxicity and tumor response. HIV-positive children with refractory or newly diagnosed malignancies will be treated with alpha IFN alone or in combination with other antiretroviral agents.

PRIOR AND CURRENT PROGRESS
As on the last COG report (Spring 2001) response was still masked and toxicity was minimal. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 8, if multi-site study.

[Ref: COG Report of Studies, Spring 2001]

CONCLUSIONS
Study is ongoing and should remain open for accrual at WRAMC.

Report Date: 26 March 2002

Work Unit # 6387

# DETAIL SUMMARY SHEET

TITLE: POG 9421: Phase III Evaluation of Standard vs. High-Dose Ara-C Induction Followed by the Randomized Use of Cyclosporin A as an MDR Reversal Agent Compared to Allogeneic BMT in Childhood AML

KEYWORDS: allogeneic, BMT, AML

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 28 March 1995

## STUDY OBJECTIVE

1. Determine the effect of high-dose vs. standard-dose Ara-C induction on complete response (CR) and event-free survival (EFS) in childhood AML

2. Compare the EFS in childhood AML after three cycles of consolidation with or without the multi-drug resistance (MDR) modulator cyclosporin A.

3. Compare the EFS between patients genetically randomized between allogeneic BMT and chemotherapy.

## TECHNICAL APPROACH

To test, in a randomized study, the role of HD Ara-C in military health care beneficiaries who are <21 years of age presenting with newly-diagnose acute myeloid leukemia who have had no prior therapy.

## PRIOR AND CURRENT PROGRESS

This study was closed to accrual on 15 August 1999. Final accrual was 654 subjects group wide. Of those, 624 were evaluable. There were no new registrations at WRAMC since the last APR, leaving the total at five. Two of these patients are still being followed at WRAMC and are in CR; two have been transferred to other military POG institutions; one patient registered at WRAMC died of progressive disease after a BMT in first CR. Of the 624 evaluable patients, 559 (89.6%) entered remission (530 had M1 marrow and 29 had M2a marrow). Death accounted for 18 of the 65 induction failures (27.6%); the other 48 patients who failed to enter remission had resistant disease. The remission rate for 57 Down syndrome patients was 54/57 (94.7%). The remission rate for patients who received induction of DAT was 250/286 (87.4%), similar to the remission rate of 255/281 (90.7%) for patients who received induction of HDAT (p=0.10). The mean (+SE) rates of event-free and overall survival three years after randomization were 41.2 $\pm$ 2.8% AND 55.6$\pm$2.7%, respectively. There was no statistical difference in remission rate, OS, or EFS between non-BMT groups. The estimated rates of remission duration for patients who received Allo. BMT (N=83) and for all other patients (N=422) were 67.2 $\pm$ 7.3% and 37.2 $\pm$ 3.3%, respectively. Myelotoxicity has been significant but as anticipated. Benefits to patients include the possibility of remission of disease.

[Ref: COG Fall Report of Studies, October 2001]

## CONCLUSIONS

Study should remain open to follow WRAMC registrants.

Report Date: 15 May 2002 Work Unit # 6388

# DETAIL SUMMARY SHEET

TITLE: POG 9201 ALinC16: Treatment for Patients with Lesser Risk Acute Lymphoblastic Leukemia -- A Pediatric Phase III Study

KEYWORDS: acute, lymphoblastic, leukemia

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Hartman, Kip COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 23 May 1995

## STUDY OBJECTIVE

1) Confirm the outstanding results in patients with lesser-risk non-T, non-B acute lymphoblastic leukemia (ALL) treated in a fashion similar to the least intensive arm of POG 8602 (ALinC 14, Arm A).
2) Study laboratory correlates from POG 9400 and clinical correlates with outcome in pooling studies 9201, 9405, and 9406.

## TECHNICAL APPROACH

Military health care beneficiaries who are $\leq$ 21 years of age with newly-diagnosed ALL will be prospectively identified to be at lowest risk of treatment failure based on the new consensus risk groups and through the use of trisomies 4 and 10 in a trial to confirm the very favorable results of ALinC #14.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study was closed to accrual on 14 November 1999, with a final group-wide accrual on the phase III part of this study of 625. There are four WRAMC registrations; no additional registrations since the last APR. One of these four have transferred to another POG institution. WRAMC has accepted two transfer patients on protocol from other POG institutions. Four patients, therefore, are followed on this protocol at WRAMC, and all four remain in CR. There are no reports of adverse reactions at WRAMC. Group-wide there were three induction deaths amongst 622 eligible Phase III patients. Aside from the three induction deaths all patients achieved remission. Event-free survival at four years is 90% (SE=1.7%) and at five years it is 86% (SE=2.6%). Benefits to patients include the possibility of remission of disease.

[Ref: The Children's Oncology Group Current Reports, Spring 2002]

## CONCLUSIONS

Study should remain open to follow study registrants at WRAMC.

Report Date: 18 June 2002

Work Unit # 6397

# DETAIL SUMMARY SHEET

TITLE: POG 9354/CCG 7932: Phase III Evaluation of Intensified Vincristine, Doxorubicin, Cyclophosphamide, Ifosfamide, and Etoposide in the Treatment of Newly-Diagnosed Ewing's Sarcoma or Primitive Neuroectodermal Tumor of Bone or Soft Tissue

KEYWORDS: newly-diagnosed, Ewing's sarcoma

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijszuk, Askold COL MC; Hartman, Kip COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 12 July 2001

## STUDY OBJECTIVE

To compare the event-free survival, and toxicity in patients with Ewing's sarcoma treated with a 48-week course of standard-dose vincristine, doxorubicin, cyclophosphamide, ifosfamide, MESNA, and etoposide plus G-CSF with that of patients treated with the same agents given in a 30-week dose-intensified regimen.

## TECHNICAL APPROACH

Patients less than or equal to 30 years of age with newly-diagnosed Ewing's sarcoma or PNET of bone or soft tissue will be randomized to receive either the 48-week course of standard-dose vincristine, doxorubicin cyclophosphamide, MESNA and etoposide plus G-CSF, or the 30-week dose-intensified regiment using the same agents.

## PRIOR AND CURRENT PROGRESS

This study has met accrual goals and was closed to further accrual on 15 September 1998. There were 492 group-wide registrations. Three patients have been registered at WRAMC. Of those three, one was transferred to another POG institution and two are followed at WRAMC and are alive and in remission. Mucositis and grade 4 toxicity was more common on Regimen B than Regimen A. There were a total of seven toxic deaths and four were on regimen A. Two of the seven were due to post-surgical complications. Adverse drug reactions seem equally distributed between the two regimens. Secondary leukemia has been reported in nine patients (five on Regimen A and four on Regimen B). At this time, the incidence of secondary leukemia appears to be no greater than that reported in previous studies. Response: Regimen A: 72.2% (CR 2.4%; PR 69.8). Regimen B: 78.7% (CR 3.5%, PR 75.2%). Overall event-free survival and survival are 74.7 (SE 2.3) and 83.0 (SE 2.1), respectively, at three years. Benefits to patients include the possibility of remission of disease.

(Reference: COG Current Report of Studies, Fall 2001)

The number of subject enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is 492, if multi-site study.

## CONCLUSIONS

Study should remain open at WRAMC to follow WRAMC registrants.

Report Date: 26 August 2002 Work Unit # 6400

# DETAIL SUMMARY SHEET

TITLE: An Overview of the Research Protocol Entitled POG 9440/CCG 494: National Wilms' Tumor Study – 5: Therapeutic Trial and Biology Study

KEYWORDS: Wilms', therapeutic, biology

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 26 September 1995

## STUDY OBJECTIVE

1) Increase the survival rate of children with favorable Wilms' tumor and other renal tumors of childhood; 2) determine if loss of heterozygosity for chromosome 16q markers in tumor tissue is associated with a poorer diagnosis for children with favorable histology Wilms' tumor; and 3) determine if loss of heterozygosity for chromosome lp markers in tumor tissue is associated with a poorer prognosis for children with favorable histology Wilms' tumor.

## TECHNICAL APPROACH

Pediatric military health care beneficiaries will be registered as either studied, followed, or registered only. Study patients must be less than 16 years of age, not received chemotherapy or radiation therapy, and have a stage I-IV favorable histology Wilms' tumor, stage I-V focal or diffuse anaplastic Wilms' tumor stage I-V clear-cell sarcoma of the kidney or stage I-V rhabdoid tumor of the kidney. Patients must have undergone a nephrectomy.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study was closed to accrual on 1 June 2002. There is no update report since the last APR. There was one WRAMC registration in the past year for a total of eight. Two of the patients registered on study at WRAMC have been transferred to other COG institutions, so there are currently six patients followed at WRAMC on this protocol. Relapse-free survival for patients with favorable histology (FH) Stage I-IV tumors is consistent with historical expectations. Notably, all children who relapsed following nephrectomy only remain alive. Results for Stage I focal and diffuse anaplasia disease may not be equivalent to Stage I favorable as expected. This will be followed closely. Patients with Stages II or III with focal or diffuse anaplasia appear to be faring better on NWTS 5. Stage I CCSK currently has 100% RFS although with small numbers (8 pts). CCSK stages II-IV is also looking good with 85% 2 yr RFS. Patients with stage IV diffuse anaplasia and those with stages I-IV rhabdoid tumor continue to fare poorly despite treatment with new regimens, I and RTK, and will be reviewed for possible closure of these Phase II studies. There have been no AER/ADR's at WRAMC and none were reported by the Renal Tumors Committee. Benefits to patients include the possibility of remission of disease.

[Reference: Minutes of Renal Tumors Committee Meeting 4 November 2000]

The number of subjects enrolled to the study since last APR at WRAMC is 1 and the total enrolled to date at WRAMC is 8. The total number enrolled study-wide is (no data in last COG report), if multi-site study.

## CONCLUSIONS

Study should remain open to follow WRAMC registrants.

Report Date: 5 December 2001

Work Unit # 6401

# DETAIL SUMMARY SHEET

TITLE: Support of Pediatric Oncology Group Activities, WRAMC

KEYWORDS: cancer, grant, children

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 30 January 1996

STUDY OBJECTIVE:
The NIH grant application is to bring in the funds in support of the research conducted at WRAMC sponsored by the Pediatric Oncology Group.

TECHNICAL APPROACH:
None.

PRIOR AND CURRENT PROGRESS
Please refer to the individual POG protocols.

CONCLUSIONS
None.

Report Date: 5 August 2002 Work Unit # 6405

# DETAIL SUMMARY SHEET

TITLE: A Multicenter Study to Determine the Prevalence and Clinical Characteristics of Barrett's Esophagus in Childhood

KEYWORDS: Barrett's Esophagus, esophagitis, gastroesophageal reflux

PRINCIPAL INVESTIGATOR: COL Philip L. Rogers MC
ASSOCIATES:

DEPARTMENT: Pediatrics STATUS: O
SERVICE: Pediatric GI & Nutrition INITIAL APPROVAL DATE: 28 May 1996

## STUDY OBJECTIVE

To determine the prevalence of short segment Barrett's esophagus in pediatric patients presenting for esophagogastroduodenoscopy (EGD); 2) describe the clinical and histologic findings in patients with Barrett's esophagus; 3) correlate the clinical and histologic findings in patients with reflux esophagitis; and 4) validate the use of a gastroesophageal reflux questionnaire in the evaluation of gastroesophageal reflux disease in children.

## TECHNICAL APPROACH

The study population will consist of 650 patients consecutively enrolled who are scheduled for routine EGD by the division of Pediatric Gastroenterology and Nutrition at WRAMC and other participating centers. A gastroesophageal reflux questionnaire will be completed prior to the performance of an EGD. A standard EGD with biopsies will be performed. Additionally, a biopsy at the squamocolumnar junction will be obtained. The histologic characteristics of the esophageal biopsies and prevalence of SSBE will be determined. The clinical presentations of the patients, as determined by the questionnaires, will be compared to the histologic findings. The ability to determine esophagitis by the use of questionnaires will be determined.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 307. The total number enrolled study-wide is 307. No new patients are being enrolled.

One paper was submitted for publication in the North American Society for Pediatric Gastroenterology and Nutrition, but was rejected. This paper is currently being revised for re-submission. Data will be reviewed on the histologic and endoscopic findings of the distal esophagus (SCJ) compared with the more standard 3-5 cm above the SCJ in children with GERD symptoms. Patient questionnaire data will be analyzed in the coming year.

## CONCLUSIONS

The prevalence of Barrett's esophagus in childhood is very low, but changes in esophageal epithelial lining consistent with dysplasia can be demonstrated if tissue biopsies are carefully evaluated. In our study, two patients with possible BE had a significant history for gastroesophageal reflux. Our paper presents important descriptive data about Barrett's esophagus and highlights the fact that BE is rare, but can be present even in children. Our initial data suggests that biopsies at the squamocolumnar junction (SCJ) may be more revealing about GERD in children than the standard biopsies taken at 3.5 cm above the SCJ. This data is currently being analyzed.

Report Date: 13 June 2002

Work Unit # 6408

# DETAIL SUMMARY SHEET

TITLE: POG 9605: ALinC 16; Protocol for Patients with Newly-Diagnosed Standard-Risk Acute Lymphoblastic Leukemia (ALL)

KEYWORDS: pediatrics, lymphoblastic, leukemia

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Hartman, Kip COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 June 1996

## STUDY OBJECTIVE

1) Determine if EFS can be improved with the addition of 6 months of delayed intensification with divided-dose oral methotrexate plus oral 6 MP as divided, or once a day dose given during intensification and continuation; 2) correlate laboratory and clinical findings from this study, and POG #s 9400, 9201, and 9406; 3) assess significance of marrow findings after 2 weeks of induction; and 4) describe occurrence and prognostic significance of elevated transaminases

## TECHNICAL APPROACH

After induction and consolidation, patients are randomized to one of four late intensification/consolidation arms. Regimen 1: Weekly IM MTX plus once daily oral 6MP intensification followed by daily oral 6MP in continuation. Regimen 2: Divided dose oral MTX plus once daily oral 6MP intensification followed by daily oral 6MP in continuation. Regimen 3: Weekly IM MTX plus divided-dose oral 6MP intensification followed by divided-dose 6MP in continuation. Regimen 4: Divided-dose oral MTX plus divided-dose oral 6MP intensification followed by divided-dose 6MP continuation. All patients will receive vincristine/prednisone pulses and IT MTX/Ara-C/HC during continuation therapy.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study was closed to accrual on 15 November 1999. Final group-wide accrual is 1087. WRAMC has three registrants and two others accepted in transfer from other POG institutions. There are no new registrations at WRAMC since the last report. Three are currently being followed at WRAMC (two remain in CR1 and one has relapsed and is currently receiving chemotherapy in second remission), and two are transferred to other POG institutions. Event free survival is not reported. There are no ADRs at WRAMC. In the previous study, 21% of the patients had adverse CNS events. There are 142 ADRs reported group-wide involving the CNS. The actuarial projections for CNS events are 6.6% by the end of consolidation, and 13.1% by the end of therapy. For seizures, the projections are 2.2% by the end of consolidation and 5.8% by the end of therapy.

[Data from COG Current Report of Studies, Fall 2001]

## CONCLUSIONS

Study is closed to patient accrual but should remain open for patient follow-up.

Report Date: 19 June 2002 Work Unit # 6410

# DETAIL SUMMARY SHEET

TITLE: POG 9404: T-Cell #4 Protocol - Intensive Treatment for T-Cell Acute Lymphoblastic Leukemia and Advanced-Stage Lymphoblastic Non-Hodgkin's Lymphoma

KEYWORDS: leukemia, T-Cell, chemotherapy

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Hartman, Kip LTC MC; Crouch, Gary LtCol MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 August 1996

## STUDY OBJECTIVE

1) Determine, in a randomized trial, the effectiveness of high-dose methotrexate (HD MTX) when added to a multi-agent chemotherapy backbone (DFC1 87-001) proven effective in T-Cell acute lymphoblastic leukemias (T-all); 2) determine, in a randomized trial, the role of the cardioprotectant Zinecard (DZR) in preventing cardiotoxicity; and 3) study the biology of T-Cell lymphoid malignancies, including the correlation of minimal residual disease with event-free survival, utilizing the TAL 1 proto-oncogene, p53 and p16 tumor suppressor genes, and drug sensitivity profiles of blast cells to adriamycin, methotrexate, and cytarabine.

## TECHNICAL APPROACH

Patients with T-ALL (DR-T+) who are <22 years old, and patients with lymphoblastic lymphoma Murphy stage III or IV who are <21 years old (including those <12 months) will be randomized to receive or not receive high-dose methotrexate and Zinecard. Response rates and degree of anthracycline cardiotoxicity will be evaluated and compared.

## PRIOR AND CURRENT PROGRESS

This study closed to accrual on 10 September 2001. A total of 573 patients were accrued, and 554 were eligible. Seventy were accrued since last APR. There have been three WRAMC registrations and no new registrations since last APR. All three subjects at WRAMC are doing well in remission. On 27 September 2000, Data Monitoring Committee action led to the closure of Arms 1 and 2 due to a sequential analysis demonstrating positive efficacy of the high dose MTX (HDM). The Zinecard randomization remained open and subsequently all patients are receiving HDM. Results of the Zinecard randomization remain blinded. Toxicity has been the same in all treatment arms except for the increased incidence of grade 3 or 4 mucositis in the HDM arms. Benefits to patients include the possibility of remission of disease.

{Reference: COG Current Report of Studies, Spring 2002}

## CONCLUSIONS

Study should remain open to follow WRAMC registrants.

Report Date: 13 February 2002

Work Unit # 6414

# DETAIL SUMMARY SHEET

TITLE: Oncogene Expression in Thyroid Neoplasia

KEYWORDS: thyroid, cancer, oncogene

PRINCIPAL INVESTIGATOR: Catherine Dinauer MAJ MC
ASSOCIATES: Gary Francis COL MC

DEPARTMENT: Clinical Investigations
SERVICE: Pediatric Endocrine

STATUS: C
INITIAL APPROVAL DATE: 05 October 1999

## STUDY OBJECTIVE

This study is designed to examine the expression of various oncogenes in thyroid cancers and to correlate the expression with the risk of metastasis and recurrence.

## TECHNICAL APPROACH

Archived thyroid tumors are sectioned and either 1) stained by immunoperoxidase specific for each oncogene or 2) extracted for RNA which is then reverse transcribed and amplified (PCR) for detection of specific mutations and mRNA levels. The intensity of expression is then correlated with the risk of metastasis and recurrence.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of 32 papillary thyroid cancers, 10 follicular thyroid cancers, and 13 benign lesions have been stained for expression of various oncogene protein products, including p53, VEGF, cMET, HGF/SF, and VEGF receptors. In addition, RNA has been extracted and amplified for expression of ras and ret/PTC mutations.

The techniques for immunohistochemistry and RNA amplification have been optimized with paraffin embedded tissues. The results have been used to target several specific oncogenes in additional DCI supported protocols.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 55. The total number enrolled study-wide is N.A., if multi-site study.

## CONCLUSIONS

This study is being closed as no new samples are being collected and all experimental work is now being done under the auspices of WU # 01-65001 (PI: COL Gary Francis).

Report Date: 14 September 2001 Work Unit # 6416

# DETAIL SUMMARY SHEET

TITLE: Analysis of Parental Time Allocation in Families where Children with Special Needs Live with their Unaffected Siblings

KEYWORDS:

PRINCIPAL INVESTIGATOR: Levin, Sondra MD
ASSOCIATES:

DEPARTMENT: Pediatrics STATUS: C
SERVICE: INITIAL APPROVAL DATE: 19 November 1996

STUDY OBJECTIVE
To determine whether there is a difference in parental time allocation for siblings in families with a disabled child vs. families without a disabled child.

TECHNICAL APPROACH
Data will be compiled by having parents voluntarily complete a study questionnaire. Parents will be recruited from the general pediatrics clinic and the genetics clinic at WRAMC as well as from the University of Maryland where this study was also approved. Follow-up weekly diaries of time spent with children at home will be solicited as well.

PRIOR AND CURRENT PROGRESS
No new questionnaires completed over the past year. The number of subjects enrolled to the study since last APR at WRAMC is 0. The total number enrolled study-wide is 19, if multi-site study. No new questionnaires were completed over the past year.

CONCLUSIONS
No new data obtained so no further conclusions drawn. The study is now over five years old and closed. It will be resubmitted as a new protocol if the decision is made to continue the study.

Report Date: 25 February 2002

Work Unit # 6423

# DETAIL SUMMARY SHEET

TITLE: Sphingomyelinase and Ceramide Regulate Steroid Synthesis

KEYWORDS: ceramide, steroid hormone

PRINCIPAL INVESTIGATOR: Francis, Gary COL MC
ASSOCIATES:

DEPARTMENT: Pediatrics
SERVICE: Pediatric Endocrinology

STATUS: C
INITIAL APPROVAL DATE: 03 February 1998

## STUDY OBJECTIVE

To determine if SMAse or Ceramide have effects to the genes which control steroid biosynthesis

## TECHNICAL APPROACH

Messenger RNA will be isolated from MA-10, and IEG-3 cells incubated with either control media, or media containing SMAse or ceramide. The specific sequence encoding steroidogenic enzymes will be reverse transcribed and amplified to determine if the mRNA is increased following SMAse or Ceramide stimulation.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study.

## CONCLUSIONS

The study has been completed and has found that SMAse upregulates steroid hormone biosynthesis without inducing apoptosis. This supports the role for a novel signal transduction system (ceramide) in the control of steroidogenic cells.

Report Date: 28 May 2002 Work Unit # 6425-98

# DETAIL SUMMARY SHEET

TITLE: Power Spectrum Analysis as a Marker of Diabetic Autonomic Neuropathy in Children and Adolescents with Diabetes Mellitus

KEYWORDS: Heart Rate variability

PRINCIPAL INVESTIGATOR: Thomas R. Burklow LTC MC
ASSOCIATES: Merily Poth MD USUHS; James J. Bailey MD NIH

DEPARTMENT: Pediatrics
SERVICE: Pediatric Cardiology

STATUS: C
INITIAL APPROVAL DATE: 26 May 1998

## STUDY OBJECTIVE

1. To examine the association of heart rate variability in children with clinical symptoms of neuropathy in diabetic children.
2. To examine the association of heart rate variability in children with standard clinical testing for neuropathy in diabetic children.

## TECHNICAL APPROACH

Diabetic children and adolescents are recruited from the pediatric endocrinology clinic. A Holter monitor is applied and the patients are coached through the following maneuvers: 1) Valsalva breathing, 2) metronomic breathing, and 3) upright standing. After completion the patient is then disconnected and his or her participation is completed. The Holter monitor recording is then analyzed through a Sun workstation for analysis of heart rate variability through autoregression analysis. No modifications have been implemented since the last APR.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since beginning patient enrollment in September 1998, we have performed clinical, laboratory and electrophysiological assessments on 32 patients. An interim data analysis has demonstrated no correlations with the parameters of heart rate variability, biochemical, standard testing for autonomic dysfunction, and demographic data. As a result of this analysis, no further patients have been enrolled since August 2000. I am currently writing up the results for possible publication. No further subjects will be enrolled.

There have no adverse events recorded during the conduct of this protocol. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 32. The total number enrolled study-wide is N/A if multi-site study.

## CONCLUSIONS

No significant correlations identified. Statistical analysis will be completed in preparation of manuscript preparation.

Report Date: 01 March 2002

Work Unit #6429-99

# DETAIL SUMMARY SHEET

TITLE: Bone Mineral Density in Survivors of Childhood Thyroid Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Dinauer, Catherine MAJ MC
ASSOCIATES:

DEPARTMENT: Pediatrics
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 27 April 1999

## STUDY OBJECTIVE

This is a pilot observational study evaluating bone mineral density of patients diagnosed with thyroid cancer at <21 years of age.

## TECHNICAL APPROACH

Potential subjects are identified from pre-existing databases of pts diagnosed with thyroid cancer in childhood (databases are under WU #6398 and #6414). After obtaining consent, subjects complete a questionnaire (re: demographics, treatment and status of thyroid cancer, other medical problems, exercise habits, calcium intake, age at puberty, and, for females, menstrual history), undergo a physical exam, have blood drawn for thyroid function tests and thyroglobulin, and undergo a DEXA scan. In addition, subjects' medical records are reviewed.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is N/A if multi-site study.

There have been no adverse events and no subjects have withdrawn from the study. The PI is no longer on active duty. Dr. Patricia Powers, Chief of Pediatric Endocrinology, WRAMC, will be assuming the role of PI (forms to be submitted). In addition, personnel from Adult Endocrinology will likely become more involved in subject recruitment. (Dr. Vic Bernet has been the point of contact.)

## CONCLUSIONS

No progress was made on this study in the past year, but we are in the process of doing a change of PI. The new PI will work with the Adult Endocrinology service in an effort to identify and efficiently recruit eligible subjects for this study.

Report Date: 13 February 2002 Work Unit # 6430-99

# DETAIL SUMMARY SHEET

TITLE: Acute Pediatric Care in a Pediatric Clinic Versus a General Emergency Department: A Performance Improvement Project Comparing Outcomes and Patient Satisfaction

KEYWORDS: Acute Care, Pediatrics, Outcomes, Patient Satisfaction

PRINCIPAL INVESTIGATOR: Dinauer, Catherine A. MAJ MC
ASSOCIATES: Lucci, Ed LTC MC; Harper, Brenda COL MC

DEPARTMENT: Pediatrics
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 10 August 1999

## STUDY OBJECTIVE

This study is a Performance Improvement project designed to investigate the acute care of pediatric patients at WRAMC in two settings: the Pediatric Clinic (PC) and the Emergency Department (ED). The plan is to examine:

1) clinical outcomes,
2) functional outcomes, and
3) parent satisfaction with care in the two clinical venues.

## TECHNICAL APPROACH

The parents of patients seen in either a PC Same Day Appointment or in the ED will be contacted by telephone 7-10 days after the visit and asked to complete a survey. Parents will be informed of the survey at the time of the child's visit through a memo (explaining the study purpose and plan, voluntary nature of their participation, etc). A pilot survey of parents of 20 children (10 PC and 10 ED) will be performed initially. Once reliability and validity of the survey are assessed, quarterly surveys of the parents of 50 patients (25 PC ad 25 ED) will be performed.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A pilot survey of 20 parents was performed in early fall 2000; analysis of the survey items by the Nursing Research Service showed high reliability. Two full-fledged surveys were then performed, in October 2000 (n=50) and January 2001 (n=40). 5% of parents contacted declined participation. 11% of the phone numbers attempted were disconnected or incorrect. An analysis of these data was performed and the results were presented to the Dept. of Pediatrics and ED staff at a Performance Improvement meeting as well as at a meeting of the WRAMC Quality Outcomes Committee in spring 2001. Because parental satisfaction ratings were overall high for both the ED and the PC and due to the unavailability of study personnel to do further surveys, it was decided to not pursue this study further. Specific issues and suggestions raised by participating parents have been addressed/implemented by/in the ED and PC.

No parents withdrew from the study and there have been no adverse events. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 110. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

This study provided data that were used for quality improvement purposes by the ED and PC. The study will now be closed.

Report Date: 31 January 2002 Work Unit # 00-7102

# DETAIL SUMMARY SHEET

TITLE: A Randomized Placebo-Controlled Trial of Sertraline for Neurobehavioral Sequelae of Traumatic Brain Injury

KEYWORDS: Traumatic Brain Injury, Head Injury, SSRI

PRINCIPAL INVESTIGATOR: Deborah L. Warden, M.D.
ASSOCIATES: Joan Walter, P.A., James Ecklund, M.D., Bahman Jabbari, M.D., Laurie Ryan, Ph.D., Elisabeth Moy-Martin, RNC, M.A., Mary Coyle, RNCS, M.S.N., Maria Graves, R.N., Molly Sparling, B.A.

DEPARTMENT: Neurology
SERVICE: Traumatic Brain Injury Program

STATUS: O
INITIAL APPROVAL DATE: 21 March 2000

## STUDY OBJECTIVE

a. To investigate the efficacy of Sertraline, a selective serotonin reuptake inhibitor (SSRI), in treating neurobehavioral sequelae of irritability, depression, frustration, anxiety and other post-concussive symptoms following traumatic brain injury (TBI).
b. To explore possible relationships between anosmia (deficits in smell) and irritability/aggression.

## TECHNICAL APPROACH

As the standard of care for patients with traumatic brain injury (TBI) at Walter Reed, patients receive a multidisciplinary evaluation consisting of neurology exam, neuropsychology, psychiatry, psychosocial, EEG, MRI, phlebotomy, and family interview. Research tests include the smell test, evoked potentials, drawing and storing of the blood sample, and some questionnaires related to the subject's medication response. Blood samples (about two tablespoons) are kept at the DVHIP labeled with the patient's study number for possible future use in studies to understand better aspects of recovery from head injury. Blood samples are used in studies of genetic markers potentially related to outcome from TBI. Participants have the option of not consenting to the genetic analyses while still participating in the rest of the protocol. After signing the volunteer informed consent, patients will be randomized into an active drug or placebo group. Patients receive an increasing dose of Sertraline or placebo starting at 50mg (1 pill) and increasing to a dose of 200 mg (four pills) of Sertraline. Dose adjustment is considered every three weeks and is based on scores on the Clinical Global Improvement Scale. Family members or a close friend of the subject are asked to complete some questionnaires after giving informed consent for their participation.

The medication phase lasts twelve weeks. Patients receive standard TBI care during this period that may include a period of Convalescent Leave Home (CVL) followed by a gradual return to duty. All patients are contacted weekly during the medication phase to assess general condition, current symptoms, and assessment of compliance. If patients require a clinical medical appointment during the twelve weeks, patients are seen at WRAMC if possible. If not possible, study personnel are available to speak with the patient's clinician at a local medical facility. Patients return to WRAMC at twelve weeks for a follow-up evaluation of their symptoms, or are contacted by phone if unable to return to WRAMC for their twelve-week evaluation. Sertraline blood levels are obtained at twelve weeks as a measure of compliance and as a potential correlate to symptom amelioration. After the twelve-week evaluation, patients are tapered off Sertraline or placebo over two weeks.

If subjects have recurrent symptoms following the twelve-week evaluation that are distressing to them, or believe they need medication to keep their symptoms from recurring, pharmacological and nonpharmacologic treatments are discussed with them. Patients are offered appropriate treatment,

including Sertraline, if medically indicated. The blind is not yet broken, that is, patients are not able to learn if they were being treated with placebo or Sertraline. Subjects are contacted by phone or seen at 3, 6, 9, and 12 months following their twelve-week follow-up evaluation for an assessment of their symptoms and general level of functioning. If patients are in the area, these follow-up evaluations are done in person.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One addendum has been approved by DCI and implemented this year. The addendum modified the inclusion criteria, removing the criterion that patients must have posttraumatic amnesia (PTA). We had participants who had clear evidence of brain injury without PTA and were concerned that this criterion could exclude many otherwise eligible individuals over the course of the protocol.

We currently have enrolled ten participants. One adverse event was reported this year. The event was not related to the protocol. No patients have withdrawn from the study for any reason. A recent literature search completed 31 January 2002 revealed no new research directly relating to this protocol.

The number of subjects enrolled to the study since last APR at WRAMC is eight and the total enrolled to date at WRAMC is ten.

CONCLUSIONS

Subject enrollment is currently underway and we feel that the protocol is running smoothly.

Report Date: 25 June 2002

Work Unit # 00-7104

# DETAIL SUMMARY SHEET

TITLE: A Study of the Use of Telemedicine/Teleradiology in the Initial Management of Acute Stroke

KEYWORDS: Stroke, Cerebrovascular Disease, Telemedicine, Network, and Teleradiology

PRINCIPAL INVESTIGATOR: MAJ John Y. Choi, MC
ASSOCIATES: COL Ronald Poropatich, MC; LTC Edward Lucci, MC; LTC Robert Labutta, MC; LTC Geoffrey Ling, MC; LTC Albert Martin, MC; MAJ Mark Depper, MC; CPT Ken Kudelko, MC; Gabriele Feolo, RN, MSN

DEPARTMENT: Neurology
SERVICE:

STATUS: C
INITIAL APPROVAL: 22 August 2000

STUDY OBJECTIVE:

This study sought to establish the feasibility of telemedicine consultation in the diagnosis of stroke. Telemedicine evaluation of the neurological examination, which included the National Institutes of Health Stroke Scale (NIHSS) and brain computed tomography (CT) were evaluated.

TECHNICAL APPROACH:

This study assessed the logistics of telestroke consultations. Phase I was within WRAMC, with telestroke consultants in a physician's office evaluating subjects at the WRAMC Emergency Department. Phase I was completed on 1 March 2002 with six subjects enrolled. Department of Neurology study personnel performed the patient examinations, which consisted of patient history questions, the NIHSS and brain CT-Scans. The study personnel also handled the Telemedicine equipment for the video teleconference (VTC), presentation. Equipment used in this trial included a portable VTC unit with camera and a videocassette recorder.

The investigators obtained a written informed consent from subjects during the subjects' recruitment from the neurology clinic or ward. The volunteers either had a normal neurological examination, or an abnormal neurological examination related to non-stroke or stroke causes. A subject with a normal neurological examination gave case scenarios for symptoms unrelated to neurological diseases.

Prior to obtaining consent an investigator determined the subject's competency using the mini mental status exam. The study coordinator scheduled the volunteer for a study intervention in the ED. Volunteers were briefed prior to their ED appointment to recite a diagnosis specific case scenario during the study intervention. Scenarios included mock information about onset of signs and symptoms related to neurological or non-neurological causes. These scenarios were assigned accordingly to the appropriate volunteer groups (normal neurological examination, stroke/abnormal neurological examination or non-stroke/abnormal neurological examination) in an otherwise random order. After the subject arrived at the ED, telemetry monitoring was established. A beeper then notified the in-person neurology or telemedicine consultant, in a random order, about the subject. Only the neurology resident or the nurse coordinator knew the volunteer's prior history and physical examination findings.

Two consecutive, timed study interventions occurred in the ED. The telemedicine neurology consultant obtained the subject's history and neurological examination. The intervention's starting time was at the "timer" activation at the start of the study patient examination intervention. The end time was the moment the intervention by the telemedicine consultant was complete. Then another blinded neurology physician performed a timed in-person history, neurological examination and CT-scan reading as well. This study intervention followed the same steps and procedures as the telemedicine consultant intervention. This timed examination served as the gold standard. To minimize the effects of learning by the subjects the order the telestroke and in-person examinations were performed was randomly alternated.

Archived brain CT-scans without patient identifiers were identified form the *Impax* radiology system. Those CTs showed findings of normal brain morphology, abnormal brain morphology related to non-stroke neurological findings or old and/or acute strokes. Control group subjects' scenarios associated an archived normal brain CT scan. Stroke subjects may have had old strokes or acute stroke findings. Non-stroke subjects had CT-scan abnormalities consistent with the non-stroke neurological pathology. Brain scan evaluation time was measured from the moment the scan was loaded on the video screen until the consultant analyzed the scan under a time goal of 10 minutes +/- 5 minutes. The blinded neuroradiologist read the brain CTs with time measurements. The time it took the blinded neuroradiologist to read the CT scan served as the gold standard for the in-person neurology consultant and the telemedicine neurology consultant. CT scans had patient identifiers removed.

Video recordings of the telemedicine and the in-person consultant's interview and examination were edited to remove patient identifiers. However the patient's face was not concealed, since facial expressions are crucial for neurological evaluation. (Any subject enrolled into this trial was asked to give permission to video tapings by signing standard government audiovisual consent form). Dr. Lee Schwamm evaluated the videotape records as a technical advisor.

There were no adverse events during Phase I of this study. Study personnel assisted with patient transfers to minimize the potential risk of falling. Subjects had the option to terminate the study at any time if they felt over-stressed. Investigators had the option to terminate the study at any time if there was any indication that the subject's medical condition worsened.

*Modifications made to the methodology section since the initial IRB approval on 22 August 2000: In the methodology section, the telestroke consultant site was defined as a location within WRAMC but outside the Emergency Department. Recruitment was based on referrals and did not involve written advertisements or posters. The number of volunteers was calculated to a maximum of 10, instead of 12 as proposed initially. We added documentation regarding the availability of assistance to study volunteers during the transfer to the emergency department. We also discussed the necessity for study subjects to recite study case scenarios. MRMC IRB defined the minimum number of subjects to complete the study at 6. The coordination of the patient interview is outlined in more detail. The study personnel and the nurse coordinator will handle the equipment for the video presentation of the study. Further details about investigators' procedure for subject assessment in this study and specific relevant appendices/data record sheets are discussed. We will include a set of mock laboratory values to further simulate a patient encounter. Study personnel will be with the volunteer at all times after activation of the study intervention to serve as witnesses. There was a blinded neuroradiologist, setting the gold standard for the brain CT reading, for comparison versus the telemedicine and in-person neurology consultant. This was a time evaluation planned for 10 minutes. The possible risk of falls or worsening of medical condition was added. We added to research record review, representatives of the U.S. Army Medical Research and Material Command. We discussed preventative measures taken by study personnel to minimize the risk of adverse events to study volunteers. An outline of necessary follow up actions was added, if an adverse event had occurred. Two paragraphs were added discussing the security of confidential patient data. Only participating study personnel had access to patient information. All data collected during the trial period were handled, stored and discarded in accordance with the USAMRMC policies. Data collection, specific details on storage, record upkeep and destruction of data after the required waiting period were mentioned. Data associated with the study volunteers were collected for entry into the Command's Volunteer Registry Data Base. Time goals for telemedicine consultation and brain CT readings were defined.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 6 and the total enrolled to date at WRAMC is 6. Phase I of the trial evaluated six subjects. Phase I is concluded. There were no adverse events during Phase I of this study. There were no study subjects that have withdrawn from the study during Phase I of this clinical trial. New Related Literature: Schopp LH, Johnstone BR, Merveille OC. Multidimensional telecare strategies for rural residents with brain injury. J Telemed Telecare. 2000; 6 Suppl 1:S146-9.

CONCLUSIONS

Primary outcome measures were time requirements and accuracy of diagnosis for the telemedicine consultant. Timely telemedicine consultation was deemed successful for a mean time less than 40 minutes +/- 10 minutes and CT brain readings of 5 minutes +/- 5 minutes. Standard deviations were also calculated. Evaluations that exceeded two standard deviations in time length were examined.
Our data analysis for phase I showed feasibility of telestroke consultation in a timely fashion. We calculated mean, median, and standard deviation of total time and timed subsection (see Table 1). Wilcoxon signed ranks test were used to evaluate for statistical significance. We found NIHSS time difference was significant at exact significance 2 tail of .031. Some time inefficiencies are to be expected during the neurological NIHSS examination as the ED personnel has to be instructed to check visual fields or sensory modalities for example. History taking and brain CT reading depends very little on remote site personnel assistance accounting for similar time use compared to the in-person evaluation. Brain CT scans were read faster by the in-person examiner and the telestroke consultant than by the neuroradiologist establishing the gold standard for CT scan reading times. This difference in time used for CT scan interpretations may be due to the clinical information available to the in-person and the tele-stroke raters assisting in their interpretation of the CT scan studies. Most importantly, the telestroke evaluation was well within predefined time limits, less than 40 minutes total time. A trend toward significance regarding differences in total time, (p=.063), for all telestroke evaluations was observed. The total time difference equaled to 6.5 minutes, which is an acceptable time frame for urgent stroke evaluation.

The protocol will proceed to enroll 42 volunteers. One volunteer will be a control subject with an intact neurological examination. A successful time result should include an upper limit of the 95% confidence interval (CI) exceeding 70%. After 42 subjects have been enrolled, an analysis to calculate a 95% confidence interval of the telemedicine consultant time will be performed. Impact of this protocol on the ED will be defined. The Chief of the ED at WRAMC and his committee staff will be asked to fill out a questionnaire (see Appendix F) to determine whether this protocol helped their evaluation of stroke patients. Secondary outcomes include comparison of known patient diagnosis between the in-person versus the telemedicine consultant. Accuracy of the NIHSS determined by the in-person study personnel versus the tele-stroke consultants will also be captured and compared. Evaluation of the brain CTs by the in-person and the telemedicine consultant versus the gold standard time restricted reading by the neuroradiologists will be statistically analyzed to support the testing hypothesis and to construct a conclusion to this clinical trial.

To compare the difference between in-person and telemedicine in time of patient history, NIHSS, CT Scan, and the total time, repeated measure ANOVA will be performed with each site as a grouping factor for between subjects factors and the methods (In-person vs. Telemedicine) as the within subject factor, each site will serve as its own control in the analysis. Post hoc tests will be conducted to compare the difference for each site.

If the study find a 1.5 standard deviation (sd) change for CT-scan using telemetries approach, it will show that the mean telemedicine time is exceeding the pre-set 5 minutes limit. So the sample size of 14 per site will have a greater power of 96% to detect such difference when compared to the in-person mean. Likewise, we will plan such analysis for correct diagnosis and brain CT reading for validation of this technology in acute stroke care. We will plan to perform kappa statistical analysis to evaluate agreement among the different raters (in-person evaluator, telestroke evaluator, emergency provider evaluator) with a goal of agreement of equal or greater than 0.80.

Report Date: 09 August 2002 Work Unit # 00-7105

# DETAIL SUMMARY SHEET

TITLE: Effectiveness of Botulinum Toxin Type-A in the Treatment of Migraine Headache: A Randomized Controlled Trial.

KEYWORDS: Migraine, headache, Botox

PRINCIPAL INVESTIGATOR: Sartori, Roberto MAJ MC
ASSOCIATES: Jabbari, Bahman, COL, MC; Labutta, Robert, COL, MC; Murray, Evan, MAJ, MC; Kudelko, Kenneth, CPT, MC; Brooks, Judith, RN, MSN, CCRC

DEPARTMENT: Neurology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 26 September 2000

STUDY OBJECTIVE:
It is hypothesized that patients who receive injections of Botulinum toxin A (BTX-A) into selected pericranial muscles experience a significant reduction in the frequency of headaches and/or the average severity of attacks. We intend to evaluate the efficacy of (BTX-A) in the treatment of migraine headache.

TECHNICAL APPROACH:
This study is a prospective, randomized double-blind placebo-controlled trial comparing the efficacy of BTX-A injections versus placebo in migraine headache prevention. Patients will record the frequency and intensity of headaches in a daily diary for a one-month baseline period, and for six months after they receive a single treatment or placebo dose to selected pericranial muscles. The primary outcome measure is the average frequency of headache days measured during a 30-day blocks for six months. The secondary outcome measures are the severity of attacks using a visual analog scale (VAS) from 0-10 (0= no headache pain; 10 = most severe headache pain experienced) and the Migraine Specific Quality of Life Questionnaire (MSQ). No modifications were made to the protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE :
Forty-eight (48 subjects) have been screened since the last APR. Subjects were simultaneously screened for migraine and tension studies. The number of subjects enrolled to the study since last APR at WRAMC is 8 and the total enrolled to date at WRAMC is 19. No adverse events were reported. Several subjects reported mild, transient tenderness at the injection site and headache following injection. Both of these are expected side effects. There has been no new published data regarding the effectiveness of Botulinum toxin A (BTX-A) in migraine headache prevention.

CONCLUSIONS:
No conclusions have been obtained to date Interim data analysis will be carried out once a total of 40 patients have completed the study.

Report Date: 09 August 2002

Work Unit # 00-7106

# DETAIL SUMMARY SHEET

TITLE: Effectiveness of Botulinum Toxin Type-A in the Treatment of Tension-type Headache: A Randomized Controlled Trial.

KEYWORDS: Migraine, headache, Botox

PRINCIPAL INVESTIGATOR: Sartori, Roberto MAJ MC

ASSOCIATES: Jabbari, Bahman, COL, MC; Labutta, Robert, COL, MC; Murray, Evan, MAJ, MC; Kudelko, Kenneth, CPT, MC; Brooks, Judith, RN, MSN, CCRC

DEPARTMENT: Neurology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 26 September 2000

## STUDY OBJECTIVE

It is hypothesized that patients who receive injections of Botulinum toxin A (BTX-A) into selected pericranial muscles experience a significant reduction in the frequency of headaches and/or the average severity of attacks. We intend to evaluate the efficacy of (BTX-A) in the treatment of tension headache.

## TECHNICAL APPROACH

This study is a prospective, randomized double blind placebo-controlled trial comparing the efficacy of BTX-A injections versus placebo in tension headache prevention. Patients will record the frequency and intensity of headaches in a daily diary for a one-month baseline period, and for six months after they receive a single treatment or placebo dose to selected pericranial muscles. The primary outcome measure is the average frequency of headache days measured during 30-day blocks for six months. The secondary outcome measures are the severity of attacks using a visual analog scale (VAS) from 0-10 (0= no headache pain; 10 = most severe headache pain experienced) and the Migraine Specific Quality of Life Questionnaire (MSQ), specific to tension headaches. No modifications were made to the protocol.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is NA, if multi-site study. Subjects were simultaneously screened for the migraine and the tension studies. Of the forty-eight (48 subjects) screened only two met criteria for the tension protocol. Neither chose to participate in the study. Since no patients have been enrolled there haven't been any adverse events. There has been no new published data regarding the effectiveness of Botulinum toxin A (BTX-A) in migraine headache prevention.

## CONCLUSIONS:

No conclusions have been obtained to date. Interim data analysis will be carried out once a total of 40 patients have completed the study.

Report Date: 5 January 2002 Work Unit # 01-71001

# DETAIL SUMMARY SHEET

TITLE: Assessing States of Unconsciousness by Actigraphy

KEYWORDS: Actigraphy, Coma, Unconsciousness

PRINCIPAL INVESTIGATOR: LTC Michael Russo MC
ASSOCIATES: COL Daniel Redmond MC; COL Edward Urban MC; LTC William Campbell MC; LTC Kevin Cannard MC; LTC(P) Robert Labutta MC, MAJ John Choi MC; MAJ Al Martins MC; MAJ Evan Murray MC

DEPARTMENT: Neurology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 20 March 2001

## STUDY OBJECTIVE

In the present study, states of unconsciousness will be explored using actigraphy. Actigraphy is already an accepted tool for distinguishing wake from sleep. Actigraphy will be compared to standard available measures for the assessment of unconsciousness in a hospital setting, specifically, the clinical neurological examination. Hypotheses that will be tested are:

a. Actigraphic measures will reliably discriminate pathological unconscious states from normal sleep.
b. Actigraphic measures will reliably distinguish various levels of unconsciousness.

## TECHNICAL APPROACH

This observational study will identify level of unconsciousness using the standard clinical examination. Four levels of unconsciousness will be assessed, with 12 samples collected from each level. This clinical exam data will be used to identify segments of actigraphic signal representing a specific level of unconsciousness. The actigraphic signal from each state of unconsciousness will then be examined for features that may distinguish a level of unconsciousness from other levels. The actigraphic signals will be compared using computational techniques including neural net analysis.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:

Six volunteers signed consent. Of these six, one was not actigraphed and did not begin the study – the volunteer experienced an administrative scheduling conflict. Five volunteers enrolled. One volunteer who was actigraphed died during the study and the actigraph with data was lost. Data was collected from four volunteers. The visual inspection of the data on the four subjects shows the actigraph device to be working according to design specifications. No medications were administered during the study. No adverse effects due to the study were appreciated. The one death was due to the coma that was being studied, and not related to the actigraph device. No patients voluntarily withdrew from the study.

The number of subjects enrolled to the study since last APR at WRAMC is 5 and the total enrolled to date at WRAMC is 5.

No new literature published on this topic.

## CONCLUSIONS

No conclusions can be made at this time.

Report Date: 22 January 2002

Work Unit # 01-71002

# DETAIL SUMMARY SHEET

TITLE: Investigation of the Administration of Baclofen Injection for the Management of Spasticity Associated with Stroke, Medtronic Protocol #D98-072

KEYWORDS: Stroke, spasticity, Baclofen pump

PRINCIPAL INVESTIGATOR: Cannard, Kevin LTC MC
ASSOCIATES: Choi, John MAJ MC; Moores, Leon LTC MC

DEPARTMENT: Neurology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 27 March 2001

## STUDY OBJECTIVE

The primary objective is to evaluate functional changes as a result of Intrathecal Baclofen (ITB) therapy in the stroke population. Secondary objectives are to obtain additional data on the safety and efficacy of ITB therapy and to evaluate the quality of life changes as a result of ITB therapy.

## TECHNICAL APPROACH

In the first phase, at pre-screening, a medical history will be taken, and a medical examination will be performed. The patient will complete the Functional Independence measure (FIM) and Sickness Impact Profile questionnaires to assess function and quality of life, respectively. The patient will undergo manual muscle testing and have their spasticity evaluated with the Ashworth scale. At screening the patient must demonstrate a positive response to an intrathecal injection of 50 mcg, 75 or 100 mcg of baclofen. Spasticity will be assessed at 1,2,4,5 and 8 hours post-bolus injection. Heart rate, blood pressure and respiration will be assessed at each evaluation point of screening. A "positive response" is defined as an average one-point drop in the Ashworth score in the affected extremities as compared to the score obtained immediately prior to the bolus injection. This response must be maintained over two consecutive assessment points. IF the patient exhibits a significant reduction in spasticity, a SynchroMed Infusion System and catheter will be implanted to administer intrathecal baclofen on a chronic basis.

In the second phase of the study, patients will return for office visits within 30 days and again at 90 days post-implant. Assessments (Ashworth Scale, review of current therapies) will be done a minimum of every 90 days (which is the maximum interval between pump refills of aclofen) until study termination. Dosage requirements, system function and side effects will be assessed at each follow-up visit. The patient will repeat the FIM an dSIP at 3 months and 12 months post-implant.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Study findings obtained thus far: None. (No new study findings were reported to us from Medtronic Company).
Amendment or modifications to the research study since the last review: None.
Adverse events (AE) expected and/or serious for WRAMC site: None
Information on patients withdrawn from the study at WRAMCX: None
Information on patients withdrawn from the study at multiple centers: Thirty-four at multiple national centers.

The number of subjects enrolled to the study since last APR WRAMC is 2 the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 70, if multi-site study.

## CONCLUSIONS

No data was analyzed at this point and no new conclusions were drawn as informed by Medtronic.

Report Date: 18 March 2002 Work Unit # 01-71003

# DETAIL SUMMARY SHEET

TITLE: Genes for X-linked Torsion Dystonia-Parkinsonism in the U.S. Veterans of Panay Filipinos

KEYWORDS: X-linked torsion dystonia-Parkinsonism, genetic mutation, movement disorder

PRINCIPAL INVESTIGATOR: COL Bahman Jabbari MC
ASSOCIATES: WenLiang Yan M.D. Ph.D. DSCCIP; Diarmuid Nicholson Ph.D., Yvonne Lukes DAC; Laura Pedraza DAC

DEPARTMENT: Neurology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 15 May 2001

## STUDY OBJECTIVE

To identify the mutant gene, DYT3, causing X-linked Torsion Dystonia-Parkinsonism in the U.S. Veterans of Panay Filipinos.

## TECHNICAL APPROACH

Initial screen sample: A discordant brother trio with one affected brother and two unaffected ones are used. The blood samples of the two well brothers who are non-WRAMC beneficiaries were collected through an approved protocol in the USUHS (RO92AL01).

Experimental approaches:

a) The DNA extraction from the blood samples of the subjects is routine, with PureGene kit (Gentra System) or similar products, following the manufacturer's instructions.
b) Exon amplifications of the candidate gene are performed with regular PCR conditions together with at least 30-bp flanking splice donor or acceptor junctures. The PCR products are purified to remove primers before sequencing.
c) Cycle sequencing is using BigDye dideoxynucleotide terminators (Perkin Elmer). To reduce cost the PCR primers used in the exon amplification is employed for sequencing.
d) Mutation detection is conducted visually on the Sequencer program (Genecodes Software), comparing the sequence data from both affected and unaffected. If necessary, additional samples will be collected from the Philippines to differentiate a mutation from a polymorphism.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The minimal region harboring DYT3 mutation encompasses more than a million base pairs, according to the latest human genome map. Dozens of candidate genes have to be sequenced. The work to date has excluded the genes coding for neuroligin-3 (hNL3) and thyroid-hormone receptor associated protein 230 (TRAP230), as the mutant loci for DYT3.

A significant finding during the mutation screen is the experimental proof of an error in the genomic map used by European researchers in their quest for the DYT3 gene. The error includes missing from the map at least 50 kb DNA that contains genes coding for ITGB1BP2 and RhoG.
The current work focuses on the structural sequences of the following genes in the region (from proximal to distal):

1. ITGB1BP2 (interaction with beta1 integrin cytoplasmic domain isolated by two-hybrid screening).
2. RhoG-1 and 2 (similar to ras homolog gene family, member G, also known as LOC139125).
3. STAT (similar to STAT induced STAT inhibitor-4, also as LOC139126)

The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 2, if multi-site study. No adverse events occurred during the enrollment.

CONCLUSIONS

Torsion dystonia is the second commonest movement disorders encountered in neurological practice after Parkinsonism. The identification of the mutant gene responsible for X-linked Torsion Dystonia-Parkinsonism would significantly advance our understanding of this and other movement disorders including Parkinsonism. Significant progress has been made in the first year of project # 01-71003, which includes the exclusion of the genes coding for neuroligin-3 (hNL3) and thyroid-hormone receptor associated protein 230 (TRAP230), as the mutant loci for DYT3. A continued effort in the coming years that exhaustively examines all remaining candidate genes in the defined DYT3 genomic region will ultimately identify the genetic defect that causes this disease.

Report Date: 05 July 2002 Work Unit # 7154

# DETAIL SUMMARY SHEET

TITLE: Defense and Veterans Head Injury Program (DVHIP): WRAMC Core Evaluation Protocol

KEYWORDS: traumatic brain injury, head injury

PRINCIPAL INVESTIGATOR: Deborah L. Warden, MD

DEPARTMENT: Neurology and Neurosurgery STATUS: O
SERVICE: Traumatic Brain Injury Program INITIAL APPROVAL DATE: 31 August 1993

STUDY OBJECTIVE
To ensure that all military and DVA traumatic brain injured (TBI) patients receive TBI-specific evaluation and follow-up, while at the same time collecting standardized patient outcome data that will allow us to evaluate the relative efficacy and cost of various TBI treatment and rehabilitation strategies, and to define optimal care for individuals with TBI.

TECHNICAL APPROACH
Each subject receives neurological, neuropsychological, psychiatric examinations; and EEG and MRI testing. Following the comprehensive evaluation patients are returned to duty and followed. No significant changes have been made to the evaluation procedure over the past year.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The Core Evaluation Protocol remains active as we continue to enroll patients and follow enrolled patients over 24 months. As of 30 June 2002, 420 patients have been enrolled in the protocol and have received baseline evaluations. This year 63 subjects received baseline evaluations and 58 follow-up evaluations were completed. There have been 4 adverse events reported over the last year, none attributable to the protocol. No patients withdrew from the study this year.

CONCLUSIONS
A new Walter Reed Core Evaluation Protocol is awaiting final signatures to be submitted to DCI for review and approval by the Clinical Investigations Committee and the Human Use Committee. We are submitting an Exception to Policy concurrent with this Annual Progress Report requesting extension of this protocol until committee review and approval of the new protocol. Upon final approval of the new protocol, this protocol will be closed.

Report Date: 5 March 2002

Work Unit # 7161

# DETAIL SUMMARY SHEET

TITLE: Proton Magnetic Resonance Spectroscopic Imaging in Patients with Movement Disorders

KEYWORDS: spectroscopy, proton, movement

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC
ASSOCIATES: Rao, Krishna MD

DEPARTMENT: Neurology
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 25 April 1995

## STUDY OBJECTIVE

To determine the yield and utility of Magnetic Resonance spectroscopy (MRS) in patients with movement disorders.

## TECHNICAL APPROACH

Sixty subjects with various movement disorders will undergo MRS, a noninvasive technique that allows focused study of biochemistry within normal and diseased brains. Conventional MRI with additional special equipment and software is utilized to allow spectral analysis.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC was 0 and the total enrolled to date at WRAMC remained 38. No side effects were noted. The group consisted of a variety of movement disorders including patients with Huntington and Parkinson disease.

## CONCLUSIONS

Patients with Huntington disease (six) demonstrated a prominent glutamate peak consistent with glutamate toxicity. Patients with Parkinson's disease in general demonstrated normal MRS. The number of patients in other groups (PSP, MSA, so forth) was still to small for appropriate statistical analysis.

Report Date: 28 February 2002 Work Unit # 7162

# DETAIL SUMMARY SHEET

TITLE: An Open Label Study of Interferon Beta-la (Recombinant Human Interferon Beta) in Subjects with Multiple Sclerosis (Biogen Protocol Number, C94-801-P, Version 6) updated 20 January 1999.

KEYWORDS: multiple sclerosis, interferon, Beta-la

PRINCIPAL INVESTIGATOR: Robert J. Labutta LTC MC
ASSOCIATES: Jason Friedman CPT MC USA, Judith A. Brooks RN MSN CCRC

DEPARTMENT: Neurology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 25 April 1995

STUDY OBJECTIVE
To obtain safety information regarding the use of repeated IFN-B-la dosing in subjects with multiple sclerosis.

TECHNICAL APPROACH
Patients will be administered 30 micrograms of IFN-B-la intramuscularly once a week for two years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of 382 subjects were entered in the multicenter study, and 30 of the patients were from WRAMC. The study has been closed to enrollment since September 1996. The last patient out in the multicenter study will be mid-March 2002 with WRAMC's last patient out having been in September 2001. Database issues are in the process of being resolved. Closing the database is expected to occur sometime in the summer of 2002.

IND Safety reports were submitted for the following events that were reported across sites:
Overdose of Baclofen, missed abortion, hospitalization for epistaxis. WRAMC's serious adverse events included: hospitalizations for 1) MS related pyelonephritis, 2) MS related right leg flexor spasms 3) substernal chest pain after steroids which was probably an esophageal spasm, 4) elective carpal tunnel release, and 5) non-cardiac chest pain related to difficulty swallowing a pill.

CONCLUSIONS
There are not any changes with the data in this ongoing safety and efficacy study. The data from this ongoing safety and efficacy study again supports that Interferon-beta 1a (Avonex) remains effective in a high percentage of treated MS patients.

Report Date: 28 February 2002

Work Unit # 7166

# DETAIL SUMMARY SHEET

TITLE: An Open Label Uncontrolled Trial of Long-Term Treatment with Poly-ICLC in Patients with Malignant Gliomas and Multiple Sclerosis.

KEYWORDS: poly-ICLC, glioma, multiple sclerosis

PRINCIPAL INVESTIGATOR: Robert J. Labutta LTC MC
ASSOCIATES:

DEPARTMENT: Neurology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 23 April 1996

## STUDY OBJECTIVE

To maintain treatment and follow up of patients on intramuscular Poly ICLC for multiple sclerosis and malignant glioma.

## TECHNICAL APPROACH

Malignant glioma patients were administered Poly ICLC at 20 mcg/kg three times a week for 36 months and then tapered. The multiple sclerosis patients were receiving between 0.5-10 mg once or twice a week. They have all discontinued treatment as of December 2001.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 15. The total number enrolled study-wide is N/A, if multi-site study.
No adverse events have been reported.

## CONCLUSIONS

All MS patients have transitioned to one of the FDA approved Multiple Sclerosis medications. One glioma patient is still on Poly ICLC on a compassionate use basis. HUC committee minutes requested that an IND holder be named.

Report Date: 05 July 2002 Work Unit # 7174-98

# DETAIL SUMMARY SHEET

TITLE: Markers of Possible Vulnerability to Symptoms Following Traumatic Brain Injury

KEYWORDS: traumatic brain injury, moderate head injury

PRINCIPAL INVESTIGATOR: Deborah L. Warden, MD
ASSOCIATES:

DEPARTMENTS: Neurology and Neurosurgery
SERVICE: Traumatic Brain Injury Program

STATUS: O
INITIAL APPROVAL DATE: 04 August 1998

## STUDY OBJECTIVE

To explore possible relationships between biologic factors, i.e., certain allelic frequencies, and response to injury following TBI.

## TECHNICAL APPROACH

Genotyping banked blood samples to identify ApoE and serotonin transporter genotypes. Other allelic frequencies may be analyzed subsequently.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Over the past year, collaboration has continued with Drs. Lipsky and Goldman, NIAAA, to explore the effects of genetic markers, specifically those effecting neurotransmitter effects, on patterns of TBI recovery. As described in the APR for 2001, analyses have been performed to examine the role of the COMT polymorphism in cognitive recovery after traumatic brain injury. Results of these analyses were presented at the Annual Meeting of the American Neuropsychiatric Association Meeting in La Jolla, CA, February 2002. A manuscript describing these results has been submitted for publication to the Annals of Neurology.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 239. There have been no adverse events or withdrawals from the study this year. No addenda or other changes to the protocol have been requested over the last year.

## CONCLUSIONS

Analyses of COMT polymorphism effects on executive functioning following TBI have yielded interesting results that have been presented at the ANPA Annual Meeting and have been submitted for full publication. Future analyses will examine the relationship of other genetic polymorphisms to TBI recovery.

Report Date: 4 September 2001

Work Unit # 7176-99

# DETAIL SUMMARY SHEET

TITLE: The Neuroprotective Effect of Non-NMDA Receptors in Cultured Rat Cerebellar Granule Cells From Sprague-Dawley Rats Pups

KEYWORDS: AMPA, trans-ACPD, kainic acid, aniracetam, neuroprotection, excitotoxicity

PRINCIPAL INVESTIGATOR: Marini, Ann MD
ASSOCIATES: Krishna Banaudha, Ph.D

DEPARTMENT: Neurology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 17 November 1998

## STUDY OBJECTIVE

To determine whether non-N-methyl-D-aspartate receptors protect neurons against the excitotoxic effects of glutamate acting on N-methyl-D-aspartate receptors.

## TECHNICAL APPROACH

We are using cultured rat cerebellar granule cells to achieve our objective outlined above. These neurons are relatively homogeneous and express all of the glutamate receptor subtypes including N-methyl-D-aspartate and non-N-methyl-D-aspartate receptors. Cerebellar granule cells are pretreated with variable concentrations of specific non-N-methyl-D-aspartate receptor agonists followed by treatment with an excitotoxic concentration of glutamate (100 μM). Twenty-four hours later the number of viable cells are quantified using fluorescein diacetate.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Funding only recently received.

## CONCLUSIONS

No conclusions at this time.

Report Date: 1 February 2002 Work Unit # 00-7201

# DETAIL SUMMARY SHEET

TITLE: Naturalistic Study of Pharmacotherapy in Patients with Schizoaffective Disorder, Bipolar Disorder, and Schizophrenia

KEYWORDS:

PRINCIPAL INVESTIGATOR: Grieger, Thomas A. CDR, MC
ASSOCIATES:

DEPARTMENT: Psychiatry STATUS: C
SERVICE: INITIAL APPROVAL DATE: 14 March 2000

## STUDY OBJECTIVE

To determine the general demographic characteristics, the trends in pharmacotherapy, the reasons for hospitalization and hospital course of patients hospitalized with the diagnosis of schizoaffective disorder, bipolar disorder, and schizophrenia in a large public sector medical system.

## TECHNICAL APPROACH

The methodology has not changed since our protocol submission. Briefly, hospitalization records for all patients with a discharge diagnosis of schizoaffective disorder, bipolar disorder, and schizophrenia during the period from September 1993 - October 1999 are being reviewed, and variables including age at first onset, number of prior hospitalizations, length of stay, reason for hospitalization, medications prior to hospitalization, question of compliance, medications at discharge and reason for medication adjustment are assessed. Patterns of physician medication selection and patient response are then studied to determine both differences and similarities in the treatment of the three disorders over the time period studied.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 70 and the total enrolled to date at WRAMC is 70. The total number enrolled study-wide is N/A, if multi-site study. There were no adverse events in this retrospective chart review.

## CONCLUSIONS

This study examined changes in the pharmacological treatment of 70 patients who were hospitalized with a diagnosis of schizoaffective disorder over a six-year period. An increasing use of divalproex sodium and atypical anti-psychotics instead of lithium and typical anti-psychotics was observed. The use of a combination of an anti-psychotic and a thymoleptic medication was more common than monotherapy, and physicians tended to continue antidepressants on the basis of a history of depression. Patients with a new diagnosis of schizoaffective disorder were stabilized less quickly than those with a previous diagnosis. The use of divalproex sodium and newer anti-psychotics did not reduce the time to stabilization in routine clinical practice.

The non-availability of charts from the early years of the study precludes the comparison studies with patient with bipolar disorder and schizophrenia.

Report Date: 06 September 2002

Work Unit # 01-7201

# DETAIL SUMMARY SHEET

TITLE: Development of a Child and Adolescent Psychiatry Database

KEYWORDS:

PRINCIPAL INVESTIGATOR: Black, Nancy MAJ MC
ASSOCIATES:

DEPARTMENT: Psychiatry
SERVICE: Child and Adolescent Psychiatry

STATUS: O
INITIAL APPROVAL DATE: 17 October 2000

## STUDY OBJECTIVE

1. To gather comprehensive demographic and clinical data on consented clinic patients in order to categorize patients in terms of acuity, diagnoses and necessary treatments/interventions.
2. To create a database including clinic and telemedicine consultation patients to be utilized as a research vehicle for future retrospective and prospective studies of a military clinic population.

## TECHNICAL APPROACH

Parents/guardians of new clinic patients are approached in the child and adolescent psychiatry service (CAPS) clinic or via telemedicine sessions after completion of a standard intake paperwork packet. Consent for the study allows intake data from the clinic forms to be entered into a CAPS computerized database by the research assistant. There are no videotapes, blood draws, genetic testing, etc. performed for research purposes.

As of January 2002, CAPS switched the Ohio Scales outcomes measure. To maintain consistency within the CAPS computerized database, the research assistant has the parent/guardian complete the YOQ once they have been consented for the study.

## PRIOR AND CURRENT PROGRESS

There are no recent literature findings on child psychiatry databases. There are no study findings thus far; participants continue to be enrolled in the study. Since the last APR review, there was a change in the Principal Investigator, from Michelle Sandberg to MAJ Nancy Black. The study also underwent an audit review by the Department of Clinical Investigation in March 2002.

The number of subjects enrolled to the study since last APR at WRAMC is 32 and the total enrolled to date at WRAMC is 97. The total number enrolled study-wide is NA, if multi-site study.

There have been no adverse events.

## CONCLUSIONS

None at this time.

Report Date: 12 March 2002

Work Unit # 7279-98

# DETAIL SUMMARY SHEET

TITLE: The Frequency and Nature of Forensic Issues in an Inpatient Adult General Psychiatric Population.

KEYWORDS: Forensic psychiatry, Military psychiatry

PRINCIPAL INVESTIGATOR: Malone, Ricky LTC MC
ASSOCIATES: Daly, Christine CPT MC

DEPARTMENT: Psychiatry
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 25 March 1998

STUDY OBJECTIVE
This study will tabulate the frequency and nature of forensic issues in adult psychiatric inpatients admitted to this facility and examine for relationships between these issues and demographic and clinical variables.

TECHNICAL APPROACH
Retrospective chart review.

PRIOR AND CURRENT PROGRESS
Record review completed and preliminary data analysis in progress. A review of recent literature shows that this is an area that has still not been addressed.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 301.

CONCLUSIONS
None to date. Anticipate conclusion by June 2002.

Report Date: 7 February 2002

Work Unit # 7280-98

# DETAIL SUMMARY SHEET

TITLE: Suicidal Behavior in Active Duty Patients

KEYWORDS:

PRINCIPAL INVESTIGATOR: Ritchie, Cameron LTC MC
ASSOCIATES: William Keppler, MD: Joe Rothberg, PhD

DEPARTMENT: Psychiatry
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 10 April 1998

## STUDY OBJECTIVE

To examine the relationship between demographics, depressive symptoms, suicidal behavior, motive for self-destructive acts, substance abuse, and effect on a military member's career.

## TECHNICAL APPROACH

To review 140 charts for relevant information. An addendum described a change in the charts reviewed, to include more recent charts between 1 August 1998 and 1 March 1999 (which were on CIS).

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 140.

## CONCLUSIONS

94 % were admitted with a depressed mood. Two-thirds had a history of prior attempts or gestures. 49% had been treated with psychiatric medication prior to admission and 88% were treated with psychiatric medications while on the ward. 47% were returned to a full duty status, 29% with a recommendation for administrative separation, and 18% were recommended for a medical board. This should be viewed as a pilot study. Similar research should be done at a range of military medical facilities to help improve our suicide prevention programs.

Report Date: 4 October 2002 Work Unit # 7284-99

# DETAIL SUMMARY SHEET

TITLE: Comparison of Parental Therapeutic Alliances Before and After Initial Psychiatric Interviews: Telepsychiatry Versus In-Person Appointments

KEYWORDS: Therapeutic Alliance, Telepsychiatry

PRINCIPAL INVESTIGATOR: MAJ Nancy Black, MC
ASSOCIATES: LTC Stephen Cozza, MC; Ms. Sarah Rosquist

DEPARTMENT: Psychiatry
SERVICE: Child and Adolescent Psychiatry

STATUS: O
INITIAL APPROVAL DATE: 17 November 1998

STUDY OBJECTIVE:
The objectives of this study are to examine the elements of the developing therapeutic alliance from the first psychiatric interview based upon the parental perspective. The primary distinction will be made in determining whether there is a significant difference between the questionnaires obtained from in-person interviews and those obtained from telepsychiatry interviews. Another objective is to compare the parental opinions both before and after interviews.

TECHNICAL APPROACH:
Questionnaires approved by WRAMC human use committee will be distributed to all participants who consent in both in-person and telepsychiatry initial intakes done by staff at the Child and Adolescent outpatient clinic at WRAMC. These questionnaires are designed to quantify parents' perceptions of the potential for an alliance to be made between the provider and the patient/family. All participants will also fill out the YOUTH OUTCOME QUESTIONNAIRE (YOQ™2.0 (1) which is already part of the paperwork involved with an initial intake. Symptom Severity Data obtained from the YOUTH OUTCOME QUESTIONNAIRE (YOQ™2.0 (1) will be used to match the in-person and telepsychiatry participants by level of severity. These matched groups then will be examined to determine if any statistically significant trends regarding parental perception of the potential for alliance to form exist. A post interview questionnaire will be given to parents of the telepsychiatry group to monitor any change of their perceptions of the ability to form alliance before and after the interview. The number of complete, usable data sets is 40 telepsychiatry cases and the 100 in-person cases.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
There is no literature that looks specifically at satisfaction with child and adolescent telepsychiatry. Initial trends indicate that participants in the telepsychiatry group have higher expectations prior to their initial interview than do participants in the in-clinic group. Additionally, participants in the telepsychiatry group seem to be satisfied with the services they receive via telepsychiatry, based on the change in the mean scores from the pre-interview questionnaire to the post-interview questionnaire. (Scores decreased, and lower scores are associated with greater satisfaction.) No significance to date between research groups, but data collection is still on-going.

The number of subjects enrolled to the study since last APR at WRAMC is 48 and the total enrolled to date at WRAMC is 100. The total number enrolled study-wide is 131.

CONCLUSIONS:
Data collection is ongoing at the distant site. Data collection is complete at WRAMC. An attempt was made to recruit Fort Detrick, but was unsuccessful due to staffing/credentialing issues.

Report Date: 30 November 2001

Work Unit # 7285-99

# DETAIL SUMMARY SHEET

TITLE: Assessing Pre-Military Psychiatric Illness, Risk Factors Leading to Early Onset of Psychiatric Illness and Inter-Rater Reliability of Psychiatric Diagnosis

KEYWORDS:

PRINCIPAL INVESTIGATOR: Ritchie, E. Cameron LTC MC
ASSOCIATES: Grammer, Geoffrey G. CPT (P) MC, Cooper, Mark CPT MC

DEPARTMENT: Psychiatry
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 02 February 1999

## STUDY OBJECTIVE

1. To determine if patients had active symptoms or prodromal signs of illness prior to entering the military.
2. To examine precipitating stressful life events for military personnel admitted to inpatient psychiatric wards at WRAMC.
3. To document the accuracy of DOD diagnoses.

## TECHNICAL APPROACH

No change, retrospective chart review.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The comparison between the diagnoses made by the WRAMC physicians in the medical record and the diagnoses from the independent blinded reviewers has been completed.

The original protocol asked for permission to review up to 400 charts. These were charts of patients who were hospitalized in the first year of active duty. However, fewer charts than expected had patients who were hospitalized within a year and whose charts contained enough information to analyze.

The data from 69 inpatient charts on prodromal signs of illness had been compiled and partially analyzed. However, there were some difficulties with the initial collection and analysis of the data, and it had to be re-done. The data has been entered into a new spreadsheet. Analysis is pending.

Because of time and resource limitations, it was decided not to attempt to analyze psychological testing or MRI data. There have been no new subjects enrolled. This is a retrospective chart review. Therefore there have been no adverse actions or patients withdrawn from the protocol.

## CONCLUSIONS

There is excellent diagnostic reliability between the WRAMC physicians and blinded reviewers. The kappa for inter-rater reliability was .84. This kappa is a chance-related reliability measure. The uncorrected percent agreement between the independent psychiatrists and the Medical Board was 88%. The main source of discrepancy came from questions about the length of illness, which occasionally was not well documented in the Medical Board.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 69.

Report Date: 03 July 2002 Work Unit # 00-7301

# DETAIL SUMMARY SHEET

TITLE: Computerized Neuropsychological Assessment of Army Aviators (CNAAA): Development of a Digitized Database and Preliminary Investigator of the Relationship of ANAM, CogScreen and MicroCog to Aviator Trainee Checkflight Performances

PRINCIPAL INVESTIGATOR: Christensen, Daniel K. CPT MS
ASSOCIATES: Kelly, Mark P. DAC, Gahm, Gregory LTC MS, Leso, John CPT MS, Baggett, Mark MAJ MS, Goodlett, Georgie, B.A.

DEPARTMENT: Psychology
SERVICE: Neuropsychology

STATUS: O
INITIAL APPROVAL DATE: 1 August 2000

## STUDY OBJECTIVE

1) To develop a digitized database for computerized neuropsychological measures. 2) To develop a system to electronically transmit neuropsychological test data collected at a remote location to a centralized database. 3) To explore the relationship of select neuropsychological variables (derived from ANAM, CogScreen, and MicroCog) to initial checkflight performances during Initial Entry Rotary Wing (IERW) training.

## TECHNICAL APPROACH

All procedures described in this section will be conducted by one of the investigators (CPT Daniel Christensen, Dr. Mark Kelly, MAJ Mark Baggett, LTC Greg Gahm, CPT John Leso) or a trained civilian research assistant, Georgie Goodlet. Subjects will be given a detailed overview of the study requirements followed by a 48-hour period in which to give consent. Once consent is obtained, subjects will be scheduled for the interview and testing session within two weeks. At the interview and testing session they will then complete a brief structured questionnaire designed to gather demographic information and information about past medical history. The questionnaire data will be used to describe the sample and to make statistical comparisons based on demographic variables. For the telemedicine aspect of the study, a WRAMC Telemedicine Directorate programmer (Mr. Sun) will program (using Microsoft Access or SQL) a computerized version of the proposed questionnaire so that it can be taken on the computer. Completion of the questionnaire will be followed by a brief interview to clarify information reported on the questionnaire and to query any missing information. Following the questionnaire and interview, each subject will be given individual instructions on how to begin the first test. Once the instructions are fully understood, each subject will complete the tests by following additional instructions presented on the computer screen. All subjects will complete the three different tests during a four-hour period on the same day allowing for a 15-minute break between tests. Trained personnel will be available for questions throughout the testing period. The order of tests will be randomized to avoid order effects. All tests are computer administrated (laptop or desktop) and each test lasts approximately 45-60 minutes. The questionnaire and interview takes approximately 15 minutes to complete. All data will be saved on the testing computer and, if feasible, securely transported via electronic medium to a centralized database at WRAMC for analysis.

Data will be stored and transported using security features mandated by the NARMC Telemedicine Directorate. These features include encryption, password security and access controls. Only the investigators and the trained civilian research assistant have access to the data. Study data for individual subjects will not be made part of the subject's medical record or be made available to the chain of command. All personal identifiers will be stripped and a case number will be assigned before transmittal of the data. Personal identifying information is required in order to accurately collect Checkflight Performance scores on only the study participants and no other aviator trainees. The Principle Investigator,

or his designee, will maintain information collected in this study indefinitely in the digitized database (Microsoft Access or SQL) for future data analysis. However, at the time of final storage of data, all personal identifiers will have been stripped, thereby ensuring anonymity of data in the final database. After final storage of anonymous data, other researchers may be provided access to the data when there is a legitimate need for further scientific inquiry.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Thus far we have developed the initial database using Microsoft SQL7 (objective 1), and we have developed the "electronic data transmission" method, which involves uploading data via a secure website and to a secure server (objective 2). There have been no substantive modifications, no adverse events, and no subjects have withdrawn to date. There has not been anything in the literature in the past year that would have affected the study.

The number of subjects enrolled to the study since last APR at Fort Rucker is 27 and the total enrolled to date at Fort Rucker is 49.

CONCLUSIONS

Thus far, the findings indicate that it is feasible to electronically transmit data from a remote location using a secure server database. The implication from this finding is the possibility of greater access to neuropsychological services. Preliminary results indicate that select subtests from each of the three computerized tests (e.g., ANAM, MicroCog, CogScreen) correlate significantly with Checkflight performance scores. Final results and conclusions about the usefulness of the individual computerized neuropsychological tests are pending completion of data collection.

Report Date: 3 May 2002 Work Unit # 01-73002

# DETAIL SUMMARY SHEET

TITLE: CD-ROM Technology to Increase Appropriate Self-Care and Preventive Behaviors Among Enlisted Women

KEYWORDS:

PRINCIPAL INVESTIGATOR: James, Larry C. LTC MC
ASSOCIATES:

DEPARTMENT: Psychology STATUS: O
SERVICE: INITIAL APPROVAL DATE: 5 June 2001

STUDY OBJECTIVE
Determine if CD-ROM technology can increase preventive health knowledge in enlisted women.

TECHNICAL APPROACH
CD-Rom technology. No modification to the study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A literature search was performed and no new articles were found. No adverse events have occurred.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 6. The total number enrolled study-wide is 6, if multi-site study.

CONCLUSIONS
Slow progress with recruitment of subjects.

Report Date: 11 September 2002

Work Unit # 01-7301

# DETAIL SUMMARY SHEET

TITLE: Computer Automated Neurophysiological Assessment of Army Aviators

KEYWORDS: ANAM, CogScreen, Neuropsychology

PRINCIPAL INVESTIGATOR: Baggett, Mark MAJ MS
ASSOCIATES: Kelly, Mark P. and Christensen, Daniel

DEPARTMENT: Psychology
SERVICE: Neuropsychology

STATUS: O
INITIAL APPROVAL DATE: 30 November 2000

STUDY OBJECTIVE

Conduct a validation study comparing a computerized assessment measure Automated Neuropsychological Assessment Metric 2001 (ANAM2001) windows version (Bleiberg, Kane, Reeves, Garmoe, & Halper, submitted for publication) to CogScreen, SynWin and the Wonderlic Personnel Test (Wonderlic, 1983). The purpose of this study is to validate ANAM2001 as a future assessment tool when compared to CogScreen.

TECHNICAL APPROACH – No modification have been made.

a. **Study Design**: The design is a related measures construct-validity study (Bordens & Abbott, 1988; Campbell & Fiske, 1959; Glass & Hopkins, 1984) for one group of subjects. Specifically, the study will examine the convergent and discriminant validity, of the measures specified.

b. **Methodology**: Subjects will be asked to read and sign the consent form. The 160th SOAR Psychologist will conduct subject screening after the volunteers have implemented the consent form. Subjects will complete an online history questionnaire to determine medical, social and flight history. The background history questionnaire, ANAM, CogScreen, and SynWin will be administered by computer in a secure environment within a single 2-hour session. Testing of subjects will be conducted in a computer room at the 160th SOAR and observed by a Clinical Psychologist in groups of 6. The sequence of administration of the three tests (ANAM, SynWin and CogScreen) will be randomized to control for fatigue effects. The background questionnaire, ANAM and SynWin will be web enabled for this study. The background questionnaire and tests will be administered from a password protected web page on a secure server maintained at WRAMC, by WRAMC Telemedicine. The study will be conducted from computers at the 160th SOAR in a secure room. If it is technically feasible the CogScreen will be web- enabled. If this is not possible due to the commercial nature of the test, CogScreen will then be loaded to the local computers at the 160th SOAR. The data will up-loaded in SQL-7 from the 160th SOAR computers to a secure, password-protected server at WRAMC. The data will be saved into SPSS for later data analysis. All computers used in administration of the testing will be kept in a secure room at the 160th SOAR, which is locked when not in use. Access to the data on the computer will be gained only through passwords. All tests will include only a code number beginning with code "001." No name or social security number will be attached to the SPSS data files. Five years following the completion of the study all data files related to the study will be destroyed. Participation will be completely voluntary with the goal of enhancing US Army Aviation through developing cognitive performance screening measures. Because of limited population size of the 160th SOAR it will not be feasible to randomly sample subjects from the population. A clinical psychologist at Ft. Campbell, KY will screen all test subjects utilizing structured clinical interview and questionnaires. The Wonderlic Personnel Test (WPT) is routinely included in the 160th SOAR screening process as a requirement of entry into the regiment. The WPT is administered independent of this proposed study. The WPT is a brief group administered test that correlates highly with IQ and is widely used in personnel settings (Wonderlic, 1983). The test is administered in order to predict academic performance of pilots on flight training materials. The WPT is thought to have little relationship with actual flight performance. The WPT is part of a standard screening battery that is

c. given to all soldiers are assigned to the 160th SOAR. The scores from the WPT will be available for data comparison with their consent. To control for potential effects of fatigue, subjects will be tested in the morning following a routine night's rest.

d. **Data Collection**: A brief demographic questionnaire will be administered prior to beginning the testing. The questionnaire requires approximately two minutes to fill out. The purpose of the questionnaire is to collect medical history and demographic data that may be utilized to anonymously describe group data in any future publications. The questionnaire will not include name, social security number or other identifying information. Each subject will be assigned a code for their data e.g. "001" that will match the subjects questionnaire and tests to the same subject. A traditional measure of intellectual abilities the WPT will be used as a comparison measure of discriminant validity. The WPT is a paper and pencil self-administered test that takes 12 minutes to complete. The WPT correlates .91 to .93 with the Wechsler Adult Intelligence Scale (WAIS) Full Scale IQ (Woderlic, 1983) a measure of general intellectual ability. Unlike ANAM, CogScreen, and SynWin the WPT tasks focus on accuracy of solving a variety of problems. Extensive research has been published with the WPT in personnel assessment and selections settings. Three computerized neuropsychological measures will be administered ANAM, CogScreen and SynWin. Data from each of three computerized neuropsychological measures is collected at the time of administration.

e. **Sample Size/Data Analysis**: One hundred twenty five subjects will be recruited for this study and constitute a convenience sample. With the proposed sample size of 100 subjects, the study will have 80.5% power to detect a statistically significant result where the criterion for significance (alpha) has been set at 0.01 for a two-tailed test. This computation assumes that the correlation in the population is 0.33. If the correlation in the population were 0.47, on the other hand, then the proposed sample size of 100 subjects would have 100% power to detect a statistically significant result where the alpha has been set at 0.01 for a two-tailed test. To account for possible "dropouts" or missing data, a sample size up to 125 subjects is requested. Data analysis will focus on the correlations between ANAM2001, CogScreen, SynWin, and WPT. Descriptive statistics will be used for the variables of age and education level of the sample group. Then, a series of correlation analyses (Pearson r) will be conducted between ANAM2001, CogScreen, SynWin, and WPT to explore convergent and divergent validity. In general, data analysis will be conducted to explore the construct validity (Bordens & Abbott, 1988; Campbell & Fiske, 1959; Glass & Hopkins, 1984) of the measures administered in this study ANAM2001, CogScreen, SynWin, and WPT. Throughput, as a measure encompassing both speed and accuracy of performance, was selected to serve as an appropriate summary measure of performance efficiency for each subtest. ANAM2001 produces 14 throughput scores for its 14 different subtests. A series of correlation analyses (Pearson r) will be conducted between each ANAM2001 subtest throughput score and each CogScreen subtest throughput score. ANAN2001, CogScreen, and SynWin throughput/composite scores will be compared to the WPT composite score. SynWin is a measure of divided attention; ANAM2001 contains no equivalent divided attention measure. CogScreen does contain a single subtest of divided attention that will be compared to the SynWin composite score. A summary of correlations scores for ANAM2001, CogScreen, and SynWin displayed in a correlation matrix to allow easy visual examination of convergent validity (Campbell & Fiske, 1959). In a separate correlation matrix, ANAM2001, CogScreen, SynWin throughput scores will be correlated with the WPT estimated IQ to examine discriminant validity.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The findings are pending. 33 subjects have completed the study at Ft. Campbell. No adverse events have been identified. No recent literature has been found related to this study other than that reviewed in the protocol. No subjects have withdrawn from the study. No complaints about the study have been filed. Several subjects have informally complained about the length of the consent form. Subjects have made no other significant comments. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 33, if multi-site study.

CONCLUSIONS

Pending.

Report Date: 30 April 2002

Work Unit # 7302

# DETAIL SUMMARY SHEET

TITLE: Analysis of Component Neurocognitive Processes for the Trial-Making Test: An Examination of Age Related Changes

KEYWORDS: Trail Making Test, Aging

PRINCIPAL INVESTIGATOR: Jones, Alvin Ph.D., DAC
ASSOCIATES: Kratz, Kris E. MA; Bluestein, Brendon W. MA

DEPARTMENT: Psychology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 8 July 1997

## STUDY OBJECTIVE

There are three objectives:

(1) To determine if the component neurocognitive process (motor speed, visual scanning etc.) can be determined and reliably measured for the Trial Making Test;
(2) To examine the effects of age on the component neurocognitive processes;
(3) Establish preliminary normative data for clinical interpretation of test results.

## TECHNICAL APPROACH

There are three phases of research:

(1) Development of standardized test materials;
(2) Establishing test-retest reliability for the testing material;
(3) Collection of data to examine how performance changes on the component neurocognitive process over the life span. The final stage will also provide preliminary normative data for clinical interpretation of test results.

## PRIOR AND CURRENT PROGRESS

Phase I has been completed and work is continuing on Phase II. No modifications have been made to the study. No adverse events have occurred and no participants have withdrawn from the study. No new literature related to study.

The number of subjects enrolled to the study since last APR at WRAMC is 53 and the total enrolled to date at WRAMC is 56.

## CONCLUSIONS

No conclusion can be drawn at this time.

Report Date: 2 April 2002 Work Unit # 00-7502

# DETAIL SUMMARY SHEET

TITLE: A Prospective Study of Stress in Army Reservists

KEYWORDS: Army Reservists Occupational Stress; Longitudinal Study

PRINCIPAL INVESTIGATOR: LTC Laura R. Brosch
ASSOCIATES: Jacqueline Agnew, Ph.D.

DEPARTMENT: Nursing
SERVICE: Nursing Research

STATUS: O
INITIAL APPROVAL DATE: 16 May 2000

## STUDY OBJECTIVE

The overall goal is to apply the newly developed Reserve-Specific Stress Inventory to a cohort of selected reservists in a prospective study design. This will allow the identification of stressors related to reserve, civilian job, and family roles that are associated with adverse health outcomes. The subscales of the Inventory will enable examination of individual and organizational factors that mitigate stress under high stressor conditions.

## TECHNICAL APPROACH

This study will be prospective in design, with each subject followed at six-month intervals for one year following an initial data collection session. Participants will be volunteers who have been randomly selected from unit rosters of Army Reserve units belonging to the 99th Regional Support Command in Pittsburgh. After enrolling in the study and providing signed information consent, reservists will be interviewed by telephone using a survey that will address their roles as reservists, civilian workers, students (if applicable), and family members as well as psychological health factors. The newly developed Reserve-Specific Stress Inventory will be used to assess specific stressors as well as personal and organizational resources that can mitigate stress. Outcomes will emphasize injury and stress-related experiences. The data to be collected by interview will measure components of the model that relate to the conceptual framework of the study, i.e. the demand-control model. Because of the geographic dispersion of units and need to distribute initial contact over time, subjects will be enrolled over a period of six months at the rate of approximately 30 participants per month. Total anticipated enrollment: n = 180.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study was initiated in July of 2001 following completion of previous TSNRP funded study (Work Unit # 7577-99). Activity to date on this study has included establishing plans for sampling, assembling the instrument to be implemented, and obtaining the required equipment and software to begin the study. Additionally, the departure of the post-doctoral student who was working on this grant has necessiated a change in personnel. A new student is being identified for this role.

No recent findings in the literature have been found that would impact the approach or content of the study as planned. The activation of selected reservists following the terrorist attack on 11 September 2001 has forced us to consider our sampling plan very carefully in an effort to minimize the loss of research subjects to an overseas deployment that may make their continued participation difficult.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

## CONCLUSIONS

No conclusions regarding this protocol are available at this time.

Report Date: 17 May 2002

Work Unit # 00-7503

# DETAIL SUMMARY SHEET

TITLE: Ethical Issues in Department of Army Nursing Practice

KEYWORDS: ethical issues, nursing practice, instrument development

PRINCIPAL INVESTIGATOR: LTC Laura Brosch, AN
ASSOCIATES: COL Janet Harris, AN; LTC (Ret) Janice Agazio, AN

DEPARTMENT: Nursing
SERVICE: Nursing Research

STATUS: O
INITIAL APPROVAL DATE: 22 September 2000

## STUDY OBJECTIVE

The aims of this study are: 1) identify the ethical issues experienced by Army Nurse Corps (ANC) officers and Department of the Army civilian (DAC) registered nurses (RNs) in their practices and the frequency of their occurrence; 2) identify how disturbed ANC and DAC RNs are by these ethical issues; and 3) determine the ethics education needs of ANC and DAC RNs.

## TECHNICAL APPROACH

This study involves two phases. In phase I, focus groups will be used to identify and incorporate Department of the Army and military environment-specific ethical issues into the Ethical Issues Scale. Participants for the focus groups will include ANC officers in TOE units and both ANC and DAC RNs in Medical Treatment Facilities and TOE units. Approximately 30 minutes will be required to complete the survey. Ordinal level data will be analyzed with frequency and contingency tables. Interval level data will be described with means, ranges, and standard deviations, as appropriate. Nonparametric, Chi-Sqaure, will be used to determine is there is a significant difference in the issues experienced by ANC officers and DAC RNs. This study will provide information about the ethical issues experienced in the workplace by ANC and DAC RNs. There has been no modification to the methodology.

## PRIOR AND CURRENT PROGRESS

Three focus groups have been conducted, one at Dewitt Army Community Hospital at Fort Belvoir and two focus groups at Fort Bragg. The 23 participants in the focus groups included ANC officers in TOE units and both ANC and DAC RNs in Medical Treatment Facilities. The tapes of the focus groups have been transcribed and analyzed. Additional items are being added to the Ethical Issues Scale. The revised EIS was distributed to six WRAMC nurses as a pilot test. Phase I is completed. Phase II is underway, including mailing the anonymous EIS questionnaire to all ANCs and DAC RNs in MTFs and TOE units. No adverse events occurred in this study.

The number of subjects enrolled to the study since last APR at WRAMC is six and the total enrolled to date at WRAMC (DeWitt) is fourteen. The total number enrolled study-wide is 29, if multi-site study. In phase II, to date, 3437 EIS questionnaires have been mailed; 381 to WRAMC and 846 to NARMC. It is not known how many have been returned.

## CONCLUSIONS

None.

Report Date: 17 November 2001 Work Unit # 01-75002

# DETAIL SUMMARY SHEET

TITLE: Army Nurse Readiness

PRINCIPAL INVESTIGATOR: MAJ Peter Murdock

DEPARTMENT: Nursing
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 2 January 2001

STUDY OBJECTIVE: 1. To further assess the psychometric properties of the Readiness Estimate and Deployability Index (READI) in a large, diverse population of Army nurses, and to make recommendations for the revision of the READI based on the results. 2. To compare the results of this administration of the READI between active and reserve component Army nurses in the North Atlantic Regional Medical Command.

TECHNICAL APPROACH Data collection was conducted using a modified three-mailing procedure. All participation was voluntary and confidential.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE A random selection of 425 active component nurses from nurses assigned to MTFs in the NARMC (n=536) were invited to participate. This sampling yielded a response rate of 51.8% (n=222). A random selection of 250 reserve component nurses from nurses in troop program units that deployed to an MTF in the NARMC (n=320) were invited to participate. This sampling yielded a 45% response rate (n=112). Recent literature includes a comparison of READI results in a convenience sample of active (n=118) and reserve officers (n=53) enrolled in Officer Basic Course at Fort Sam Houston. Internal consistency analysis conducted on the first three READI dimensions (Clinical Nursing Competency, Operational Nursing Competency, and Soldier and Survival Skills) were found to be highly reliable and stable as assessed by Chronbach's coefficient alpha (from 7.4 to .95).

CONCLUSIONS Developing and fielding the READI will allow Army nurses to assess their own deployment readiness using a valid and reliable instrument. The READI will provide the command with a detailed profile of how nurses rate their own deployment readiness, thereby reducing the potential for disparity between reported and perceived readiness, and identify training opportunities for corrective action before readiness declines or lives are lost. This study contributes to the body of work by Reineck, Finstuen, Connelly and Murdock (in press), and Kovats, Morris, Reineck, and Finstuen (in press), supporting the on-going development and fielding of a valid, reliable, and standardized instrument for assessing ANC readiness. This was the first successful mass-mail administration of the READI to active duty and reserve component nurses affiliated with a single Army regional medical command and achieved the largest combined sample of any previous administration (n=244). The strengths of this study were its approval by the WRAMC IRB, random selection of nurses, high response rate, and maintenance of subject volunteerism and confidentiality. The greatest challenge in completing the study was working with the reserve mail system. Depicting results in GPD format facilitates rapid understanding of results. Unit commanders, nurse leaders, operations personnel, and nurse trainers and educators can quickly assess individual and group readiness, identify deficits and strengths, make personnel decisions, and develop training plans. The READI can improve deployment readiness in a variety of ways. Groups of nurses from different sections, units, or regions can be compared and their readiness ratings matched with mission-specific casualty care projections to find the best fit between mission requirements and nursing personnel. Individual nurses can be evaluated for suitability for specific missions. New nurses can be assessed when they arrive in a unit and compared with their unit cohorts. They can be reassessed over time against unit, regional, and MEDCOM-wide READI benchmark ratings. Over time, commanders, nurse leaders, and unit historians can plot changes in readiness as the history of unit training exercises and deployments unfolds. Data from multiple READI administrations can build a profile of Army nurse skills that can aid in recruitment and ensure that elected officials and policy makers are aware of the value of Army nurses in contributing to a responsive, competent, and ready Army medical force. Future administrations are needed to compare ratings for nurses in different ranks, AOCs, and cohorts of deployed nurses before, during, and after deployment.

Report Date: 3 January 2002

Work Unit # 01-75003

# DETAIL SUMMARY SHEET

TITLE: Improving Adherence in a Coronary Disease Reversal Program with Web-Based Technology

KEYWORDS: Cardiovascular disease prevention; outcomes assessment; web-based technology; adherence

PRINCIPAL INVESTIGATOR: Spencer, Debra MAJ AN
ASSOCIATES: Walizer, Elaine LTC (ret) AN; Vernalis, Marina COL MC

DEPARTMENT: Nursing
SERVICE: Critical Care Nursing Section

STATUS: O
INITIAL APPROVAL DATE: 20 February 2001

## STUDY OBJECTIVE

The overall purpose of this study is to conduct a randomized comparative study to measure the efficacy of an Internet-based interactive communication link as an aid to promote patient adherence to a coronary artery disease reversal program. The study seeks to answer the research question: "What is the overall effect of an internet-based interactive communication link on the efficacy of a lifestyle modification program?" The study will address four research aims.

1. To determine if the use of an Internet-based interactive communication link (Health Hero Network® Online Services) between participants enrolled in the Coronary Artery Disease Reversal (CADRe) program and CADRe clinical team produces a significant change in program adherence.
2. To determine if the use of an Internet-based interactive communication link (Health Hero Network® Online Services) reduces the patient's cardiac risk factors as a result of adherence to the program? Subquestion: To determine the feasibility of using comorbid disease specific questions via the communication link to initiate a more rapid intervention if needed.
3. To determine the patient satisfaction level with use of this technology as an adjunct intervention to the CADRe program?
4. Subquestion: To determine is there is an association between the total adherence score at program exit and overall patient satisfaction with the technology.

## TECHNICAL APPROACH

A randomized comparative design will be used to determine the efficacy of an Internet-based interactive communication link (Health Hero Network® Online Services) in the adherence to a coronary artery disease reversal program. Participants will follow a controlled protocol and receive either Health Hero Network® Online Service plus standard Program or the standard Program based on randomization of the cohort upon entering the Program. In this study, the groups that do not receive the Health Buddy will be considered the control group.

Participants will be recruited from the Cardiology Service and the "Non-Invasive Coronary Artery Disease Reversal" study. Cohorts of up to 20 patients are recruited every three months for enrollment. Cohorts of patients will be randomly selected (using a random number table) to receive the Health Buddy® Appliance. Irrelevant of cohort size, at least two cohorts will use the Health Buddy® Appliance to minimize one cohort being seen as "special". The goal is 60 patients who use the Health Buddy® appliance and 60 controls. This will allow for those who choose not to participate and for dropouts. Selection for this study will be done by random pre-selection of cohorts as a whole prior to recruitment into this study. Cohorts will be randomized to the Health Buddy® group or standard Program care using a table of random numbers. If the cohort is randomized to the Health Buddy® group, participants not willing to use the Health Buddy® appliance will be offered the opportunity to decline its use and dropped from this study (not the host study), however, demographic data will be collected on those who choose not to participate. This demographic data is already collected in the host study and will be maintained in the host study research records. Those

declining use of the Health Buddy® will remain with their cohort and receive standard Program care. Patients in the randomized Health Buddy group who do not wish to use the device will not be removed from the cohort, but their data will not be used as control data. Only those patients randomized to the treatment group will be consented for this study.

The WRAMC Human Use Committee (HUC) approved this protocol on 20 February 2001 and required revisions were received on 29 March 2001. Subsequent USUHS IRB approval was received on 13 June 2001.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

### Study Addenda

On 16 August 2001, the HUC approved Addendum #1 to this protocol. During the negotiation process with Health Hero Network and the Henry M. Jackson Foundation (HMJF) on the service contract, the HMJF legal department asked to review the consent form. Since the electronic device (Health Buddy) to be used in this protocol does transmit medical information from the patient to the case manager, the HMJF legal department requested that the following language be added to the consent form: "The electronic device is to be used only for purposes of this research study. The information transmitted over the electronic device does not constitute medical advice and does not replace the professional medical judgment of your physician or health care provider. If you encounter an emergency health care situation, do not use the electronic device. Instead contact your physician or health care provider directly."

### Enrollment

The number of subjects enrolled to the study since the last APR at WRAMC is 20 (in treatment group) and the total enrolled to date at WRAMC is 20 (in treatment group). The first group to receive the Health Hero device initiated the program on 29 October 2001. Nineteen of these twenty are physically utilizing the Health Buddy device in their homes without difficulty. One subject had to delay entry into the core program due to job commitments and will hopefully be able to initiate the core program in April 2002. The April 2002 cohort has also been randomized as a treatment group. There are 101 enrolled in the core study (Non-Invasive Coronary Artery Disease Reversal). Of these 101 subjects enrolled in the CADRe program, 36 have completed the year study, 47 are actively participating in various stages of the program, 1 is on hold, and 17 have withdrawn as outlined in the core study APR. The 20 subjects in this study's treatment group are included in the 101 core study enrollment numbers.

### Adverse Events

There have been no adverse events as a result of this study.

## CONCLUSIONS

No objective conclusions can be made at this point in time. The first treatment cohort is currently in week 10 of the overall program. Patient approval with the device now seems high after some initial frustration with data entry using the electronic device. It also appears that high-risk symptoms management has improved (i.e. chest pain and blood glucose) in the past ten weeks as well as fewer high-risk behaviors (i.e. compliance with overall program components) being reported by the subjects.

Report Date: 29 May 2002

Work Unit # 01-75004

# DETAIL SUMMARY SHEET

TITLE: Job Satisfaction Among Army Nurses

KEYWORDS: Job Satisfaction, ANC

PRINCIPAL INVESTIGATOR: LTC Patricia Patrician AN
ASSOCIATES: MAJ Georgette Diggs AN

DEPARTMENT: Nursing
SERVICE: Nursing Research

STATUS: C
INITIAL APPROVAL DATE: 10 July 2001

## STUDY OBJECTIVE

The purpose of this study was to determine the level of job satisfaction among ANC officers using the McCloskey and Mueller Satisfaction Survey (MMSS, 1990). Job satisfaction was assessed along the eight dimensions of: (1) extrinsic rewards, (2) scheduling, (3) balance of family and work, (4) co-workers, (5) interaction opportunities, (6) professional opportunities, (7) praise and recognition, (8) control and responsibility.

## TECHNICAL APPROACH

Participants received a demographic data questionnaire, survey, cover letter, and a self-addressed stamped envelope. The cover letter ensured confidentiality. Participants were informed that taking part in the study was strictly voluntary and that non-participation would in no way jeopardize their employment. Surveys were delivered to unit mailboxes and no attempt was made to contact individuals a second time. Only the researcher had access to the completed questionnaires. All results were reported as aggregate data and completed questionnaires were kept in a locked box.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Of the 273 nurses to whom questionnaires were distributed, 137 responded. The sample consisted of 137 ANC officers that were employed at a military hospital. The ANC officers had been on active duty at least one year and ranged in age from 23 to 55 years old. The mean age of the participants was 36 years. Company grade officers (n=84) and field grade officers (n=53) constituted the sample. The majority (n=88) of nurses were female, had bachelor degrees (n=79), and practiced in specialty areas (n=77) The participants in the study exemplified extrinsic and intrinsic behaviors.

Research Question One: How do ANC officers perceive job satisfaction? A total job satisfaction score was established at 104 out of a possible range of 31 to 155. Based upon the Likert scale, 94 was the lowest composite score indicative of job satisfaction (Misener et al., 1996).

Research Question Two: What are the factors associated with job satisfaction? Satisfaction with job benefits (M=4.19) ranked the highest, followed by the amount of vacation and the level of interaction with peers. Participants were least satisfied with child care facilities followed by opportunities to interact with College of Nursing and part-time work opportunities.

Research Question Three: Is there a difference in job satisfaction of ANC officers in medical centers when compared to those in ambulatory care centers? The difference between total satisfaction means in relationship to the place of employment was not statistically significant ($t=1.758$, $p=0.08$).

Research Question Four: Is there a difference in job satisfaction of field grade officers when compared to company grade officers? The difference between total satisfaction means in relationship to rank was statistically significant ($t= - 3.258$, $p=.001$). Total job satisfaction for field grade officers (M=111) was significantly higher than total job satisfaction for company grade officers (M=100). Scheduling ($t= - 4.343$, $p=.000$) was the most statistically significant variable followed by professional opportunities ($t= -3.286$, $p=.001$) and extrinsic rewards ($t= -2.687$, $p=.008$). Of the eight subscales, interaction opportunities, praise/recognition, and control/responsibility were the only variables that were not statistically significant.

Research Question Five: Is there a difference in job satisfaction of ANC officers working in a medical-surgical arena when compared to those working in a specialty area? The difference between total satisfaction means in relationship to work arena was not statistically significant (t=.020, p=.984). Total job satisfaction for both groups was equal (M=104). In this study of ANC officers, analysis found that Chronbach's Alpha coefficient for each of the components ranged from .49 to .89. The alpha for the global scale was .84.

The number of subjects enrolled to the study since last APR at WRAMC is 120 and the total enrolled to date at WRAMC is 120. The total number enrolled study-wide is 137, if multi-site study.

CONCLUSIONS

This study revealed that the majority of the ANC officers indicated a sense of satisfaction with extrinsic rewards, co-workers, and levels of praise and recognition. The ANC officers indicated a sense of dissatisfaction with scheduling, balance of family and work, interaction opportunities, professional opportunities, and control and responsibility. The majority of the ANC officers revealed that they were moderately satisfied with their pay compared to the O'Rourke (2000) study in which pay ranked second lowest in overall job satisfaction. Of all the extrinsic factors, participants rated vacation benefits and the military benefits as the greatest satisfiers. These findings were not similar to the data presented by Crose (1999) that reported that opportunities to work days, having flexible work schedules, and having some weekends off were the greatest satisfiers.

Dissatisfaction with the balance of family and work was not uncommon in a military setting. This was especially true in the medical arena due to peacekeeping or humanitarian assistance missions and shift work. Moreover, the majority of the participants were married with a mean age of 36 years old. During middle career stages, commitments to family and to community were not uncommon (Shaw, 1999). Based on the results, the field grade officers indicated a higher level of job satisfaction than company grade officers. Although both groups scored above the lowest possible score that was indicative of job satisfaction, field grade officers were more satisfied with extrinsic rewards, flexible scheduling, having a balance of family and work, co-workers, and professional opportunities compared to company grade officers. This finding was similar to a study by Freudenheim and Villarosa (2001) that revealed dissatisfiers of young nurses to be a lack of flexible scheduling, professional opportunities, and extrinsic rewards.

As tenure increased within an organization, the employee's potential for formal benefits such as promotion and informal benefits such as gaining a higher status also increased (Hellman, 1997). This was likewise true in the ANC. Satisfaction with extrinsic rewards among field grade officers was by virtue of their rank and years of tenure. Satisfaction with scheduling and professional opportunities among the field grade officers was most likely due to the level of autonomy allowed an officer of higher rank. Professional autonomy was ranked as one of the most important factors contributing to the nurses' sense of job satisfaction (Finn, 2001). The most desirable organizational structure to nurses was one that supported autonomous decision-making (Kangas, Kee, & McKee-Waddle, 1999). Nurses' work schedules were an important factor that influenced turnover. Stable work schedules created less work-related stress and lowered the level of anticipated nurse turnover (Shader et al., 2001). Registered nurses also reported that there was no incentive to work weekends (Shader et al.,). Participants in this study likewise rated compensation for working weekends as a dissatisfier.

Although studies have shown that specialization was an important contributor to job satisfaction (Kangas et al., 1999; O'Rourke, 2000), the participants in this study showed no evidence of a variation in their job satisfaction scores based upon specialty versus nonspecialty designations. This finding was not congruent with O'Rourke (2000) who concluded that specialty care nurses were more satisfied with professional status and interaction and nonspecialty nurses were more satisfied with organizational policies. Likewise, there was no evidence that ANC officers stationed in a Medical Center had a different level of satisfaction when compared to ANC officers in an Ambulatory Care Center.

Herzberg (1959) identified intrinsic factors as achievement, recognition, the nature of the work, a sense of responsibility, opportunities for advancement, and potential for professional growth as being satisfiers. In this study, intrinsic and extrinsic factors were satisfiers. Intrinsic satisfiers were having a sense of satisfaction with immediate supervisors, the amount of responsibility, recognition of work from peers, and having opportunities for career advancement. Herzberg (1959) stated that extrinsic factors or dissatisfiers emerged from the surroundings in the work environment. Interpersonal relations, working conditions, salary, status, security, and supervision were dissatisfiers. In this study, dissatisfiers emerged from both extrinsic and intrinsic factors. From the eight extrinsic and intrinsic factors, ANC officers categorized 50% of the extrinsic factors as dissatisfiers and 56% of the intrinsic factors as dissatisfiers.

Report Date: 28 May 2002 Work Unit # 01-75005

# DETAIL SUMMARY SHEET

TITLE: Medication Error Reporting and the Work Environment in a Military Setting

KEYWORDS: medication errors, patient safety, work environment

PRINCIPAL INVESTIGATOR: LTC Patricia Patrician, AN
ASSOCIATES: LTC Laura R. Brosch, AN

DEPARTMENT: Nursing
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 10 July 2001

STUDY OBJECTIVES:
1) Assess the differences in medication error reporting between an anonymous report and the current formal incident report system. Only those errors that occur on inpatient wards will be considered.
2) Assess civilian and military nurses' perceptions of the nursing work environment, reasons for medication errors, reasons for non-report and extent of non-report.
3) Examine the relationship of the nursing work environment (unit-based and shift-specific factors) and medication error reporting in an Army Medical Treatment Facility (MTF).

TECHNICAL APPROACH: This study consists of a cross-sectional anonymous survey and anonymous longitudinal daily coupons completed by nurses over a 30-day period. The cross-sectional surveys assess the qualities of the work environment as well as the degree of and reasons for non-report of medication errors. The longitudinal coupons assess on a daily basis, whether a medication error was committed, whether a near miss occurred, or whether the shift was uneventful in terms of medication errors. Each nurse answers the daily questions based of their assigned patients. The plan was to survey 14 inpatient units at WRAMC in two phases. Six units participated in the first phase of the study, from mid-January to mid-February. The response rate was unusually low (12% for the cross-sectional surveys and 10% for the longitudinal surveys), thus the research team decided to stop the study temporarily until we could ascertain why the response rates were so low. An addendum was sent to the IRB and approved allowing us the contact Performance Improvement Facilitators (PIFs) on each unit and have them invite the nursing staff to focus groups or individual interviews, or, as a last resort, to query the staff to find out reasons for the low response rates. Three of the six PIFs responded to our request. Reasons for non-response included being too busy, forgetting to turn in longitudinal coupons, fear that the survey was not anonymous, and the exclusion of LPNs.
To address these issues, another addendum was sent to the IRB and approved, allowing us to include LPNs in the second phase of data collection (the remaining 8 units) and to designate a "champion" on each unit who would remind the staff to turn in surveys and coupons. We plan to resume data collection in mid-June 2002.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
See explanations above for addenda to the study. Thus far, from the six units surveyed to date, we have 18 cross-sectional surveys returned and 182 longitudinal coupons. There have been no adverse incidents concerning this study. The data will not be completely analyzed until all data have been collected.
While the literature on medication errors addresses the causes and consequences of medication errors, and efforts to reduce their occurrence, no new literature has been published dealing with reasons for not reporting medication errors. MEDCOM has recently conducted a patient safety organizational climate survey and results show that a "culture of blame" for errors in health care (not only medication errors) still exists within the Army health care system, although this information has not yet been published.

CONCLUSIONS: There are no conclusions at this time.

Report Date: 16 May 2002 Work Unit # 01-75006

# DETAIL SUMMARY SHEET

TITLE: Research Utilization of Registered Nurses in U.S. Army Hospitals

KEYWORDS: Research Utilization, research based-practice

PRINCIPAL INVESTIGATOR: LTC Laura Brosch, AN

DEPARTMENT: Nursing STATUS: O
SERVICE: INITIAL APPROVAL DATE: 20 July 2001

## STUDY OBJECTIVE

To determine the extent that nurse in US Army MTFs use research findings for their own practice, to describe the ways in which research findings are used among different levels of nurses, and to describe both professional and organizational factors that enhance or hinder research utilization.

## TECHNICAL APPROACH

Participants at three sties (Walter Reed Army Medical Center (WRAMC), Womack Army Medical Center (WAMC), and Ireland Army Community Hospital (IACH)) were asked to complete two survey instruments. One assessed research utilization and professional factors that may affect it. The other identified organizational factors that may impact implementation of research findings in practice. IACH was used as a pilot site to corroborate reliability and validity of these instruments for use with this population. A personal visit to each Chief Nurse was made to discuss questions and concerns regarding the study. The investigator requested a name only list of all RNs working at each facility. This was used expressly for the purposes of personalizing the first mailing of the survey and providing a directed second mailing and reminder letters if necessary. At the time of study commencement, a reminder explanatory letter was sent to the Chief, Department of Nursing, at each of the facilities. The study aims, purpose, and procedures were discussed, as well as time frames for the study, IRB approval, and compliance. Packets sent to all the nurses in each facility included a cover letter providing details of the study, iterating that participation was voluntary, and that confidentiality of responses would be strictly maintained. It also included the two survey instruments and a postage-paid return-mailing envelope. Voluntary return of the surveys to the associate investigator constituted consent to participate in the study.

Survey mailings to the pilot site (IACH) commenced on 5 November 2001 following an announcement letter to the Chief Nurse and flyer distribution. Data collection proceeded according to the stated protocol, and ended on 17 December 2001. A 43.2% (n=38) return on the surveys was realized. Survey mailings for WAMC began on 7 January 2002 with an announcement letter to the Chief Nurse and flyer distribution. Surveys were mailed out beginning 21 January 2002. The final thank you letters were sent on 11 March 2002. Survey mailings to WRAMC began on 27 February 2002, following an announcement letter to the Chief Nurse and flyer distribution. Final thank you letters were sent on 27 March 2002. Thus far, there has been a 31.6% (n=84) return on the surveys from WAMC and 37.2% (n=188) return from WRAMC. Surveys are still coming in. The order of mailings for IACH (n=38) was inadvertently switched, where the second mailing of surveys was sent prior to the reminders. This was corrected for WAMC and WRAMC.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Newer literature in this area of study is now tending to focus on the organization as a system of change, rather than on the individual making practice changes, based on evidence. In addition, the term "research utilization" appears to have been replaced with the terms "evidence-based practice" and "knowledge utilization". These new terms are broader and recognize that research is not the only source of knowledge for best practice.

Preliminary data analysis of this study tends to support the past literature, in that perceived barriers to research utilization include time to access knowledge and implement it, attitudes toward research, and lack of

organizational support. In addition, the organizational factor of purposive information flow appears to be significant in whether or not RNs use research findings to change their practice. It has been assumed that educational level is directly correlated to increase use of research in practice, yet, in this study, the mean research utilization scores are slightly lower than those of a civilian comparison group where the mean educational level is lower. Further analysis will attempt to uncover the reason for this.

Thus far, 310 of 860 surveys have been returned from the three study sites, for a return rate of 36.0%. Two returned blank surveys contained attached notes stating that the survey was too long, and that they had filled out many others. Seven were only partially filled out and were not usable. Thus the total number of useable surveys for the study stands at 301. Because this study only consists of surveys and participation was voluntary, it is assumed that there have been no adverse events associated with it at any of the three sites. None have been reported.

The number of subjects enrolled to the study since last APR at WRAMC is 182 and the total enrolled to date at WRAMC is 182. The total number enrolled study-wide is 301 if multi-site study.

CONCLUSIONS

It is expected that few, if any, surveys will be returned at this point. Data analysis is ongoing. Any remaining returned surveys can easily be added to the data and included in the analysis. Any surveys returned after 1 June 2002 will not be included. The final report/dissertation will be completed in July 2002. It is expected that findings will parallel those of past studies, though the military culture differs from the civilian arena. However, the results of this study within the military environment will provide some direction in which to pursue interventions and intervention studies toward evidence based nursing practice.

Report Date: 28 May 2002 Work Unit # 01-75007

# DETAIL SUMMARY SHEET

TITLE: Army Hospitals: Work Environment, Quality of Care, and Intent to Leave

KEYWORDS: Hospital nursing, work environment, retention, quality of care

PRINCIPAL INVESTIGATOR: LTC Patricia A. Patrician, AN
ASSOCIATES: LTC Laura R. Brosch, AN; COL Melissa Forsythe, AN

DEPARTMENT: Nursing
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 10 July 2001

## STUDY OBJECTIVES

1) describe work environment attributes, affective responses to the job (burnout and job satisfaction), perceived quality of care and intent to leave the Army workforce from the perspective of military and civilian staff nurses working in Army hospitals,
2) explain the relative contributions of individual attributes, work environment attributes, and affective responses to the job in explaining intent to leave the Army workforce, and
3) examine the added contribution of nurses' perceptions of the quality of care they provide in explaining intent to leave the Army workforce

## TECHNICAL APPROACH

This is a multi-site, cross-sectional study of nurses who work in inpatient units in the Army Medical Department. The plan for this study was to obtain lists of units and names of the nurses who work there from each medical treatment facility (MTF). We then planned to conduct surveys in accordance with the Dillman method of survey methodology. However, at least one site (MAMC) objects to releasing the names of their nurses to the research team and prefers to generate the list of names and codes locally and distribute the surveys to each nurses' mailbox. This would further protect against any inadvertent breeches of confidentiality as we would not have access to those nurses' names at all. We would receive the surveys by mail at WRAMC and provide MAMC the codes of the returned surveys. They would then track responses and re-send surveys to those who did not respond to the first mailing.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study.

We are still in the process of obtaining IRB approval at the remaining 7 sites throughout the Army. Currently MAMC and TAMC have given verbal IRB approval, but we are awaiting formal notification prior to commencing the study at those sites. Because nurses at WRAMC have received too many surveys during this fiscal year, we are waiting until September to survey the NARMC, including WRAMC. Our plan at this time is to survey TAMC, MAMC and the Western Regional Medical Command (Ft Irwin and Ft Wainwright). In September, we would survey the NARMC, the South East Regional Medical Command and the Great Plains Regional Medical Command.

There has been no published literature that definitively links the work environment or quality of care to intent to leave a job, however, my dissertation research found that one of the work environment variables, the adequacy of resources available to the bedside nurses, was associated with actually resigning from a hospital nursing job.

## CONCLUSIONS

There are no conclusions at this time.

Report Date: 06 June 2002

Work Unit # 01-75008

# DETAIL SUMMARY SHEET

TITLE: Examining the Weight Management and Exercise Behaviors Among Active Duty Nursing Personnel in Maintaining Compliance with the Army's Weight Control Standards

KEYWORDS: weight management behaviors, exercise behaviors, self-efficacy, barriers, benefits

PRINCIPAL INVESTIGATOR: LTC Patricia A. Patrician, AN
ASSOCIATES: CPT Patricia A. Coburn AN, Barbara M. Sylvia Ph.D. RN, Col Martha Turner USAF NC

DEPARTMENT: Nursing
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 17 July 2001

STUDY OBJECTIVES This comparative descriptive study was undertaken to examine, among active duty nursing personnel, the 1) weight management and exercise behaviors, 2) perceptions of benefits and barriers to exercise, and 3) self-efficacy for exercise.

TECHNICAL APPROACH This study used a comparative descriptive research design to first describe the weight management and exercise behaviors, perceived benefits and barriers to exercise, and the self-efficacy to exercise in the face of barriers. Second, to compare these factors by weight category (i.e. overweight versus non-overweight). Pender's Health Promotion Model (HPM) was the organizing framework for this study. An 89-item questionnaire was distributed to nursing personnel in the National Capital Area (NCA). The questionnaire consisted of three different instruments used to examine variables that assess positive and negative weight management and exercise behaviors, determine the benefits and barriers to exercise, and determine self-efficacy expectations related to the ability to continue exercising in the face of barriers. Descriptive statistics were used to examine the data for the groups. Statistical comparisons between the groups were accomplished using Chi-square and t-tests for categorical and continuous data respectively. The Statistical Packages for Social Sciences (SPSS) v. 10.0 was used to code and analyze data.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 166. As of February 2002, all data had been collected. There were no adverse events. This literature review focused on studies that examined trends in overweight and obesity and the weight management and exercise behaviors in the military.

CONCLUSIONS Weight Management Behaviors utilized by overweight versus non-overweight nursing personnel: Significant differences were found between these groups on the following weight management behaviors; severely restrictive diets ($X^2$ 12.29, p>.001), popular diet regimes ($X^2$ 9.41, p=.002), laxatives ($X^2$ 3.95, p=.047), and both prescription ($X^2$ 13.55, p>.001) and over-the-counter medications ($X^2$ 12.29, p>.001), with the overweight group indicating a greater practice of each behavior. No significant differences were found between the groups in the use of self-induced vomiting ($X^2$ 1.28, p=.258) or diuretic use ($X^2$ 3.28, p=0.70). Eight percent (6) of the overweight group, and 2% (2) of the non-overweight group reported using diuretics as a form of weight management. Fourteen percent (10) of the overweight group and 5% (5) of the non-overweight group reported a weight change of at least ten pounds in the last month.

Exercise Behaviors of overweight and non-overweight respondents: There was a significant difference between groups in regularly exercising, with the normal weight group reporting this behavior to a greater extent. ($X^2$ 4.27, p=.039). There was also a significant difference between groups in the use of running as a form of exercise, with the normal weight group again more frequently engaging in this activity ($X^2$ 5.59, p=.018). No significant differences were found between groups in their use of the following exercises: walking, aerobics, weight lifting, and cycling.

Perceived Benefits and Barriers: The average perceived benefit score was 97.74 (SD 12.87) for the entire sample. The mid-point score of 95 was much higher than the mid-point score of 87 for the original use of the scale in a civilian population. There was no significant difference between the overweight and non-overweight

group for the average perceived benefit scores of 98.88 (SD 12.4) and 96.39 (SD 14.75) respectively. The mid-point score was 95 for both groups. There was also no significant difference between the overweight and non-overweight groups relative to perceived benefits to exercise (t=-1.15, p=.252). Greater than 50% of both groups agreed that exercise allowed them to carry out normal activities without being tired and that exercise improved the quality of their work. Detecting differences in the perceived benefits to exercise among overweight and non-overweight respondents was accomplished by collapsing the four-point Likert scale into a two point agree and disagree scale. The average perceived barrier score was 40.20 (SD 6.09). The mid-point score of 40.0 was just slightly lower than the mid-point score of 41 for the original use of the scale. There was no significant difference (t=1.056, p=.292) between the overweight and non-overweight group for the average perceived barrier scores of 39.67 (SD 5.85) and 40.68 (SD 6.27) respectively. The mid-point score for the overweight group was 39.0 and 40/0 for the non-overweight group. Twenty-five percent of both groups reported that exercise took too much time, and 20% of both groups reported that exercise facilities did not have convenient schedules for exercising. The difference in the perceived barriers to exercise among overweight and non-overweight respondents was accomplished by collapsing the four-point Likert scale into a two point agree and disagree scale.

Self-Efficacy: The mean self-efficacy score for the total sample was 5.55 (SD 2.38) on a scale of zero to ten. The mean self-efficacy score of the overweight group was 5.33 (SD 1.97)), and 5.69 (SD 2.64) for the non-overweight group indicated there was no significant difference in the two groups (t=0, p=0). There was also no significant difference in the overweight versus non-overweight group's self-efficacy towards exercising at least three times a week for twenty minutes. Greater than 50% of both groups reported ratings of five or higher, indicating a high degree of self-efficacy toward exercising when the weather was bothersome, if they had to exercise alone, or if they felt tired, stressed or depressed. However, greater than 50% of both groups reported a rating of less than five, indicating a low degree of self-efficacy toward exercising when they felt pain or did not enjoy it.

The finding that the overweight group engaged in more maladaptive weight management strategies than the normal weight group was not surprising, but nonetheless, has significant health care implications for this group of active duty military health care providers. The use of severely restricted diets and laxatives to maintain weight can lead to nutritional and fluid volume deficiencies, especially if these strategies are used in conjunction with increased activity levels, such as during the Army Physical Fitness Test (APFT). The use of over-the-counter medications is also problematic, given the side effects of these substances, to include sudden increases in blood pressure and stroke. Sixty percent of participants in the overweight group and 75% in the non-overweight group reported that they engaged in regular exercise, defined as at least thirty minutes in duration and at least three times per week. Although this difference was statistically significant, it is heartening that, given the nature of military nursing personnel's work (e.g. shift-work and overtime), and although it was less that the 85% reported by Decker, overweight individuals are engaging in regular exercise. Every effort should be made to support and encourage this behavior.

The lack of statistically significant differences between the overweight and non-overweight groups on the total score of the barriers and benefits to and self-efficacy for exercise scales was unexpected. The research team expected that the overweight group would perceive fewer benefits and greater barriers to exercise and less self-efficacy for exercise. This finding might be explained by the fact that the study participants were health care personnel and have been exposed to information about the benefits of exercise in their educational programs. That the barriers weren't significantly different between groups is perhaps more telling. The overweight personnel did not report more barriers, as was expected, and actually reported fewer barriers to exercise with a mean barrier score of 39.67 (SD 5.85) versus the non-overweight group barrier score of 40.68 (SD 6.27). This may be due to the cultural norm in the military that "there's no excuse" for not exercising. The military culture requires personnel to remain physically fit, and multiple measures are in place to ensure compliance. These measures, which Pender refers to as external cues to action, may provide the impetus for both overweight and normal weight soldiers to continue to exercise in addition to other weight management behaviors.

Report Date: 5 July 2002

Work Unit # 01-75009

# DETAIL SUMMARY SHEET

TITLE: Patient Handling at a Major Military Medical Facility

KEYWORDS: patient handling, nursing

PRINCIPAL INVESTIGATOR: LTC Laura R. Brosch AN
ASSOCIATES: LTC Patricia Patrician AN, COL Mary Lopez SP

DEPARTMENT: Nursing
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 26 September 2001

STUDY OBJECTIVES:
The overall goal of this study is to describe the patient handling demands based on patient dependency level, type of transfer, and physical exertion that occur during a 24-hour period on inpatient units at a major military medical facility.

TECHNICAL APPROACH:
Two surveys were developed and consisted of single item measures. These instruments (demographic survey and patient handling coupons) are designed to measure discomfort level, physiological effects, and productivity baselines.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
Approximately 283 nursing personnel were on duty on the inpatient units at Walter Reed Army Medical Center on 7 November 2001. 175 demographic surveys were completed, giving an overall response rate of 62%. 111 people completed at least one coupon, giving an overall response rate of 39.4%. Respondents were 65% female and 35% male. The mean age of the staff population was 35 years (SD=10.7), ranging from 21 to 63 years old. The staff respondents were 46% military, 42% civilian, and 12% contractor. The mean age of the military personnel was 29 years (SD=6.4) and the mean age of all civilians including contractors was 40 years (SD=10.5). 57.7% of nursing staff has experienced neck and shoulder discomfort in the last 12 months. 49% of nurses have experienced upper/lower back discomfort in the last 12 months, and 58% of all upper-lower back discomfort was reported as a result of patient handling and care. 28% of nursing staff felt lower back pain at baseline. The median number of lost days for neck and shoulder injuries was found to be five days, for upper/lower back 5.5 days, for upper extremity 24 days, and lower extremity 4 days. Respondents had been working in nursing for a median of six years (SD=10); the minimum was 0.5 and the maximum was 38 years.

The number of subjects enrolled to the study since last APR at WRAMC is 175, and the total enrolled to date at WRAMC is 175.

CONCLUSIONS:
Our findings yield important findings that can be implemented as an intervention for at least the units we found to be high risk, namely the ICU and surgery units. Focus should be placed on lateral repositioning and bed-to-bed transfer interventions, in addition to ergonomic education and training. Equipment options have greatly advanced and are increasingly biomechanically sound, of durable quality, and easy to use. For example, according to Owen (2000) nurses perceived significantly less physical exertion and as patients were significantly more comfortable when a friction-reducing pad was used for the transfer. Focus should be placed on providing lateral transfer devices such as friction reducing sheets for all patients on these units. Additional equipment should be purchased as is specifically necessary for the unit, including motorized lateral transfer devices, and full sling lifts. In conjunction with purchasing the equipment, the staff should be well trained in the use of the equipment. Additionally, further research should incorporate nurse and supervisor training on equipment, maintenance, education of the problem, and available solution.

Report Date: 27 September 2001 Work Unit # 01-7501

# DETAIL SUMMARY SHEET

TITLE: A Comparison of Three Different Laryngeal Mask Airway Cuff Pressures on the Incidence and Severity of Post-Operative Sore Throat

KEYWORDS: Cuff pressure, LMA, Sore Throat

PRINCIPAL INVESTIGATOR: Saunders, Kenneth CPT AN
ASSOCIATES: McElhone, Patrick CPT AN

DEPARTMENT: Nursing
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 24 October 2000

## STUDY OBJECTIVE

To determine whether there is an increase incidence and/or severity of sore throat associated with increasing LMA cuff pressures.

## TECHNICAL APPROACH

A convenience sample was selected from military health care beneficiaries who met the study inclusion criteria. Inclusion criteria for this study were patients over the age of 18, ASA category I or II. The patient will be undergoing elective surgery requiring a general anesthetic and will maintain spontaneous ventilation throughout the course of the anesthetic. The surgery length should be less than four hours. Any patient that met the above criteria was given an informed consent and asked to participate in this study during their pre-anesthesic assessment.

Exclusion criteria for this study included patient refusal to participate in this study. A patient was excluded if the use of the LMA was contraindicated for reasons described earlier, or if the patient was undergoing a surgical procedure that required endotracheal intubation. Patients were also excluded from this study if they presented on the morning of surgery with a sore throat. If greater then three attempts were made to place the LMA in the patient's airway, the patient was excluded from the study. Finally, if the minimal sealing pressure was determined to be greater than 40 $cmH^2O$, the patient was excluded from the study.

Power analysis was done to determine the sample size for this study. Using an alpha set at 0.05 and a power of 0.80, the sample size was calculated to be 84 subjects, with 28 subjects in each treatment group. Subjects were randomly assigned to one of three treatment groups. The treatment groups differed only by the cuff pressure of the LMA. In one group, the LMA cuff pressure was equal to the minimum pressure needed to maintain ventilation and prevent leakage. The LMA cuff pressures in the other two groups were 45 $cmH^2O$ and 60 $cmH^2O$, respectively. Random assignment of the subjects to each treatment groups was accomplished by the statistical web page Research Randomizer.

Demographic data was collected on each patient. The data collected included the patient's height, weight, age, gender, ASA and Mallampati score. The demographic data was analyzed to compare the different treatment group.

Information about the anesthetic and surgery was also collected on the data collection tool. This information included the presence of a sore throat prior to surgery, size of the LMA used, the number of insertion attempts, the ease of insertion, the cuff pressure of the LMA after insertion into the patient's laryngopharynx, the cuff pressure at which a minimal seal was heard, total time LMA was in place, and the total volume of air withdrawn from the cuff prior to removal of the LMA. The amount of anesthetic agents used during the case was documented. After removing the LMA, it was inspected, and the presence of blood or emesis was recorded on the sample data sheet, with additional information.

Verbal descriptor scale was used to evaluate the severity of the patient's sore throat, the patient was asked to rate the sore throat on a scale from 1-4. The score of 1 means the patient did not have a sore throat. The score of 2 is indicative of a mild sore throat, present only when the patient swallowed. The score of 3 corresponds to a moderate sore throat that was constantly present, however, the patient did not require medication to maintain comfort. Finally, a score of 4 represents severe sore throat that was constantly present, and required the patient to take medication maintain their comfort.

A manometer was used by each researcher to measure the cuff pressure of the LMA. The cuff pressure was measured in $cmH_2O$. The manometer was calibrated as needed based on the manufacturer's reccomendation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There has been no recent literature obtained that had any significant relevance to this research study. There has been no amendments or modifications to the research study since it's last review. No subject had an adverse outcome secondary to this research study.

The number of subjects enrolled to the study since last APR at WRAMC is 5 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is 28, if multi-site study. The remaining subjects were enrolled at Ft. Meade, MD.

CONCLUSIONS

Analysis of descriptive data is being completed at this time. The treatment effects groups were smaller then anticipated, with only either 5 or 6 subjects in each treatment group. A chi-squared test of homogeneity could not be used to analyze nominal level data and a Knuskall-Wallis ANOVA could not be used to analyze ordinal level data, because when these treatment groups were arrayed into cells on a table, 80% of the cells did not have a frequency greater than 5 and cells often had a frequency of zero. This violated an assumption of both statistical tests and prevented the Chi-squared test of homogeneity and the Knuskall-Wallis ANOVA from being used to analyze data. Anecdotally, it does not appear that cuff pressure influences sore throat since none of the subjects in the minimal sealing pressure group complained of sore throat. Also, ten of the eleven subjects that were dropped from the study were male. This may indicate that males may need a larger size LMA, although further research is needed.

Report Date: 24 July 2002 Work Unit # 01-75010

# DETAIL SUMMARY SHEET

TITLE: Increasing Testicular Self-Examination in Active Duty Soldiers: An Intervention Study

KEYWORDS: testicular self-examination, testicular cancer

PRINCIPAL INVESTIGATOR: Brown, Carlton G. CPT AN
ASSOCIATES: Brosch, Laura LTC AN; Patrician, Patricia LTC AN

DEPARTMENT: Nursing STATUS: O
SERVICE: INITIAL APPROVAL DATE: 14 September 2001

## STUDY OBJECTIVE

Assess the knowledge and health beliefs regarding testicular cancer (TC) and testicular self-examination (TSE) in active duty soldiers.
Identify the proportion of active duty soldiers who practice monthly TSE.
Assess the impact of the distribution of printed TC/TSE educational materials on the a) knowledge of and health beliefs regarding TC/TSE, and b) the monthly performance of TSE in active duty soldiers.
Assess the impact of the presentation of TC/TSE peer-taught educational video together with printed material on the a) knowledge of and health beliefs regarding TC/TSE, and b) the monthly performance of TSE in active duty soldiers.
Determine which of two educational interventions based on the Health Belief Model is the most effective in increasing the proportion of active duty soldiers who practice monthly TSE.

## TECHNICAL APPROACH

Approximately seven weeks prior to offering the interventions, subjects in the three groups were mailed a baseline survey of knowledge, health beliefs regarding TC/TSE and their self-reported frequency of TSE. This baseline survey, along with a cover letter, instructions, and a self-addressed stamped envelope was distributed via the US Postal system. Two weeks following the mailing of the questionnaire, all 450 subjects received a post card thanking them for their participation and reminding them to complete the survey if they had not completed it yet. Two weeks later, all the subjects who had not completed the first survey were mailed a second survey, along with a cover letter, instructions, and a self-addressed stamped envelope. The subjects had two final weeks to complete the baseline survey. The deadline for acceptance of surveys was 24 hours before one of the interventions was offered.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 416 and the total enrolled to date at WRAMC is 416.

We received only a 15% response rate (61 surveys returned/413 deliverable). Sixteen subjects responded after the first mailing, eighteen responded after the post cards, and twenty-seven responded after the second surveys. In our original proposal, we needed a sample size in each group of 65 (43%) to detect a statistically significant difference in our primary outcome variables between groups. The current sample size is inadequate to detect group differences. However, our descriptive analysis revealed some important findings. Of the 61 respondents, 70% had never heard of testicular self-examination. Perhaps the most shocking result was that only 15% performed testicular self-exam correctly, which is once a month according to the American Cancer Society. Finally, 70% of the men surveyed did not know the age group hat was at highest risk for testicular cancer. Conversely, the men at highest risk for testicular cancer were the subjects surveyed. These results are equivalent to many other studies that have been done, which show that men are not educated about testicular cancer and TSE, even when they are in the age group at highest risk for this disease. The study team was both perplexed and disappointed with the results. We considered other factors and surrounding events that might

have contributed to the low response rate. When we originally wrote the proposal in February 2001, we could not have predicted the magnitude of the effects reverberating from the September 11 tragedy.

Because of the low response rate, we have requested, through the WRAMC IRB committee, a modification in the study proposal. This request is currently pending approval. Initially, this study was designed as a quasi-experimental non-equivalent delayed intervention comparison group pre-test/post-test design to assess the impact of the two Health Belief Model-base educational interventions tested in this study. The study team has requested permission to modify the study design, and mail post-tests (Men's Self-Health Surveys) to all soldiers who were assigned to the units that received the three interventions. This modification would essentially change the study design to a "post test only design" for all but the 61 soldiers who completed the initial survey. While we realize that a post-test is a less optimal method to use, it can be used to assess the impact of the interventions. We plan to assess for a significant difference in the knowledge and practice of TC and TSE between the groups tested The problem with this design is that there is no baseline to assess a change in knowledge and behavior, and it may lead to a false confidence in the validity of the findings. We want to survey those soldiers who were present for the health education intervention, and are still present on 30 July 2002, when the second survey is to be administered.

CONCLUSIONS

None.

Report Date: 1 March 2002 Work Unit # 7576-99

# DETAIL SUMMARY SHEET

TITLE: E-mail as a Communication Tool in Army Nursing Management

KEYWORDS: email, computer-mediated communication, nursing, management, grounded theory

PRINCIPAL INVESTIGATOR: Brosch, Laura LTC AN
ASSOCIATES: Lasome, Caterina MAJ AN

DEPARTMENT: Nursing
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 09 February 1999

## STUDY OBJECTIVE

The purpose of this grounded theory study was: 1) to determine the impact of computer-mediated communication (CMC) on the management relationship between Head Nurses (HN) and Clinical Staff Nurses (CSN) in a military health care setting, and 2) to determine the consistency between perceptions versus actual messages sent by CMC. The specific aim of this study was to qualitatively describe the experiences of HNs and CSNs who use email technology and to generate a substantive theory that described and explained the use of CMC in military nursing middle management.

## TECHNICAL APPROACH

Data were collected using semi-structured individual interviews and CMC transcripts between HNs and CSNs. Participants completed a demographic data sheet and signed informed consent. Interviews were conducted over a 13-month period with participants working in three military treatment facilities located within the Walter Reed Health Care System (WRAMC, KACC, and DACH). A textual analysis of a two-week sample of CMC between HNs and their respective CSNs was conducted concurrently. Interviews were tape-recorded and transcribed verbatim. Prior to the conclusion of data collection, HN and CSN focus groups were convened to clarify and validate themes that emerged from the data. CMC text was analyzed in its original form. Descriptive statistics were used to describe the sample (age, gender, frequency of email use, etc.). Data were analyzed using the constant comparative method. The QRS NUD*IST™ software program was employed to manage the large volume of text-based data.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Twenty-two active duty Army nurses participated. Access to participants in the three Army medical facilities occurred without complication. Interviews proceeded according to the planned protocol using tape recorders and note taking techniques. No participants refused to complete their interviews nor offered complaints about the interview process. There were no adverse effects during the conduct of this study.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 22. The total number enrolled study-wide is 22, if multi-site study.

## CONCLUSIONS

*Basic Social Problem*

The basic social problem that emerged was the effect of ambiguity in CMC within the HN/CSN dyad. Ambiguity was defined as a quality or state of uncertainty or doubtfulness with regard to CMC. This ambiguity arose for a variety of reasons, in a variety of situations, and was manifested in a variety of forms. One source of ambiguity was a lack of clear rules governing the use of CMC. Other sources included the importance of CMC in light of redundant communications systems that are in use ("why bother with CMC if my HN is going to tell me what I need to know anyway"). Lack of training was another source of ambiguity; people were unsure of how to use CMC properly. An ill-defined culture surrounding CMC use also pervaded many of the participants' responses. Finally, lack of non-verbal cues left questions about

message interpretation and/or comprehension by both parties (HN and CSN). All of these sources of ambiguity were complicated by the fact that there were two disparate CMC systems available to users within the organization (Microsoft Outlook and CHCS). Confusion reigns related to the purpose, use, and intended audience for each system. There were several participants who had the perception that different systems were for different levels of users.

*Basic Social Process*

Regardless of the source of ambiguity, each person employed a basic social process of personal adaptation to overcome ambiguity in CMC. The "Personal Adaptation" process was characterized by 3 mutually exclusive strategies: 1) observing & testing, 2) modeling, or 3) engaging. The decision about which strategy to adopt for dealing with ambiguity a CMC encounter was influenced by a set of interacting circumstances or situations in which the CMC was embedded. These 7 interacting circumstances or situations (called conditions) were: 1) nature of message content, 2) experience, 3) competence, 4) authority/role, 5) access, 6) awareness, and 7) personal attributes and preferences. These findings resulted in a substantive grounded theory of personal adaptation to ambiguity in computer-mediated communication.

Report Date: 6 December 2001 Work Unit # 7577-99

# DETAIL SUMMARY SHEET

TITLE: Development of a Reserve-Specific Stress Inventory

KEYWORDS: Army Reserve, Stress, Psychosocial Factors

PRINCIPAL INVESTIGATOR: Brosch, Laura LTC AN
ASSOCIATES: Jacqueline Agnew, PhD COL AN USAR, Johns Hopkins University

DEPARTMENT: Nursing
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 09 February 1999

## STUDY OBJECTIVE

The overall goal is to develop a tool to be used in research programs and eventually interventions that address the health, and therefore readiness status, of reservists. This reserve-specific occupational stress inventory will be based on a review of the literature and qualitative results from previous research funded by the TriService Nursing Research Program (TSNRP). Common occupational stress models form the framework for elements of the instrument.

## TECHNICAL APPROACH

Volunteer participants are members of the selected reserves, a group whose health status has received very little study. They were randomly selected from unit rosters of Army Reserve medical units subordinate to the 99th RSC in Maryland, Pennsylvania, Virginia, West Virginia and the District of Columbia. Methods included development of potential stress inventory items from previously administered interviews and focus group study results. The development of the proposed instrument included a series of eight cognitive interviews. An initial administration of this preliminary instrument to 100 volunteers yielded a database for item analysis and reduction. A second administration of the revised instrument was planned to obtain a target population of 300 randomly selected individuals to allow further refinement and validation of the stress inventory. Finally, a subgroup of 75, are being asked to repeat the second instrument for assessment of reliability.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date is 0. The total number enrolled study-wide is 511.

The no-cost extension for the study expired 28 February 2001, and the final report was delivered to the TSNRP. All steps of the protocol have been completed: cognitive interviews (n=8), administration and analyses of the preliminary instrument (n=101), administration and preliminary analyses of the revised instrument (n=402), and the repeat administration for analysis of test-retest reliability (n=73). Of the questionnaires received, 98, 387, and 73 (respectively), were usable for analysis. Following the APR of 12 December 2000, an additional fourteen surveys were received. The recruitment total of 402 for the second administration exceeded the initial goal of 300 due to an unexpected increase in the response rate during the second half of data collection. This finding was explained in a memorandum and accompanied the previous APR. One manuscript was submitted and approved at USUHS. Data analysis and manuscript preparation is continuing at this time.

No recent research reports address the topic of this research. The importance of research addressing the readiness status of military reservists and the impact of multiple psychological stressors from both the civilian and military spheres will continue to be an important area of inquiry.

CONCLUSIONS

The operational readiness of the US military depends on high levels of health and mission-oriented training of all members, including those of the reserve components. In the Army Reserves, nurses have a major role in maintaining and restoring the health of service members, and thus have many opportunities to impact on readiness. Protecting the health of the selected reserve population, however, may be complex because of the multiple roles of these service members as they perform their civilian and military jobs as well as meet family obligations. Reservists experience unique combinations of stressors and resources from their multiple occupational settings.

This study built on previous work to develop a reserve-specific stress inventory that is psychometrically sound and can be used in models such as those employed in occupational stress studies. The conceptual framework of such studies commonly incorporates domains such as job demands and degree of control associated with a job, as well as job-related social support and resources. These domains, therefore, were represented by separate subscales in the Reserve-Specific Stress Inventory (RSSI) that was developed. In addition, early data from reservists indicated that various aspects of fatigue were attributed to their reserve work experience. A new scale to measure reserve-specific fatigue was therefore also developed.

The newly developed scales (RSSI and Fatigue) were subjected to a series of qualitative and quantitative methodologies to revise and refine them and to assess their psychometric properties. Volunteer reservists participated in four major steps, building on work that had been done in key informant interviews, focus groups, and literature reviews to develop the initial draft instruments. Eight reservists participated in cognitive interviews, 98 reservists completed the first survey to assess psychometric properties, and 387 completed the more comprehensive final survey. In addition, a subgroup of 73 from the final survey repeated the set of new scales at a three-month interval to assess test-retest reliability.

Analyses of several measures of internal reliability demonstrated impressive performance of all new scales of the RSSI and the Fatigue scale. For example, for each of the final scales, alpha coefficients ranged from .81 to .92. Three of the scales demonstrated differences between groups as evidence of their validity. Officers scored higher on the measure of job demands while women reported lower scores on the measure of job control and higher scores on the fatigue measure. .A final test of predictive validity of the new scales examined their performance in three sets of regression models that looked at fatigue, reserve job satisfaction, and mental health as outcomes. Three of the RSSI scales figured prominently in the final models and performed according to expectations. Both the Demands and Resources scales were significantly associated with all three dependent variables in models that included demographic and other characteristics. The Social Support variable predicted level of mental health. Only the Control variable was not retained in the stepwise model. Finally, test-retest results for all scales at a three-month interval showed reliability coefficients to be at least .71 for all new scales.

These results indicate that unique tools are now available for use in studies of Army Reserve populations. With further information regarding their generalizability, their uses will be better defined. These scales definitely have potential for guiding interventions to decrease stress and increase health and readiness of Army Reservists.

Report Date: 18 June 2002 Work Unit # 7578-99

# DETAIL SUMMARY SHEET

TITLE: Development and Evaluation of the Military Nursing Moral Distress Scale

KEYWORDS: Military Nursing, Moral Distress; Crisis Deployment

PRINCIPAL INVESTIGATOR: LTC Laura Ruse Brosch, AN
ASSOCIATES: COL Ann Hurley, DNSc, (RET), Sara T. Fry, PhD, Barbara Jo Foley, PhD, COL, AN (RET)

DEPARTMENT: Nursing
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 27 July 1999

## STUDY OBJECTIVE

The purpose of this project is to develop and test the Military Moral Distress Scale (MMDS), a tool to measure moral distress in the military nurse. Specific Aims of the project are 1) Identify the phenomenon of moral distress in nurses' stories of patient care; 2) Develop the content of items for constructing the Military Distress Scale (MMDS); 3) Develop a tool to measure military moral distress in U.S. Army Nurses; and 4) Conduct the psychometric evaluation of the military Moral Distress Scale.

## TECHNICAL APPROACH

Phase one of the study included the analysis of interviews and focus group discussions to identify and validate the construct of moral distress in military nurses. Using interview data, researchers wrote the items for the Moral Distress in Military Nurses Scale. Focus group discussions with respondents and experts in moral distress were used to assure that we saturated the universe of the content domain of moral distress and items were congruent with theoretical definitions, clearly stated and described experiences common to nurses. In phase two, researchers further developed the content validity through use of judges who were U.S. Army Nurse Corps Officers with crisis military deployment experience and doctoral prepared nurses with expertise in ethics. The last step was to pilot test the wording by administering the tool in person to 10 Army nurses did no participate in any of the preceding steps. After final revisions we mailed packets including the Military Nursing Moral Distress Scale, a letter providing informed consent information, instructions and a return envelope with postage to be paid by Northeastern University. This mail system avoided the use of a postmark and was another step in preserving the anonymity of respondents. We do not know the number of participants under the aegis of the WRAMC IRB, but obtained a total of 1500 returned scales. Addendum: On February 10, 2000 we requested approval to examine the test-related stability of the scale in a subset that agreed to participate. Approval to incorporate the changes requested was granted on April 20, 20000, by the WRAMC Human Use Committee.

## PRIOR AND CURRENT PROGRESS

Phase I (analysis of interviews and focus group discussions) and phase II (establishing content validity and readability) were completed. A total of 38 subjects participated in phases I and II of the study. Total enrollment was 1538. No adverse events were noted or reported. No subjects withdrew from the study. There were no direct benefits to Nurse Officer subjects in the study. However, several subjects have reported that they valued the study and its goals.

## CONCLUSIONS

We have received 1500 completed responses to the Military Nursing Moral Distress Scale (MNMDS). All questionnaires were returned anonymously; therefore we cannot report the number of subjects from WRAMC or from other sites. Data were entered and analyzed using an SPSS computer program.

Sample: Packets with missing data or all zeros in the MNMDS were deleted. Descriptive analysis of the remaining sample (n=959) indicated that 529 officers had been crisis deployed either inside the US, outside the US, or both. The remaining officers (n=430) had not been crisis deployed. The deployed group was older and

had completed more years of military service that the non-deployed group. The two groups were similar in level of education, years of completed full time, non-military nursing service, and rank.

Evaluation procedures including 1) item analysis, 2) confirmatory principal components analysis (PCA), 3) internal consistency reliability, and 4) construct validity procedures were conducted. Since the model of military nursing moral distress was developed using interviews of military nurses who were crisis deployed, the item analysis, PCA, and internal consistency reliability were conducted on data from the crisis-deployed sample. Construct validity by the contrasted groups approach used deployed and non-deployed groups.

Findings:
Based on item-total correlations of .5 and above, 25 of the original 82 items were retained in the scale. Chronbach's alpha for the 25-item scale was .92. Confirmatory principal components analysis resulted in a three-factor solution, i.e. scale items formed three distinct factors. The three factors: Effects and Consequences of Moral Distress, Initial Moral Distress, and Reactive Moral Distress were consistent with the domains of moral distress identified in the qualitative phase of the study. The three scales formed by these factors all yielded Chronbach's alphas between .80 and .90, thus meeting internal consistency criteria appropriate for a new scale. Construct validity was established using the contrasting groups method. MNMDS scores of the 25 items in the deployed sample (n=529) and the non-deployed sample (n=430) were compared using the independent t-test. The mean MNMDS score for the deployed group (M 26.2, SD 212.2) was significantly higher (t=6.4, p=.000) than the mean MNMDS score (M 117.8, SD 19) of the non-deployed group. This difference was expected since the military moral distress phenomenon was developed based on interviews of military nurses who were crisis-deployed and was related to the circumstances of crisis-deployment. This finding supported the construct validity of the MNMDS.

Implications:
Evidence of the MNMDS's reliability and validity indicates that researches can confidently use the MNMDS. However, further refinement and use in other military nurse populations (i.e. Navy and Air Force) with unique crisis deployment situations is strongly suggested. When military nursing moral distress is demonstrated, measures to prevent or decrease its occurrence such as facilitating discussion of barriers that cause initial distress, devising strategies to overcome barriers, and providing ethical counseling to help nurses understand and manage moral distress should be developed and tested.

Report Date: 04 June 2002 Work Unit # 7579-99

# DETAIL SUMMARY SHEET

TITLE: Nurses Influence on Patient Outcomes in US Army Hospitals

KEYWORDS: Nurses, Patients, Outcomes

PRINCIPAL INVESTIGATOR: Patrician, Patricia LTC AN

DEPARTMENT: Nursing
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 27 July 1999

## STUDY OBJECTIVES

The overall purpose of this study was to apply Donebedian's structure, process, and outcome model to explore nursing organization, nursing practice, and patient outcomes in military hospitals. The principle aim of the research was to describe patient outcomes in active duty personnel, military retirees, military dependents, nursing organizational structures, processes, and hospital characteristics. Patient outcomes included the occurrence of adverse events such as injury-sustaining falls, length of stay, and severity-adjusted mortality. Following discharge from the hospital, outcomes included patient satisfaction with nursing care, satisfaction with how symptoms were managed, and functional health status. Nursing organizational structures included nursing practice model, nursing skill mix, and the education and experience level of registered nurses (RNs). Nursing organizational processes included RN job satisfaction, degree of autonomy in nursing practice, the discretionary judgment accorded nurses in the work environment, the level of RN and physician collaboration, the degree of clinical expertise, and the extent to which an ethical work environment is present.

## TECHNICAL APPROACH

### Setting and Sample

Data for this study were collected at two military medical centers. One had 172 beds and the other had 216 beds. Both hospitals also support large outpatient care services. Data were collected from four patient care units at each facility. These eight units represented four specialty units and four mixed bed units at the two hospitals. The patient population at both hospitals consisted of active duty personnel, military retirees, and family members eligible for military health care. The non-probability patients' sample included active duty military personnel, retired military personnel, and their dependents. Using quota sampling, approximately equal percentages of patients for each of these three categories of beneficiaries and hospital units, specialized or mixed bed, were sought. Each of the chief nursing administrative officers for the two hospitals was interviewed, as were all of the head nurses on the selected units. The registered nurse (RN) staff represented a mix of active duty military, civilian, and agency nurses. A total of 94 registered nurses worked in the four units in the first hospital, and 91 in the four units in the second hospital. The non-probability RN sample included all Army Nurse Corps (ANC) and civilian nurses on the selected units. Data were collected so that ANC nurses could be distinguished from non-ANC nurses.

### Instruments

Data were collected using existing instruments and instruments developed for this study.

Patient Instruments: Instruments used to collect patient data included form to record data about the patient hospitalization and a mailed survey. The survey was mailed directly to the most recently discharged patients. The survey included a patient satisfaction scale, a scale measuring satisfaction with symptom (pain) management, and a scale to assess functional health status that encompassed physical and psychosocial health.

Organizational structure instruments consisted of a Chief Nursing Administrator Interview, an Organizational Structure Survey, a Nurse Unit Head Interview, a Unit Organizational Structure Survey, and a Monthly Workload Management System for Nursing Report (WMSN).

Nurse Instruments: Along with a form to gather demographic and background information about the nurses, three existing instruments were used in this study. The Nursing Work Index-Revised was used to measure autonomy, control over practice, and collaborative relationships. The Manifestations of Early Recognition (MER), a newly developed instrument, was used to measure clinical nursing expertise. The Ethical Environment Questionnaire (EEQ) measured ethical parameters in the work setting.

Data Collection

Collection of the patient data at the two institutions was sequential in time so that it was nearly complete in the first institution when it began in the second institution. In the first institution, lists of the most recently discharged patients were obtained from the selected units, and surveys mailed out to those patients with an informed consent form to sign and return with their survey. Medical record data were obtained concurrently. In the second institution, lists of the most recently discharged patients were obtained, surveys mailed out to those patients, along with an informed consent form to sign and return giving express approval to access their medical records for data collection. Medical record data were collected for patients who deceased during the data collection period. Approximately equal numbers of patients were sought for mixed beds and specialty units and for military status category. Collection of the organizational structure data was accomplished as part of the nurse data collection phase at the two hospitals. Appointments were made with each of the Chief Nurses and head nurses (wardmasters) for both the interviews and specific questionnaires.

Data Analysis

Data were entered into Epi-Info because this software allows for double entry. Data are entered twice to that entry errors are marked at the entry point and corrected when found. The verified data were then imported into the Statistical Package for the Social Sciences (SPSS) for actual data analysis. At this point, data were analyzed using descriptive and correlation statistics.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 284.

## CONCLUSIONS

*Discussion of Patient Findings*

It is important to emphasize that because quota sampling was used, the data presented do not reflect the "average" patient population in military hospitals. Estimates for average percent of hospitalized military beneficiary from each hospital showed that about 19% would be active duty personnel, 25% would be retired military, 54% would be dependent, and 2% would be other (emergency admissions and the like). As was the intent for this study, the quota sampling procedure resulted in about equal categories of these beneficiary groups. With this qualification, these patients were diverse in terms of age, gender, education, and ethnicity. Interpretation of results in terms of number of surgical procedures, category of admitting diagnosis, frequency of ANA adverse event occurrence, length of stay, and Apache II scores requires comparison with data from civilian hospitals and national data, where available, for meaningfulness. As a group, patients were well satisfied with the nursing care they received, and fairly satisfied with pain management. Functional health status scores were midrange for total scores, low for return to role function, but high for mental status. This indicates that recovery was not complete but that mental status was quite good. Mental status influences recovery, so that long-term outcomes would be expected to be good. Regression procedures showed that severity of illness and pain severity contributed to functional health status although not to a great degree. Only satisfaction with pain management and LOS contributed to satisfaction with nursing care. Neither of these variables contributed in a major way to the outcome variables, however. Apache scores, SF36 scores, and satisfaction with pain management all contributed to self-ratings of health. At least one measure of pain was significant in all three equations, a result that supports the recent requirement that standards of pain control be met. The differences found by military category (active duty, retired, dependent) were also expected. Active duty personnel were younger as a

group than dependents and retired personnel. Active duty personnel also returned to function faster than those who were retired, again an expected finding.

*Discussion of Organizational Findings*

The size of these military hospitals was roughly equivalent to the size of civilian hospitals in mid-sized cities. Anecdotal reports indicate that use of agency nurses is as high as 80% for civilian hospitals in one metropolitan area so that these military hospitals have a more stable workforce. The chief nursing administrators in both hospitals had similar philosophies of management. This philosophy encouraged communication through formal and informal routes. Nurses were present on committees and had a voice. Of particular importance was the presence of viable nursing research offices. Staffing patterns reflect those in civilian hospitals where more nurses are placed in specialized units than mixed bed units. Nursing practice models varied, which may indicate that the model used is a response to the needs of particular nurses working in particular units and hospitals.

*Discussion of Nurse Findings*

Some of the limitations identified in this study were that all nurses did not respond to the questionnaire and responses were not evenly distributed across the units selected for the study. Also, the MER is a new instrument that, while reliable for this sample, has not been widely tested. Examining demographic differences revealed the military nurse respondents outnumbered the civilian nurse respondents. Compared to the civilian RNs in these military hospitals, the military RNs had higher educational levels, were more likely to be men, and more apt to be Caucasian. The civilian nurses were older and had more nursing experience than the military nurses. A demographic comparison of all RNs in this study to a national sample of nurses (Communications Staff 2002) highlights distinctions between nurses working in civilian hospitals and nurses working in these military hospitals. Nurses in this study were a) younger by an average of nine years, b) more racially diverse, c) more likely to be men, and d) more likely to be educated at the BSN level. Aiken, Haven, and Sloan (2000) view the level of education of the nursing workforce as a contextual attribute because the ability to recruit and retain well-educated nurses reflects positively on the institution's managerial practices. Scores on autonomy, control over practice, and nurse-physician relationships were all near or above midpoint for all respondents as a group indicating positive work environments in both of the military hospitals studied. Scores on the MER were all well above midpoint, indicating a desirable level of clinical expertise. These findings all reflect favorably on the military hospital work environment at a time when shortages are regularly reported. When scale scores were compared for differences between mixed bed and specialty unit nurse respondents, autonomy was higher for nurses on the mixed bed units. This was an unexpected finding. Studies with civilian hospitals generally show autonomy to be higher on specialty units. This may be an artifact unique to this study or reflect a real difference between military and civilian hospitals. Consistent with the literature, control over practice was higher in the specialty units. Clinical expertise, as measured by the MER, was higher on the specialty units. Perhaps this reflects both higher patient acuity and intense interactions with patients, their families, and other healthcare colleagues. The most notable difference found between the military and civilian nurses working in these military hospitals was autonomy. Autonomy scores were higher for the military nurses, perhaps because of their officer status. The civilian nurses reported more certifications than the military nurses. Obtaining certification from a professional organization is a visible recognition of achievement. Perhaps certification is a way for civilian nurses working in military hospitals to show achievement similar to the way that rank shows achievement for military nurses. Alternately, because the civilian nurses were older, and had more experience, they may have had more time to pursue specialty certification. Nursing expertise as measured by the MER was related to the number of certifications. A study of certified nurses indicates that certification is associated with competency and expertise (Cary 2001) so this association would be expected. This finding also provides evidence for validity of the MER as a measure of nursing expertise. Because reports in the literature on autonomy, control over practice, and nurse-physician collaboration are exclusively based on experiences in civilian hospitals, data from this study were compared with civilian hospital data reported by Aiken and Patrician (2000). Scores on both autonomy and control over practice were slightly lower for the military specialty units than scores reported by Aiken and Patrician for civilian specialty units. Similarly, scores for autonomy on the mixed bed units

in military hospitals were lower than Aiken and Patrician's civilian mixed bed units in magnet hospitals. Scores on control over practice were lower for the military mixed bed units than for Aiken and Patrician's civilian mixed bed units. However, scores on nurse-physician relationships were higher for both mixed bed and specialty units in the military hospitals than those reported by Aiken and Patrician for all mixed bed and specialty unit magnet and non-magnet civilian hospitals. Although not an a priori purpose of this study, this comparison illuminates areas of differences between military and civilian hospitals. The general finding that scores on autonomy and control over practice were lower for nurses in military hospitals than those in Aiken and Patrician's civilian hospitals might be attributable to several factors. Most important among these is that during the time of this study, military deployments for humanitarian missions were higher than at any time since the Vietnam War. It is conceivable that these military staff nurses might have anticipated momentary deployment, a factor certainly not under their control. In addition, military personnel in executive leadership positions are routinely transferred every two to three years. At least some change would be expected with the arrival of each new leader so that feelings of uncertainty and less control over work life might always be present to some degree in military hospitals. Finally, military hospitals are by nature hierarchical with lines of authority more clearly and visible demarcated than in civilian hospitals so that the perception may be one of less autonomy and control over practice. Alternatively, it may be that today's health care settings as well as the military milieu require more teamwork and collaboration, thereby making it more desirable to attenuate individual autonomy and control over practice to attain a more collaborative practice environment. Overall, these study findings are intriguing. The RNs in this study of military hospitals had remarkably similar scores on all study variables whether they were military or civilian nurses, or whether they worked in mixed bed or specialty units. It may be that the military culture is a leveling factor. Most personnel, as well as their patients, share a common military background. This background bears some similarity to a shared cultural orientation. It is also possible that many of the civilian nurses working in these military hospitals were military reservists, former active duty personnel, or spouses of active duty of retired military so that their perspectives were more reflective of the military culture in which they were employed. Although the military RNs scored higher on both the NWI-R and MER than did the civilian RNs, they had remarkably similar scores. The expectation that nurses in military hospitals would have excellent nurse-physician relationships was supported. The investigators tend to attribute this in part to the officer status held by RNs in the military. Officer rank accords nurses relatively equal footing with the physicians with whom they work and promotes a more collaborative working environment. Perhaps the status accorded the military nurses creates an environment according status to the civilian nurses as well. Since gender is often identified as the source of problematic nurse-physician relationships, these excellent nurse=[physician relationships could also be due to the fact that both military hospitals had a relatively high proportion of male nurses, muting power issues related to gender.

*Discussion of Additional Analyses*

The two hospitals and the specialty and mixed bed units were roughly the same for outcomes for patient satisfaction with nursing care and for subscales of the SF36. Patients from the specialty units rated nurses slightly higher in technical proficiency, but the difference was too slight to be clinically important. Patients from hospital 2 were slightly higher for the SF36 subscale of mental health than those in hospital 1. The findings for satisfaction with pain management are different, however. Patients in the specialty units at hospital 1 rated satisfaction with pain management higher than those in the mixed bed units. In hospital 2, there were no substantial differences for satisfaction with pain management between specialty and mixed bed units. The regression equations testing predictors for patient satisfaction with nursing care and the SF36 did not identify any meaningful contributors, and the variance accounted for was small for both. The equation examining variables contributing to patient satisfaction with pain management found that estimated worst pain episode, estimate of pain treatment effectiveness, and the nurses NWI subscale variable of control over practice were significant contributors to the variance in satisfaction.

*Conclusions for Patient Findings*

The patient population seemed younger, had high numbers of male patients, showed a preponderance of Caucasians, and was better educated than what might be expected in metropolitan civilian hospitals of a

similar size. Again, at least some of these data are an artifact of the quota sampling procedure. The demographic picture of the retired patient group reflects a historical cohort difference for gender and race/ethnicity. Tomorrow's retirees will demonstrate more diversity on these variables. Length of stay showed great variability with 12% having hospital stays of longer than eleven days. As managed care begins to take full effect, length of stays would be expected to be shorter. Those in the specialty units were older and sicker as one would expect in any civilian hospital. As a whole, this patient population seemed to have discharge support in place with most able to return home. Those who had lower functional health scores after discharge were more likely to report more use of health care services at that time. Satisfaction with nursing care was high as was satisfaction with the pain treatment patients received.

*Conclusions for Organizational Findings*
Features of the organizations that were particularly advantageous were the presence of multiple routes of communication throughout administrative levels, various ways for nurses to provide input to administration, and the presence of nursing research offices. The mix of civilian and military nurses was complementary in terms of nursing experience, education, and status.

*Conclusions for Nurse Findings*
The work environment of nurses in military hospitals is different in certain respects than the work environment of nurses in civilian hospitals. Research into how autonomy and control over practice are defined in military hospitals, and whether these definitions are consistent with those in civilian hospitals, is one avenue for future research. Other studies advocate using the patient care unit as the level of analysis because of unit culture variations even within the same hospital. Unit cultures in this study were more homogeneous than reported in the literature for civilian units. The nurses in this sample were also quite distinctive in terms of age, gender, race, and education. Nurses are visibly valued in military hospitals. Military rank is displayed on the uniform and accords a degree of status. Both hospitals participating in this study had designated nursing research services with physical space and full-time staff. The military culture seemed to permeate the work lives of both military and civilian nurses working in these military hospitals in similar and positive ways. Nurse-physician relationships were excellent, and would logically be expected to contribute to good patient outcomes. The status of nurses in military hospitals, the high proportion of male nurses, and the high educational level of the military nurses seem to contribute to an environment that promotes job satisfaction and collegial relationships as measured by the NWI-R. Additional research is needed to confirm this, but these might be factors for civilian nursing administrators to consider in influencing the work environment. Current and projected nationwide shortages in professional nurse staff mandate that factors contributing to both recruitment and retention be identified. Isolating these factors will help identify effective interventions. Constructing satisfying work environments is essential on both the institutional and the personal level. Nursing work is largely similar regardless of setting, but nurses' work settings differ. Where nurses work and whom they work with affects their sense of the work environment and whether nurses stay or leave as a result. In commenting on a recent study linking patient outcomes to nurse staffing, the Director for the Agency for Healthcare Research and Quality commented that "Excellent nurses may have difficulty providing excellent care if they are working in conditions that are not conducive to quality care." (Health Resources and Services Administration 2001.) Assessing different work environments, such as those in military hospitals, offers additional insight into ways to construct environments that foster quality care by nurses.

*Conclusions for Additional Analysis*
Few meaningful differences were identified between hospitals and between specialty and mixed bed units for patient or nurse variables when examined as aggregated data. This implies a similarity across hospitals and unit type. Satisfaction with pain management was affected by the degree of pain and pain treatment effectiveness as well as by a nurse variable. Nurses have a role in pain management, and this was important to patient satisfaction in this analysis. Appropriate pain management has received increasing attention over the past few years, and the role that nurses have in seeing that pain control is at least adequate needs continued explication for effects on patient satisfaction.

Report Date: 2 May 2002

Work Unit # 00-8101

# DETAIL SUMMARY SHEET

TITLE: A Prospective Study to Evaluate the Testing of Individual Donor Units from Voluntary Blood Donation for the Presence of HIV-1/HCV RNA

PRINCIPAL INVESTIGATOR: MAJ Francisco J Rentas, MS
ASSOCIATES: Sherri S. Hall, GS-10, MAJ Michael J. Lopatka, MS

DEPARTMENT: Fort Knox, KY
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 20 June 2000

## STUDY OBJECTIVE

The overall study objective is to collect scientific data from individual donor samples with documented serological assay results for anti-HIV and anti-HCV in support of the intended use of the TMA HIV-1/HCV Assay. TMA results will be compared to results from licensed antibody (HIV-1 and HCV) and p24 Ag (HIV) tests. The primary objective is to determine whether the TMA HIV-1/HCV Assay allows earlier detection of HIV-1/HCV infection than serological screening tests. This clinical study is a collaboration between Camp Memorial Blood Center (CMBC) and Gen-Probe Inc., San Diego, CA.

## TECHNICAL APPROACH

Blood donations from volunteer allogeneic donors accepted for routine donation at approved military blood collection centers were included in this study. Blood was screened for anti-HIV, HIV p24 Ag, and anti-HCV using FDA licensed tests. The TMA HIV-1/HCV Assay was used to test plasma samples and results were compared to the screening results. Donors who tested TMA HIV-1/HCV positive were added to the follow-up study. Follow-up for HCV reactive donors is monthly for one year; for HIV reactive donors it is weekly for three months, or when seroconversion occurs. Follow-up also will take place for any seropositive samples resulting in a non-reactive or equivocal final TMA Assay result. This plasma is shipped frozen to Gen-Probe for an alternate NAT test. All NAT data was released to Gen-Probe Inc. for incorporation into demographic studies. Gen-Probe analyzed the data and forwarded their findings to the FDA to support licensing of this test. There has been one Amendment, #02, approved by the WRAMC IRB on 13 November 2001.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 14,923 and the total enrolled to date is 27,735. There have been zero adverse reactions for this study. CMBC has not identified any cases where a donor tests TMA positive, EIA negative. These donors would be placed in the follow-up study to determine seroconversion status. The advantage would be in the earlier detection of an HIV/HCV positive donor. This increases the safety of the military blood supply.

## CONCLUSIONS

Of the fifty TMA HIV-1/HCV Reactive Donors, seventeen were seropositive by Enzyme Immunoassay (EIA) Testing. Sixteen of these donors confirmed positive by supplemental testing. One donor was indeterminate. There were 33 samples that initially tested TMA reactive, but were negative upon repeat TMA testing (false positive). There were 63 cases where the EIA test was reactive with a non-reactive TMA result (27 anti-HCV, 20 anti-HIV, and 1 HIV p24 Ag). Supplemental RIBA 3.0 testing indicated that none confirmed positive, seven were indeterminate, and twenty confirmed negative for HCV. Supplemental Western Blot testing for the 21 HIV cases indicated eight were indeterminate and eleven confirmed negative. Two were quantity insufficient for testing and are pending confirmation. There were zero HIV confirmed positive cases that were TMA negative. For all HCV and HIV indeterminate cases, a frozen sample was sent to a reference lab for alternate NAT testing. All results have returned with no positives for HCV or HIV. All those tested for alternate NAT were negative, indicating quantity for alternate NAT testing and are not interpretable. There were no donors who confirmed positive for HIV or HCV through TMA testing alone.

Report Date: 17 December 2001 Work Unit # 01-83001

# DETAIL SUMMARY SHEET

TITLE: Factors Related to Infant Feeding Choices

KEYWORDS:

PRINCIPAL INVESTIGATOR: MAJ Michael R. Bell, MC
ASSOCIATES:

DEPARTMENT: Fort Belvoir STATUS: C
SERVICE: Occupational and Environmental Medicine INITIAL APPROVAL DATE: 13 February 2001

## STUDY OBJECTIVE

This study will assess the rates of breastfeeding of infants by active duty mothers, identify barriers to breastfeeding, and determine if there is an association between breastfeeding and decreased absenteeism. It will also compare health care costs between mother-infant pairs who are breastfeeding, and mother-infant pairs whom are formula feeding. The information obtained from the study would be very valuable for planning programs to support breastfeeding, if needed, in the military population. Ultimately, these programs may allow active duty mothers and infants to have a better chance of enjoying the health benefits of breastfeeding.

## TECHNICAL APPROACH

Prospective mother-infant pairs will be enrolled in this study in their third trimester of pregnancy. Data will be collected via a series of internet-based questionnaires using *Test Pilot III*© software that is licensed for multiple uses at USUHS. Participants who do not have web access may use computers available in the DHCS Wellness Clinic, the DHCS library, the NNMC library, the DDEAMC library, the DACH library, the MAMC library, or the MGMC library to reach the web site. If this is not practical for the participant, she will be mailed the questionnaires appropriate intervals, and be asked to fill them out and return them in the provided self-addressed, stamped envelopes. After delivery, study participants will be asked to keep a diary. Using their diaries, the participants will be asked to answer follow-up questionnaires that will be administered at 2 weeks, 2 months, 4 months, and 6 months post-partum.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Several recent events made accomplishment of study objectives impossible. Since 11 September 2001, the Principal Investigators at the two largest clinical sites (National Naval Medical Center and Darnall Army Community Hospital) withdrew due to increased tempo of operations and deployments. The PI at Dwight D. Eisenhower Army Medical Center left active duty and a replacement was unavailable. The PI at the Malcolm Grow was re-assigned to Hawaii and a replacement was unavailable. This loss of study sites effectively cripples the study, since a large sample size was needed to test the hypotheses of interest. None of the sites listed above had begun enrollment of subjects. Enrollment at Dewitt Army Community Hospital was discontinued by the PI. Dewitt was the only active site. There were ten mothers, (1 American Indian/Alaskan Native, 2 African Americans, 7 Caucasian), and two infants, (1 African American male, one Caucasian female), enrolled at Dewitt. Of the ten enrolled mothers, only two completed the first follow-up questionnaire (which automatically enrolled their infants), despite periodic reminders as described in the protocol. It was questionable whether any further follow-up questionnaires would be completed. A preliminary analysis of the completed questionnaires was underway, but based on the loss to follow-up, and the small number of subjects enrolled, it was unlikely that any valid conclusions could be drawn from the information.
There were not any adverse events reported among study participants.

## CONCLUSIONS

Principal Investigator will notify the subjects of the closure of the study in writing as soon as he receives approval from the IRB.

Report Date: 16 November 2001

Work Unit # 8500-99

# DETAIL SUMMARY SHEET

TITLE: An Analysis and Comparison of Pharmacy Service Provider Selection Among Military Beneficiaries for Maintenance Medication

KEYWORDS: customer satisfaction, pharmacy services

PRINCIPAL INVESTIGATOR: Spain, John MAJ MS
ASSOCIATES: Julia Gannon; Dr. Dong-Churl Suh

DEPARTMENT: Pharmacy
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 05 January 1998

## STUDY OBJECTIVE

To analyze and compare costs, satisfaction with pharmacy services, beneficiary quality of life, and beneficiary selection criteria associated with three pharmacy benefit options: Military pharmacy, TRICARE retail network pharmacy, and mail order pharmacy. The following identifies specific objectives.

## TECHNICAL APPROACH

A questionnaire will measure differences in quality of life and customer satisfaction between the prescription plan options available. The impact of pharmaceutical care initiatives on provider selection and willingness to accept a co-payment for non-stocked medications at MTF pharmacies will be assessed.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This project has been an experience in working bureaucracy. The bottom line is that two out of the three groups that PI required patient data from have decided not to provide it (legal concerns, etc). The mail order folks are concerned about releasing patient information. The retail folks want to get paid for providing information for this survey. At this point PI feels it is futile to continue since those with access to the information needed will not release it for the reasons listed above. Their willingness to provide information has changed as people in positions of authority have rotated to new positions. Without their support, a determination of customer satisfaction is unattainable.

## CONCLUSIONS

Principal Investigator wishes to close the study in light of an inability to access the necessary patient information to carry it out.

Report Date: 20 May 2001 Work Unit # 00-8501

# DETAIL SUMMARY SHEET

TITLE: Prevalence of Helicobacter pylori Seropositivity in Allergic Rhinitis and Asthma

KEYWORDS: Helicobacter pylori, asthma, allergic rhinitis

PRINCIPAL INVESTIGATOR: COL Francis Morris MC
ASSOCIATE INVESTIGATOR:

DEPARTMENT: Landstuhl Regional Medical Center STATUS: C
SERVICE: Allergy-Immunology INITIAL APPROVAL DATE: 11 January 2000

STUDY OBJECTIVES:
Determine if there is a difference in the prevalence of Helicobacter pylori colonization between the two study groups: asthma patients and allergic rhinitis patients without asthma. A positive result may suggest a causative or protective role for Helicobacter pylori in these two disease processes.

TECHNICAL APPROACH:
Patients were recruited from the usual patient flow through the Allergy/Immunology Clinic at Landstuhl Regional Medical Center. Each research subject had a blood specimen drawn for the measurement of antibodies against Helicobacter pylori.

PRIOR AND CURRENT PROGRESS:
Fourteen patients with pure allergic rhinitis and ten patients with asthma were recruited and serum drawn. An ELISA kit was obtained from Dade-Behring for measuring serum IgG to Helicobacter pylori. Of the fourteen patients with pure allergic rhinitis, two were positive for Helicobacter pylori and twelve were negative. Of the ten patients with asthma, four were positive and six were negative. Since the background rate of seropositivity in the active duty population is 30 to 40 percent (and 20 to 30 percent in the general population), these results are not significantly different from the background population (and my preliminary work showed a very low prevalence in the asthma population and a higher prevalence in the allergic rhinitis population). My data do not support a protective or causative role for Helicobacter pylori in the pathogenesis of asthma. The remaining serum specimens have been disposed of.

CONCLUSIONS:
The rate of Helicobacter pylori seropositivity in the two study groups did not differ significantly from the rate in the background population. These results do not support the hypothesis that Helicobacter pylori protect against asthma.

Report Date: 20 May 2002

Work Unit # 00-8502

# DETAIL SUMMARY SHEET

TITLE: Tele-Psychiatry in the Division: A Study of Diagnostic Reliability and Cost Benefits Using Desktop VTC

KEYWORDS: Tele-Psychiatry, Tele-Mental Health, VTC, Diagnostic Reliability

PRINCIPAL INVESTIGATOR: Schneider, Brett CPT MC

DEPARTMENT: Landstuhl Regional Medical Center
SERVICE: Division Mental Health

STATUS: O
INITIAL APPROVAL DATE: 18 July 2000

## STUDY OBJECTIVE

- Determine the diagnostic agreement of clinical psychiatric examinations using in-person, face-to-face evaluations vs. VTC evaluations at a 384kb connection.
- Explore patient satisfaction with examinations using VTC
- Estimate the cost (direct, lost productivity, and lost time) savings of using VTC vs. traditional face-to-face consultations.

## TECHNICAL APPROACH

Each patient enrollment will involve initial brief and consent. The division mental health staff at the Schweinfurt clinic will recruit patients. Only patients that are being evaluated in the clinic will be recruited. Upon completing initial intake evaluation in the Schweinfurt clinic for both command and self referred patients, if, in the view of the provider seeing the patient, a medication evaluation is warranted for the patient, the provider will at that time inform the patient regarding the study being conducted in the clinic. If they say yes, they will be scheduled for an f/u appointment with another provider in the clinic on the same day that they will perform the SCID examination. That provider will perform the informed consent prior to the patient beginning the study.

Patients who have been identified as warranting a medication evaluation will have an appointment set up for them with one of the mental health technicians at the Schweinfurt clinic who has not been involved with their treatment to date. This appointment will occur on the same day that the provider who is performing the SCIDs is available. Because there are only 4 providers in the clinic and the recruitment of patients will be coming from each of the provider's patient load, we will be unable to have only one person perform all informed consent, as it would disqualify all of his or her patients from the opportunity to enroll in the study. The NCOIC of the clinic will be responsible for scheduling all of the patients identified as potential candidates for the study for both the informed consent meeting and the subsequent SCID evaluation. The patient will then be administered the SCID. The patient will also be asked to fill out an O-Q (outcome questionnaire) at the time of SCID. Neither psychiatrist will know the results of the SCID until after the patients participation in the study has ended. After the initial evaluation, one of the two psychiatrists will be assigned as the primary provider for the patients requiring follow up. The results of the SCID and the O-Q can be made known to them. Patients will then be assessed by Psychiatrist #1 using either face-to-face or VTC as outlined above. Psychiatrist #2, who will be blinded to the results of the previous exams, will then see the patients. Psychiatrist #2 will use the opposite interviewing technique of psychiatrist #1 (VTC or face-to-face). After each assessment, the clinician will document a maximum of two diagnoses and a GAF (global assessment of function) score. The psychiatrist seeing the patient in person will be responsible for the clinical note and chart maintenance and will render the actual clinical diagnosis for the patient's active chart. The GAF is part of the routine psychiatric Axis I-V diagnostic framework. At the end of the interviews, the patient will be given an evaluation sheet to collect demographic information to help evaluate costs and to document patient satisfaction with the VTC experience. The patients will be asked to complete a satisfaction survey using a 10cm visual analog scale following each interview.

Patients will then be released from the clinic unless clinical intervention is warranted. The psychiatrist who saw them in person will follow patients evaluated for medications who actually need medication treatment. The results of the SCID and tele-psychiatry evaluation will be made known to the provider prior to the first follow up appointment in order to help the provider confirm his diagnosis, which could be beneficial to the patient.

The SCID has been shown to have excellent interater agreement for broad diagnostic categories such as Psychotic disorders (kappa, 1.00), mood disorders (kappa, .93), anxiety disorders (kappa, .82) and substance use disorders (kappa, .93). Reliability was as follows for specific diagnoses; schizophrenia (kappa, .94), major depression (kappa, .93), dysthymia (kappa, .88), generalized anxiety disorder (kappa, .95), panic disorder (kappa, .88), alcohol use disorder (kappa, .96), cyclothymia (kappa, .80), PTSD (kappa, .77), bipolar disorder (kappa, .79), adjustment disorder (kappa, .74), and obsessive-compulsive disorder (kappa, .40). 10 Few studies exist comparing diagnostic reliability between the SCID and a routine psychiatric evaluation. One study by Fennig et al (1994) showed agreement as follows for an initial evaluation; major depression (kappa .75), schizophrenia (kappa .86), and bipolar disorder (kappa .89).

The OQtm-45.2 has been shown to have a test-retest reliability correlation coefficient of 0.84. In an outpatient psychiatric clinic population it was found to have validity ranging from 0.71 to 0.84.12.

The GAF scale has been shown to have a validity of –0.73 when compared to other Zung Depression Scale. The original GAF has an interater reliability of .62. A modified version of the GAF has a higher interater reliability of 0.81. The authors of this scale and the study comparing the original GAF to the modified GAF suggested that the modified GAF might be a better scale to use in research protocols. The correlation between the original GAF and the modified GAF was shown to be high (0.80).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR is 3 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 3, if multi-site study. No amendments or modifications since study received approval. No adverse events to report. No patients have withdrawn from the study.

A Medline literature review was performed to ascertain if any new literature pertaining to the subject matter had been published. The following articles were found:

1. Miller PR; Dasher R; Collins R; Griffiths P; Brown F Psychiatry Res 2001 Dec 31;105(3):255-64 .
This study attempts to look at the problem of diagnostic accuracy in psychiatric practice, as does ours, but unlike our study, this one does not make use of any telepsychiatry interviews, using only variations of face-to-face interviews.

2. Jones BN; Johnston D; Reboussin B; McCall WV J Geriatr Psychiatry Neurol 2001 Summer;14(2):66-71.
This study suggested that observational items on the BPRS were less reliable using low-bandwidth equipment than by face-to-face assessment. Our study is different in that we are using higher bandwidth equipment and are using a standard clinical assessment, not the BPRS.

CONCLUSIONS

No findings have been obtained to date.

Report Date: 30 May 2002

Work Unit # 00-8503

# DETAIL SUMMARY SHEET

TITLE: Genetic Investigations of Pseudofolliculitis Barbae, (PFB), in United States Armed Forces

PRINCIPAL INVESTIGATOR: MAJ Daniel J. Schissel, MC
ASSOCIATES:

DEPARTMENT: Landstuhl Regional Medical Center
SERVICE: Dermatology

STATUS: O
INITIAL APPROVAL DATE: 15 August 2000

STUDY OBJECTIVE:
This study will investigate the association of PFB with the cytokeratin K6hf mutation found in the hair follicle.

TECHNICAL APPROACH:

Research blood sample collection from selected male and female individuals will be obtained after written informed consent and processed as outlined below:

a. Isolation of blood DNA
b. PCR amplification of distinct segments of the human K6hf gene.
c. Agarose gel separation of PCR products
d. Extraction of PCR products from agarose gels
e. Automated sequencing of the PCR products
f. Mutation analysis of the keratin sequences
g. Statistical evaluation of the results

Diagnostic confirmatory histological punch biopsies (procedure considered standard of care) will be done on the initial ten PFB patients to ensure clinical diagnosis is consistent with histopathological diagnosis. If 70% or more of the clinical PFB patient do not have histological evidence of PFB, the study will be halted.

Control subjects will be recruited from orthopedic clinic and will have no clinical history or physical evidence of PFB. Control subjects will be asked to have one red-top tube of blood drawn in the hospital lab, which will be sent to the German Cancer Research Center. Control subjects will be part of this study only for the one day their blood is drawn.

Skin biopsies: (1) 4mm punch biopsy will be selected in a standard fashion using the clinic standard operating procedure from the initial ten PFB patients to insure clinical histopathological conformation of the disease process as outlined above in the plan.

Plucked hairs will be selected in the initial ten PFB patients to insure clinical histopathological conformation of the disease process as outlined above in the plan.

Digital clinical photos of representative diseased areas (usually the lower face) of the PFB research subjects will be obtained, as is the standard operating procedure for the dermatology clinic, and is considered a standardized means of tracking improvement. The photos are stored on a computer system (Canfield Clinical Systems) for teaching purposes in the clinic, clinical purposes, and research/publication. Photos will be taken at each follow-up visit. Once the study is complete, the photos will be stored indefinitely. They will be filed by disease process and without any patient identifiers. The digital photos will only be accessible by the PI.

Questionnaire: The patient will complete the questionnaire during the examination by the physician. The physician will answer any questions or clarify any terms during the visit.

Follow up procedures: Only the first ten PFB patients who undergo biopsy will return for follow-up in seven days for suture removal, or as a walk-in, should there be a wound complication. Otherwise, PFB subjects will be seen as per routine clinical follow-up, but will not have any data or samples collected for research purposes beyond the time of initial enrollment.

The protocol is designed as a stratified case-control study with the aim of determining the relative risk of the mutation for the occurrence of cutaneous problems among shaving persons. Within each stratum, one investigates a group of PFB cases and a control group who do not exhibit the skin condition when shaving. The prevalence of the mutation is estimated to be greater than 80% among PFB cases, and to be less than 10% among controls.

All data of the individual being tested/screened will be documented on protocol screening sheets and will be anonymized using indirect identifiers. Birth data is required for age calculation. For each sub-population, cases and controls are described statistically using frequency tables and means with 95% confidence intervals and standard deviations or standard errors where necessary for all demographic and clinical characteristics recorded at protocol entry. Graphic tools will be used to compare the four subgroups and to illustrate the differences between cases and controls.

The analysis of the main endpoint of the study, (the odds ratio), is performed using logistic regression and by calculating 95% confidence intervals according to Breslow & Day (1980, chapter 6.3). Adjustments for confounders and clinical characteristics are achieved by multiple regression and testing of interactions. Statistical analysis will be performed by SAS statistical software using proc frequency.

Data analysis consists of comparison of the presence of the mutation between controls and PFB subjects. Examination will be made with the chi-square test, using the Mantel-Haenszel procedure to test for heterogeneity among the strata.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
Summary of any recent literature, amendments or modifications to the research study since the last review: None.

Number of subjects enrolled since last APR review and the total enrollment to date

| | | | |
|---|---|---|---|
| African-American males, with clinical signs of PFB | 56 | / | 56 |
| African-American males, without clinical signs or family history of PFB | 6 | / | 56 |
| African-American females with clinical signs of PFB | 11 | / | 56 |
| African-American females, without clinical signs or family history of PFB | 3 | / | 56 |
| Non-African-American males with or without clinical signs of PFB | 42 | / | 56 |
| Non-African-American females with or without clinical signs of PFB | 14 | / | 56 |
| Total | 132 | | 336 |

All adverse events (AEs) expected and/or serious for HDB site – none. LRMC – none.
Information on patients withdrawn from the study – none.

CONCLUSIONS:
Study ongoing without difficulty.

Report Date: 2 August 2002

Work Unit # 00-8504

# DETAIL SUMMARY SHEET

TITLE: Racial Differences in Central Corneal Thickness Between Caucasian and African-American Subjects

KEYWORDS:

PRINCIPAL INVESTIGATOR: Hess, Todd LTC MC
ASSOCIATES:

DEPARTMENT: Landstuhl Regional Medical Center
SERVICE: Ophthalmology

STATUS: O
INITIAL APPROVAL DATE: 19 September 2000

## STUDY OBJECTIVE

To determine whether there is a clinically significant difference in central corneal thickness as measured by ultrasound between a group of African-American and a group of Caucasian subjects.

## TECHNICAL APPROACH

Corneal applanative pachymetry is performed on subjects after consent and with topical corneal anesthesia. Three measurements are taken per eye and the lowest is recorded.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Initial findings suggest that there is indeed a statistically significant difference between central corneal thickness in African-American and Caucasian subjects. No additional subjects have been enrolled since the last APR review. No adverse events have occurred. Data is still being analyzed and an attempt is being made to calculate a conversion factor for modifying applanation results in light of central corneal thickness to better estimate true intraocular pressure. No contributory literature has been published since the last APR.

The number of subjects enrolled to the study since last APR at WRAMC is 260 and the total enrolled to date at WRAMC is 260.

## CONCLUSIONS

Initial findings suggest that there is indeed a statistically significant difference between central corneal thickness in African-American and Caucasian subjects. An attempt is being made to calculate a conversion factor for modifying applanation results in light of central corneal thickness to better estimate true intraocular pressure.

Report Date: 22 October 2001 Work Unit # 8502-99

# DETAIL SUMMARY SHEET

TITLE: Highly Toxic Clone of *Actinobacillus actinomycetemcomitans* and Polymorphism in Interleukin I and Tumor Necrosis Factor alpha gene

KEYWORDS:

PRINCIPAL INVESTIGATOR: Etzenbach, John LTC, DC
ASSOCIATES:

DEPARTMENT: Landstuhl Regional Medical Center STATUS: C
SERVICE: Dental INITIAL APPROVAL DATE: 15 December 1997

STUDY OBJECTIVE
To detect risk factors for early onset periodontitis and compare genetic differences between European Caucasian and African-American populations.

TECHNICAL APPROACH
No changes have been made to the original protocol. No further patients have been sampled during the last year. Previous protocol is as follows: Patients receive a comprehensive periodontal examination, to include measurement of probing depths, attachment levels, plaque levels, and bleeding points on probing. Additionally, plaque samples are obtained from the saliva, left and right buccal mucosa, and dorsal surface of the tongue. Finally, a finger stick is done to obtain two drops of blood on a piece of absorbent paper for further research in the lab.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been no modifications to the study since the last review

Other recent publications:


1. Müller HP, Heinecke A, Zöller L, Fuhrmann A, Eger T: Gingivitis in young adults with Actinobacillus actinomycetemcomitans. Clin Oral Invest 2001 (in press)
2. Müller HP, Heinecke A, Fuhrmann A, Zöller L: Intraoral distribution of Actinobacillus actinomycetemcomitans in young adults with minimal periodontal disease. J Periodontal Res 2001; 36: 114-123
3. Müller HP, Heinecke A, Eger T: Site-specific association between supragingival plaque and bleeding upon probing in young adults. Clin Oral Invest 2000; 4: 212-218
4. Macheleidt A, Müller HP, Eger T, Putzker M, Fuhrmann A, Zöller L: Absence of an especially toxic clone among isolates of Actinobacillus actinomycetemcomitans recovered from army recruits. Clin Oral Invest 1999; 4: 161-167


The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 73. There were no adverse events related to the study and no patients were withdrawn from the study.

RESULTS
The overall periodontal conditions showed no significant differences between the 73 African-Americans (A-A) and the 100 German-Caucasian (G-C) soldiers. The number of sites examined was 170±19.6 in the A-A group and 170.9±13.9 in the G-C group. Average probing pocket depth was 2.5±0.2mm (A-A) vs. 2.0±0.3mm (G-C). *A.a.* was isolated in 16 (16%) of 100 Caucasian recruits of the German Armed Forces and 19 (26%) of 73 African-Americans. There were also no significant differences in all clinical parameters between *A.a.*-carriers of both groups to non-*A.a.*-harboring controls. In the Caucasian group 49

clones, and in the African-American group 72 clones were isolated and identified with PCR-methods for *ltx* and 16SrDNA. In one proband a maximum number of 4 genotypes and 2 genotypes in another case were found. In all other cases, only one genotype of *A.a.* was present. Seventeen different genotypes were observed. The three most common genotypes comprised 64 % of isolates in the G-C group. Especially virulent strains with 530bp –Deletion in the promoter region of the leukotoxin gene of *A.a.*, were found in two African-American soldiers with gingivitis.

A positive IL-1 genotype existed if a minimum of one copy of allele 2 in IL-1α (+4845) and IL-1β (+3954) gene was found. It was found in 26 (26%) of 100 German-Caucasian soldiers and 14 (19%) of 73 African-American soldiers. One copy of allele 2 in IL-1α (+4845) and IL-1β (-511) gene was found in 32% of German-Caucasians and African-Americans. One copy of allele 2 in IL-1α (+4845) as well as IL-1β (-511) and IL-1β (+3954) gene was found in 19% of the German-Caucasians and 16% of the African-American soldiers. One copy of allele 2 in IL-1α (+4845), IL-1β (-511) or IL-1β (+3954) gene was found in 32% of the German-Caucasian and 34 % of the African-American soldiers. One copy of IL-1β (+3954) was found in all African-American and 97% of the German-Caucasian soldiers. In soldiers who were homozygotic for allele 2 in IL-1α (+4845) and IL 1β (+3954), the potential periodontal pathogen *Actinobacillus actinomycetemcomitans (A.a.)* was never found in our study. However, 30% of the German-Caucasian and 38% of the African-American soldiers who were homozygote positive for allele 2 IL1β (-511) harbored *A.a.* Furthermore in the German-Caucasian group, an increased frequency of allele 2 and 4 could be observed in IL 1 Rn –locus. In the African-American group mainly allele 1 (93.2%) was detected.

CONCLUSIONS

*Actinobacillus actinomycetemcomitans* (*A.a.*) is part of the normal oral flora in African-American and German-Caucasian soldiers.

The results indicate that oral infections with highly toxic strains of A.a. were found only in African-American probands. A large clonal diversity of A.a. from periodontically healthy or gingivitis subjects exists. IL-1 haplotype may be of limited value for the prognosis of the occurrence of periodontal disease in African-American and German-Caucasian soldiers currently without periodontal disease.

Periodontal resistance is probably determined by the IL-1ra Allele 1 haplotype in African-Americans and German-Caucasians. Further investigations should look on other A.a. chemotaxis and phagocytosis inhibiting functions as well as genetic risk factors for A.a.-carriers.

Report Date: 24 January 2002 Work Unit # 01-86001

# DETAIL SUMMARY SHEET

TITLE: Efficacy of Stretching and Mobilization with Neutral Wrist Splinting Versus Neutral Wrist Splinting Alone in Patients with Carpal Tunnel Syndrome: A Randomized Trial

KEYWORDS: Carpal Tunnel Syndrome, Nerve Conduction Studies, Randomized Trial

PRINCIPAL INVESTIGATOR: CPT Matthew K. Walsworth, SP
ASSOCIATES: CPT Guy Terry, SP

DEPARTMENT: Aberdeen Proving Grounds
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 16 January 2001

STUDY OBJECTIVE:
To determine the efficacy of neutral wrist bracing and flexor tendon mobilization vs. wrist bracing alone in the treatment of carpal tunnel syndrome.

TECHNICAL APPROACH
There have been no changes to the methodology.
Experimental design and methods:
Subjects presenting to the physical therapy clinics at Kirk U.S. Army Health Clinic and Kimbrough Ambulatory Care Clinic will be invited to participate in the study; after agreeing to participate, a medical history will be obtained. The history will ensure that the patient's symptoms are consistent with carpal tunnel syndrome and will rule-out the known presence of any of the exclusion criteria mentioned previously. If there is any question as to the presence of any of such exclusionary condition, the patient will be referred back to their primary care manager for appropriate examination and laboratory testing. Information will also be collected to determine the nature, duration, severity, and irritability of the patient's symptoms. Physical examination will be performed to determine presence of signs and symptoms consistent with carpal tunnel syndrome and to rule out other nerve injury in the cervical spine or upper limb. Electrophysiologic examination will also be performed using standardized protocols in order to determine presence of median sensory and/or motor fiber compromise at/about the carpal tunnel region. See inclusion / exclusion criteria for more detailed descriptions of clinical and electrophysiologic criteria.

Those persons who meet the inclusion criteria and are willing to participate in the study will then be assigned randomly to one of the two groups ("splinting only" or "splinting and mobilization"). To randomize subjects, a computerized random number generator will be used. Odd numbers will place the subject in the exercise group and even numbers will place the subject in the splinting only group (this is considered "standard of care" for carpal tunnel syndrome). Subjects with bilateral CTS will be stratified separately and then randomized. They will then be managed in the same way with both of their wrists being assigned to the same group. Treatment will be the same regardless of limb dominance. Typically, splinting as an initial treatment for carpal tunnel syndrome could be considered the standard of care. Mobilization and splinting is more experimental, but does have some research and theoretical evidence to support use as a treatment.

Treatment for all subjects:
All patients will be given a prefabricated neutral wrist splint. Both groups will be encouraged to wear the splints as much as tolerable throughout the day and night. Subjects in each group will keep a log of the number of estimated hours per day that they wore their splint and subjects in the exercise group will keep a log of their exercise performance as well.

Treatment for the exercise group:

Exercises will be instructed by one of the researchers in the study and will be modified as needed based on the patient's response to the exercises and the physical therapist's judgement. The exercise group will be instructed in three exercises to mobilize the median nerve and flexor tendons as follows:

1. Thumb IP, MCP, CMC joint extension/ abduction stretch with small range, gentle oscillations with the wrist in extension.
2. Finger DIP, PIP, and MCP joint extension stretch with small range, gentle oscillations with the wrist and elbow in extension.
3. Median neural mobilization techniques with the fingers/ wrist/ elbow in extension, shoulder in depression/extension, and providing gentle cervical sidebending oscillations in the opposite direction.

They will perform each exercise for 30 seconds and perform two sets of each exercise during five daily exercise bouts. Subjects will be encouraged to perform the exercise with bouts spread throughout the day. Ideally, they might perform one bout in the morning upon awakening, a second bout mid-morning, the third bout at lunch, a fourth bout in the afternoon, and the final bout before going to bed in the evening. Again, a log will be used to monitor their compliance.

Follow-up and testing of all subjects:
The splinting and exercise compliance logs will be kept for 6 weeks. Patients will return to the clinic weekly during this time to review their compliance, address any questions or concerns and to check and modify their exercises as indicated for the exercise group. In the event that patients are unable to attend weekly follow-ups, three of the six follow-ups may be performed by telephone. Each group will be encouraged to continue their treatment independently after the first six weeks. The CTS symptom and function questionnaires will be administered at 6 weeks, 3 months, and 6 months after beginning the study. Nerve conduction studies (NCS) needed for the CSI and distal median motor NCS will be performed at these same intervals. While initial electrophysiologic examination is part of routine clinical practice, these follow up nerve conductions studies are experimental and will be used to assess for change in neurophysiologic function. However, EMG or NCS other than those needed to assess changes in the CSI or median motor NCS will not be performed unless there is a reason that it is clinically indicated (new or worse symptoms). Any significant increase in the symptoms will warrant discussion with the participant, appropriate medical referral, and potentially removing the subject from the study if there is electrophysiological evidence supporting further slowing of nerve conduction. Again, subjects will be allowed to remove themselves from the study at any time. Participants will be allowed to discontinue their involvement with the study at any time. Termination of the study will be at six months from entry.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Only two participants were enrolled in the study. Both had to withdraw due to a PCS relocations. There are no subjects enrolled currently. No literature updates.

CONCLUSIONS
None at this time.

Report Date: 02 April 2002 Work Unit # 01-87001

# DETAIL SUMMARY SHEET

TITLE: The Comparison of Digital Camera Running Gait Analysis to the Telemedicine Consult System: A Pilot Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Mark Jacobs, MA DoD, Shari Tomasetti
ASSOCIATES:

DEPARTMENT: Telemedicine STATUS: O
SERVICE: INITIAL APPROVAL DATE: 29 May 2001

STUDY OBJECTIVE:
Research Question:
In a group of study participants presenting for running gait analysis at the Pentagon Running Shoe Clinic, is there an agreement of the diagnostic finding for a participant recorded by a rater at two time points?

Expectation:
We expect at least 80% agreement in diagnostic categories reviewed by a rater.

TECHNICAL APPROACH
The first assessment, given by an Exercise Physiologist (rater), will be a Digital Video Clip (DVC) of the subject's running gait from only a lower extremity posterior view. This view protects against the identification of the subject and bias of the rater recall. Six barefoot running gait clips will be selected and stored on a Zip drive.

After the first diagnosis a running shoe will be recommended according to the diagnosis. Individuals also will be put into different weight categories. Midsole material and durability are the discriminatory features that separate shoe models for those under and over the weight guidelines Two weeks later the DVCs will be downloaded through the telemedicine consult system and analyzed by the same rater for a second assessment. The rater will be blinded as to which subject's DVC is being assessed, and also as to any previous diagnosis of the subject he/she is evaluating. All data will be recorded on separate data sheets and later combined into one. Second diagnosis on subjects will be compared to the initial analysis.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There has been minimal study findings obtained thus far, and no amendment or modifications to the research study since the last review. These findings are noted as data collection. Ten subjects have been enrolled to date. There have been no adverse events expected and/or serious adverse events for WRAMC site; serious AEs for other sites if multi-center study, and information on patients withdrawn from the study.

The number of subjects enrolled to the study since last APR at WRAMC is 10 and the total enrolled to date at WRAMC is 10.
There have been no publications from, nor any publications recently printed, that would affect this study.

CONCLUSIONS
No conclusions have been made.

Report Date: 01 October 2001

Work Unit # 8700

# DETAIL SUMMARY SHEET

TITLE: Evaluation of Telesurgical/Robotic Presence

KEYWORDS: Telesurgical mentoring, urology, telestration, robotics

PRINCIPAL INVESTIGATOR: Schenkman, Noah LTC MC
ASSOCIATES:

DEPARTMENT: Telemedicine
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 25 November 1997

## STUDY OBJECTIVE

The purpose of this study is to establish a telesurgical presence program between Walter Reed Army Medical Center, John Hopkins University and Ft Detrick, MD and evaluate the feasibility of telementoring less experienced surgeons, fellows, residents and medical students during open surgical cases and endoscopic surgery. Additionally, the use of a remotely controlled robotic arm to hold a laparoscope, as the laparoscopist's assistant, will be evaluated at these longer distances to determine the effect if any on remote telementoring. This system will in turn serve as the test bed for future telesurgical applications as they are: developed and as a remote site for future deployed telesurgical systems.

## TECHNICAL APPROACH

This proposal will evaluate the feasibility of telementoring both laparoscopic and open surgical procedures using telecommunications links between John Hopkins University, Ft. Detrick and Walter Reed Army Medical Center. We will use a T-1 PRI telecommunications link for Video Tele-Conferencing (VTC) and remote control of the AF-SOP robotic arm that holds the laparoscope. We will also employ a white-boarding function to telestrate the procedures. Our goal is to establish that this sort of remote mentoring of surgical procedures is feasible and can be potentially applied to the far-forward military medical facilities in times of combat and also for medical education procedures.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

We have not accrued any patients on this study due to delays in installation of the MEDNET communications network to the Walter Reed Operating Rooms. The Operating room renovation project has been significantly delayed. Once the correct high-bandwidth communications network is installed, we will be able to make progress.

## CONCLUSIONS

Project on hold until completion of OR renovations.

Report Date: 10 June 2002 Work Unit # 8701-98

# DETAIL SUMMARY SHEET

TITLE: Clinical Evaluation of a High-Resolution Digitized Stereo Video Slit Lamp for Use in Teleophthalmology

KEYWORDS: telemedicine, ophthalmology, diagnosis, digital images, slit lamp biomicroscopy, anterior segment

PRINCIPAL INVESTIGATOR: Bower, Kraig LTC MC
ASSOCIATES: CPT Erik Niemi, MC; COL (Ret) Kenyon Kramer; LTC Edward Trudo, MC

DEPARTMENT: Telemedicine
SERVICE: Ophthalmology

STATUS: O
INITIAL APPROVAL DATE: 7 July 1998

## STUDY OBJECTIVE

The purpose of this study is to compare the clinical diagnostic performance of the high resolution digitized stereo video slit lamp with in-person slit lamp examination in patients presenting to a general ophthalmology clinic.

## TECHNICAL APPROACH

This is a prospective observational study. Investigators at Walter Reed Army Medical Center Ophthalmology Service and the John Moran Eye Center at the University of Utah will select consecutive patients from their clinics according to the previously published inclusion/exclusion criteria. A total of 50 patients will be recruited from each site. Each patient will be identified with a distinct ID number. The investigator will perform a standard clinical slit lamp exam on both eyes and note all findings in the patient chart and on the study exam report form. The patient will then be examined with the video digital slit lamp according to a standard protocol. The patients will resume the intended course of treatment for the remainder of their appointment. The video, digitized exams will be evaluated by masked reviewers at both institutions at a time subsequent to the actual patient exams. Using the live exams as the gold standard, the proportion of correct diagnosis made using the video exam will be described using proportions with 95% confidence intervals (CI).

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No further patients have been enrolled in the study. A modification was requested to look at a specific subset of patient with corneal transplants to see if remote post-op management is reliable and safe. So far, no patients have been enrolled under that modification.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 29. The total number enrolled study-wide is 71, if multi-site study.

## CONCLUSIONS

None at this time.

Report Date: 17 February 2002

Work Unit # 8836

# DETAIL SUMMARY SHEET

TITLE: A Phase I Dose Escalation Study of Polyclonal CD4 T Cell EX Vivo Expansion for Immune System Restoration of HIV Infection

KEYWORDS: immune reconstitution, HIV, CD4 infusions

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL, MC
ASSOCIATES: Thompson, J MAJ MC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: C
INITIAL APPROVAL DATE: 30 September 1997

## STUDY OBJECTIVE

Determine the safety and feasibility of CD4 cell ex vivo expansion and reinfusion in HIV infected patients. Study endpoints are plasma HIV RNA measures and circulating CD4 lymphocyte mass. As a secondary objective, the safety of escalating doses of CD4 lymphocyte infusions will be evaluated.

## TECHNICAL APPROACH

Antilogous CD4 lymphocytes are acquired by leukapheresis from HIV infected persons and expanded ex vivo using anti CD3/anti CD28 antibodies in the presence of antiretroviral therapy. Reinfusion of 10 to 10 range CD4 cells is performed. Six addenda have been approved.

## PRIOR AND CURRENT PROGRESS

Four patients were enrolled at WRAMC, six at NNMC. Two patients at NNMC were terminated; one when he was found the have at T cell tropic (CXCR4 dependent) HIV strain, and another when he was found to have elevated liver associated enzymes with a new diagnosis of Hepatitis C. Both did not receive any infusions. One WRAMC patient was terminated early, because the HMJF/NMRI laboratory closed and that the growup of lymphocytes was no longer available. The patient was informed of this development and had received a total of 6 infusions prior to that time. One WRAMC patient did not continue through the dose escalation phase at the advice of her physician. She had normalized her CD4 count and had a CD4/CD8 ratio greater than one, also developed anemia, weight loss and had rigors with the last infusion. She continued to be followed until the study closed. Grade 1 or 2 toxicities were seen in 32 of 50 infusions, mainly fever, chills, sweats, fatigue and skin changes. There was one episode of grade 2 orthostatic hypotension. Reactions tended to occur at the higher doses of cells and were prevented or abrogated with acetaminophen. No SAEs were reported on the WRAMC enrolled. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 10, if multi-site study. We request that this study be terminated at this time because it is completed. The study was closed except for data and laboratory sample analysis with the APR of July 2001.

## CONCLUSIONS

Serial infusions of antilogous ex vivo co-stimulated CD4+T cells in H IV infected patients are safe and feasible with minimal toxicity, which can be abrogated with acetaminophen. CD4 levels and CD4/CD8 ratios can be improved without a rise in HIV viral load. Sustained increases in the fraction of cytokine secreting T cells and decreases in CD4+CCR5+ cells noted suggest enhanced function and possible resistance to HIV infection. Increased CD4_Ki-67+ cells increased whereas cells with TRECs decreased suggesting that expansion of the peripheral T cell pool mediated the increase in CD4 counts noted.

Report Date: 2 August 2002 Work Unit # 8837

# DETAIL SUMMARY SHEET

TITLE: Molecular Epidemiology of HIV-1 in Military Populations.

KEYWORDS: HIV, military, seroconvertors

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 30 September 1997

## STUDY OBJECTIVE

To describe the subtype and viral resistance patterns of HIV seroconverting military personnel correlating this with information regarding deployment, risk behaviors, potential contributing factors, in order to target military populations for intensive prevention training programs.

## TECHNICAL APPROACH

All military seroconvertors (in past 4 years) are eligible. Serum is obtained for genetic HIV subtype testing. Genotypic HIV viral resistance determinations are performed on all samples with detectable viral loads. The participant fills out a confidential survey instrument. Addendum to assess phenotypic resistance in a subpopulation. Addendum to allow banking of samples by patient identification number in the HIV repository. Addendum submitted currently to assess Kaposi Sarcoma Virus (KSV) and Herpes Simplex Virus Type II antibodies correlated with reported risk exposures. Subject enrollment will stop 31 July 2001 at all study sites.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 86. The total number enrolled study-wide is 603. There are no adverse events reported and no withdrawals from the protocol at WRAMC. Information at other sites is not known. No direct benefit accrued to participants. A protocol deviation was submitted November 2001 due to funding withdrawal and end of support of database entry at NHRC. Two subjects were not given the follow-up six-month repeat questionnaire.

## CONCLUSIONS

About 4% of WRAMC HIV seroconvertors were non B HIV subtype and 14% that were HIV drug naïve had genotypic signs of resistance to at least one antiretroviral. Acquisition of non B HIV subtypes is associated with overseas deployment. HIV seroconversion was associated with high use of alcohol, poor condom compliance, and frequent casual sex partner exposure in the seroconvertor window. Numerous areas for further intervention for prevention of HIV in active duty military have been identified.

Report Date: 13 March 2002

Work Unit # 8838-98

# DETAIL SUMMARY SHEET

TITLE: A Tri-service Study of Human Immunodeficiency Virus Disease in United States Military Beneficiaries

KEYWORDS:

PRINCIPAL INVESTIGATOR: Hawkes, Clifton LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 31 March 1995

## STUDY OBJECTIVE

To systematically document the natural disease progression of HIV infection and the effect of therapeutic intervention on the course of the disease. To study factors related to HIV transmission in sexual partners not yet infected with HIV. To develop and evaluate new and/or improved laboratory methods for diagnosing and staging HIV disease.

## TECHNICAL APPROACH

Medical information related to HIV disease is routinely being collected as part of the standard of care for HIV patients. This information will be collected and organized into a computerized database, which will facilitate scientific review and assist in the generation of hypotheses, which can then be tested utilizing various statistical analyses. Blood that is collected will be used to identify new methods of detecting replicating HIV virus, as well as patterns and mechanisms of resistance. Safeguards to patient confidentiality are met. This database forms the core around which other specific protocols can be built.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 17 and the total enrolled to date at WRAMC is 437. The total number enrolled study-wide is 1600, if multi-site study. There have been three (3) serious adverse events involving the deaths of study participants. Those in which an immediate cause of death could be identified included one with Cytomegalovirus/Dementia, one accidental death, and the third with primary cause of death unknown. Only the CMV related death was felt to be part of the natural progression of this disease. No study participants withdrew informed consent. One (1) patient transferred to another study site.

## CONCLUSIONS

No final conclusions reached during this reporting period; data collection continues.

Report Date: 4 November 2001 Work Unit # 8839-99

# DETAIL SUMMARY SHEET

TITLE: A Phase I/II Study of the Safety, Survival, and Trafficking of Autologous CD4-zeta Gene-Modified T Cells with and without Exogenous IL-2 in HIV Infected Patients

KEYWORDS: HIV, gene therapy

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Wortmann, Glenn LTC MC; Bernstein, Wendy COL MC; Gibbs, Barnett MAJ MC, Mulhall, Brian MAJ MC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 19 January 1999
Six-Month Review

## STUDY OBJECTIVE

To assess the safety, tolerability, and feasibility of administering an infusion of autologous CD4 zeta gene modified CD4+ T cells in an outpatient setting of highly active antiretroviral therapy (HAART) with and without IL-2 at a maximum non-toxic daily dose of 1.2 M IU/$m^2$ subcutaneously daily for 56 days. Assess the effect of daily subcutaneous IL2 on the persistence and trafficking of CD4 zeta gene-modified T cells in the circulation and lymphoid (rectal) tissue. Determine the effect of CD4 zeta infusions with and without IL-2 on viral load (plasma HIV-1 RNA, tissue HIV-1 RNA, and frequency of latent replication-competent HIV-1 in PMBC).

## TECHNICAL APPROACH

This 3-arm, randomized study of gene modified costimulated T cells (about $10^{10}$ infused) with or without daily subcutaneous IL-2 in HIV patients with undetectable viral load has an active interventional duration of 20 weeks. Replication competent retrovirus will be intermittently checked for as long as the individual aggress to participate. Rectal biopsy and peripheral blood mononuclear cells will be assessed for viral load and latent replication, as well as CD4 zeta. Assays to include cytotoxic lymphocytes, neutralizing antibody and lymphocyte proliferation assays are planned to assess the helper effect of CD4 zeta T cell infusion.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study started enrolling in May 2001 and the interventions to date are well tolerated. There has been one serious adverse event occurring in the screening period (before any intervention received) of grade 4 toxicity of liver function tests. This is being evaluated by the subject's primary care provider, and he is "on hold" for the study until this is resolved. There have been no withdrawals. We have recently learned of sponsor manufacturing changes that deliver a product with CD4 and CD8 cells of significant proportions. We are modifying the protocol to reflect this, and suspending enrollment and interventions until this is approved by the HUC.

The number of subjects enrolled to the study since last APR at WRAMC is 6 and the total enrolled to date at WRAMC is 6. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

To date, the IL-2 and CD4 zeta gene modified T cell infusions seem well tolerated by the four subjects who have entered the interventional phase of the protocol. Great patient interest has been shown, and we anticipate good enrollment once the study is re-opened.

Report Date: 11 May 2002

Work Unit # 8839-99

# DETAIL SUMMARY SHEET

TITLE: A Phase I/II Study of the Safety, Survival, and Trafficking of Autologous CD4-zeta Gene-Modified T Cells with and without Exogenous IL-2 in HIV Infected Patients

KEYWORDS: HIV, gene therapy

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Wortmann, Glenn LTC MC; Bernstein, Wendy COL MC; Cash, Brooks LT MC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 19 January 1999
Six-Month Review

## STUDY OBJECTIVE

To assess the safety, tolerability, and feasibility of administering an infusion of autologous CD4 zeta gene modified CD4+ T cells in an outpatient setting of highly active antiretroviral therapy (HAART) with and without IL-2 at a maximum non-toxic daily dose of 1.2 M IU/$m^2$ subcutaneously daily for 56 days. Assess the effect of daily subcutaneous IL2 on the persistence and trafficking of CD4 zeta gene-modified T cells in the circulation and lymphoid (rectal) tissue. Determine the effect of CD4 zeta infusion with and without IL-2 on viral load (plasma HIV-1 RNA, tissue HIV-1 RNA, and frequency of latent replication competent HIV-1 in PMBCs).

## TECHNICAL APPROACH

This 3-arm, randomized study of gene modified costimulated T cells (about $10^{10}$ infused) with or without daily subcutaneous IL-2 in HIV patients with undetectable viral load has an active interventional duration of 20 weeks. Replication competent retrovirus will be intermittently checked for as long as the individual aggress to participate. Rectal biopsy and peripheral blood mononuclear cells will be assessed for viral load and latent replication, as well as CD4 zeta. Assays to include cytotoxic lymphocytes, neutralizing antibody and lymphocyte proliferation assays are planned to assess the helper effect of CD4 zeta T cell infusion.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study started enrolling in May 2001 and the interventions to date are well tolerated. There has been one serious adverse event occurring in the screening period (before any intervention received) of grade 4 toxicity of liver function tests. This was attributed to acute hepatitis C. This subject was terminated as per protocol. Since last annual progress report we have submitted two addenda: one updating the protocol based on manufacturing changes and one adding a questionnaire to assess the long term knowledge regarding trial in subjects who have completed the intervention.

The number of subjects enrolled to the study since last APR at WRAMC is 4 and the total enrolled to date at WRAMC is 10. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

To date, the IL-2 and CD4 zeta gene modified T cell infusions seem well tolerated by the five subjects who have entered the interventional phase of the protocol. Good patient interest has been shown, and despite a hiatus this winter due to manufacturing changes, we anticipate good continued enrollment.

Report Date: 24 January 2002 Work Unit # 8900-99

# DETAIL SUMMARY SHEET

TITLE: Antibiotic Treatment of Gulf War Veterans' Illnesses

KEYWORDS: Gulf War Veterans' Illnesses, antibiotic, doxycycline, Mycoplasma, chronic fatigue, neurocognitive dysfunction, joint pain

PRINCIPAL INVESTIGATOR: Engel, Charles LTC MC
ASSOCIATES: Chung, Raymond COL MC

DEPARTMENT: Deployment Health Clinical Center
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 23 March 1999

## STUDY OBJECTIVE

The primary objective is to determine whether a 12-month course of doxycycline treatment in deployed Gulf War veterans presenting with Gulf War Veterans Illnesses and testing as mycoplasma positive improved patients' functional status.

The secondary objectives are to determine whether doxycycline treatment reduces symptoms of Gulf War Veterans Illnesses, including pain, fatigue and neurocognitive concerns, whether doxycycline treatment converts mycoplasma (+) patients to mycoplasma (-) status. If so, it will be determined whether these subjects revert to mycoplasma (+) status when doxycycline treatment terminates. Also, the relationship of changes in mycoplasma status will be associated with changes in functioning and symptoms. Finally, we will determine if the benefits of 12 months doxycycline treatment persist after termination of treatment.

## TECHNICAL APPROACH

The study employs a randomized, double blind design that compares two groups of patients. All veterans who were on active duty, or in the National Guard, or the Reserves between August 1990 and August 1991 and were deployed to Gulf region during that time are considered for participation. To be eligible, a veteran must have at least two of the following four symptoms that began after August 1990, have lasted for more than six months and are occurring up to the present:

a) Fatigue that limits usual activities (work, recreation, or social)
b) Musculoskeletal pain involving two or more regions of the body
c) Neurocognitive dysfunction (self-reported difficulties in memory, concentration or attention)
d) Must test as mycoplasma positive on PCR testing by central laboratory.

Patients meeting all enrollment criteria and who give informed consent to participate in the study are randomized to one of the following two groups. In the first group, the patients will be treated with doxycycline for 12 months and the second group will be treated with placebo for 12 months. Patients who are assigned doxycycline receive 200mg/day. They are instructed to take their pill the same time each day, preferably in the morning. Patients assigned to the placebo group receive identical appearing medication preparations. Because doxycycline can cause photosensitivity to sunlight, all patients are provided with a potent sun-block preparation. All patients receive the study drugs for one year. Patients are followed for an additional six months after cessation of study drugs to determine relapse rates. Major patient assessments are completed at baseline and at 3,6,9,12 and 18 months. Major assessment consists of the SF-36V, the McGill Pain Questionnaires, the Multidimensional Fatigue Inventory, the Cognitive Failures Questionnaire and the Gulf War Illness Questionnaire. Monthly follow-up visits are done to dispense medication, check compliance, and obtain data on hospitalizations and clinic visits. The use of PCR for detection and identification of *Mycoplasma* species is done at 0, 6, 12 and 18 months.

Report Date: 28 January 2002

Work Unit # 8901-99

# DETAIL SUMMARY SHEET

TITLE: A Randomized, Multicenter, Controlled Trial of Multi-Modal Therapy in Veterans with Gulf War Illnesses

KEYWORDS: aerobic exercise, Gulf War Veterans Illness, cognitive behavioral therapy, fatigue, memory loss, joint pain

PRINCIPAL INVESTIGATOR: Engel, Charles LTC MC
ASSOCIATES:

DEPARTMENT: Deployment Health Clinical Center
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 23 March 1999

## STUDY OBJECTIVE

### Primary Hypothesis

The primary hypothesis of this study is that both aerobic exercise and cognitive behavioral therapy will significantly improve physical function (as measured by the Physical Component Scale of the SF-36V) in veterans with Gulf War Illness (GWI), and the combination of cognitive behavioral therapy and aerobic exercise will be more beneficial than either therapy alone.

Central to this hypothesis is the belief that GWI is an unexplained illness within the same spectrum as fibromyalgia and CSF, and modalities effective in these other conditions can successfully treat GWI. Although some data support the independent efficacy of these two modalities in fibromyalgia and CFS, no randomized, controlled trial has examined the combined effects of these two treatments. Multi-modal programs may be more efficacious than individual therapies and there may be an added benefit to combining these two modalities, but this hypothesis has not been tested with GWI.

### Secondary Hypothesis

1. Both aerobic exercise and CBT will lead to improvements in the cardinal symptoms of GWI (e.g., pain as measured by the short form of the McGill Pain Questionnaire, fatigue as measured by the Multidimensional Fatigue Inventory and cognitive difficulties as measured by the Cognitive Failures Questionnaire.)
2. Both aerobic exercise and CBT will lead to decreased levels of distress in persons with GWI, as measured by the MM-5 of the SF-36V.
3. Both aerobic exercise and CBT will lead to improvements in emotional functioning in persons with GWI, as measured by the Mental Compound Scale of the SF-36V.

### Tertiary Objectives

1. To determine which "process measures' play a role in achieving the desired outcomes. There are several reasons that patients may improve in response to the two interventions. These include changes in: 1) a physiological effect mediated by increased aerobic fitness, 2) the person's overall pain threshold (measured by dolorimetry), 3) attitudes regarding illness and symptoms, and 4) satisfaction with previous and current treatment. We will assess which of these mechanism correlate with changes in each of the primary and secondary outcome variables, i.e., which process measures are mediators of outcome.
2. To develop a focus group consent document and compare its utility with the original study consent document with respect to patient-centered outcomes (recall, expectation of participation, availability of study personnel) and adherence to assigned therapy.
3. To develop a minimally clinically important difference for the Physical Component Scale of the SF-36V.

TECHNICAL APPROACH

This clinical trial will study Gulf War era veterans who have unexplained chronic physical symptoms such as pain, fatigue and/or cognitive difficulties. Patients will be randomized to one of four groups: 1) CBT plus aerobic exercise, 2) aerobic exercise alone, 3) CBT alone and 4) usual and customary care. The primary outcome will be a clinically meaningful improvement in the Physical Component Summary scale of the SF-36V at one year relative to baseline. All patients will be followed over for one year and outcome will be measured at 3 months (immediately following the end of treatment), 6 months and 12 months post randomization.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 63. The total number enrolled study-wide is 1092, if multi-site study.

CONCLUSIONS

The results are currently undergoing peer review so cannot be released.

Report Date: 25 August 2002

Work Unit # 00-9201

# DETAIL SUMMARY SHEET

TITLE: Role of Focal Adhesion Kinase and E-Cadherin in Differentiated Thyroid Cancer

KEYWORDS: thyroid cancer

PRINCIPAL INVESTIGATOR: Gary L. Francis COL MC
ASSOCIATES: Yvonne Lukes

DEPARTMENT: Clinical Investigation
SERVICE: Research Operations

STATUS: C
INITIAL APPROVAL DATE: 5 October 1999

## STUDY OBJECTIVE

This protocol was designed to determine the expression of focal adhesion kinase and E-cadherin in archived formalin fixed thyroid tissues.

## TECHNICAL APPROACH

Tissues were sliced and immunostained for focal adhesion kinase and E-cadherin. Both were detected in the majority of thyroid tumors, and there was no difference in intensity between indolent and aggressive thyroid cancers.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since the last APR at WRAMC is 55 and the total enrolled to date at WRAMC is 55. The total number enrolled study-wide is 55, if multi-site study. A total of 55 samples have been stained. There is no correlation with tumor size, metastasis, or recurrence. We are therefore holding this data for future correlations with other studies.

## CONCLUSIONS

The study has shown that FAK and E-Cad are expressed by thyroid cancers. No further study is planned for these stains or samples.

Report Date: 16 November 2001 Work Unit # 01-92002

# DETAIL SUMMARY SHEET

TITLE: A Prospective, Randomized, Multicenter, Open-Label, Comparative Safety Study of Pegasys® vs. Pegasys® plus Ribavirin Treatment vs. A Twelve-Week Treatment Delay in Patients with Chronic Hepatitis C

PRINCIPAL INVESTIGATOR: Sjogren, Maria COL MC
ASSOCIATES: Kent Holtzmuller COL MC

DEPARTMENT: Clinical Investigation STATUS: O
SERVICE: INITIAL APPROVAL DATE: 23 January 2001

STUDY OBJECTIVE:

1. Primary:
   - To compare the safety profiles of Pegasys® plus Ribavirin vs. Pegasys® monotherapy, through week 72 (safety defined as the following adverse events: fatigue, depression, anemia, grade 3 or 4 neutropenia, or any clinically significant infections requiring treatment).
2. Secondary:
   - To compare the safety profiles of Pegasys® plus ribavirin vs. Pegasys® monotherapy, through week 24 (safety defined as the following adverse events: fatigue, depression, anemia, grade 3 or 4 neutropenia, or any clinically significant infections requiring treatment).
   - To compare the safety profiles of Pegasys® plus ribavirin vs. Pegasys® monotherapy, through week 12 (safety defined as the following adverse events: fatigue, depression, anemia, grade 3 or 4 neutropenia, or any clinically significant infections requiring treatment).
   - Evaluate virologic response rates at week 24 and at week 72 – Proportion of patients with non-detectable HCV-RNA ( < 50 IU/ml by Amplicor® HCV test v2.0) at week 24 and at week 72.
   - Evaluate virologic response rates at week 12 – Proportion of patients with non-detectable HCV-RNA ( < 50 IU/ml by Amplicor® HCV test v2.0) or a 2-log drop at week 12.
   - Evaluate the predictability of week-12 HCV-RNA to week 24 and to week 72 non-detectable HCV-RNA for Pegasys® plus ribavirin vs. Pegasys® monotherapy.

TECHNICAL APPROACH

This is a prospective, randomized, open-label, multicenter, safety and efficacy study. Randomization will be centrally controlled. Patients will be given the option of selecting one of two cohorts for randomization.

Planned program size: 1,500 subjects nationwide, 10 at WRAMC. Patient population: Male or female patients ≥ 18 years old with serogically proven CHC. Patients should have quantifiable HCV-RNA (> 600 IU/ml by Amplicor HCV Monitor™ test v2.0), abnormal alanine amniotransferase (ALT) and compensated liver disease, with or without cirrhosis.

Cohort 1: Patients who are willing to delay treatment for 12 weeks if randomized to Arm C, will be randomized into Arm A or B in a 3:1 ratio, respectively.

- Arm A -- Pegasys® plus ribavirin
- Arm B -- Pegasys® monotherapy
- Arm C – Twelve-week treatment delay

At 12 weeks, Arm C patients will be randomized into Arm A or B in a 3:1 ratio, respectively. For the secondary objective, comparing Pegasys® plus ribavirin vs. Pegasys® monotherapy vs. treatment delay, analysis will be done on Cohort 1 patients only.

Cohort 2: Patients who opt not to be randomized to Cohort 1 because of the possibility of being randomized to a delayed treatment arm, will be randomized into Arm A or B in a 3:1 ratio.

- Arm A - Pegasys® plus ribavirin
- Arm B - Pegasys® monotherapy

Patients will receive treatment for 48 weeks and then be followed for an additional 24 weeks for safety.

For the primary objective, Cohort 1 and Cohort 2 data will be pooled together for analysis. Subjects will be randomly assigned to treatment via an interactive voice response telephone system. Subject randomization numbers are to be allocated sequentially in each respective cohort, in the order in which patients are enrolled. Randomization will be in blocks of five (5) for the 3:1:1 randomization, and in blocks of four (4) for the 3:1 randomization.

Discontinuation scheme: Patients who do not have undetectable HCV-RNA levels (< 50 UI/ml by Amplicor® HCV test v2.0) after 24 weeks of study treatment will be considered non-responders and treatment will be discontinued. Patients responding at 24 weeks will receive additional 24 weeks of treatment. All patients discontinuing early from study treatment will complete assessment as defined for week 48 prior to follow-up.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Recent literature: The field of treatment of hepatitis C is rapidly evolving. Pegylated interferons are new drugs with limited known ability to induce permanent HCV eradication. Recent studies have shown a sustained viral response (SVR) of 52% when using a different treatment regimen (Peg-Intron + ribavirin) while the SVR was reported as 56% for the combination of Pegasys and ribavirin. However, the SVR is lower when using Pegasys alone. In this protocol eight (8) subjects were randomized to combination therapy (PegIFN + ribavirin) and two (2) subjects are receiving PegIFN alone. Because of the recent data, the sponsor (Hoffman-La Roche) has petitioned the FDA to allow all monotherapy-treated subjects to be switched to combination therapy. The FDA approved this addendum and it is to be submitted to WRAMC IRB in the near future to allow the best therapy for subjects enrolled in this study.

Amendments

April 03 2001: The central laboratory cited in the protocol has changed to ICON Laboratories, Inc. 260 Smith St., Farmingdale, NY 11735-9097. A new form FDA 1572 has been filled out.

July 17 2001: The following documentation is to be included in this protocol:
Self-Injection Chart: This is a step-by-step guide to subcutaneous self-injection. Frequently Asked Questions: This form will be used by a call center to respond to common questions asked by the callers. Roche will be using a call center for both recruitment and educational purposes. The call center will be available for potential subjects. Call Guide: This is the script that will be used by the call center.

July 23 2001: Clinical tests are to be performed by WRAMC laboratory in addition to the ones performed at Roche's central lab – ICON laboratories -- in order to screen eligible patients for the protocol.

August 10 2001: ROCHE has submitted the following changes to this protocol: One additional visit at week 1 where a CBC will be done. Additional RNA level testing at week 12.

The number of subjects enrolled to the study to date at WRAMC is 10. The total number enrolled study-wide is 1240 among 177 sites.

The following serious adverse events have been reported by other study sites outside of WRAMC:

- January 4 2001 – Study # NO16007 Adverse Event: Papilledema/Scotoma. Optic neuropathy.
- March 8 2001 – Study # M78014 Adverse Event: Chorioretinitis.

- April 16 2001 – Study # M78020 Adverse Event: Unexplained Death.

April 19 2001 – Study # BV16209 Adverse Event: Liver Transplant Rejection. Work Unit # 01-92002

- June 20 2001 – Study # M78014 Adverse Event: Prepatellar Bursitis. Study # NR16161 Adverse Event: Serum Sickness.
- July 3 2001 – Study # NO16006 Adverse Event: Avascular necrosis of the hip bones (left and right femoral heads, left acetabulum, right greater trochanter, the iliac border of the right sacroiliac and both borders of the left sacroiliac).
- August 1 2001 – Study # NR15961 Adverse Event: Secondary Adrenocortical Insufficiency. The AE relationship to study drugs cannot be excluded.
- August 3 2001

MCN 262904: Study # JV047 Adverse Event: Intervertebral Disc Herniation.
MCN 262918: Study # M78014 Adverse Event: Neurodermatitis. A causal relationship between worsening of neurodermatitis and treatment with Peginterferon alfa-2a and Ribavirin is somewhat likely and it can not be excluded.
MCN 263644: Study # M78014 Adverse Event: Ophthalmalgia.
MCN 264334: Study # M78014 Adverse Event: Orthostatic Hypotension.

- August 7 2001 – HIV-HCV co-infection.
- August 16 2001

MCN 262297: Study # M23153 Adverse Event: Ischemic Colitis.
MCN 263648: Study # BV16209 Adverse Event: Breast Abscess.

- August 20 2001 - Study # BV16209 Adverse Event: Breast Abscess. Indeed, the causal association between the use of Ribavirin and the establishment of a breast abscess is not likely.
- August 23 2001

MCN 261550: Study # JV15724 Adverse Event: Hyperammonemia.

- September 10 2001 – Study # NR15963 Adverse Event: Left Bundle Branch Block.
- September 13 2001 – Study # M78019 Adverse Event: Loss of Vision.
- September 19 2001 – Study # Bv16209 Adverse Event: Pulmonary hypertension.
- October 11 2001 – Study # Non-Roche. Adverse Event: Increased Lactic Acid.

CONCLUSIONS

As of today, we have enrolled ten (10) patients of whom 6 are on week twelve, 2 are on week eight, 1 is on week four and 1 is on week one of treatment. Eight (8) subjects have been randomized to Peg-Interferon and ribavirin treatment and two (2) have been randomized to Peg-Interferon alone. Overall, this on-going protocol has shown that among all adverse events being assessed fatigue and neutropenia have shown to be the most predominant ones in the very beginning of treatment. Around week twelve, these adverse events have shown to be subsided or diminished. Viral count for week 12 has just started to be tested and as of today, out of three subjects tested two have shown negative HCV viral count (< 50 UI/ml by Amplicor® HCV test v2.0). We are in the process of testing HCV viral counts on the remaining subjects for week twelve.

Report Date: 3 January 2002

Work Unit # 01-92003

# DETAIL SUMMARY SHEET

TITLE: Hepatitis C Virus Infection: Mechanism of Disease Progression

KEYWORDS: Hepatitis C; virus; liver; cirrhosis; HCV RNA; epidemiology; US military

PRINCIPAL INVESTIGATOR: Sjogren, Maria COL MC

DEPARTMENT: Clinical Investigation
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 20 February 2001

STUDY OBJECTIVE: The principal hypothesis of this study is that active duty members infected with HCV genotype 1, liver disease progresses more rapidly than in subjects infected with non-HCV non-genotype 1. Assessment on other variables which might influence histologic progression of liver disease including age, race, rank, deployment, alcohol consumption, HCV RNA level will be determined as well. Specific objectives are as follow:

1. To compare the rate of progression of liver disease based on histologic severity scale in military subjects infected genotype 1 to the rate of progression in those infected with non-genotype 1.
2. To identify other predictors of histologic liver disease
3. To determine risk factors for acquisition of genotype-1 compared to non-genotype 1 HCV
4. To describe the natural history of HCV infection in a large group of a military population including morbidity and mortality

TECHNICAL APPROACH: This is a study of active duty military men or women who have the diagnosis of chronic HCV infection. Subjects who seek medical care at the Gastroenterology Service/Liver Clinic for HCV infection are informed about this study by the principal investigator or clinical trial coordinator. Clinical status (status of liver disease, presence of co-morbid medical conditions, markers of hepatic synthetic function) and a serum sample stored at - 70 °C for future analysis will be assessed at follow-up visits every six months. A questionnaire will be administered every six months regarding ongoing risk factors for HCV infection and quality of life (modified SF-36).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE: To date 41/45 potential volunteers were enrolled in this study, two subjects did not fulfill eligibility criteria, and 2 did not want to participate. Preliminary findings have showed ethnic groups as follows: 29.3% African Americans, 4.9% Asians, 58.5% Caucasians, 2.4% Latino/Non-Black, 4.9% Latino/Black. Age groups were distributed as younger than 40 years old (36.6%) and older than 40 years old (63.4%). Males constituted the majority of subjects (85.4%) and females accounted for 14.6% of these subjects. The military rank distribution showed 75.7% of enlisted and 26.4% of officers. Laboratory tests showed abnormal alanine aminotransferase in 58.5%, detectable HCV RNA in 92.7% with a mean HCV RNA of 1.2 x 106 IU/mL. The most prevalent genotype was 1a (42.5%), followed by 1b (25%), other (30%) and not determined (2.5%). Liver biopsies interpreted using the Knodell system showed a 45% of fibrosis with portal expansion, 22.5% of bridging fibrosis (portal-portal or portal-central linkage), 17.5% of cirrhosis, 12.5% of normal and 2.5% inconclusive. Under the Child-Pugh's criteria, two subjects were classified as group C while all the rest were classified as group A. One patient received a liver transplantation and another is expecting to receive one in the near future. One subject (ID #03) died in November 01 from an unrelated cause. He developed a brain tumor (hemangioblastoma). His death was reported to HUC.

CONCLUSIONS:
The study is progressing well. Additional data is needed in order to delineate a more in depth analysis of hepatitis C mechanism of transmission as proposed in the original grant.

Report Date: 14 August 2002 Work Unit # 01-92004

# DETAIL SUMMARY SHEET

TITLE: Interleukin-6 and Tumor Necrosis Factor-Alpha Role In Alcoholic Liver Cirrhosis

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rojkind, Marcos M.D.
ASSOCIATES:

DEPARTMENT: Clinical Investigation STATUS: O
SERVICE: INITIAL APPROVAL DATE: 11 September 2001

## STUDY OBJECTIVE

To determine the role of the acute phase response and the cytokines of the acute phase response on collagen gene expression in the liver. Although this protocol overlaps with 01-92005, it was submitted as a means to start the experimental part in vitro using cell cultures. No animal usage is contemplated for this particular protocol. Prior to receiving approval for animal usage (see 01-92005), this protocol allowed the PI to start his work and comply with the requirements of NIH, the sponsoring institution for this grant proposal.

## TECHNICAL APPROACH

Analyze the molecular mechanisms whereby the cytokines of the acute phase response (mainly tumor necrosis-α) (TNF- α) modulate the expression of collagen and matrix metalloproteinases by hepatic stellate cells.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is n/a and the total enrolled to date at WRAMC is n/a.

## CONCLUSIONS

Studies performed up to date have revealed that TNF- α downregulates the expression of α1(I) collagen gene by a mechanism dependent on the activation of Jun kinase (JNK) and decreasing the phosphorylation of p38MAPK. Moreover, we demonstrated that inhibitors of p38MAPK reproduce the downregulation of the collagen gene induced by TNF- α. Interestingly, downregulation of the collagen genes is accompanied by upregulation of matrixmetalloproteinases. We concluded that both genes are reciprocally modulated. This work was performed in collaboration with a former fellow in my laboratory, currently working in Pamplona, Spain.

Report Date: 14 August 2002

Work Unit # 01-92005

# DETAIL SUMMARY SHEET

TITLE: The Role of the Acute Phase Response in Alcoholic Liver Cirrhosis

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rojkind, Marcos M.D.
ASSOCIATES:

DEPARTMENT: Clinical Investigation
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 14 September 2001

## STUDY OBJECTIVE

To determine the role of the acute phase response and the cytokines of the acute phase response on collagen gene expression in the liver of rats fed alcohol. Although this protocol overlaps with 01-92004, it required animals. Because the approval of this protocol took a long time, only six control animals have been used for cell isolation. The *in vitro* work that includes experiments performed with cell cultures is being reported in 01-92004.

## TECHNICAL APPROACH

For these experiments, rats will be fed alcohol with or without the administration of endotoxin and/or a choline-deficient diet. We will measure the effects of these treatments on type I collagen, collagenase, and TIMP-1 genes expression in total liver and in hepatic stellate cells and hepatocytes isolated from those livers.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Thus far, only six control rats have been used for liver perfusion and cell isolation. We expect to start some groups of animals shortly. In addition, we performed experiments with livers of rats that received the experimental treatments while the PI was a faculty member at AECOM. The animal committee of AECOM had approved these experiments. The results suggest that ethanol feeding induces an oxidative stress response. In addition, leptin levels are induced.

## CONCLUSIONS

The results obtained are insufficient to draw any conclusions at this time.

Report Date: 14 August 2002 Work Unit # 01-92006

# DETAIL SUMMARY SHEET

TITLE: Alcohol Induced Liver Fibrosis: An In Vitro Model

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rojkind, Marcos M.D.
ASSOCIATES:

DEPARTMENT: Clinical Investigation STATUS: O
SERVICE: INITIAL APPROVAL DATE: 14 September 2001

STUDY OBJECTIVE
To study the effects of ethanol and its metabolite acetaldehyde on collagen and collagenase gene regulation.

TECHNICAL APPROACH
For these studies, the PI will take advantage of the numerous cell lines of HSC developed in his laboratory and of human HSC provided by investigators from the Mount Sinai School of Medicine and North Carolina School of Medicine. Cultured cells are treated with acetaldehyde and harvested at various time-points for total RBA extraction and levels of mRNA determined by Northern blot analysis and/or semiquantitative PCR.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is n/a and the total enrolled to date at WRAMC is n/a.

CONCLUSIONS
From the experiments performed this year, we have determined signal transduction pathways involved in acetaldehyde-mediated upregulation of the type I collagen genes. A manuscript containing some of these experiments will be submitted shortly for publication.

Report Date: 24 October 2001

Work Unit # 01-9201

# DETAIL SUMMARY SHEET

TITLE: Hepatitis G Virus and Aplastic Anemia

KEYWORDS: GBV-C/HGV, stem cell disease, aggressive viral infection, spousal co-infection

PRINCIPAL INVESTIGATOR: Jana Bednarek PhD DAC
ASSOCIATES: COL KC Holtzmuller MC, DE Nicholson PhD DAC

DEPARTMENT: Clinical Investigation
SERVICE: Research Operations

STATUS: O
INITIAL APPROVAL DATE: 5 December 2000

## STUDY OBJECTIVE

The purpose of this study was to examine and determine the differences between Hepatitis G viral genomic sequences and its translation into proteins in genotypically similar HG viruses isolated from serum of an asymptomatic patient and one with serious aplastic anemia, a case study of patient and his spouse.

## TECHNICAL APPROACH

Serum of patient was obtained at the initial diagnosis and his spouse's a few days later. Both were stored at -76°C. When the protocol was approved, the patients signed informed consent form. We then prepared the hepatitis G viral RNA from the serum aliquot and stored that at -76°C as well. RNA was converted to cDNA by reverse transcription. Specific areas of the viral genome were enhanced with the use of PCR reaction and specific primers designed for this purpose. They were visualized as single bands in electrophoretic separation on agarose gel stained with ethidium bromide. For sequencing we removed PCR primers from PCR products by centrifugation using Amicon 100 filters. Purified cDNA was subjected to direct sequencing using sense or antisense primers. DNA sequencing was performed by dideoxy chain termination method using BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems). Sequencing reaction products were purified through Centri Sep Spin columns and separated electrophoretically on Perkin Elmer ABI Prizm 310 Genetic Analyzer with Power MacIntosh. Nucleotide analysis was carried out with the help of NIH program Blast.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Hepatitis G virus (HGV) has a controversial association with aplastic anemia. Our study included one patient and his spouse who developed an acute viral syndrome. The patient developed hepatitis and aplastic anemia. The spouse recovered uneventfully. All tests for suspected viruses and autoimmune antibodies were negative except for HGV RNA found in both. We sequenced substantial portions of HGV genome: 5'Untranslated-Core-Envelope-1-Envelope-2 region, Nonstructural-3 helicase and Nonstructural-5A were sequenced showing that the patient (H) and his spouse (W) were infected with the same HGV strain. Patient's HGV had one amino acid substitution in E2 protein that his spouse's virus did not have. This was caused by one nucleotide difference. In pre-core the H genome had two nucleotide changes, and the W genome had four. The recently proposed ambisense and overlapping genes that produce core-like proteins were translated: each had one amino acid change in patient's HGV only.

The similarity of initial symptoms in the patient and his spouse, combined with the HGV RNA findings, suggest that the patient experienced an acute illness from HGV that was associated with the development of aplastic anemia. The patient was treated with bone marrow transplantation from his sibling and recovered. There is no direct benefit of our study to these patients. There were no new papers published on the subject on HGV association with aplastic anemia since this protocol was approved in December of 2000. Study on proposed overlapping gene translation was published and we incorporated that additional new approach into our HGV genome analysis.

The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 2.

CONCLUSIONS

We have completed all planned experiments on the initial serum of the patient and his spouse. These serum aliquots were stored at -76°C and made available to us when the patients signed informed consent. The patients are now living mostly in Texas, and we have not yet been able to obtain a follow-up serum of these two patients.

The similarity of initial symptoms in the patient and his spouse, combined with the HGV RNA findings, suggest that the patient experienced an acute illness from HGV that was associated with the development of aplastic anemia.

Report Date: 11 March 2002

Work Unit # 9206

# DETAIL SUMMARY SHEET

TITLE: Are Heat Shock Proteins Target Antigens of the Immune System in Renal Allograft Recipients?

KEYWORDS: heat shock protein, kidney transplantation, immunology

PRINCIPAL INVESTIGATOR: Yuan, Christina LTC MC
ASSOCIATES: John Swanson, Shirley Polly, Erin Bohen, Joyce Hershey

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 09 April 1996

## STUDY OBJECTIVE

A. To determine retrospectively and prospectively whether heat shock proteins (hsps) are target antigens of the immune system in renal allograft recipients. More specifically to determine if renal allograft recipients develop antibodies and/or cellular immune response specific for hsps.
B. To correlate development of humoral and/or cell-mediated immune responses specific for hsps with renal allograft outcome.

## TECHNICAL APPROACH

Phase I: This phase of the study is a retrospective cohort study. Fifty patients who have previously received a renal transplant and fifty age, sex and race matched controls will be selected for testing for anti-hsps antibodies (by ELISA), and for circulating T cells reactive to hsps (by flow cytometry).
Phase II: This phase of the study is a prospective cohort study. Forty consecutive subjects undergoing first cadaveric renal transplantation will be tested for anti-hsps antibodies and for T cells reactive to hsps immediately pre-transplantation and at serial time points post transplantation.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Phase I: All patients and controls have been entered into this phase of the study -- 50 of each -- for a total of 100 subjects. ELISA assays are completed. Preliminary results show that Hsp70 antibody levels are relatively less in patients vs. controls, as are Hsp27 antibody levels. Anti Hsp60 antibody levels were not statistically different between the two groups. Chart review is completed, as is data entry regarding donor-recipient matching. Data analysis is ongoing analysis. Phase II will not be undertaken. This study is closed to accrual and open only for data analysis at this time. There have been no new developments in the literature.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 100 (Phase I). The total number enrolled study-wide is NA, if multi-site study.

## CONCLUSIONS

See progress above.

Report Date: 24 October 2001 Work Unit # 9212

# DETAIL SUMMARY SHEET

TITLE: Hormonal Regulation of the Vitamin D Receptor

KEYWORDS:

PRINCIPAL INVESTIGATOR: Lukes, Yvonne DAC
ASSOCIATES:

DEPARTMENT: Clinical Investigation STATUS: C
SERVICE: Research Operations INITIAL APPROVAL DATE: 09 December 1997


STUDY OBJECTIVE
To determine the effects if different steroids on and number of Vitamin D receptors in four different cell lines; MDA-MB-23 1, T4-7D, Hep G2, and HL-60.

TECHNICAL APPROACH
Each cell line is exposed to stripped fetal calf serum for 24 hours followed by the addition of tretinoic acid, prednisone, 17-B estradiol, or T3 for 72 hours, 48, 24, and baseline 0.

PRIOR AND CURRENT PROGRESS
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

CONCLUSIONS
The change in the VDR level in T-47D cells following incubation with $10^{-8}$ M 1,25(OH)2D3 showed maximum stimulation occurred within the first 24 hours ($P<0.05$) and decreased 43% by 72 hours. Pre-incubation of T-47D with increasing concentrations of 1,25(OH)2D3 showed an up regulation from $10^{-6}$ to $10^{-9}$ M ($P<0.05$). The receptor level was found to be higher in well differentiated T-47D cells (12254/25ng total RNA) than in the less differentiated MDA-MB-231 (2992/25ng total RNA) whereas in the poorly differentiated cell lines of Ewing's' sarcoma, ES-SK-1 and ES-SK-MC, the number of copies were 86 and 544/25ng total RNA. Human kidney, a high expresser of VDR, had approximately 22291 copies as compared to 260 copies in human liver. We conclude our data correlates well with the degree of differentiation in human tumors and real time quantitative PCR may serve as a useful tool for detecting these differences.

Report Date: 28 September 2001

Work Unit # 9219-99

# DETAIL SUMMARY SHEET

TITLE: Molecular Marker of Radiation Induced Thyroid Disease Developing In Subjects Who Lived Downwind of the Hanford Nuclear Power Plant During Childhood

KEYWORDS: radiation, thyroid, cancer

PRINCIPAL INVESTIGATOR: Gary L. Francis, COL MC
ASSOCIATES: Yvonne Lukes, DAC

DEPARTMENT: Pediatrics
SERVICE: Endocrinology

STATUS: C
INITIAL APPROVAL DATE: 17 November 1998

## STUDY OBJECTIVE

To determine the pattern of oncogene activation in paraffin embedded tissue samples from subjects exposed to Hanford Nuclear Power Plant radiation in the 1950's.

## TECHNICAL APPROACH

Paraffin embedded thyroid samples (benign and malignant) that were collected for clinically indicated reasons and exist on the shelf at the time of approval of this project will be collected by collaborators at Fred Hutchinson Cancer Center. This protocol has also been approved by the Fred Hutchinson Cancer Center IRB. Samples will be provided to the WRAMC DCI laboratory for oncogene analysis. Corresponding clinical data and radiation dose reconstruction data will be maintained by collaborators at Fred Hutchinson Cancer Center.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

## CONCLUSIONS

The study was approved, but no samples were received from Mike Tuttle, MD for analysis. At this time, it is requested that the protocol be cancelled, and a new protocol will be submitted in the event of any samples forthcoming.

Report Date: 28 September 2001 Work Unit # 9220-99

# DETAIL SUMMARY SHEET

TITLE: Molecular Markers of Radiation Induced Thyroid Disease Developing in Subject Treated with External Beam Irradiation for Tinea Capitus as Children

KEYWORDS: radiation, thyroid, cancer

PRINCIPAL INVESTIGATOR: Gary Francis COL MC
ASSOCIATES: Yvonne Lukes, DAC

DEPARTMENT: Pediatrics STATUS: C
SERVICE: Endocrinology INITIAL APPROVAL DATE: 17 November 1998

## STUDY OBJECTIVE

To determine the pattern of oncogene activation in paraffin embedded tissue samples from subjects exposed to external beam irradiation for Tinea Capitus as children in the 1950s.

## TECHNICAL APPROACH

Paraffin embedded thyroid samples (benign and malignant) that were collected for clinically indicated reason and exist on the shelf at the time of approval of this project will be collected by collaborators at in Israel. This protocol has also been approved by appropriate IRB in Israel. Samples will be provided to the WRAMC DCI laboratory for oncogene analysis. Collaborators in Israel will maintain corresponding clinical data and radiation dose reconstruction data.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total to date at WRAMC is 0.

## CONCLUSIONS

No samples have been obtained from collaborators in Israel. For this reason, it is requested that protocol be closed. In the event samples are ever provided to Michael Tuttle, MD and new protocol will be submitted to outline proposed studies.

Report Date: 16 November 2001

Work Unit # 9221-99

# DETAIL SUMMARY SHEET

TITLE: Combination of Ribavirin with Interferon Alfacon-1 or with Interferon Alfa 2b as Initial Treatment for Chronic Hepatitis C

KEYWORDS: hepatitis C, interferon, ribavirin, human trial

PRINCIPAL INVESTIGATOR: Sjogren, Maria COL MC
ASSOCIATES: Kent Holtzmuller COL MC

DEPARTMENT: Clinical Investigation
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 15 December 1998

## STUDY OBJECTIVE

To observe the response to a new interferon (alfacon-1) in combination with ribavirin as compared to standard therapy (interferon alfa-2b and ribavirin) in volunteers with chronic hepatitis C infection.

## TECHNICAL APPROACH

Subjects with established diagnosis of chronic hepatitis C (serology and liver biopsy) are randomized to one of two groups of therapy: interferon alfacon-1 and ribavirin or interferon alfa-2b and ribavirin. Volunteers receive treatment for 24 weeks; at this point HCV RNA is tested in serum. If detectable, the volunteer does not continue therapy (both groups) - If HCVRNA is undetectable, treatment continues on for up to 48 weeks. Therapy is stopped at 48 weeks and volunteers are monitored for an additional 24 weeks. A final test of HCVRNA is done at 72 weeks. If negative, the volunteer is a responder; if positive, the volunteer is a non-responder. A second liver biopsy will be done in patients who are responders. In March 2000 an addendum was approved to increase WRAMC enrollment to 100 subjects.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

### Recent literature

The field of therapy for hepatitis C is rapidly evolving. New formulations of interferon have become available in the recent past. Few weeks ago, pegylated-interferon alfa 2b in combination with ribavirin became commercially available. This new formulation affords convenience (one injection an week versus three injections a week). This new formulation appears to be more efficient than interferon alfa-2b in eliciting sustained viral response (SVR). The pivotal trials showed a 52% SVR for pegylated interferon alfa 2b + ribavirin versus 47% SVR for interferon alfa 2b + ribavirin. Because of this increased efficiency we will not longer treat subjects with one of the arms of this study and we plan to submit an addendum to allows us to randomize to pegylated interferon + ribavirin instead. The other arm will not be modified because of excellent results superior to pegylated interferon as explained below. Enrollment has been stopped until addendum is approved.

To date 127 subjects have been enrolled (all sites), 75 at Walter Reed. During the last year, 31 new subjects were enrolled, 16 at WRAMC. See attached graphs showing the sustained viral response of 70 subjects who have finished the entire study period (72 weeks).

Serious AE have been reported to IRB for 9 subjects and are summarized as follows:
CL – hypothyroidism
GM- variceal bleeding
AR – gastrointestinal complaints
PH – persistent cough
CS-P – skin rash
DP – kidney stones

DM – palpitations and anemia
GW – hypothyroidism
WS – psychiatric side effects
All serious AE led to discontinuation of antiviral treatment. However, no long-term sequelae were observed in these patients.

Expected side effects were:

| IFN alfa-2b + ribavirin | CIFN ribavirin |
|---|---|
| Fever 37% | 67% |
| Fatigue 95% | 100% |
| Aches 84% | 89% |
| Headache 84% | 89% |
| Nausea 68% | 67% |
| Cough 79% | 78% |
| Depression 68% | 83% |
| Anemia 13% | 16% |
| Neutropenia 13% | 12% |

All side effects were mild to moderate in intensity and resolved on their own or with dose modification or symptomatic therapy.

Overall discontinuation from the study

| | |
|---|---|
| Positive HCV RNA at week 24 (by protocol design) = | 31 |
| Adverse events | 9 |
| Withdrew consent | 8 |
| Investigator discretion | 1 |
| Total | 49 |

No deaths occurred in this study.

CONCLUSIONS
Both combination treatments appear to be safe. The combination of consensus interferon and ribavirin appears to result in an overall higher HCV RNA sustained clearance than the combination of interferon alfa 2-b plus ribavirin (56% vs. 31%, p= 0.032). This difference was also observed in subjects deemed hard-to-treat (high viral load and genotype 1) where the difference was 41% vs. 18% (p=0.07).

Report Date: 25 February 2002

Work Unit # 9222-99

# DETAIL SUMMARY SHEET

TITLE: Significance of Tyrosine Kinases in Differentiated Thyroid Cancer

KEYWORDS: Tyrosine Kinase, Thyroid cancer

PRINCIPAL INVESTIGATOR: Ramirez, Raul LTC MC
ASSOCIATES: Francis, Gary COL, MC, Jeff Anderson, Yvonne Lukes

DEPARTMENT: Clinical Investigation
SERVICE: Research Operations

STATUS: C
INITIAL APPROVAL DATE: 02 March 1999

## STUDY OBJECTIVE

This protocol was designed to quantitatively determine the mRNA levels encoding 21 different tyrosine kinase enzymes in a limited number of fresh-frozen thyroid cancers.

## TECHNICAL APPROACH

RNA was successfully isolated from 5 tumors, reverse transcribed, and amplified using primers specific for each of the tyrosine kinases. Levels of the mRNA were determined using the ABI 7700 sequence detection system. The levels of two of these tyrosine kinases, cMET and VEGF appear to be increased in several samples. Current activity is focused on repeat determination of these levels to confirm this observation, as well as improved definition of the VEGF mRNA amplified.

## PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study.

## CONCLUSIONS

This study has validated the methods required to perform real time RT-PCR quantitation of mRNA encoding tyrosine kinases in thyroid cancer specimens. A larger proposal is currently being submitted to the NIH for consideration of fuding based on the preliminary data from this study. At this time, there are no plans to continue this study with any of the tissues approved for 9222-99 and the study is closed.

Report Date: 18 March 2002 Work Unit # 9223-99

# DETAIL SUMMARY SHEET

TITLE: An Investigation of Oxidative Damage to Proteins in Thyroid Autoimmunity

KEYWORDS:

PRINCIPAL INVESTIGATOR: COL Henry B. Burch MC
ASSOCIATES:

DEPARTMENT: Clinical Investigation STATUS: O
SERVICE: INITIAL APPROVAL DATE: 06 April 1999

STUDY OBJECTIVE

The objective of this protocol is to study the oxidative damage to proteins in thyroid autoimmunity. It has been established previously that compound Dityrosine is formed as a result of oxidation of proteins by free radicals. The free radicals are formed more in the disease condition than normal. Therefore, monitoring the level of Dityrosine is a useful tool to determine the oxidative stress in Autoimmune Thyroid disease. The protocol involves in the determination of the Dityrosine in the serum of Normal, Graves' and Hashimotos thyroidities patients. The protocol proposes to assess the actual modification of the thyroid patients i.e. Thyroglobulin in the serum of patients with autoimmune thyroid disease by isolating and characterizing Tg in the serum.

TECHNICAL APPROACH

Extraction and purification of Dityrosine from the serum was done by the following procedures:

a. Digestion with Proteinase K to cleave Dityrosine from the proteins
b. Separation and purification of the cleaved Dityrosine were done by centrifugation using Micron Centrifugal Filter devices.
c. Eluate containing Dityrosine and other components of Mol.Wt. below 3,000 were treated with chloroform and 0.1% trifluoroacetic acid, centrifuged and aqueous layer collected and dried. The dried sample was dissolved in 0.1% TFA and injected to HPLC column. The chromatographic separation of the Dityrosine was achieved using Weaters HPLC system, detected in Fluorescence detector. The mobile phase used for the separation of Dityrosine from the other components in the serum as following A) HPLC water with Pic B (1- Heptane Sulfonic Acid), B) 100% methanol with Pic B, C) 100% methanol, D) HPLC water. We used Waters Nova pack C 18 column and proper gradient profile.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Identification and quantitation were done by comparing the retention time of pure Dityrosine previously synthesized and characterized by Mass Spect. A standard curve was also developed with pure Dityrosine. We plan to determine the actual modification of the thyroid protein i.e. Thyroglobulin (one of the thyroid antigens) by the following procedures: 1. Isolation of using antibody to Tg.3. HPLC separation of the Tg and comparison of the peaks in pure and modified Tg.3. further characterization of the Tg from the serum of the group of patients studied using Sepharose CL 6B çolumn. 2. Identification of Tg in the collected fraction using Mass Spect (TOF).

The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is N/A. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS

Oxidative protein damage is a concomitant change with thyroid autoimmunity.

Report Date: 4 January 2002

Work Unit # 9400-99

# DETAIL SUMMARY SHEET

TTTLE: Absorption Rate of a New Bioabsorbable Membrane- A Pilot Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Theberge, Daniel COL DE
ASSOCIATES: Tempel, Carl G. MAJ DE

DEPARTMENT: DENTAC
SERVICE: Oral/Maxillofacial Surgery

STATUS: C
INITIAL APPROVAL DATE: 02 February 1999

STUDY OBJECTIVE

1. To determine the absorption rate of a new bioabsorbable membrane in a human patient.
2. To study the histologic process of membrane absorption.

TECHNICAL APPROACH

Place ten dental implants, each covered with an identical bioabsorbable membrane (Resolut XT), into an edentulous maxillary or mandibular arch. Serially uncover the implants and place healing abutments, using a tissue punch and local anesthetic at 1,2,3,4,6,8,12,16,20,24 and 28 weeks. Examine the tissue punch specimens histologically.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study.

CONCLUSIONS:

PI requests that this research protocol be closed. Due to new research and developments in this particular research area, the utility of this particular research protocol is reduced to the point where is it is no longer reasonable to consider continuing to try to initiate and complete the protocol.

Report Date: 22 April 2002 Work Unit # 00-9601

# DETAIL SUMMARY SHEET

TITLE: Skin-Contact Monochromatic Infrared Irradiation on Lateral Epicondylitis

KEYWORDS:

PRINCIPAL INVESTIGATOR: Paul F. Pasquina, MAJ, MC
ASSOCIATES:

DEPARTMENT: Orthopedics and Rehabilitation STATUS: O
SERVICE: Physical Medicine & Rehabilitation INITIAL APPROVAL DATE: 22 February 2000

## STUDY OBJECTIVE

Determine whether the pain response after application of Skin-Contact Monochromatic Infrared Irradiation differs from that of placebo in the treatment of lateral epicondylitis.

## TECHNICAL APPROACH

Randomized, double blind, placebo controlled prospective study of active vs. placebo unit.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is N/A, if multi-site study.

## CONCLUSIONS

We have had trouble recruiting patients. Dr. Earwood has PCS'd, as have my contacts with physical therapy. I would still like to continue with the study. There have been no adverse effects from the treatment. Since it is a double-blind treatment, no report as to the efficacy can be determined.

Report Date: 26 July 2002

Work Unit # 00-9602

# DETAIL SUMMARY SHEET

TITLE: Comprehensive Prospective Gait Evaluation of Patients with Spinal Cord Pathology

KEYWORDS: Gait Analysis, Spinal Cord Injury, Spinal Cord Pathology

PRINCIPAL INVESTIGATOR: LTC Steven Shannon, MC
ASSOCIATES: LCDR Sean Kelly, MC; COL Bahman Jabbari, MC

DEPARTMENT: Orthopedics and Rehabilitation
SERVICE: Physical Medicine and Rehabilitation

STATUS: O
INITIAL APPROVAL DATE: 18 April 2000

STUDY OBJECTIVE:
To describe the gait characteristics of subjects with spinal cord pathology (SCP) during the first year after diagnosis.

TECHNICAL APPROACH
SCP subjects and controls will be tested with a computerized 3-D gait laboratory including a dynamic EMG machine, and descriptive statistics will be presented and analyzed.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

CONCLUSIONS
Study hampered by loss of principle investigator, and shift in focus of gait lab to another DSCCIC protocol. Decision pending about the continuation of this study.

Report Date: 29 April 2002 Work Unit # 00-9603

# DETAIL SUMMARY SHEET

TITLE: Comparison of Biochemical Markers Between Active Duty U.S. Service Members with Chronic Myofascial Pain Syndrome (MPS) and Matched Controls

KEYWORDS: myofascial pain, musculoskeletal pain, chronic pain

PRINCIPAL INVESTIGATOR: J. Gambel LTC, MC
ASSOCIATES: Lynette Scott, PhD S. Shannon, M. Rubertone, R. Howard, R. Gerwin

DEPARTMENT: Orthopedics and Rehabilitation
SERVICE: Physical Medicine and Rehabilitation

STATUS: C
INITIAL APPROVAL DATE: 6 Jun 2000

## STUDY OBJECTIVE

To evaluate the association of four common metabolic markers (uric acid, TSH, FT4, and serum ferritin) with chronic myofascial pain syndrome in active duty military population and matched controls.

## TECHNICAL APPROACH

A case group was composed of U.S. military active duty patients with chronic MPS from a Physical Medicine and Rehabilitation outpatient clinic. Each patient had a history of myofascial pain of at least six months duration with active trigger points. Cases were assigned a case date of approximately one year after the onset of their symptoms. Closest available sera prior to case date were obtained for cases and for matched controls from the U.S. Department of Defense Serum Repository. All sera were batch tested for uric acid, thyroid stimulating hormone (TSH), free T4 (FT4), and ferritin.

## PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The study is complete. Case and control groups each included 32 participants. On average, the sera were drawn approximately ten months prior to the case date. No significant differences were found between the laboratory test results of case and controls with regards to uric acid, TSH, FT4, and ferritin.

## CONCLUSIONS

In the study population, no association was identified between the four metabolic markers and chronic MPS. The relatively equal proportion of study participants by gender may have obscured potential differences in the case and control groups that were used to track the three clinical conditions: hypometabolism, iron deficiency, and hyperuricemia. Laboratory testing may be more revealing if these markers were assessed prospectively over the clinical course of those diagnosed with MPS.

Report Date: 15 July 2002

Work Unit # 00-9604

# DETAIL SUMMARY SHEET

TITLE: Determination of Low Back Muscle Usage by MRI Before and After Stepper Machine Exercise

KEYWORDS: MRI, exercise, back musculature

PRINCIPAL INVESTIGATOR: LTC Raul Marin MC
ASSOCIATES: MAJ Phil Dinauer MC; MAJ Roberto Perez-Millan MC; LTC Jeffrey Gambel MC; CPT Deydre S. Teyhen MS

DEPARTMENT: Orthopedics and Rehabilitation
SERVICE: Physical Medicine and Rehabilitation

STATUS: O
INITIAL APPROVAL DATE: 19 September 2000

STUDY OBJECTIVE Compare the effect of two methods of using the stepper machine on the recruitment ("usage") of back muscles in normal subjects using MRI.

TECHNICAL APPROACH Male and female subjects between the ages of 18 and 39 years. Volunteers were recruited by word of mouth. This was intended to be a prospective, randomized complete block, crossover single blinded trial. Because of our inability to recruit equal numbers of males and females, we were unable to stratify the subjects into gender specific blocks. The order of the stepping method was randomized via a computer generated randomization table.

A baseline MRI (baseline scan # 1) of the gluteal muscles with the subject at rest was performed initially. The radiologist performing the MRI readings was blinded as to the condition (rest, regimen 1, or regimen 2) associated with the films being read. Each subject began exercising in the stepper machine doing either six inch short stepping technique with subject's hands free from the bars so to maintain the upper body weight supported exclusively by the back extensor musculature, or full length stepping technique with subject's hands holding the support bars. A five-minute warm-up preceded the exercise session. Intensity of exercise was determined by the rate of perceived exertion. MRI scanning occurred immediately after this first exercise session (post-exercise scan # 1), followed by a ten-minute rest period. The rest period was followed by a baseline re-test in the MRI scanner (baseline scan # 2). Then the subject began second exercise regimen. Re-scanning followed immediately after this second exercise regimen (post-exercise scan # 2). Thus, each subject was scanned four times (baseline # 1, post-exercise # 1, baseline # 2, post-exercise # 2). The placement of each subject in the MRI table was clearly marked, utilizing bony landmarks to ensure that the subsequent scanning sequences occurred with the subject lying in the exact position as he/she was during the first scanning.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE The number of subjects enrolled to the study since last APR at WRAMC is eleven and the total enrolled to date at WRAMC is seventeen. No adverse events occurred.

The "dosage" of exercise intensity was determined by stepping method with the six-inch hands off method presumably being the most strenuous (this is one point that we wanted to assess in this protocol). Water content changes in exercising muscle are dependent on the intensity of the exercise, and these changes determine the MRI's ability to identify muscle usage. At sub-maximal workloads, extracellular water volume increases more than the intracellular water volume, and with maximal workloads the opposite is true. The higher the intracellular water content, the higher the MRI signal intensity post-exercise, thus allowing for better definition of actual muscles used and the determination of which exercise regimen provided the highest challenge to the lumbar musculature. We were expecting that the back musculature would behave in the same fashion as the leg muscles, as described by Zimmermann, who found that faster cadences (as in the six inch hands off method) result in increased muscle use of the gluteus maximus, quadriceps, and gastrocnemius while performing stepper machine exercise. Unexpectedly, a preliminary evaluation of the first six subjects tested (MRI focused exclusively on the lumbar paraspinal muscles) showed no differences between the exercise methods. Since the majority of subjects reached their target exercise intensity halfway through the exercise session (and one did not reach it at all), it was felt that the lack of differences was due to inadequate challenge due to short duration of exercise. Furthermore, a review of the literature was done, and it was found that the

function of back extension is a coupled action involving the back extensor muscles *and* the hip extensors (Gluteus Maximus and Hamstrings). Thus, the lack of differences noted could be explained by the inability of the stepper exercise to train the back muscles in isolation and by a larger than expected contribution of the gluteal musculature.

As a result, an addendum was submitted to the HUC 16 October 2001 requesting a change of the MRI scanning from the paraspinal muscles to the gluteal muscles. The addendum also requested permission to recruit six additional subjects. These requests were granted. A second addendum was submitted to the HUC on 11 January 2002 in which a protocol variance was reported (two subjects recruited as a result of the permission granted to the 16 October 2001 addendum underwent fifteen instead of the protocol-mandated ten minutes of exercise per session). This addencum also requested an increase of the exercise time from ten to fifteen minutes and a change in the protocol title to reflect the new focus of the MRI scanning on the gluteal musculature.

A third addendum submitted on 8 February 2002 requested permission to re-study subjects #7 and #8 due to the corruption of MRI discs. The HUC had questions concerning this request, and these were answered by a fourth addendum dated 22 March 2002. The HUC granted permission to re-study these two subjects, but only as a "last resort" if, at the conclusion of the recruitment of subjects, it was evident that the data on the two discs could not be salvaged. During the data analysis for the preparation of this APR, the following findings were noted:

a. Subjects enrolled: 17
b. Subjects studied: 17 (six with MRI of the paraspinal muscles, eleven with MRI of the gluteal muscles). Note that maximum of subjects allowed by WRAMC IRB is sixteen. The additional subject relates to the two subjects whose MRI disc was corrupted and the data rendered unavailable. HUC had approved the re-study of these two subjects only as a last resource. Thus, we treated these two subjects as lost data and made the mistake of scheduling substitutes for these subjects as opposed to re-studying them as the "last resort" option allowed by HUC. We studied the first substitute as our last subject to be enrolled on 17 May 2002. Shortly after, and before recruiting and scheduling the second substitute, the MRI company to which the discs were sent came through and provided/salvaged the MRI data from the discs. Hence, the second substitute was not recruited, but the first was, giving us a total of one additional subject above what the WARMC IRB had approved.
c. Two subjects were excluded because they never reached REP of 13.
d. Results: (Exertion and demographic information involves all sixteen subject's studies. MRI data is confined to the eleven subjects whose MRI focused on the gluteal muscles.)

Mean age 32.8 years (SD 34.5); mean height 68.88 inches (SD 69.5); mean weight 166.9 pounds (SD 164); 18.8 female and 81.2% male. Time to reach Rate of Perceived Exertion of 13 (i.e. fatigue): Statistically significant difference ($p=.001$) with little steps reaching fatigue faster than big step. Stepper machine intensity level at which fatigue was reached: Statistically significant difference ($p=.022$) with the little steps reaching fatigue at lower intensity than big step. All sixteen subjects reported little step technique to be more demanding than big step technique. MRI T2 signal intensity comparison of buttocks at rest #1 (baseline scan #1) vs. rest #2 (baseline scan #2); no statistical difference between the two rest MRI scans ($p=.308$ for right buttock and $p=.683$ for left buttock) thus confirming no cross-over or carry-on effect from the first exercise session to the second exercise session. Preliminary MRI T2 signal intensity comparison of the gluteals post big step technique vs. little step technique: no significant difference between the two exercise techniques ($p=.286$ for the right and $p=.894$ for the left). Further analysis of this data set is pending to correct for high variability in MRI T2 signal intensity readings.

CONCLUSIONS Exercising with the stepper machine using the little step no-hands-on-grab-bars technique appears to be much more challenging and demanding than using the big step technique, both subjectively and physiologically. Furthermore, there is documented gluteal muscle usage with both stepping techniques and there was no crossover effect between the first and second exercise sessions. The findings on the MRI comparisons between techniques were disappointing. However, there is much work yet to be done in the statistical analysis of the data. Depending on the results of this further analysis, the investigators may submit an addendum to the HUC requesting permission to enroll ten additional subjects so as to correct for the small sample size apparent inability to correct for the unexpected high variability on MRI T2 signal intensity readings.