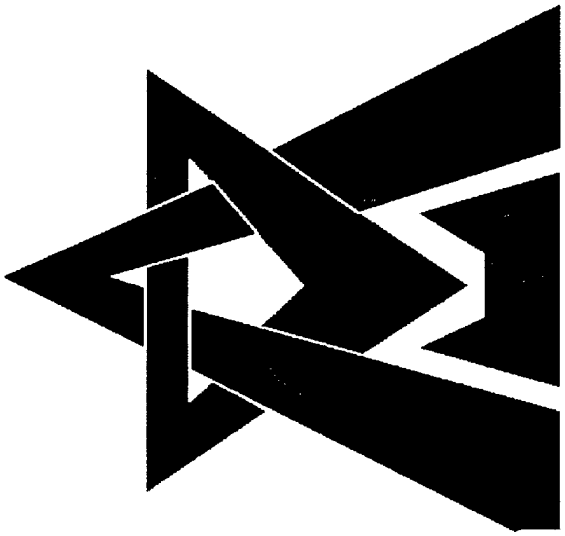
Madigan Army Medical Center
Department of Clinical Investigation

Annual Progress Report





Fiscal Year 1998

19990511 064

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REPORT DOCUMENTATION PAGE

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Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	30 September 1998	Annual 1 October 1997 - 30 September 1998

4. TITLE AND SUBTITLE
Annual Research Progress Report
Department of Clinical Investigation

5. FUNDING NUMBERS

6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Department of Clinical Investigation
Madigan Army Medical Center
Tacoma, WA 98431

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

Clinical Investigation Regulatory Office
U.S. Army Medical Center and School
Fort Sam Houston, TX 78234-6125

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT

Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

This report covers all research protocols that were administratively or technically supported by the Department of Clinical Investigation, Madigan Army Medical Center, during FY 1998. Included in the individual reports are title, investigators, funding, objective, technical approach, and progress for FY 1998. Also included in the report are personnel rosters for the Department, funding information, and presentations and publications emanating from Madigan Army Medical Center during FY 1998.

14. SUBJECT TERMS

Research protocols, investigators, objectives, progress, technical approach

15. NUMBER OF PAGES
581

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	UL

REPORTS CONTROL SYMBOL RCS-MED-300(R1)

ANNUAL PROGRESS REPORT

30 SEPTEMBER 1998

DEPARTMENT OF CLINICAL INVESTIGATION

MADIGAN ARMY MEDICAL CENTER

TACOMA, WASHINGTON 98431

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FISCAL YEAR 1998

DEPARTMENT OF CLINICAL INVESTIGATION
MADIGAN ARMY MEDICAL CENTER
TACOMA, WASHINGTON 98431

Introduction

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals" as prepared by the Committee on the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Institutes of Health, and Title 9, Subchapter A, Parts I, II, and III of the Code of Federal Regulations. The investigators adhered to Title 21, Part 50 of the Code of Federal Regulations and the recommendations from the Declaration of Helsinki in the performance of investigations involving human subjects.

Acknowledgements

I would like to take this opportunity to thank Nancy Whitten, Barbara Jones, Troy Patience, and Genie Hough for their effort, in the compilation, preparation, and editing of this publication.

Foreword

The continued expansion of scholarly activity at Madigan Army Medical Center (MAMC) during a time of re-engineering, downsizing, and increased clinical productivity is a tribute to the commitment to excellence of the MAMC community of clinical investigators. Madigan experienced reductions in graduate medical education programs, house-staff assigned, and certified faculty yet produced scholarly activity at historical levels simultaneous with increased patient contacts, care and service. Madigan Department of Clinical Investigation (DCI) supported 114 new research protocols and 439 on-going protocols (359 staff protocols, 17 fellow protocols, 56 resident protocols, 3 intern protocols and 4 external protocols). IRB approved protocols involving 330 house-staff, 24 fellows, 106 residents, five interns, and 105 investigators from external institutions. The emphasis and priority for Military Unique Clinical Investigation continues to be increased. DCI has initiated outreach programs to provide pre-review and design support for our medical executives seeking to improve the quality of care through a more scientific approach to managed care.

The very important Graduate Medical Education mission at Madigan continues to receive strong support from DCI through leadership in curriculum development, medical education research, and the unique training opportunities available through the departmental programs (i.e. PALS, ATLS, etc.). The following number of interns, residents, fellows and faculty participated: 1. "Introduction to Clinical Investigation Course" (35), 2. "Molecular Biology Workshop" at SAFMLS (52), and 3. 'Surgical Training Protocols'; i.e., PALS and ATLS (154).

The First Annual Madigan Research Day was held 28 May 1998 and offers the best benchmark available for the vigor of scholarly activity and clinical research at our institution, and within our region. Sixty-six abstracts were submitted and reviewed by subcommittees and 21 selected for podium presentations. Moderators presented several additional presentations to focus the research efforts in the areas of Military Unique Clinical Investigation (LTC C. Ray Dotson, MS, Assistant Chief, DCI), Scientific Approach to Managed Care and Outcome Studies (COL Bonnie Jennings AN, Chief Nurse), Improvement Award Program (COL Lester Reed, MC, Chief, Medicine), Medical Education Research (COL Patrick Kelly MC, GME), Experimental Design (Dr. Katherine Moore, Ph.D., Senior Scientist, DCI), and Case Reports (COL Romeo Perez, MC, Chief, Ob/Gyn). The COL Patrick S. Madigan, M.D. Foundation and The Geneva Foundation supported the effort from conception to execution to include the Program Brochure, Open House, and recruitment of Judges. Twenty-four individuals donated their time to act as judges for the oral presentations, they included Admiral (Ret) Whitney, Major General (Ret) Gamble, COL (Ret) Vanetta, COL (Ret) Bales, COL Pasternak (USAR), LTC (Ret) Roye, COL McCaffery.

BG George J. Brown's opening comments set the stage for the challenge and celebration of scholarly activity at MAMC: "Madigan Army Medical Center's First Annual Research Day celebrates those who have the courage to be curious in public". Four presentations were awarded Army Achievement Medals in the following areas: 1. **Change of Practice** - "The Effect of Loaded Foot Marching vs Running on Injury, Fitness, and Performance In US Army Light Infantry Soldiers" presented by CPT Dan C. Norvell, SP, 2. **Discovery** - "Purple Toes" presented by CPT Brian P. Mulhall, MC, 3. **Innovation** - "Tracheal Mucosal Healing in Response to Moderate Mucosal Injury Induced by Expandable Metallic Stents" presented by LCDR Keith Ulnick, MC, USN, and 4. **Interdisciplinary**.- "The Routine Pregnancy Process: Framework for Clinical Pathway Genesis" presented by 1LT Cristen Brandsma, AN. The inaugural recipient of the BG George J. Brown Mentor's Cube was COL Patrick Kelly, MC. The Madigan Research Day Proceedings were published in the U.S. Army Medical Department Journal (AMEDD Journal), July-September 1998 edition, and are included in this publication with the permission of the Editor, Bruce Nelson. In the AMEDD Journal "preface" Major General James B. Peake provided the following summation, "Shows the diversity and depth of ongoing scholarly activity at just one of the Army's Medical Centers". The Second Annual Madigan Research Day will be held 1 April 1999.

Unit Summary

A. Objective:

To provide the facilities and environment to stimulate an interest in clinical and basic investigations within Madigan Army Medical Center and its region.

B. Technical Approach:

All research, investigational and training activities within the Department of Clinical Investigation are conducted under the guidance of AR 40-7, AR 40-38, AR 70-25, AR 70-18, and HSC Reg 40-23. Careful monitoring of all approved protocols is conducted in order to assure strict compliance with the applicable regulations.

C. Staffing:

Name	Rank	MOS	Title
Hume, Roderick F., Jr.	COL	60J9A	Chief, DCI
Dotson, Carroll Ray	LTC	71A67	Asst Chief, DCI; Chief, Research Administration Service
Sherman, Richard A.*	LTC	71F67	Chief, Surgical Research Service
Nielsen, Ronald E.	MAJ	75C64	Chief, Laboratory Animal Resources Service
Aldous, Wade K.	CPT	71A67	Microbiologist
Qabar, Aziz N.	CPT	71B67	Biochemist
Trotman, Ian C.	MSG	91K5X	NCOIC, DCI
Ngala, Vickie R.	SFC	91T4R	Senior Animal Care NCO
Collins, Sherri L.	SGT	91T20	Senior Animal Care Sergeant
Williams, Iridiana**	SGT	91K20	Medical Laboratory Specialist
Long, Brett W.	SPC(P)	91T10	Animal Care Specialist
Fogleman, Sandra D.	SPC(P)	91T10	Animal Care Specialist
Moore, Katherine H.	GS13	00601	Chief, Research Operations Service
Matej, Louis A.	GS11	00644	Medical Technologist
Wright, James R.	GS11	00644	Medical Technologist
DeHart, Mary Jo	GS11	00644	Medical Technologist
Bullock, Jeff M.	GS11	00644	Medical Technologist
Patience, Troy H.	GS09	1530	Statistician (Medicine)
Whitten, Nancy J.	GS09	1087	Research Protocol Specialist
Kaeo, Curtis K.	WG07	4749	Maintenance Worker
Hough, Eugenia R.	GS06	0318	Secretary/Steno
Jones, Barbara A.	GS05	0303	Clinical Research Associate

* Retired, ** Detailed out

Personnel:	Authorized	Required	Assigned
Officers -	4	10	6
Civilians -	8	12	10
Enlisted -	8	12	6

D. Funding FY 98

Civilian Payroll	$494,100	
Incentive Awards	$1,600	
Military Payroll	$648,583	
Operations	$90,000	
Printing	$1,543	
CEEP	$34,603	
TDY	$5,700	
Services	$10,000	
	Total:	**$1,286,129**
	MEDCASE:	**$0**
MRMC	$7,707	
Air Force	$1,525	
POG	$0	
SWOG	$0	
GOG	$0	
Geneva Foundation Grants	$312,143	
Grants Federal:	**$321,375**	
FACT	$2,135	
Geneva Foundation Escrow	$351,954	
Jackson Foundation	$4,353	
Grants Non-federal:	**$358,442**	
	Grants Total:	**$679,817**
	FUNDING TOTAL:	**$1,965,946**

E. Progress

During FY 98, there were 439 active protocols that received administrative and/or technical support during the year. Of these, 263 are presently ongoing, 4 are in a suspended status, 95 were completed, and 77 were terminated. The principal investigator distribution was as follows: 359 staff protocols (includes 200 group oncology protocols), 56 resident protocols, 17 fellow protocols, 3 intern protocols, 1 USDA protocol, 2 active duty student protocols, and 1 Weed Army Community Hospital protocol. There were 114 new protocols.

There were 57 publications in nationally recognized journals. 86 presentations at regional or national medical association meetings.

F. Fellowship/Residency Program Support

Fellowship/Residency programs supported by DCI: 21 residencies and 5 fellowships, they are: *Residencies*: Emergency Medicine, Family Practice, General Surgery, Internal Medicine, Neurology, Obstetrics and Gynecology, Occupational Therapy, Ophthalmology, Oral and Maxillofacial Surgery, Orthopaedic Surgery, Otolaryngology, Pathology, Pediatrics, Pediatric Psychology, Pharmacy, Physician Assistance Program (Emergency Medicine & Orthopaedics), Podiatry, Preventive Medicine (Public Health), Radiology, Transitional Year, and Urology.

Fellowships: Developmental Pediatrics, Faculty Development (Family Practice), Geriatrics, Maternal-Fetal Medicine, and Urogynocology.

117 protocols involving 56 residents
108 protocols involving 17 fellows

Other training programs supported by DCI:
Training protocols: Department of Surgery: 2
Department of Emergency Medicine: 2
2nd Battalion, 75th Ranger Regiment: 1

Other protocols supported:
USDA protocol
Weed Army Community Hospital protocol

G. Committee Members

Clinical Investigation Committee
Katherine H. Moore, Ph.D.
Chairman

Chief or delegated representative of:

- Department of Emergency Medicine
- Department of Family Practice
- Department of Medicine
- Department of Nursing
- Department of OB/GYN
- Department of Pathology
- Department of Pediatrics
- Department of Radiology
- Department of Surgery
- Pharmacy Service
- Physical Medicine & Rehabilitation Service
- Department of Clinical Investigation:
  - Biochemistry Section
  - Microbiology Section
  - Lab Animal Resources Service
  - Medical Statistician
  - Research Administration Service

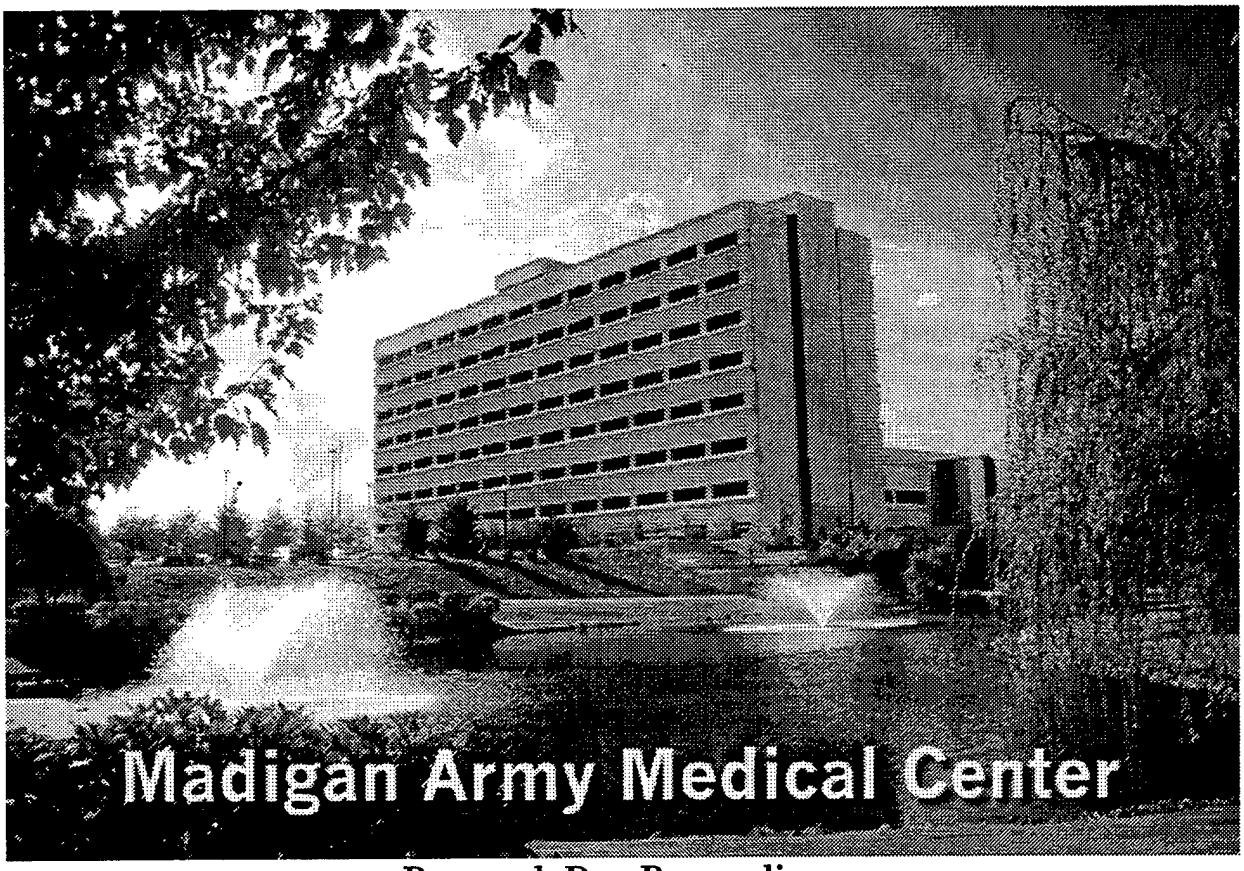
G. **Committee Members (cont'd)**

Human Use Committee
Katherine H. Moore, Ph.D.
Chairman

Chief or delegated representative of:
- Department of Nursing
- Department of Pediatrics
- Department of Radiology
- Department of Ministry and Pastoral Care
- Department of Clinical Investigation
- Pharmacy Service
- Social Work Service
- Center Judge Advocate
- Non-institutional Member

Animal Use Committee
COL Roderick F. Hume, Jr.
Chairman

Chief or delegated representative of:
- Department of Nursing
- Northwest Veterinary Support Service Area
- Non-institutional Member
- Research Operations Service, DCI
- Laboratory Animal Resources Service, DCI
- NCOIC, Laboratory Animal Resources Service, DCI



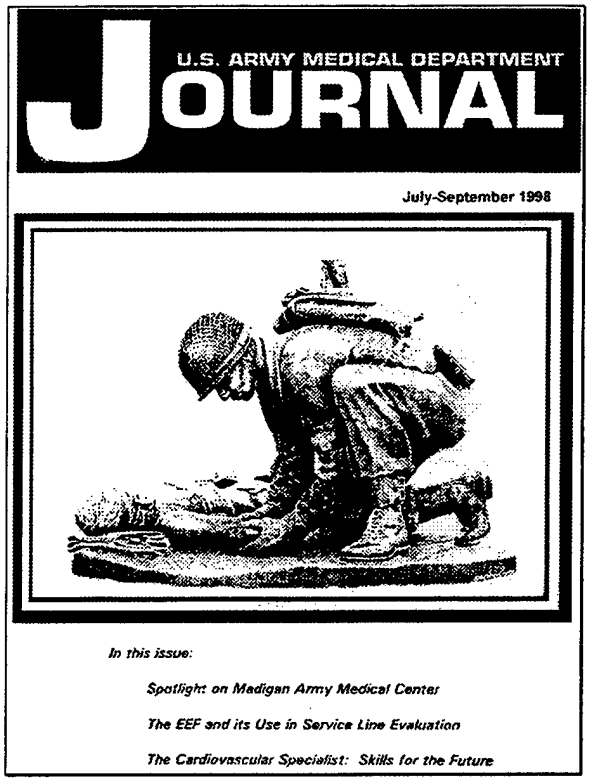
Research Day Proceedings

for

28 May 1998, Letterman Auditorium,
Madigan Army Medical Center
Fort Lewis, Washington

The goals for this program where threefold: Celebrate the Exceptional Scope of Scholarly Activities at MAMC, Incite Enthusiasm (for Further Studies, Grant Submissions, and Publications at MAMC), and Attract Grant Support for MAMC.

Four presentations have been nominated for awards (Army Achievement Medal): Innovation, Interdisciplinary, Discovery, and Change In Practice.



INTRODUCTION

You can think that you are good!
You can even believe that you are good.
It's something else to have the courage to submit your best effort to peer review...
If your peers think its good, then you are good!!!

Research occurs because of extra effort, requiring a voluntary sacrifice of personal time, and risking criticism of one's ideas. It's a good thing. And it's something for which we can all be proud. Madigan Army Medical Center's First Annual Research Day celebrates those who have the courage to be curious in public.

Brigadier General George J. Brown
Commander, Madigan Army Medical Center

Military Unique Clinical Investigation
Moderator: LTC C. Ray Dotson

EMERGENCE OF MILITARY MEDICINE:

Historically, the purpose of military medical service was to salvage manpower for the defense forces. Today, not a single major military establishment in the world is without a formal military medical service. Medicine is a dynamic, technology-based profession, the practice of which is being continuously modified by the new knowledge and new technology being produced by the massive civilian biomedical research and development community within which the military medical system is immersed.

It is essential for the "readiness" mission that the military medical departments practice high quality, technologically up-to-date medicine in peacetime. The operation of accredited Graduate Medical Education (GME) programs in military medical centers and facilities provides necessary institutional mechanism for making this feasible and successful both militarily and medically. Each military medical department anticipates that in wartime it should be prepared to deal with large numbers of patients with traumatic injuries or massive exposure to toxins or infectious disease agents. The training that military health care providers receive in peacetime in military medical facilities is intended to assure that the health care providers in these medical departments have the necessary military and medical skills to provide the services required of them in support of the military mission.

Our teaching medical centers are aware that the purpose of the GME training programs is to train physicians to support the operational missions of the armed forces. In fact, the clinical care element of the military training programs is often indistinguishable from that in the civilian hospital community with the same and similar medical training programs. The main difference between residency programs in military facilities and those in the civilian counterparts is that the DOD programs orient the physician trainee to the military system providing the background for practicing their essential skills under conditions of conflict or national emergency.

GME PROGRAMS (CLINICAL RESEARCH):

The most respected civilian graduate medical programs provide strong, well-funded clinical research programs to residents and fellows. In these matters, clinical research is widely accepted as a measure for "outstanding" physicians and the clinical training programs which prepare them for their professional challenges. Retention of high quality GME by the Department of Defense (DOD) is essential to readiness and in the current funding constraints, it is consistent with the cost control realities of today's Defense Establishment. Currently, most civilian medical schools and graduate training programs do not adequately teach the principles of combat medicine. Therefore, the military must rely upon itself even more to provide the medics capable of practicing their trade in unique settings and be prepared to support the combat mission at any location worldwide.

THE PATH

We need facts to produce new theories, but we also need theories to produce new facts. Basic research is the first step in a multistep process to develop new theories and facts. This is followed by applied research and development of the pathways which may lead to the implementation of these findings. Clinical investigation then takes the theories and facts another step, into the medical setting where promising findings are tested in clinical trials. Finally, demonstration programs are established and instituted resulting in new

health care delivery, improved disease control, or new prevention and treatment matrices. Clinical Investigation in the military setting is a process, the way to develop and refine medical care practices to support the soldier, airman, and sailor in the conditions which are peculiar to them and their dependents.

MILITARY UNIQUE CLINICAL INVESTIGATION:

The care and welfare of our soldiers, airmen, and sailors is the central concern of our (military) research efforts. The essential process required to preserve and maintain the fighting strength (...salvage our manpower for the unique military missions...) is to anticipate the threat, solve the problems, and work through the medical challenges that the deployed soldier may encounter. At the Joint Services Graduate Medical Education Selection Board, Secretary Martin coined the term 'Military Unique Clinical Investigation'. Subsequently, the Surgeon General (SG) from each of the DOD services stated that more military unique curriculum development and more military unique research were needed. This message was clear and anticipated here at Fort Lewis by both Madigan Army Medical Center (MAMC) and I Corps leadership. There is already an existing tradition of collaborative militarily relevant clinical investigation efforts between MAMC and I Corps and this remains a fundamental element of future plans at this installation.

Our first presentation this morning is a command initiated inquiry, a study designed to help the commander do the 'right thing' in training the troops. The second presentation describes initiatives in the enlisted female readiness arena and describes the translation of the recently developed Department of the Army's "Female Soldier Readiness Leader's Guide" into an Air Force version compliant with their policies and procedures. Both these models can now be considered for "Regional" implementation. Next, we hear a report of a study seeking to achieve improved resolution of broken bones to return the service member to the military forces to 'fight' another day.

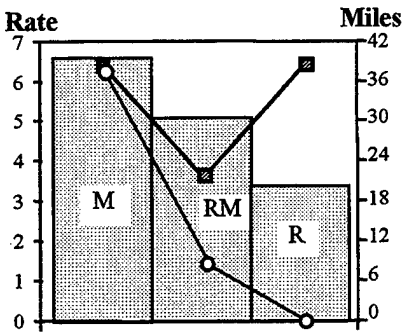
Your presence and participation at the **"FIRST ANNUAL MADIGAN ARMY MEDICAL CENTER RESEARCH DAY"** is appreciated and is part of the success story being told here. I wish to extend my gratitude and appreciation to each of today's presenters and their mentors, co-investigators, and supporters.

The Effect of Loaded Foot Marching vs Running on Injury, Fitness, and Performance In US Army Light Infantry Soldiers

CPT Dan C. Norvell, SP[a], COL Joseph R. Dettori, SP[a], CPT Drew C. Peterson, MC[c], Troy H. Patience, BS[b]

[a]Physical Therapy, Physical Medicine & Rehabilitation Service and [b]Department of Clinical Investigation, Madigan Army Medical Center, Ft. Lewis, WA and [c]Brigade Surgeon, 1st Brigade, 25th Infantry Division (Light), Ft. Lewis, WA

The mission of the light infantry soldier is to road march several miles with a heavy load prior to engaging in battle. Presently, Army soldiers' fitness and physical readiness is measured by the Army Physical Fitness Test (APFT) which includes pushups, sit-ups, and a timed two mile run. Most light infantry soldiers spend their physical training (PT) time doing these three activities rather than foot marching. Some units are increasing their marching mileage for the purpose of training more specifically. The purpose of this study is to determine the effects of loaded foot marching versus running performed during PT on injury rates, fitness, and performance. Three light infantry companies were divided into the following PT groups: march only (M, n=92), run/march (RM, n=101), and run only (R, n=103). PT was performed 3times/week. The APFT, 12 mile loaded foot march, marksmanship range and an obstacle course were performed at the beginning and end of the study. While there was no difference in injury rates among the groups (11.8, 11.7, and 11.4 per 100 soldiers/mo. respectively), those who marched with 50-pound ruck sacks injured themselves more during PT (figure, circles are marching/mo., squares are total miles/mo). Compared to the beginning of the study, the R and RM groups were faster in their 2 mile run times (28 seconds and 14 seconds, respectively), while the M group was slower by 43 seconds (ANOVA, $p<0.0001$). There were no significant differences in marksmanship following the 12 mile loaded foot march but runners significantly outperformed both marching groups in the obstacle course ($p=0.003$). We conclude that military leaders and health professionals must consider the negative effects of loaded foot marching. Marching is more combat oriented and therefore should not be avoided. However, loaded foot marching in place of running for PT is associated with more injuries during PT, decreased fitness, and decreased performance.



Presenter: CPT Daniel C. Norvell, SP
Mentor: COL Joseph R. Dettori, SP



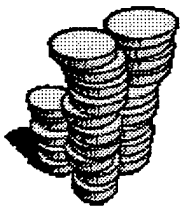
RESEARCH DAY AWARD WINNER
"Change in Practice" Category

Female Airman Readiness: A Leader's Guide

A1C Kelly A. Hartley, USAF[a] and LTC Byron C. Calhoun, MC, USAF[b]
[a]62nd Medical Group, McChord AFB, WA and [b]Maternal Fetal Medicine Service, Department of OB/GYN, Madigan Army Medical Center, Ft. Lewis, WA

Every military leader is a manger; of time, resources, and people. This presentation outlines our introduction of the Leader's Guide, a handbook for leaders responsible for managing a growing segment of the military personnel pool-the female airman. The military is well on its way to providing challenging and rewarding career paths for all its service members. How a leader utilizes and develops these resources depends upon knowledge of the many potential missions as well the unique attributes of each team-member. The handbook and the resources references within it are meant to help leaders integrate this knowledge into the planning process, eliminating potential problems before they can disrupt the mission. The handbook covers the areas which usually leave leaders guessing, such as pregnancy profiles, exercise during pregnancy, post-partum recovery, field needs of females, and preventive measures for the dormitory environment. The handbook is intended mostly for leaders at the level where the command chain ends and the work begins. The responsibility for female readiness ultimately falls to the female airman themselves. Readiness requires preparation based upon specialist expertise and field experience.

Presenter: A1C Kelly A. Hartley, USAF
Mentor: LTC Byron Calhoun, USAF



Received Command Sergeant Major's Coin

Does Insertion of a Cortical Bone Screw into Bone Change the Torsional Strength? A Biomechanical Study.

MAJ George K. Bal, MC
Orthopedic Surgery Service, Department of Surgery, Madigan Army Medical Center, Ft. Lewis, WA

Purpose: To determine if the torsional strength of a cortical bone screw is compromised by a single insertion and removal. This occurs when a bone screw is placed intra-operatively, judged to be to long, and removed.
Methods: We studied 3 different cortical bone screw sizes: 2.7 mm, 3.5 mm, and 4.5 mm (Synthes, USA, Paoli, PA 19301). The screws were divided into 4 test groups of 10 screws each: I- a control group of screws tested to torsional failure, II- screws inserted into bone, removed, and tested to torsional failure, III- screws placed through a plate, into a centered hole in bone, removed, and tested to torsional failure, and IV- screws placed through a plate, into an eccentric hole in bone, removed, and tested to torsional failure. All screws were inserted with a calibrated, digital, torque screw driver into drilled, tapped holes in fresh-frozen, human femora. All screws were then tested to failure on a materials testing machine. Results: The average failure torque for the 2.7 mm screws was 1.45 ± 0.09 N-m, 2.67 ± 0.07 N-m for the 3.5mm screws, and 5.35 ± 0.09 N-m for the 4.5 mm screws. There were no significant differences among the 2.7 mm and 3.5 mm screw Groups. For the 4.5 mm screws, Group III and IV showed a significant decrease in torsional strength of 0.08 N-m, and 0.13 N-m, respectively, when compared to Control Groups.

Conclusions: Single insertion and removal of 2.7 mm and 3.5mm cortical bone screws does not result in a change in the torsional strength of the screw. The 4.5 mm cortical bone screws did show a small decrease in torsional strength after a single insertion through a plate, and thus the re-use of 4.5mm screws cannot be completely supported.

Presenter: MAJ George K. Bal, MC
Mentor: Stephen Benischke, MD

Scientific Approach to Managed Care (Outcomes Study)

Moderator: COL Bonnie Jennings AN

This section will focus on a portfolio of studies that represent the scientific approach to managed care. Some would find that to be an interesting coupling--science and managed care. Some would argue that managed care has nothing to do with science. Rather it's about mystic, magic, money and a madness insofar as it is creating a seismic heave in this nation's health care.

One way to take the madness out of managed care is through science, or at least through using a scientific approach to examine the world of managed care; to examine what works, what does not, and at what cost. The goal of such examinations is to ensure cost effectiveness is in balance with a complimentary to quality patient care.

This particular scientific approach detours from many classic methodologies. In many respects, we are talking about a new genre of science--a burgeoning field known as outcomes studies. Outcomes studies is a rubric that encompasses both outcomes research, or those studies that examine which interventions are most efficacious, and outcomes management, or those studies that examine efficiency or how to reduce unintended variation and evaluate resource consumption. It is studies in this latter group that mandate a new research prototype. It is also studies in this group that are driven by the pragmatic questions emanating from the operational world of health care delivery. Because of concerns about the cost and quality of care, it is not surprising that outcomes studies are growing exponentially. Rather than viewing quality and cost as opposing forces, our patients are better served if we consider the words of Roper and Hackbarth who noted, "The quality and cost of health care services are as tightly intertwined as fibers of fine silk".

Outcomes management studies have not yet achieved the same level of sophistication and scientific rigor, overall, as more traditional research. And yet, because they focus on compelling questions and issues derived from the real world of health care delivery, we must develop some level of comfort and understanding in dealing with how these sometimes softer data can help us make the hard decisions that surround us today. The series of presentations in this segment of the program exemplify some of the possibilities in outcomes analysis; some of the potential that can be realized by using a scientific approach to managed care.

Using Animated Computer Simulation to Determine the Optimal Resource Support for the Endodontic Specialty Practice at Fort Lewis.

LTC Donald L. Gebhart, MS
U.S. Army-Baylor University Graduate Program in Healthcare Administration

Animated computer simulation was used in this study to determine the optimal resource support (dental assistants and dental treatment rooms) for the endodontic specialty practice at Fort Lewis, Washington. MedModel® Healthcare Simulation software was used to compare five scenarios or models with varying numbers of dental assistants and dental treatment rooms. The models were run for 250 repetitions to simulate one year of operation. Then the model output data were analyzed with statistical tests, and the models were compared using a decision matrix which incorporated the Dental Activity Commander's preferences and the relative performance rating of each model. One-way Analysis of Variance tests indicated that there were significant differences ($p<0.0001$) in the five computer models. The model with two dental assistants and three dental treatment rooms was determined to have the best overall performance, and therefore, to possess the optimal resource support. Based on the results of this study, it was recommended that the endodontist be assigned two dental assistants and be given access to three dental treatment rooms, if possible.

Presenter: LTC Donald L. Gebhart, MS
Mentor: COL William Cahill, MS

The Routine Pregnancy Process: Framework for Clinical Pathway Genesis

1LT Cristen Brandsma, AN
Department of Nursing, Madigan Army Medical Center, Ft. Lewis, WA

Objective: A multidisciplinary approach to track the involvement of routine obstetrical patients from enrollment as outpatients until postpartum discharge was initiated to explore implementation of an early discharge program.
Design: The use of the interdisciplinary team utilizing nursing services as a major and consistent role in each area of expertise was seen as the key to success. The impact of providing comprehensive and holistic care in the context of the five step nursing process: assessing, diagnosing, planning, intervention, and evaluation were utilized. From the analysis, team members were enlisted from obstetrical outpatient nursing services, pediatric nursing, neonatal nursing, family practice department, labor and delivery nursing, pediatric well-child nursing services, obstetrics/ gynecology department, social services, community health nursing, referring hospitals, and pregnant patients including dependent wife and active duty enlisted/ officer members to map out the flow of the patient through the entire pregnancy process.
Setting: The obstetrical, family practice, and pediatric outpatient clinics along with L&D and postpartum inpatient services.
Patients/Participants: The control group were uncomplicated patients seen under the previous system (prior to pathway process) from 1 Mar-31 Aug 94 and the uncomplicated obstetrical study patients seen after the early discharge program (post pathway) from 1 Mar-31 Aug 96.
Interventions: Implementation of the early discharge program after pathway initiation.
Main Outcome Measure(s): Elucidation of framework for how to proceed with a clinical pathway process nesting nursing process in a complicated inpatient and outpatient setting was achieved. Objective outcomes included: patient satisfaction with an early discharge program, identification with barriers to care, recognition of areas for increased quality of care, and cost consequence analysis (previously presented in detail elsewhere).
Results: There were 1,042 total control patients with routine vaginal delivery from 1 Mar-31 Aug 94 totaling 2668 hospital days with a mean number of hospital days of 2.56 per patient (SD-0.878). The study group of early obstetrical discharge patients from 1 Mar-31 Aug 96 with uncomplicated vaginal delivery encompassed 1,050 patients with 1,965 days averaging 1.87 hospital days per patient (SD-1.48) without concomitant increase in unscheduled clinic or emergency room visits. These findings demonstrated a statistically significant decrease ($p<0.05$) in admission length of stay in the early discharge vaginal delivery gravidas. (See Table 1) The total cost of admissions fell from $3,257,628 to $2,399,625 ($1,221/day) showing a cost saving of $858,003 over six months. The average cost per admission fell from $3,126 to $2,285 without an increase in postpartum pediatric or maternal readmissions.
Conclusions: Using a multidisciplinary approach to the nursing paradigm involving the five step nursing process we were able to elucidate the process necessary to identify critical nodes patient care and satisfaction while providing significant cost savings.

Presenter: 1LT Cristen Brandsma, AN
Mentor: LTC Elizabeth Mittelstaedt, AN



RESEARCH DAY AWARD WINNER
"Interdisciplinary" Category

Reduction in HIV Patient Hospitalizations after Adopting HAART

CPT Sue Ellen Fitzgerald, MC[a], LTC Joseph T. Morris, MC[a], MAJ Robert Gibbons, MC[b], COL Ronald Cooper, MC[a]

[a]Infectious Disease Service, Department of Medicine and [b]Department of Medicine, Madigan Army Medical Center, Ft. Lewis, WA

In 1996, the Infectious Disease Service at Madigan Army Medical Center, Ft. Lewis, WA began recommending high activity anti-retroviral therapy (HAART) for all HIV infected patients with a measurable viral burden regardless of CD4 count. Such therapy tends to be highly effective in suppressing the infection and allowing the immune system to recover at least some of its function. Although HAART is expensive, there might be a net savings for the hospital if the admission rate of HIV patients were decreased while on this therapy. To explore this possibility, the hospitalization rates of the HIV positive population followed at the MAMC infectious disease clinic were determined before and after initiation of HAART. The military medical system provides a unique opportunity for evaluating the impact of such a policy because the patients are followed as clinic outpatients, receive their prescriptions, undergo diagnostic studies, and are hospitalized as inpatients in the same institution. In 1997, only 10.3% of patients were hospitalized. In 1994 and 1995, the two years prior to initiation of HAART, 33.3% ($p=0.0003$) and 32.2% ($p=0.0005$) of patients were admitted respectively. Furthermore, a decrease in all cause mortality was noted after initiation of HAART from 13.0% ($p=0.036$) and 12.9% ($p=0.076$) in 1994 and 1995 respectively, to 5.2% in 1997. This decrease in mortality was statistically significant for HIV-related (non-traumatic) deaths. Despite the high cost of these medications, we believe that this reduction in hospitalizations will help to offset the cost of these medicines and that their use in the military HIV positive patient population is appropriate despite the military population's tendency to be diagnosed at an earlier stage in their disease.

Presenter: CPT Sue Ellen Fitzgerald, MC
Mentor: LTC Joseph T. Morris, MC

A Prospective, Randomized, Double-Blinded, Placebo Controlled Trial of Cisapride after Colorectal Surgery

CPT Tommy A. Brown, MC[a], CPT Jerome McDonald, MC[b], CPT Alec Beekley, MC[a], LTC William Williard, MC[a]

[a]General Surgery Service, Department of Surgery and [b]Department of Surgery, Madigan Army Medical Center, Ft. Lewis, WA

INTRODUCTION: The predominant factor prolonging hospitalization and delaying oral intake after colorectal surgery continues to be return of large bowel function. We investigated the effect of the cisapride on postoperative bowel motility.

METHODS: Patients were started on cisapride versus a placebo on postoperative day one after colorectal surgery. Medication was continued throughout the hospitalization. Endpoints included the time to patients' first bowel movement, time of advancement to regular diet, total time of hospitalization, and cost analysis. Results were analyzed using Mann-Whitney U tests.

RESULTS: A total of 37 patients were entered in the study with 17 in the cisapride group and 18 in the placebo group. The median time to first bowel movement, advancement of diet and discharge was 1 day less in the cisapride group compared to the placebo group ($p<0.02$). This effect appeared to be similar for patients undergoing emergent and elective surgery, although sample size was too small to demonstrate this statistically. The cost savings were $1400.00 per hospitalization based on median hospital stay.

CONCLUSIONS: Cisapride use results in statistically significant improvement in post-operative bowel motility after colorectal surgery promoting earlier oral intake, decreasing hospital stay, and improving costs. Cisapride should be added as adjunct treatment in postoperative care after colorectal surgery.

Presenter: CPT Tommy Brown, MC
Mentor: LTC William Williard, MC

Improvement Award Program (IAP)
Moderator: COL Lester H. Reed, MC

Organizational Approach. MAMC is the largest military medical facility and the center of both primary and referred care in Region 11 of the DOD's managed healthcare program TRICARE. This region serves much of the western half of the United States, including Alaska. How can MAMC use incentives to stimulate improvements? The medical center is organized into functional areas which emphasize the "process" of care rather than the departmental delivery of care. The IAP was conceived by a multidisciplinary group including representatives from all major functional areas in our hospital. That same group chartered a ten-member team to produce a plan for review in Sep 96. The resultant program, called the IAP, was to provide both financial and human motivational incentives for generating improvements. Specifically, the improvements were to make managed medical care a success by changing the process of operations as outlined below under the listed award criteria. The current IAP was presented, approved, and funded by our governing body and interdisciplinary fiscal board with final approval by the Commanding General. Individual training in Total Quality Management (TQM) is required for all employees at MAMC and is the basis for the corporate culture of our matrix organization. An annual program of $100,000 was established for incentives to groups which satisfied the IAP competitive objective award criteria. The IAP was empowered to distribute these funds to the teams which showed quantifiable superiority using 1) multidisciplinary and 2) process oriented improvement which increases 3) efficiency, 4) quality or standard, 5) resource management, 6) productivity, and 7) reduces deficit.

Execution. The IAP team solicited "grass roots" proposals for improving the Root Cause issues hindering the process of delivering managed health care. These proposals were submitted by groups organized by those actually performing the work. Continuous Quality Improvement (CQI) was the tool used to develop both the IAP as well as the programs submitted by each award winning team. Standardized electronic template submission forms contained objective competitive categories such as resource, productivity, and fiscal analysis. Successful competition for these awards required development of a "best practice" program. The ten IAP board members objectively evaluated each proposal with the seven point format listed above, resolved reviewer variation, and set requirements for minimum scores. Summaries from the original electronic submissions and the results of these semi-annual boards were delivered in formal, well-attended, and dramatic community ceremonies, published in local news media, forwarded in 1997 to the Army Medical Department (AMEDD) for distribution, and briefed in 1997 to the AMEDD Surgeon General.

Results. In 18 months, 39 projects were selected for awards. These projects included 364 participants, for an average team size of 9.35 people per project. The total resource "saving" or cost avoidance was $11.1 million; thus, a mean of $285,010 per project. The 10 MAMC board members validated the cost avoidance estimates for each project and presented awards in denominations between $1,000 and $10,000. These funds were used locally by the workforce which generated the project to augment education and development at MAMC. The average Return on Investment was $65.39 for each $1.00 invested. The increase in staff involvement in the IAP by ~8%/year, for a 11/2- year total of 12%, indicates MAMC staff supports the program.

Obstetrical Prepacks: Quality Improvement, Enhanced Efficiency, and Cost Containment

COL Carla Howley-Bowland, MC, USA[a], LTC Roderick F. Hume, MC, USA[b], COL William Cahill, MSC, USA[c], CW Susan Willig, (ret) USA[d], MAJ Karen Winter, NC, USAFR[a], Capt Veronica L. Ventura, MC, USA[e], Lt. Col Byron C. Calhoun, MC, USAF[b]
[a]Deputy Commander for Clinical Studies, Womack Army Medical Center, Ft. Bragg, NC and [b]Maternal Fetal Medicine, Department of Obstetrics/Gynecology, [c]Chief of Staff/Deputy Commander for Administration, [d]Logistics Division, [e]Department of Obstetrics/Gynecology, Madigan Army Medical Center, Ft. Lewis, WA

Objective: The purpose of this study was to determine if by applying cost-containment management principles the cost of obstetrical delivery could be reduced.

Study Design: With the logistical database, the previous cesarean and vaginal delivery packs were evaluated for design, equipment and competitive pricing with new prototypes tested for physician acceptability.

Results: The cost of the cesarean pack decreased from $110 to $86 per delivery saving us $9,600 with 10 minutes saved per procedure and the vaginal delivery pack decreased from $37 to $20 savings $30,000 per year with 5 minutes saved per procedure while providing an indefinite shelf life, latex-free, single packaging.

Conclusions: By the use of simple, multidisciplinary re-engineering techniques applied to the logistical arena we were able to save significant amounts of money by simplifying our packing to a non-expirable, latex-free, and single unit package. If these changes are applied across the total DoD births of 60,354 including 10,717 (16.1%) cesarean sections the potential savings is $257,208 and 1,786 technician hours/year and for 49,637 vaginal deliveries (83.9%) and 4,136 technician hours/year.

Presenter: MAJ Karen Winter, RN, USAF
Mentor: LTC Byron C. Calhoun, MC, USAF

Impact of Clinical Pharmacists on Pharmaceutical Expenditures and Patient Satisfaction

CPT C. Becket Mahnke, MC[a], David L Whaley, Pharm.D.[b], David J. Tomich, Pharm.D., FASHP[b], Jill Tanner, Pharm.D.[b], and COL Patrick C. Kelly, MC[a]

Departments of [a]Pediatrics and [b]Pharmacy, Madigan Army Medical Center, Ft. Lewis, WA

In attempting to control costs, managed care organizations have implemented various methods to reduce pharmaceutical expenditures. We studied the effect of a clinical pharmacist enforcing compliance with prescribing guidelines, with regard to cost avoidance and patient satisfaction. Our clinical pharmacist screened prescriptions for medications in five therapeutic classes, and informed practitioners when their choices did not comply with our established prescribing guidelines. A prescription was changed if authorized by the provider, and cost avoidance and patient satisfaction were assessed. Data collected revealed a cost avoidance of $26,727 over the 6 week data collection period; simply projecting this figure over a 12 month period suggests an annual drug cost avoidance of $230,000. With regards to patient satisfaction, over 70% of respondents "strongly agreed" with being pleased with the medication dispensed, and only 11% "strongly disagreed." We conclude that significant pharmaceutical cost avoidance can be realized via the use of clinical pharmacist enforcement of prescribing guidelines, without loss of patient satisfaction.

Presenter : CPT C. Becket Mahnke, MC
Mentor: COL Patrick C. Kelly, MC

Mentor's Cube Presentation

LTC (P) Roderick F. Hume, Jr., MC

The First Annual Madigan Center Research Day celebrates the breadth and depth of scholarly activity performed at MAMC. The basis for this event is a legacy of innovation, discovery, and interdisciplinary collaboration. We give high quality clinical care, while giving our students the capability to provide excellent care in future assignments. And we learn how to give better care, and better teaching through our investigational efforts. We are willing to evaluate our performance and use this feedback to continually improve our process. At the core of this process is the mentor.

A mentor is both teacher, and coach. A guide through the new territory of the attainment of special knowledge and skills. But the mentor facilitates this transformation of the student to become a wise master in their own right. One capable of turning to the next generation to continue the loop of learning. A mentor is an exemplar, not aloof, but not necessarily your "friend". A mentor does not give wisdom, rather a mentor perceives the opportunities for the student to attain wisdom. Being a mentor is painful, hard work. Being a mentor is difficult, and easily misunderstood. A mentor will say just what needs to be said, when it needs to be said, leaving it to the recipient to discover the truth for themselves. This is often not what the protege wants, or thinks that they need. However, the mentor persists by empowering the student in their pursuit. The lever is learning, an active interactive experience. Mutual understanding, subtle communication, direct and frank dialogue are the most critical skills. The mentor always, and at all times, keeps the student's perspective in mind. Not to coddle or protect the protege from life's experiences, but to help them extract the meaning of life's messages. This process is always an integrated activity just below the level of perception. But the student must recognize the mentor. Mentoring must be requested to be received. A mentor is always a leader, a clarion, a coach, a guide, a joker, a teacher. The mentor is the one with the simple image which clarifies during times of confusion, the laugh in the face of adversity, the light touch, the subtle clue. The mentor understands the process and is a master of the interrelated network of growth and development, ever mindfull of the level of maturity of each person involved. A mentor does not choose the protege. Everyone is their student.

A mentor is the master communicator who holds your experience up for your inspection, in all of its facets, so that you can see from many angles. A mentor gives the protege the cube of the shared experience. It is up to the student to build upon that foundation. The first MAMC Mentor's Cube is presented to COL Patrick Kelly, MC.



Research Day Mentor's Cube renamed
the **BG George J. Brown Mentor's Cube**

Medical Education Research

Moderator: COL Patrick Kelly, MC

Medical Education Research seeks to determine the best method to teach, to instruct. How do we take the lead in learning? Curriculum development is only the beginning. How do you impart enthusiasm for life long learning in our students? What is the outcome by which we measure our success? MAMC teaches teachers, cultivates mentors, and empowers the investigator to question our educational process. The presentations today focus upon health care providers in the ambulance, at a clinic, and in a Graduate Medical Education Program.

Consultation Rates for Navy Independent Duty Corpsman in an Acute Care Clinic

CDR (sel) John R. Holman, MC, USN
Department of Family Practice, Madigan Army Medical Center, Ft. Lewis, WA

Purpose: Family physicians manage 90 percent of patients' problems without consulting our specialist colleagues. The consultation practices of mid-level providers such as physician assistants, nurse practitioners and Navy independent duty corpsmen (IDCs) working in family practice clinics have not been described. Having a family physician review consults from a physician extender may prevent excessive specialty consultation.

Methods: For four months, consultation rates were recorded for Navy IDCs seeing patients in the hospital staff sick call. Staff family physicians were available as needed for supervision. Specialty consultation was allowed without restraints. Over the subsequent four months, the IDCs were instructed to discuss all consultations with the supervising family physician. The IDC and family physician together arrived at the best management plan for that patient. Means and confidence intervals were calculated for the consultation rate for each period. The paired, two-tailed t-test was used to compare the data sets for statistical significance.

Results: In the four months without review, the mean consultation rate was 26 percent [18-34 percent, 95 percent confidence interval (CI)]. In the four months with review, the mean consultation rate decreased 64 percent to 9 percent [(2-16 percent, 95 percent CI), two-tailed p=0.01]. With an average of 140 sick call visits each month, 24 fewer specialty consults were written each month when family physician review was required.

Conclusions: Family physician review of Navy IDC consults from a hospital staff sick call significantly reduced the number of specialty consults obtained by these physician extenders. Under managed care, careful scrutiny of a clinic's practice patterns is essential to optimizing the delivery of top quality and cost-conscious health care.

Presenter: CDR (sel) John R. Holman, MC, USN
Mentor: COL Joseph Yetter, MC

Paramedic Decisions with Out-of-Hospital Intravenous Placement

Steve Pace, MD[a] and Fritz Fuller, REMT-P[b]
[a]Department of Emergency Medicine, Madigan Army Medical Center, Ft. Lewis, WA and
[b]American Medical Response, Tacoma, WA

Study Objective: Determine rate of unnecessary (over-treatment) EMS intravenous line (IV) placements. We hypothesized > 10% over-treatment IV placement rate. More occurrences with transport times > 10 minutes, paramedic experience < 2 years, and when a paramedic student was present.

Methods: Consecutive EMS patients were prospectively followed to determine whether an IV was placed or not. Over-treatment was any patient with EMS initiated IV not used in the field or within 60 minutes of the ED stay for fluid bolus or medication administration. We analyzed data on placement and use of IV, ED initiation and/or use, EMS transport times, years of paramedic practice, and presence of a paramedic student. Proportions are expressed with 95% confidence intervals. All IV placements were at the discretion of the paramedic.

Results: 290 patients over 34 days. 165 had IV initiated (147) or attempted (18). 29% ± 5% (84/290) of the patients received an over-treatment EMS IV. 125 patients had no EMS IV. 7 later required IV during first 60 minutes of ED stay. Under-treatment rate was 2.4% ± 1.8% (7/290). Odds ratios (95% CI) are: transport times > 10 minutes, 1.3 (0.7-2.4), < 2 years of experience as a paramedic, 1.1 (0.4-2.7), and paramedic student, 2.4 (1.0-5.4). Conclusions: Over-treatment rate was common at 29% ($p<0.01$). A paramedic student increased the odds (2.4) of over-treatment ($p<0.05$). Under-treatment rate was 2.4%. Paramedics frequently over-treat with little under-treatment.

Presenter: Fritz Fuller, REMT-P
Mentor: Steve Pace, MD

Continuity of Care and Patient Satisfaction in a Family Practice Clinic

MAJ Eric Morgan, MC and LTC Mike Pasquarella, MC
Faculty Development Fellowship, Department of Family Practice, Madigan Army Medical Center, Ft. Lewis, WA

Purpose: Continuity is a tenant central to Family Practice. While short and long-term continuity have both been associated with satisfaction in populations that select and easily change their providers, little is known about the importance of continuity in environments where patients are assigned a provider.

Methods: One-week waiting room survey on all Family Practice Clinic (FPC) patients. Responder's demographic characteristics were compared to a computerized record of the week's clinic visits. Results were analyzed using Chi-square, unpaired t-Test and correlation matrixes. A multiple logistic regression was generated for patient satisfaction based on access, long-term continuity rates and satisfaction with the Primary Care Provider (PCP).

Results: 196 surveys were returned. Distribution rate was 61.6% with a response rate of 68.3%. While responders were more likely to be retired ($p<.05$), responders were not more likely to be seeing their PCP on the survey date ($p=.31$). For the immediate visit, most patients tolerate seeing any provider, with satisfaction only slightly diminished. ($p=.08$) Patients desire greater PCP continuity as annual use increases. ($r=.16$). Although the desire for continuity is not associated at all with FPC satisfaction ($r=.05$), obtaining long-term continuity is. Logistic regression of patient satisfaction reveals that 12% was determined by long-term continuity rates, 23% by PCP satisfaction, and 17% by how easy it was to make the appointment. ($R2=.30$) With high clinic use, PCP satisfaction and long-term continuity rates now account for 78% of patient satisfaction. ($R2=.42$) There is a subset of patients (13%) who value choice of appointment time or provider over continuity. Satisfaction is not diminished in this group despite poor long-term continuity rates. Patients who saw their PCP on the survey date average seeing their PCP twice as often in the long-term. ($p<.0001$). However, it was much more difficult to see one's PCP than to see any provider. ($p=.03$)

Conclusions: With high annual usage, satisfaction becomes increasingly dependent on achieving long-term continuity with a provider the patient likes. While continuity is important, flexibility in allowing patients to see other providers and to change providers is also important. Continuity and satisfaction rates are linked with ease of appointment. Facilitating appointments is important if continuity is to occur for the majority of FP patients.

Presenter: MAJ Eric D. Morgan, MC
Mentor: COL Joseph Yetter, MC

Experimental Design

Moderator: Katherine H. Moore, Ph.D.

The category of "Experimental Design" encompasses the basic science projects. This type of research typically will investigate a fundamental principle of cell biology or physiology, and is the easiest in which to appreciate the values of hypothesis, objective and experimental design. The importance of adherence to these values becomes clear in the ethical imperatives of clinical research. These ethical imperatives involve protection of research subjects, whether animal or human. Above all, rigorous experimental design, facilitates the search for truth, aiding investigators in avoiding fatal flaws. These flaws may remain unrecognized and could lead to false conclusions. We have seen in the papers already presented today that the importance of a hypothesis, objective and good experimental design is consistent throughout any research, including approach to managed care, military unique research and medical education.

The range of topics and experimental models that were submitted is impressive. Mechanisms of inflammation are investigated in two studies, one using an in-vitro human placenta model, the other a laboratory animal (mouse) model. Another animal model (young pigs) was used by the scientists developing new ways to treat airway injuries. One study utilized cells grown in dishes, but could be potentially applied to patients. Two studies have utilized human subjects to answer a clinically important question and lead to the development of new tests for cancer, or therapies to ease patient discomfort after surgery.

Some may view basic science research projects as less important or necessary in a setting such as Madigan compared to other types of research. However, another view is that basic science projects and the disciplined approach necessary for their success are a critical step in the training of physicians and nurses who then proceed to complete other projects and become the mentors for the next generation. The principles of study design, execution, and data analysis that are learned in a laboratory or carefully designed project utilizing human subjects are relevant to the success of any research project. As in industry, in medicine the time lag between an idea being in the realm of basic science and practical application is becoming much shorter. I would not be surprised to find that some of the ideas presented in today's Experimental Design section will soon be applied to patient care. In many ways, researchers at Madigan are at the front of the wave that is leading the pathway of change in medicine.

The Effects of Lipopolysaccharide, an Inflammatory Stimulus, on Placental Production of Interleukin-6 in the Isolated Dually Perfused Placental Cotyledon

MAJ Richard K. Wagner, MC[a], MAJ Christina Apodaca, MC[a], Roger M Hinson, MC[b], Byron C. Calhoun, MC[a], Katherine H. Moore, Ph.D.[c], LTC(P) Roderick F. Hume, MC[a]
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Objectives: Interleukin 6 (IL-6) is a multifunctional cytokine produced in variety of inflammatory conditions. It has been isolated from placental tissue, and increased levels in the amniotic fluid shown to predict intrauterine infection. No studies have examined the ongoing production of IL-6 in the isolated placental cotyledon. Our purpose was to determine if the isolated dually perfused placental cotyledon actively produces IL-6, and to investigate the effects of an inflammatory stimulus on this production.

Study Design: Two cotyledons from each of nine placentas were perfused. The intervillous spaces and fetal circulation of the control cotyledon were perfused with an oxygen-enriched Hank's Balanced Salt and Albumin solution. The intervillous space of the study cotyledon was identically perfused, but the fetal circulation received one of three different concentrations of Lipopolysaccharide, a potent inflammatory stimulus. Effluents from the fetal circulations of both cotyledons were collected at regular intervals and IL-6 concentrations subsequently determined using a commercially manufactured Enzyme Linked Immunosorbant Assay. Perfusion pressures within each group were recorded at regular intervals.

Results: Data was analyzed using repeated measures analysis of variance. Interleukin-6 concentrations were identified and demonstrate a statistically significant increase over time in both the study and control groups ($p = 0.002$). No statistically significant difference between the concentrations of IL-6 in the study and control groups is apparent ($p=0.848$) and no dose-dependent effects of LPS on IL-6 production are revealed in this experiment ($p=0.709$). There is no statistically significant difference in perfusion pressures between the study and control groups.

Conclusions: Interleukin-6 is detectable in the venous effluents of the isolated perfused placental cotyledon and is produced in increasing quantity directly proportional to time. LPS does not appear to modulate the production of IL-6. Treatment with LPS is not associated with a significant change in fetoplacental vascular tone.

Presenter: MAJ Christina Apodaca, MD, MC
Mentor: LTC Byron C. Calhoun, MC, USAF

Effect of a Perfluorocarbon on Interleukin-6 Secretion by Murine Peritoneal Macrophages

CPT Victoria W. Cartwright, MC
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Background: Perfluorochemicals (PFC) when used for partial liquid ventilation have been noted to decrease pulmonary inflammation. Several in vitro studies have demonstrated that PFC decreased inflammatory mediator release, but this effect has not been well documented in vivo. We used a murine peritoneal model to determine whether PFC was pro or anti-inflammatory. Specifically, we hypothesized that the PFC perfluorophenathrene would attenuate inflammation (as assessed by peritoneal lavage fluid IL-6 levels) when administered in combination with pristane, a potent stimulator of IL-6 production.

Methods: Groups of female BALB/c mice were injected intraperitoneally with either 0.5 ml of PFC (n=15), 0.5 ml of pristane (n=6), or 0.5ml each of PFC and pristane (n=14). Peritoneal lavages were performed at five and seven weeks post injection, and lavage fluid IL-6 levels were measured with a commercial ELISA.

Results: IL-6 levels, expressed as mean (SD) in units of pg/ml were as follows: at week five, PFC group 29 (42), Pristane 138 (86), PFC+Pristane 137 (117). At week seven, PFC group 42 (31), Pristane 120 (88), PFC+Pristane 124 (104). Two-way ANOVA identified no significant intra-group differences between values obtained at weeks five and seven, but it did detect a significant between group effect. The PFC group had significantly lower IL-6 levels than either the Pristane ($p<0.01$) or PFC+Pristane group ($p<0.001$), but the IL-6 levels of the Pristane and the PFC+ Pristane groups were not significantly different ($p=0.99$).

Conclusions: Our data indicate that, in this mouse model, pristane induced IL-6 production by peritoneal macrophages was not attenuated by perfluorophenathrene. In fact, this PFC was mildly pro-inflammatory, though much less so than pristane. These results contrast with several in vitro studies which have demonstrated decreased inflammatory mediator production by PFC laden macrophages. Possible explanations for this include differences in the methods of inducing inflammation, the model used to assess inflammation, and the brand of PFC used.

Presenter : CPT Victoria W. Cartwright, MC
Mentor: MAJ Roger M Hinson, MC and LTC Edward Carter, MC

Telomerase Activity in Solid Transitional Cell Carcinoma, Bladder Washings and Voided Urine

MAJ Raymond S. Lance, MC[a], CPT Wade K. Aldous, MS[b], CPT Jason Blaser, MC[c], and MAJ J. Brantley Thrasher, MC[a]

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Telomerase activity has been detected in a wide variety of human malignancies. It appears to be one of the fundamental ingredients necessary for cellular immortality. We sought to determine the incidence of telomerase activity in solid transitional cell carcinoma (TCC) specimens, benign urothelium, bladder washings, and voided urine from patients with TCC identified cystoscopically compared to controls.

Telomerase activity was measured in 26 solid bladder cancers, and 13 benign urothelial specimens using the telomere repeat amplification protocol (TRAP), a polymerase chain reaction (PCR) based assay. Telomerase activity was further measured in the centrifuged cellular material obtained from the bladder washings of 26 patients with TCC, and 40 with benign urologic disease found to have a normal cystoscopy. All patients with hematuria were additionally evaluated with an upper tract radiographic examination and found to be free of malignancy. Voided urine was likewise evaluated in 11 patients with TCC, 12 with benign urologic diseases, and 56 asymptomatic control subjects.

Telomerase activity was detected in 25/26 (96%) solid specimens, 21/26 (81%) bladder washings, and 6/11 (54%) voided urine specimens from patients with histologically confirmed TCC. In the control group, 2/13 (15%) benign urothelial specimens, and 2/56 (4%) voided urine specimens from the asymptomatic volunteer group demonstrated telomerase activity. Of those with benign urologic disease, 16/40 (40%) bladder barbotage specimens, and 6/12 (50%) voided urine specimens demonstrated telomerase activity. Sensitivity and specificity of telomerase as a marker for TCC in the bladder washings group was 81% and 60% respectively, and 54% and 50% in voided urine, respectively.

These data indicate that activation of telomerase is frequent in solid TCC and appears to be a sensitive marker in bladder washings of patients with TCC. We noted an unexpectedly high false positive detection rate in patients with benign urologic diseases, especially those with symptomatic BPH. Further study of a larger number of both bladder cancer patients and those at risk is necessary to determine if telomerase activity could play a role as a diagnostic and/or surveillance marker of TCC.

Presenter: MAJ Raymond S. Lance, MC
Mentor: MAJ J. Brantley Thrasher, MC

Effects of Tamoxifen on Telomerase Activity in Breast Cancer Cell Lines

Amber Marean, BS[a], Mary Jo DeHart, BS[b], Louis Matej, BS[b], Katherine Moore, PhD[b], LTC Kenneth Bertram, MC[c], and CPT Wade K. Aldous, MS[b]

[a] Red Cross Volunteer (Department of Clinical Investigation), [b]Department of Clinical Investigation, and [c]Hematology/Medical Oncology Service, Department of Medicine, Madigan Army Medical Center, Ft. Lewis, WA

Introduction: We tested the effects of Tamoxifen at 4 different concentrations with MCF-7 and MDA-MB-231 breast cancer cell lines. MCF-7 cells are a known estrogen receptor positive cell line, whereas MDA-MB-231 cells, previously thought to be estrogen receptor negative are now shown to have the estrogen receptor beta.

Methods: Both cell lines were grown in the presence of Tamoxifen 10^{-6} through 10^{-9} M for 10 day periods. Cells in separate flasks were harvested daily for determination of total cell number, protein was extracted for determination of telomerase activity, and RNA was extracted for Northern and RT-PCR analysis to measure expression levels of telomerase components and estrogen receptors.

Results: Total cell counts of both cell lines with 10^{-8} M Tamoxifen treatment were lower than control cells and other Tamoxifen treatments from days 4 -10. Telomerase activity levels from 10^{-8} M Tamoxifen treated cells were lower than controls and other Tamoxifen treatments from days 4 - 10. All Tamoxifen treated cells showed recovery with cell growth and telomerase activity within 4 days except the 10^{-8} M treatment.

Summary: Tamoxifen has an effect on cell count and telomerase activity only within the 10^{-8} M concentration. Cells were able to overcome drug inhibition at all other doses after 4 days.

Presenter: Amber Marean, B.S.
Mentor: CPT Wade Aldous, MS

Tracheal Mucosal Healing in Response to Moderate Mucosal Injury Induced by Expandable Metallic Stents

CPT Keith Ulnick, MC[a], MAJ Jonathan Perkins, MC[a], MAJ Kenneth Azarow, MC[b]

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Background/Purpose: To assess tissue inflammation and wound healing from airway stenting with an expandable metallic stent in the pig (Sus Scrofa) trachea.

Method: A prospective, randomized, controlled study involving 32 young pigs, divided into 4 groups of 8, animals (7 experimental and 1control) was conducted. Under direct visualization, a stent was placed endoscopically After stent placement, Groups 1 and 2 underwent euthanasia 3 and 7 days, respectively. Groups 3 and 4 had stents removed on day 7 and were euthanized at day 14 and 21, respectively. Controls underwent bronchoscopy alone. Segments of trachea were evaluated grossly and underwent for H&E and immunohistologic staining.

Results: Tracheal mucosa was minimally impacted by stent placement. Granulation tissue was noted at the proximal end of the stented segment in 90% of the animals. All granulation tissue disappeared after stent removal. Histopathology confirmed the endoscopic and gross findings. Tracheal growth and animal weight gain were unaffected.

Conclusions: Metallic stents induce minimal mucosal reactivity in the pig trachea, as compared to controls. When stents are removed there is resolution of inflammation and rapid wound healing. These findings illustrate the potential advantages of this type of stent as an adjunct in airway reconstruction.

Presenter: CPT Keith Ulnick, MC
Mentor: MAJ Jonathan Perkins, MC



RESEARCH DAY AWARD WINNER
"Innovation" Category

The Effectiveness of 5-Hydroxytryptamine Type 3 (5-HT3) Receptor Antagonists in the Treatment of Narcotic Induced Intrathecal Pruritus: Ondansetron Versus Naloxone

1LT Laura E. Francis, R.N., M.S.N.
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Epidural narcotics are frequently indicated in the control of pain in post operative patients. Pruritus with epidural morphine is reported in 41-100% of patients. To date, naloxone is the treatment of choice to relieve this type of pruritis. Naloxone often reverses analgesia while having a shorter half-life than intrathecal morphine, thus requiring multiple doses to sustain relief from pruritis. Several theories point to the role of seretonin (5-HT) in the regulation and transmission of nociceptive information including pruritis. Ondansetron, a 5-HT3 antagonist, may relieve pruritis with a single dose and will not reverse the analgesia of morphine. The sample population for this study includes 120 OB/GYN patients presenting for non-emergent surgical procedures who's anesthetic plan calls for administration of intrathecal morphine (duramorph) for postoperative pain relief. Once informed consent is obtained, the patients are randomly assigned to medication administration groups (ondansetron or naloxone). Each patient receives duramorph 0.3-0.5mg. intrathecally. Pruritis, pain, nausea and headache are recorded each hour for six hours using a self scored visual analogue scale. At the patient's request a standard pruritis relieving dose of naloxone 0.1mg or ondansetron 4mg intravenously is administered in a double blind manner. If the pruritis is not relieved by the first dose, a second dose may be repeated one time after 30 minutes have elapsed. Mean scores will be tallied and analyzed using an analysis of variance. To date fourteen patients have been recruited into the study. Only two have requested treatment for pruritis.

Presenter: 1LT Laura E. Francis, R.N., M.S.N.
Mentor: LTC Melissa Forsythe, AN, PhD

Case Reports

Moderator: COL Romeo Perez, MC

The critical importance of the timely observation, thoughtfully researched, and carefully presented for review by ones peers remains the keystone for most of the advances in clinical investigation and clinical practice. It is through these little discoveries that specific hypotheses can be formulated and tested in well designed clinical studies. New diagnostic methods or therapies validated through clinical trials. All of this must begin with the precise question: Why did this happen to my patient? What does it mean to others?

"In the beginning is the end, and in the end the beginning." [T.S. Elliot] So we present a few of the many significant case reports presented each year from the Madigan community. Last of the day, but no less important. The most significant contributions made by many distinguished academic physicians were simple case reports. Think of congenital rubella. Think of thalidomide.

We began the days presentations with marching feet, and we end with purple toes. We chase a BB down the airway of a distressed patient. And we discover that a proven medical modality might expose our female soldiers to an unintended consequence. What does each case reveal about the importance of the process of the practice and documentation of medicine. What cases will be measured by great gains.

Madigan Research Day should provide a forum for the significant positive growth in attracting grant support, new ideas, coinvestigational teams, and mentors for our young investigators. I appreciate your outstanding achievement and your willingness to support the success of the First Annual Madigan Research Day.

Decline in Bone Mineral Density with the Development of Stress Fracture in a Female on Depo-Provera®

CPT Gerald J. Harkins, MC[a], COL Gary D. Davis, MC[a], COL Joseph R. Dettori, SP[b], COL Milo L. Hibbert, Mc[a]

[a]Department of Obstetrics and Gynecology and [a]Physical Therapy, Physical Medicine & Rehabilitation Service, Madigan Army Medical Center, Ft. Lewis, WA

Depot medroxyprogesterone acetate (Depo-Provera®) is a popular contraceptive choice among young, physically active women. However, its administration has been linked to a relative decrease in estrogen levels. Since bone resorption is accelerated during hypoestrogenic states, there has been growing concern about the potential development of osteoporosis and fractures with the use of this contraceptive measure.

A physically active 33 year old woman demonstrated a 12.4% drop in femoral neck bone mineral density (BMD), 6.4% drop in lumbar BMD, and 0.8% drop in total BMD with the subsequent development of a tibial stress fracture while on depot medroxyprogesterone acetate. Bone mineralization rapidly improved and the stress fracture resolved with the discontinuation of the medication.

The long-term effects of depot medroxyprogesterone acetate on bone mineralization in physically active women should be more thoroughly evaluated.

Presenter: CPT Gerald J. Harkins, MC
Mentor: COL Milo Hibbert, MC

Combined rigid and flexible endoscopic removal of a steel BB from a peripheral bronchus: a case report

CPT Joseph Ruegemer, MC and MAJ Jonathan Perkins, MC
Otolaryngology/Head and Neck Surgery Service, Department of Surgery, Madigan Army Medical Center, Ft. Lewis, WA.

Removal of aspirated foreign bodies (FB) in the peripheral tracheobronchial tree is challenging, particularly for sharp or smooth non-food objects. FB may become lodged from progressive migration, small size, and repeated attempts at removal. Various removal techniques have been described. We present an alternative technique for removal of a BB impacted in the peripheral lung. The location and nature of the FB required a unique approach for successful removal. The combination of rigid and flexible bronchoscopy provided excellent visualization and maneuverability, ultimately avoiding open surgical removal. This case emphasizes the advantages for bronchoscopists to be familiar with both rigid and flexible techniques.

Presenter: CPT Joseph Ruegemer, MC
Mentor: MAJ Jonathan Perkins, MC

Purple Toes

CPT Brian P. Mulhall, MC
Internal Medicine Service, Department of Medicine,
Madigan Army Medical Center, Ft. Lewis, WA

72 yo Black male with recent PMH significant for right Middle Cerebral Artery Cerebrovascular Accident (started on Coumadin) with outpatient course complicated by DVT (aspirin initiated). Pt. developed a "cellulitis" at an IV site with 2 of 6 screening cultures positive for Staph aureus, and a clinical picture thought consistent with endocarditis. However, all further cultures were negative, as was TTE and TEE. Tagged WBC scan showed diffuse lower extremity endothelial inflammation thought secondary to "bacterial seeding", so pt. received a full 6 week course of antibiotics. Prior to scheduled (repeat) tagged WBC scan, pt. developed symptoms consistent with Congestive Heart Failure. His step-wise, progressive renal failure now corresponded to a markedly depressed Left Ventricular Ejection Fraction (15% vs. 40% one month prior). On hospital day 8, the patient developed painful, necrotic lesions on the toes of both feet thought consistent with embolic phenomenon. All blood cultures were negative, as was evaluation for vasculitis. Due to suspicions regarding cholesterol embolization, a skin biopsy was performed-which was negative. Given a high clinical suspicion, anti-coagulants were stopped. Patient's creatinine stabilized and repeat ECHO showed a return of his LVEF to 40%. At his request, patient was discharged to home. Clinically, he worsened; due to his progressive lethargy, he was again taken to a hospital where he was found to be markedly azotemic. He proceeded into cardiac arrest and could not be resuscitated. Autopsy confirmed the diagnosis of cholesterol microembolization syndrome (CMES).

After case presentation, the diagnosis of CMES (typical presentation and epidemiology) will be discussed; the interesting facets (uncommon presentation in blacks, the endothelialitis, the temporal cardiomyopathy) will be high-lighted; and recent developments and considerations regarding pathophysiology will be introduced.

Presenter: CPT Brian P. Mulhall, MC
Mentor: LTC Joseph Morris, MC; MAJ Maureen Arendt, MC



RESEARCH DAY AWARD WINNER
"Discovery" Category

RESEARCH DAY AWARDS

Each of the 66 presentations were eligible for the 4 awards. The awards were based on judges voting for the best in each of the following categories: Change of Practice, Discovery, Innovation, Interdisciplinary.

The winners were:

Change of Practice - "The Effect of Loaded Foot Marching vs Running on Injury, Fitness, and Performance In US Army Light Infantry Soldiers" presented by CPT Dan C. Norvell, SP

Discovery - "Purple Toes" presented by CPT Brian P. Mulhall, MC

Innovation - "Tracheal Mucosal Healing in Response to Moderate Mucosal Injury Induced by Expandable Metallic Stents" presented by LCDR Keith Ulnick, MC, USN

Interdisciplinary.- "The Routine Pregnancy Process: Framework for Clinical Pathway Genesis" presented by 1LT Cristen Brandsma, AN

Byron L. Stager Research Award

This award is given to residents, submissions are judged on their scientific merit, relevance, objectivity of evaluation, interpretation of results, and the potential importance of the subject of the research.

Recipient of this award for 1998:

The Effect of the Palmaz Balloon Expandable Metallic Stent in the Trachea of Pigs by CPT Joseph L. Ruegemer, MC, Otolaryngology Service, Department of Surgery

Titles of other submissions were:

Evaluation of the Normal Stress Angle of the Subtalar Joint

The Anterior-T Frame External Fixator: A Treatment Option for High Energy Tibia Fractures

The Association Between Telomerase, p53 and Clinical Staging in Colorectal Cancer

Atypical Hyperplasia in the Era of Stereotactic Core Needle Biopsy

The Effect of Perfluorocarbon on Interleukin-6 Production in a Murine Mouse Model

Cost Consequences of Implementation of the Group B Streptococcus Risk Assessment Treatment Guidelines at a Military Teaching Hospital

NM23 "Antimetastatic" Gene Product Expression in Head and Neck Squamous Cell Carcinoma

Success of Preoperative Imaging and Unilateral Neck Exploration for Primary Hyperparathyroidism

Langerhans Cell Density in Human Oral Mucosa: Relationship to Tobacco, Alcohol Consumption and Squamous Cell Carcinoma

The Contribution of the Donor Cornea to Final Corneal Curvature Following Penetrating Keratoplasty

Fellow's Research Award

This award is given to fellows, submissions are judged on their scientific merit, relevance, objectivity of evaluation, interpretation of results, and the potential importance of the subject of the research.

Recipient of this award for 1998:

Neuromotor Development of Low Birth Weight Premature Infants: Results Through Age 2 Years from the Infant Health and Development Program by MAJ Robert I. Miller, MC, USAF, Department of Pediatrics

Titles of other submissions were:

Consultation Rates for Navy Independent Duty Corpsmen in an Acute Care Clinic

Executive Summary Regarding the Family Physician Continuity of Care and Patient Satisfaction Survey

Joyce Award

This award is given to staff, submissions are judged on their scientific merit, relevance, objectivity of evaluation, interpretation of results, and the potential importance of the subject of the research.

Recipient of this award for 1998:

Trimeric Type I Repeats of TSP1 Disrupt Alignment of Human Microvascular Endothelial Cells In Vitro by CPT Aziz N. Qabar, MC, Department of Clinical Investigation

Titles of other submissions were:

Stage Specific Detection and Inhibition Studies of Plasmodium falciparum Telomerase
The Effect of Prednisone on Influenza Vaccine Response in Asthmatic Children

Airway Management in Children with Carniofacial Anomalies

Iatrogenic Airway Stenosis with Recurrent Respiratory Papillomatosis

Otitis Media Health Status Evaluation: A Pilot Study for the Investigation of Cost-Effective Outcomes of Recurrent Acute Otitis Media Treatment

PUBLICATIONS

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Detail Summary Sheets

Dental Command, Western Regional

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/053 **Status**: Completed

Title: A Survey of Sedation and General Anesthesia Techniques of the Oral and Maxillofacial Surgery Practitioner

Principal Investigator: MAJ David K. Fiaschetti, DE

Department: Western Regional Dental Command **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
02/21/1997	Nov 97	09/30/1998

Study Objective: 1) Establish current trends in sedation and general anesthesia techniques used by practitioners in Oral and Maxillofacial Surgery. 2) To determine pharmacological agents used and methods of administration of these agents. 3) Determine availability and usage of monitoring and emergency equipment.

Technical Approach: A national survey of members of the American Association of Oral and Maxillofacial Surgeons will be conducted to update information on sedation and general anesthesia techniques used by Oral and Maxillofacial Surgeons. A statistical set number of randomly selected members will be mailed questionnaires. Practitioners will be questioned concerning their anesthetic techniques to include anesthetic drugs used, methods of delivery, composition of the anesthesia team, as well as anesthesia, monitoring and emergency equipment available. Demographic data will be collected on years in practice, solo vs. group practice, location and practitioner's training. Establishment of current patterns and trends will be made.

Progress: This protocol has been completed. One thousand (1000) questionnaires were mailed to randomly selected members of the American Association of Oral and Maxillofacial Surgeons; 487 usable responses were received. The average age of respondents was 49 with the average time in practice of 18 years. There were responses from all states except North Dakota and Wyoming, with over 50% from ten states. It was found that anesthesia techniques tend to be uniform throughout the practice of Oral and Maxillofacial Surgery. No trends in techniques could be contributed to the practitioner's age, number of years in practice, or geographic region of practice. This study confirmed that oral and Maxillofacial surgeons are well trained at providing office ambulatory anesthesia and are well prepared to handle anesthetic emergencies. Oral and Maxillofacial surgeons are accepting of newer drugs and techniques, but are also not quick to abandon established and tested agents. A manuscript is in preparation.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/046 **Status**: Ongoing

Title: Evaluation of the Efficacy of Post-operative Antibiotics After Orthognathic Surgery

Principal Investigator: MAJ Henry W. Marcantoni, DE

Department: Dentistry **Facility**: MAMC

Associate Investigator(s): LTC Charles R. Weber, DC; COL Andrew A. Vorono, DE; MAJ Timothy Bandrowsky, DE; MAJ Thomas J. Borris, DE

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/19/1996	Nov 96	09/30/1998

Study Objective: To compare the efficacy of a standard perioperative antibiotic regiment with and without a one week postoperative antibiotic regimen for patients undergoing orthognathic surgery in a prospective, randomized, double-blind study.

Technical Approach: Either isolated mandibular bilateral sagittal split ramus osteotomies, isolated maxillary Lefort I osteotomies, or a combination of the two procedures will be performed on all patients enrolled in the study. Patients in each operative group will be further subdivided randomly into one of two groups. The experimental group will receive prophylactic antibiotics as follows: one preoperative dose and intraoperative doses at two hour intervals for the duration of the surgery. The control group will receive the same preoperative and perioperative regimen along with a seven day oral postoperative regimen. The patients will be monitored for objective signs of infection, and WBC counts will be drawn preoperatively and post-operatively at one week.

Progress: Fifty additional patients were entered in FY 98 for a total of 100 subjects entered in the study.

Detail Summary Sheets

Department of Emergency Medicine

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/055 **Status**: Completed

Title: A Randomized, Double-Blind, Multicenter Trial Comparing 10 Days of Oral Therapy with Trovafloxacin - CP-99,219 and 14 days of Oral Clarithromycin for the Treatment of Acute Sinusitis

Principal Investigator: LTC John D. Charette, MC

Department: Emergency Medicine **Facility**: MAMC

Associate Investigator(s): Steven A. Pace, MD; MAJ Janice C. Stracener, MC; CPT Daniel Mcilmail, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/21/1997	Apr 98	09/30/1998

Study Objective: To compare the safety and efficacy of Trovafloxacin (CP-99,219) and Clarithromycin in the treatment of subjects with acute sinusitis.

Technical Approach: A total of 250 ambulatory subjects, aged 18 or more with a medical history and clinical and radiological findings consistent with acute sinusitis will be included. Subjects with acute sinusitis will be randomized in a double-blind fashion to receive either Trovafloxacin 200 mg once daily for 10 days or Clarithromycin 500 mg twice daily for 14 days.

All subjects enrolled will be evaluated at baseline for clinical signs and symptoms of acute sinusitis, including purulent sinus discharge, facial pain, headache, hyposmia, nasal congestion and jaw pain on mastication. In addition, subjects must have findings of acute sinusitis on sinus X-ray. Sinus puncture for microbiological diagnosis is desirable but not required.

Clinical response to therapy will be assessed by the investigator at day 4, end of therapy (day 15), and end of study (day 28). The clinical response will be based primarily on the global assessment of the clinical presentation of the subject at the evaluation time point but compared to the pretreatment assessment. It will be strongly recommended that subjects who fail to respond to treatment should undergo trans-antral aspiration of the sinus for microbiological assessment.

Routine laboratory safety tests will be undertaken pre treatment, at day 4, and end of therapy (day 15). They will be repeated at day 28 if an abnormal result is detected at the end of therapy visit.

Progress: Eight patients were entered in this study, which is completed. It is a milticenter drug trial and results were forwarded to the sponsor.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/061 **Status**: Completed

Title: Second Multicenter Asthma Research Collaboration (MARC-2x): An Observational Study of Acute Asthma Management in Adults

Principal Investigator: LTC John D. Charette, MC

Department: Emergency Medicine **Facility**: MAMC

Associate Investigator(s): MAJ Richard S. Swinney, MC; Steven A. Pace, MD; Jane E. Kelly, R.N.; CPT Earl D. Davis, AN; CPT Viki J. Leefers, AN;

Start Date:	Est. Completion Date:	Periodic Review:
03/20/1998	May 98	N/A

Study Objective: To develop an emergency department (ED) research network for future participation in randomized trials of acute asthma therapy, and to describe current management of acute asthma in participating ED's.

Technical Approach: Eligible patients (ages 18-54) presenting with acute exacerbation of asthma will be enrolled 24 hours a day for one or two weeks (if >10 patients are enrolled in week one, enrollment will stop). During the course of routine management, patients will be interviewed for 15 minutes about their asthma. Important diagnostic and therapeutic details of the ED visit will be collected by chart review after the ED interview. About two weeks later, enrolled patients will be contacted by telephone for a 10 to 15 minute follow-up interview.

Progress: Eight patients were entered in this multicenter observational study. Data were sent to a central coordinating team for analysis.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/116 **Status**: Completed

Title: Incidence of Intravenous Prochlorperazine-Induced Akathisia

Principal Investigator: CPT Daniel L. Drotts, MC

Department: Emergency Medicine **Facility**: MAMC

Associate Investigator(s): CPT Richard D. Brantner, MC; CPT David R. Vinson, MC

Start Date:	Est. Completion Date:	Periodic Review:
07/18/1997	Nov 97	08/20/1998

Study Objective: To determine the incidence of IV prochlorperazine-induced akathisia.

Technical Approach: Akathisia, the syndrome of motor restlessness, is an intensely unpleasant, fairly common side effect of prochlorperazine. This study will investigate the incidence of akathisia in Emergency Department patients who receive intravenous prochlorperazine as per usual standard of care. The study patient (any ED patient for whom prochlorperazine alone is indicated) will receive IV prochlorperazine as per published PDR guidelines. Occurrence of akathisia will be determined by a previously validated akathisia scale at time 0, 30 minutes. We intend to use this incidence data in a follow on study using the same akathisia tool and study setting. This second, prospective, double-blinded, placebo-controlled study, will be designed to determine the efficacy of diphenhydramine in preventing prochlorperazine-induced akathisia.

Progress: This study has been completed. Forty-four of 100 patients receiving prochlorperazine developed prochlorperazine-induced akathisia (PIA) within one hour. Diphenhydramine improved PIA in 29 of 34 patients. Three other patients developed delayed PIA within 48 hours. None of the 40 controls developed akathisia. Single-dose prochlorperazine induced akathisia within one hour in 44% of patients. Delayed PIA was uncommon. Diphenhydramine may prove useful as a therapeutic agent for PIA. A paper was presented at the American Academy of Emergency Medicine meeting and was published in the abstracts.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 97/020	**Status**: Ongoing

Title: A Model for Prehospital 12-Lead Acquisition Without A Dedicated 12-Lead ECG Machine

Principal Investigator: Steven A. Pace, MD

Department: Emergency Medicine	**Facility**: MAMC

Associate Investigator(s): Fritz Fuller, N.R.E.M.T.-P; COL Alice M. Mascette, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/21/1997	May 96	09/30/1998

Study Objective: To verify that a 12-lead ECG obtained with a cardiac monitor/defibrillation unit is comparable in accuracy to that of a dedicated 12-lead ECG machine.

Technical Approach: The management of ischemic chest pain and acute myocardial infarction hinges on early diagnosis and treatment with thrombolytic agents if indicated. It has been shown that prehospital recognition of acute MI using 12-lead electrocardiography and interpreted by nurses/paramedics trained in ECG evaluation can result in significantly faster times to thrombolytics compared to patients who did not receive a prehospital ECG. Today there are several portable 12-lead machines with computer assisted diagnosis available, but they have only recently became available and are very expensive. By utilizing a portable 12-lead machine (Lifepak 10) and demonstrating that it can produce diagnostic quality ECG's, we hope to make available to a large group of prehospital providers 12-lead capability without an increased monetary investment.

Progress: Fifty subjects (100 tracings) have been entered. Data acquisition by ECG readers is still in progress.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/028 **Status**: Completed

Title: Prospective, Randomized, Double-Blind Comparison of the Safety and Efficacy of BAY 12-8039 400 mg QD x 10 Days vs 400 mg QD x 5 Days vs Clarithromycin 500 mg BID x 10 Days for the Treatment of Patients with Acute Exacerbations of Chronic Bronchitis

Principal Investigator: Steven A. Pace, MD

Department: Emergency Medicine **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
11/15/1996	Jan 98	11/21/1997

Study Objective: To compare the safety and efficacy of BAY 12-8039 QD x 5 days vs BAY 12-8039 400 mg QD x 10 days vs clarithromycin 500 mg BID x 10 days for the treatment of acute bacterial exacerbations of chronic bronchitis. The study will include comparisons of the clinical and bacteriological responses of the three regimens during, at the end of therapy and at the follow-up time points. The safety of the three treatment regimens will also be compared.

Technical Approach: This is a prospective, randomized, double-blind, multicenter study comparing the safety and efficacy of BAY 12-0839 400 mg QD x 5 days vs. BAY 12-0839 400 mg QD x 10 days vs clarithromycin 500 mg BID x 10 days for the treatment of patients with acute exacerbations of chronic bronchitis. The duration of therapy will be 10 days of study drug with a 21-28 day follow-up period. Patients will be seen on day 3-5 of treatment, 2-4 days after treatment, 7-14 days after treatment and 21-28 days after treatment. A sputum culture will be obtained at each visit, and CBC and chemistries will be monitored periodically for abnormalities.

Progress: This study was closed to enrollment 27 Feb 98 because the target enrollment quota had been reached. This site enrolled 5 patients who have all completed the study with no serious adverse events.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 97/133	**Status**: Completed

Title: Pain Treatment and Documentation by Paramedics

Principal Investigator: Steven A. Pace, MD

Department: Emergency Medicine	**Facility**: MAMC

Associate Investigator(s): Fritz Fuller, N.R.E.M.T.-P

Start Date:	**Est. Completion Date**:	**Periodic Review**:
10/17/1997	Nov 97	09/30/1998

Study Objective: To determine the frequency of out-of-hospital documentation of pain and morphine administration to trauma patients who are in pain. Subgroups including burns and long bone fractures will be identified and frequency of morphine use in these groups will also be determined. Other variables such as age, gender, documentation of the presence of pain, mental awareness and recent drug or alcohol use will be analyzed to determine their associations with morphine use.

Technical Approach: Patients will be identified by a manual search of all patient care records from Shepard Paramedics for the 6 month study period. Records meeting inclusion criteria will then be copied and attached to a standardized data collection form. Someone blinded to the purpose of the study will then abstract the relevant data from these sheets. One of the authors will then pull the data from the abstraction sheets and enter it into a computerized data base for analysis.

Progress: This study has been completed. In this retrospective study it was found that 18 of 350 injured patients received morphine sulfate. Emergency Medicine Technicians-Paramedics (EMT-P) administered morphine sulfate to 89 of 256 patients with fractures or burns and documented the presence of pain for 237 of 256. Odds ratios were calculated for children, females, patients with alcohol or drug use, and patients with altered mental status. Treatment time in minutes (mean +/- 95% confidence interval) for patients who received morphine sulfate was longer than for patients who did not receive morphine sulfate. Conclusion: 5% of trauma patients received out-of-hospital morphine sulfate for pain. EMT-P administered morphine sulfate to 35% and documented pain in 93% of patients with fractures or burns. The presence of an altered mental status or short treatment time decreased the use of morphine sulfate. An abstract was present at the Joint Services Emergency Medicine meeting and published in the Aug 98 issue of the Annals of Emergency Medicine, page 288.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/139 **Status**: Completed

Title: A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Study to Investigate the Efficacy and Safety of Inhaled Zanamivir (GG167) 10 mg Administered Twice a Day for Five Days in the Treatment of Symptomatic Influenza A and B Viral Infections in Adolescents and Adults

Principal Investigator: Steven A. Pace, MD

Department: Emergency Medicine **Facility**: MAMC

Associate Investigator(s): CPT Michael A. Miller, MC; CPT Mark Buettner, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/19/1997	Apr 98	09/30/1998

Study Objective: 1) To evaluate the efficacy of inhaled zanamivir compared to placebo in the treatment of influenza A and B viral infections; 2) to evaluate the safety and tolerability of inhaled zanamivir compared to placebo in the treatment of influenza A and B viral infections; 3) to evaluate the efficacy, safety and tolerability of inhaled zanamivir compared to placebo in the treatment of influenza A and B viral infections in "high risk" patients; and 4) to assess the impact of treatment of influenza A and B viral infections with zanamivir on patient productivity and healthcare resource use.

Technical Approach: This is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study. All study subjects will receive study medication twice daily for five days. The first dose will be administered at the First Treatment Visit (Day 1). Subjects will attend a Post-Treatment Visit (Day 6) on completion of study treatment and a Follow-up visit on Day 28. Subjects will also be contacted by telephone on Day 3 (during treatment) and day 14 (on completion of the first diary card). Subjects will maintain a dairy with symptom assessment, adverse event and concomitant medications. Safety evaluations will include lab analyses of blood (hematology and biochemistry) and clinical adverse event inquires. Prior to initiating the treatment trial, Madigan will participate in a surveillance study to identify the presence of the influenza virus in the community. Patients will be consented with a short surveillance study form and a throat swab will be performed.

Progress: This study has been closed. Sixteen patients were entered at MAMC. No serious problems occurred. The data have been sent to the sponsor for analysis.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/002	**Status**: Ongoing

Title: Emergency Surgical Procedures Laboratory Training Using the Goat (Capra hircus)

Principal Investigator: Steven A. Pace, MD

Department: Emergency Medicine	**Facility**: MAMC

Associate Investigator(s): MAJ Nathan T. Rudman, MC; MAJ James T. Vandenberg, MC; CPT Garrett R. Baer, SP

Start Date:	**Est. Completion Date**:	**Periodic Review**:
10/17/1997	Oct 00	N/A

Study Objective: The objective of this training exercise is to teach physicians one safe method of performing six life-saving procedures for trauma patients.

Technical Approach: This protocol was rewritten to replace MAMC #94165 (same title) which expired 21 Sep 97.

Procedures to be performed under the supervision of a staff member and the veterinarian assigned to Clinical Investigation include: (1) chest tube insertion, (2) thoracotomy, (3) pericardiocentesis, (4) diagnostic peritoneal lavage, (5) venous cutdown, and (6) cricothyroidotomy. All animals will be anesthetized and then will be sacrificed immediately after the procedures.

Progress: One training session was held in FY 98, utilizing four animals. Twenty medical personnel were trained.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/021 **Status**: Ongoing

Title: Predicting Emergency Medicine Resident Success from Prospective Resident Application Materials

Principal Investigator: Steven A. Pace, MD

Department: Emergency Medicine **Facility**: MAMC

Associate Investigator(s): MAJ Nathan T. Rudman, MC; Stacie J. Patterson ; Terri L. Blake

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/18/1997	May 98	N/A

Study Objective: To identify items in the application materials that correlate with successful completion of the residency by a retrospective review of emergency medicine resident files at MAMC.

Technical Approach: Resident files for DEM residents who commenced training between 1978 and 1993 (approximately 100) will be examined. Resident files will be scored for positive and negative predictor variables dealing with residency candidate academic ability, work ethic, and interpersonal skills. The predictor variables will be statistically analyzed to determine the degree to which they correlate with successful completion of residency training.

Progress: Approximately 120 records have been reviewed and data entry is in progress.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/028 **Status**: Ongoing

Title: Pediatric Intubation Training Utilizing the Ferret (Mustela putorius furo) Model

Principal Investigator: Steven A. Pace, MD

Department: Emergency Medicine **Facility**: MAMC

Associate Investigator(s): CPT Daniel Mcilmail, MC; MAJ Nathan T. Rudman, MC; MAJ James T. Vandenberg, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/18/1997	Dec 00	N/A

Study Objective: To improve the skill of physicians and other health care providers in pediatric endotracheal intubation, thereby improving the outcome of pediatric patients they treat.

Technical Approach: Ferrets will be anesthetized and course participants will be given the opportunity to intubate a ferret employing a laryngoscope and endotracheal tube. Administration and monitoring of anesthesia will be directly supervised or performed by the attending veterinarian. The veterinarian will be present at all times to assist, modify, or terminate the procedure.

Progress: This protocol was rewritten to replace MAMC #94152 (same title) which expired 16 Aug 97.

Four training sessions were held in FY 98, utilizing a total of 22 animals. Approximately 100 medical personnel were trained.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/109 **Status**: Ongoing

Title: A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Study to Investigate the Efficacy and Safety of Inhaled Zanamivir 10 mg Administered Twice daily for Five Days in the Treatment of Influenza in Patients 12 years or over Diagnosed with Asthma or Chronic Obstructive Pulmonary Disease

Principal Investigator: Steven A. Pace, MD

Department: Emergency Medicine **Facility**: MAMC

Associate Investigator(s): MAJ Peter J. Benson, MC; Roger Wang

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/15/1998	Apr 99	N/A

Study Objective: To evaluate the efficacy of inhaled zanamivir administered twice daily over 5 days in the treatment of influenza A and B in patients, 12 years and over, diagnosed with asthma or COPD and to assess the impact of treatment of influenza with zanamivir on patient productivity and health care resource use.

Technical Approach: All subjects will receive study medication twice daily for five days. The first dose will be administered at the First Treatment Visit (Day 1); subjects will attend a Post-Treatment Visit (Day 6) on completion of study treatment and a Follow-up Visit on Day 28. Telephone contact will be made on Day 56 to complete the resource utilization data. Additional unscheduled visits may occur as required (due to exacerbations of underlying disease). Subjects will maintain a diary with symptom assessment, adverse event, pulmonary function results and concomitant medications. Safety evaluations will include lab analyses of blood and clinical adverse event inquires.

Prior to initiating the treatment trial, Madigan will participate in a surveillance study to identify the presence of the influenza virus in the community. Patients will be consented with a short surveillance study form and a throat swab will be performed.

Progress: This protocol has only recently been approved and no patients have been entered.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/062 **Status**: Completed

Title: Third Multicenter Asthma Research Collaboration (MARC-3x): An Observational Study of Acute Asthma Management in Children

Principal Investigator: LTC William S. Powell, MC

Department: Emergency Medicine **Facility**: MAMC

Associate Investigator(s): MAJ Richard S. Swinney, MC; Steven A. Pace, MD; Jane E. Kelly, R.N.; CPT Earl D. Davis, AN; CPT Viki J. Leefers, AN; CPT Michelle L. Heflin, AN

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/20/1998	May 98	N/A

Study Objective: To develop an emergency department (ED) research network for future participation in randomized trials of acute asthma therapy, and to describe current management of acute asthma in participating ED's.

Technical Approach: Eligible patients (children ages 2-17 presenting with an acute exacerbation of asthma) will be enrolled 24 hours a day for one or two weeks (if >10 patients are enrolled in one week, enrollment will stop). During the course of routine asthma management, enrolled subjects and their parents or guardians will be interviewed for approximately 15 minutes about the child's asthma. Important diagnostic and therapeutic details of the ED visit will be collected by chart review after the ED interview. About two weeks later, the parents/guardians of enrolled patients will be contacted by telephone for a 5 to 10 minute follow-up interview.

Progress: Eight subjects were entered at MAMC. Completed surveys have been sent to the central coordinating team for analysis.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/089 **Status**: Completed

Title: A Survey of Physicians to Determine Difficulties with Standard Suctioning Equipment in the Emergency Department During Advanced Airway Management

Principal Investigator: MAJ James T. Vandenberg, MC

Department: Emergency Medicine **Facility**: MAMC

Associate Investigator(s): MAJ John G. McManus, Jr., MC

Start Date:	Est. Completion Date:	Periodic Review:
05/22/1998	May 98	N/A

Study Objective: To survey emergency physicians to determine if standard suctioning equipment is adequate for emergency airway management.

Technical Approach: Physicians attending the annual SAEM meeting, who meet the inclusion criteria, will be asked to complete an anonymous questionnaire about the Airway Management systems they are currently using. Questions include number of emergency intubations performed during the last year, types of suction devices used during resuscitations, physician's feelings on adequacy of these airway management systems, any problems experienced with their current suction system, whether their patients had suffered aspiration, hypoxia, surgical airway, or other unexpected event and physician's opinion if their current emergency suction system should be changed.

Progress: 350 questionnaires were mailed; 304 responded and 266 met the criteria. Eighty-two percent (82%) used the blunt nose yankauer as the primary suctioning device; 15% felt the suction system they used did not clear the airway in an expeditious manner. The most common problems reported with current suction systems were slow evacuation time (35%) and obstruction (29%). Thirty eight percent (38%) reported that one of their patients had suffered due to adequate suctioning and 32% reported that their current suction system should be modified. A manuscript is in the process of being written.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/051 **Status**: Completed

Title: Randomized, Controlled, Double-Blind Trial of the Efficacy of Diphenhydramine in Preventing Prochlorperazine-Induced Akathisia

Principal Investigator: CPT David R. Vinson, MC

Department: Emergency Medicine **Facility**: MAMC

Associate Investigator(s): CPT Daniel L. Drotts, MC; MAJ Peter J. Benson, MC; CPT Timothy P. Barron, MC; CPT Helen M. Sung, MC; CPT Joe L. Sellers, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/16/1998	Sep 98	N/A

Study Objective: To demonstrate the efficacy of IV diphenhydramine in decreasing the incidence of IV prochlorperazine-induced akathisia.

Technical Approach: The study subject (any ED patient cared for by one of the investigators for whom prochlorperazine alone is indicated) will receive IV prochlorperazine and either diphenhydramine or saline. Occurrence of akathisia will be determined by a previously validated akathisia scale both before and after administration of the study drugs.

Progress: This study is completed. One hundred patients were entered in the study . Adjuvant diphenhydramine decreased the incidence of single-dose prochlorperazine- induced akathisia by about 60%. There was a small but significant increase in sedation with co-administration.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/110 **Status**: Ongoing

Title: Randomized, Double-Blind, Comparative Trial of 15-minutes vs 2- minutes Infusion Rates on the Incidence of Prochlorperazine-Induced Akathisia

Principal Investigator: CPT David R. Vinson, MC

Department: Emergency Medicine **Facility**: MAMC

Associate Investigator(s): CPT Alexandre F. Migala, MC; Chad M. Bentsen; CPT Walter A. Fink, Jr., MC; Marcus A. Trione; MAJ James T. Vandenberg, MC

Start Date:	Est. Completion Date:	Periodic Review:
09/15/1998	Jun 99	N/A

Study Objective: To assess the impact of a slow-infusion on the incidence of prochlorperazine-induced akathisia.

Technical Approach: Subjects will receive in a randomized, double-blind fashion both a 2-minute infusion and a 15-minute infusion of saline, one syringe of which will also contain 10-mg prochlorperazine. The presence of akathisia will be assessed in the customary fashion and the incidences will be compared. Data will be gathered to assess the influence of a slow infusion of prochlorperazine on the incidence of prochlorperazine-induced akathisia.

Progress: This is a newly approved study. Only five patients have been entered.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 97/127	**Status**: Ongoing

Title: Efficacy of Clonidine for Prophylaxis of Acute Mountain Sickness

Principal Investigator: CPT Ian S. Wedmore, MC

Department: Emergency Medicine	**Facility**: MAMC

Associate Investigator(s): CPT Alexandre F. Migala, MC; MAJ John G. McManus, Jr., MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
07/18/1997	Oct 98	07/17/1998

Study Objective: A double blind placebo controlled study to determine if clonidine is effective in preventing or reducing the incidence of acute mountain sickness (AMS).

Technical Approach: Climbers will take a study drug dose the night prior to climbing and BID thereafter until returning to sea level. ESQs will be completed at sea level, 6000 ft, 10000 ft, and 14400 ft elevations. These will be completed 15 minutes after arrival at each altitude. Should the climb be terminated due to weather or any other objective condition preventing arrival at the summit, an ESQ will be conducted at the high point obtained. Four doses of study drug will be utilized, this will allow drug to be started 12 hours prior to beginning the climb and continued on a q12 hour basis until the completion of the climb. Results of the ESQs will be analyzed to determine if subjects meet criteria for AMS.

Progress: Forty subjects have been entered (30 in FY 98). Data entry and analysis are in progress to determine if enough subjects have been entered to obtain meaningful results.

Detail Summary Sheets

Department of Family Practice

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 96/127	**Status**: Ongoing

Title: Incidence of Exercise Induced Hematuria After the Army Physical Fitness Test (APFT)

Principal Investigator: CPT Yong H. Chun, MC

Department: Family Practice	**Facility**: MAMC

Associate Investigator(s): MAJ Charles Payne, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/21/1996	Aug 96	08/20/1998

Study Objective: 1) To determine the incidence of hematuria in a young healthy population. (2) To determine the effect of routine exercise such as the APFT on urinalysis for blood and protein. (3) To modify a guideline for assessment of painless hematuria after routine exercise.

Technical Approach: The purpose of this study will be to identify the incidence of exercise-induced hematuria secondary to routine physical training and develop guidelines for proper urine collection and triage of patients found to have hematuria after exercise. 500 male and female ROTC Cadets will be recruited during routine physical examinations which includes a urinalysis. A questionnaire will be completed and urine will be collected following a standard APFT. Urinalysis will check for blood and protein. If positive for blood, the specimen will be forwarded for microscopic study to determine of >3 RBC/HPF are present. If so, the participant will be asked to provide specimens at 24 hrs, 48 hrs, 72 hrs, and 1 week after the APFT. The data will be collected and analyzed as part of a descriptive study.

Progress: One hundred twenty-nine (129) subjects were entered. Data analysis is in progress.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/050 **Status**: Ongoing

Title: Unintended Pregnancy Prevention Program

Principal Investigator: MAJ Diane M. Flynn, MC

Department: Family Practice **Facility**: MAMC

Associate Investigator(s): LTC Jeffrey D. Gunzenhauser, MC; COL Roderick F. Hume Jr., MC; Ann K. Lancaster, CHN; LTC Jeffrey B. Clark, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/21/1997	Mar 97	09/30/1998

Study Objective: The purpose of this study is to evaluate the effect of an intervention consisting of education and facilitated access to contraception on the unintended pregnancy rate of active duty US Army soldiers serving at Ft Lewis, WA.

Technical Approach: This research project is a randomized clinical trial designed to determine the effect of education and facilitated access to contraception on unintended pregnancy rates among female soldiers at Ft Lewis. Effectiveness of the intervention will be determined by: 1) Calculating annualized pregnancy rates using SIDPERS data and positive beta-HCG results from the MAMC clinical laboratory; unintended pregnancy rates will be determined from a survey completed at prenatal care orientation. 2) A questionnaire mailed to women in the Intervention Group and the Control Group one year after the intervention designed to assess contraception use, whether the intervention affected contraception use, and the rate of unintended pregnancy.

Progress: Unintended Pregnancy Prevention Program classes given to 500 active duty women. Surveys administered to approximately 300 pregnant women. Data analysis is in progress. Presentations were made at the US Army Family Practice meeting in March 98, the Washington State Family Practice Conference in April 98, and has been accepted for presentation at the Washington State Conference on Health in October 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/149 **Status**: Terminated

Title: Primary Prevention of Otitis Media Using a Parental Education Model to Reduce Risk Factors

Principal Investigator: LCDR Robert C. Marshall, MC USNR

Department: Family Practice **Facility**: MAMC

Associate Investigator(s): LT Mark Flynn, MC USNR; LT Joan Morris, NC USN

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/16/1995	Aug 96	06/19/1998

Study Objective: The objective of this study is to reduce the incidence of acute otitis media by educating parents to modify known risk factors.

Technical Approach: All infants born at Naval Hospitals Bremerton and Oak Harbor for the month of April, May, June and July 1995 will be screened for exclusion criteria or Tri-care assignment to primary care portal outside of USNH Bremerton or Oak Harbor. If acceptable, the patient will be stratified and randomized to intervention and control groups. Each infant will be given a random number derived from a random number table. The control group will receive usual information on child care. In addition to this information, the intervention group will also receive a parental handout on risk factor modification of known behaviors that increase the risk of otitis media and a 10-15 minute talk by a nursery nurse or corpsperson about modifying these factors. All parents will complete a newborn risk factor questionnaire. At each well baby visit, ER visit and acute clinic visit, the child will be evaluated for otitis media using published criteria for diagnosis and a check-off sheet. Parents and infants in both groups will receive only routine care and counseling subsequent to the initial encounter. Follow-up questionnaires will be mailed at 6 and 12 months.

Progress: This study, in which 211 subjects were enrolled, was terminated due to a greater than 50% dropout rate and a lack of support from other clinics in enrolling new patients.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/101 **Status**: Completed

Title: Postresidency Army Family Practice Inpatient Care and Implications on Residency Training

Principal Investigator: MAJ Eric D. Morgan, MC

Department: Family Practice **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
06/20/1997	Jun 98	06/19/1998

Study Objective: 1) To describe what family practice inpatient work is being done after residency; 2) to describe what inpatient work is being done at residency training locations; and 3) to identify clinically significant differences between post-residency sites and medical center based training and community hospital based training programs.

Technical Approach: Family practice residency involves three intensive years of training to learn and master the breadth of hospitalized and ambulatory medical practice. Training programs are supposed to simulate what graduates encounter after completing residency. This information can derive from anecdotes, impressions, surveys or descriptive studies. There have been no formal descriptive studies in over 10 years evaluating what inpatient care family practitioners are involved in. During this same time period, inpatient medicine has changed substantially. Multicenter retrospective descriptive study generated from chart reviews of approximately 1000 charts from each broad training category of USA MEDDAC post-residency sites, medical center based FP training sites, and community hospital based training FP sites. Data is also reviewed that had been collected, but not previously published, from Fort Sill in the mid-1980s. Descriptive statistical analysis will be performed on data from each site. Residency and post-residency sites are then compared with each other utilizing chi-square analysis. Post-residency sites are similarly compared to historical data from the mid-1980s to demonstrate trends in Army family practice care. Study should objectively demonstrate trends in Army post-residency family practice inpatient care. It should also demonstrate what care the residency training programs are actually involved in. This study will identify priority areas of inpatient training. Areas involving misallocation of resources will also be identified. This will permit better allocation of family practice training time and resources to pertinent inpatient problems.

Progress: This study describes the type of inpatients US Army Family Practice (FP) doctors will encounter after completing residency training and compares it with what they are exposed to during their training. The rank order and frequency of diagnoses differ substantially between the residency and postresidency sites, primarily due to differing population distributions with active duty soldiers underrepresented in the residency inpatient population. The rank order differs even more between the current study and previous studies from more than 10 years ago, probably due to both population differences and changes in inpatient medicine. Focusing on the number of diagnoses per provider per year identifies 32 primary diagnoses commonly encountered in the postresidency sites where residents will not gain individual exposure during their training. To compensate for these deficiencies, Army FP residencies can use the list of deficient inpatient experiences to focus learning from secondary problems, learning from other inpatient team member's problems, focus didactic lessons, or to insure experiences through other departments. Increasing the number of active duty admissions so that resident inpatient experiences more closely parallel practice populations will also help resolve the training deficiencies.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/090 **Status**: Ongoing

Title: Treatment of Nocturnal Leg Muscle Cramps: A Double-Blind Placebo-Controlled Crossover Trial of Magnesium Oxide

Principal Investigator: LTC Guy P. Runkle, MC

Department: Family Practice **Facility**: MAMC

Associate Investigator(s): MAJ Alan J. Barker, MC; CPT John P. Barrett, MC; LTC Bruce A. Woolman, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/19/1996	Jul 96	06/19/1998

Study Objective: To determine the effectiveness of magnesium oxide in reducing or eliminating nocturnal leg muscle cramps when compared to placebo.

Technical Approach: No current pharmacologic agent is approved for use in the treatment or prevention of nocturnal leg muscle cramps. Quinine appears to be an effective remedy but sufficient evidence for its efficacy and safety are lacking. Magnesium supplementation has been given trial in Europe for the treatment of night leg cramps. No studies have been done in this country to assess the efficacy of magnesium. Patients with a history of nocturnal leg muscle cramps and who are experiencing 2 or more cramps per week will be considered for enrollment in this study. Patients will be primarily identified from Family Practice Clinic physician panels with open invitation to other interested patients who are eligible DOD beneficiaries not followed in MAMC FP Clinic. Subjects will be observed via a 2 week symptom diary prior to treatment for 2-weeks with either magnesium oxide or placebo. During the full four weeks of the study, patients will keep a daily symptom diary that will be given to one of the investigators at each clinic visit. These symptom diaries will record the number, severity and duration of muscle cramps experience. The data obtained will be analyzed for statistical significance.

Progress: No additional patients were added in FY 98; four had been entered in FY 97. When Dr. Woolman PCS'd in June 1998, the PI was changed to Dr. Guy Runkle who plans to work on the protocol as soon as time permits.

Detail Summary Sheets

Madigan Cancer Institute

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/071	**Status**: Completed

Title: Breast Health Knowledge and Practice of Female ROTC Cadets

Principal Investigator: Charlene P. Holt, M.D.

Department: MCI	**Facility**: MAMC

Associate Investigator(s): COL Walter K. Imai, MC; Cynthia K. Toft

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/22/1998	Jun 97	N/A

Study Objective: To determine the level of knowledge and preventive practices of this population of college women regarding breast health and cancer prevention.

Technical Approach: Female ROTC cadets participating in the ROTC Advanced Camp at Ft. Lewis will be asked to complete the ROTC Soldier Breast Health Questionnaire while waiting for their physicals in the MAMC Gynecology Clinic. Participants will be instructed not to fill out their Social Security Number or write their names on the questionnaire or answer sheet provided. The descriptive data compiled will include family history, age, ethnic background, menarche, hormonal medication, and knowledge of breast cancer risk factors and mammography recommendations. These data will be added to a database of like information from the two previously held ROTC Advanced Camps in which this questionnaire was previously submitted to cadets.

Progress: Approximately 1200 subjects were studied. Data analysis is in progress and a paper is being written to submit to Military Medicine for publication.

Detail Summary Sheets

Cardiology Service, Department of Medicine

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/007 **Status**: Terminated

Title: Antiplatelet Therapy vs Lovenox plus Antiplatelet Therapy for Patients with an Increased Risk of Stent Thrombosis (ATLAST)

Principal Investigator: MAJ Karen A. Hicks, MC

Department: Medicine/Cardiology **Facility**: MAMC

Associate Investigator(s): COL Alice M. Mascette, MC; MAJ Maureen A. Arendt, MC; LTC Karl C. Stajduhar, MC; MAJ David T. Schachter, MC; CPT John A. McHenry, MC; COL Roger F. Chamusco, MC; MAJ James P. Olson, MC; MAJ Michael D. Eisenhauer, MC; CPT Allan B. Wicks, MC; CPT Kenneth M. LeClerc, MC; MAJ Steven E. Miller, MC

Start Date:	Est. Completion Date:	Periodic Review:
10/18/1996	Nov 97	10/17/1997

Study Objective: The primary objective is to demonstrate that a 14 day regimen of enoxaparin, compared to placebo, reduces the 30 day combined clinical endpoint incidence of death, non-fatal myocardial infarction and urgent revascularization, when each is added to the same concomitant antiplatelet regimen of ticlopidine (14 days) and aspirin (> 6 mos) in patients at increased risk for stent thrombosis.

Secondary objectives include: 1. The comparative composite clinical endpoints at 14 days and 6 months after stent implantation. 2. The comparative incidence of major and minor hemorrhage and specified clinical laboratory changes and adverse events at day 14 (or within 48 hours after ending study-drug treatment) and Day 30 after stent implantation.

Technical Approach: This is a phase III, randomized, double-blind, multi-center, placebo-controlled, parallel group study. Immediately after sheath removal, following stent implantation during percutaneous intervention, eligible patients will be randomly assigned to receive either subcutaneous enoxaparin or matching placebo injections for 14 days, in addition to a concomitant oral antiplatelet regimen of aspirin and ticlopidine. Patients will have follow-up visits at days 5, 14, and 30 when labs will be drawn and they will be assessed for adverse events and clinical endpoints. A follow-up phone call will be made at 6 months.

Progress: The Data and Safety Monitoring Board for the sponsor met on August 10, 1998 , to review the interim analysis data for the ATLAST trail. Based on this review, they concluded that the trial was "unlikely to answer the original question posed or to result in a clinically relevant result," and recommended that it not be continued in its present form. They indicated that changes could be made to the protocol in order to capture an acceptable enrollment. However, those changes would modify the current protocol to such an extent that it would essentially be an entirely new trial. Therefore, it was terminated. Five patients were entered at MAMC. There were two adverse events at MAMC. One subject was admitted for crescendo angina after completion of the treatment phase. The event was not felt to be related to the study drug and the episode resolved satisfactorily. The other patient with a serious adverse event was admitted to the hospital for recurrent angina after stent placement. During the hospital stay, oozing at the femoral sheath removal site was noted. This was treated with a Fem stop and the bleeding ceased. There have been no further bleeding problems .

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/142 **Status**: Completed

Title: A Parallel Dose-Response Study of Sustained-Released Moxonidine in Patients with Congestive Heart Failure

Principal Investigator: LTC James J. King, MC

Department: Medicine/Cardiology **Facility**: MAMC

Associate Investigator(s): COL Alice M. Mascette, MC; MAJ Karen A. Hicks, MC; MAJ James P. Olson, MC; MAJ Maureen A. Arendt, MC; MAJ David T. Schachter, MC; CPT Kenneth M. LeClerc, MC; CPT Allan B. Wicks, MC; MAJ Steven E. Miller, MC; MAJ Theresa A. Horne, AN

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/19/1997	Nov 98	09/30/1998

Study Objective: To evaluate the dose-related change in plasma norepinephrine from baseline to 4 hours post dose after approximately 19 weeks of therapy with placebo or SR moxonidine (up to 1.5 mg BID) in patients with NYHA Class II-IV CHF.

Technical Approach: This is a randomized, placebo-controlled, parallel dose response, multicenter study in patients with congestive heart failure (NYHA Functional Classes II-IV). Each patient's study duration will be approximately 23 weeks, consisting of five phases: Screening, Baseline/Randomization, Dose Optimization, Dose Maintenance and Study Drug Washout. The study is double-blind during the Dose Optimization and Maintenance Phases, and is single-blind during the Placebo Run-In, Baseline, and Study Drug Washout Phases. Doses will be increased at 1 week intervals by 0.3 mg BID until the patient reaches the randomized or maximum tolerated dose (whichever is less). During Dose Optimization, if a patient experiences significant blood pressure reduction, symptomatic hypotension, or other symptoms of intolerance, the dose can be maintained or reduced rather than increased as per protocol. The randomized or maximally tolerated dose will be maintained for a minimum of 12 weeks. Following maintenance phase, patients will receive placebo during a 2-week study drug washout period. Patients will be seen for a screening and then baseline visit, weekly during the 7-week dose optimization period, 4 times during the 12-week maintenance period, and then 2 weeks after study drug washout. Safety assessments will include adverse event questioning, physical exams, ECG and Holter monitor at selected time points, and laboratory tests.

Progress: This study has been closed to patient enrollment. Six patients were enrolled at MAMC, but only one actually was randomized into the study. Of the remaining five patients, two patients had active co-morbid conditions that made them screening failures. One patient dropped out per choice. One patient was dropped per physician's choice. No significant adverse reactions occurred in the patient who completed the study. She is doing well.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/079 **Status**: Ongoing

Title: The Effect of Acute Norepinephrine Infusion on Exercise Oxygen Uptake Kinetics and Efficiency in Patients with Congestive Heart Failure and Normal Adults

Principal Investigator: CPT Kenneth M. LeClerc, MC

Department: Medicine/Cardiology **Facility**: MAMC

Associate Investigator(s): Wayne C. Levy, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/22/1998	Aug 98	N/A

Study Objective: To evaluate the effect of acute norepinephrine infusion on the exercise oxygen kinetics in patients with stable congestive heart failure as well as normal adults; and to evaluate slow oxygen uptake kinetics during a submaximal workload, oxygen debt and deficit, perceived exertion, blood pressure and heart rate responses, and serum lactate responses.

Technical Approach: Norepinephrine or IV placebo will be infused into both normal adults and patients with heart failure, while they do light to moderate exercise for six to ten minutes. Calorimetry will be used to measure oxygen use before, during, and after this exercise.

Progress: Exercise testing and initial data analysis have been conducted on 11 healthy adult subjects and on two heart failure subjects. The procedure has been well tolerated. Too early for any other conclusions.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/140 **Status**: Ongoing

Title: A Double-Blind, Placebo-Controlled, Parallel Design Study to Determine the Effect of 75 or 100 mg of Orally Administered Azimilide Dihydrochloride versus Placebo on Survival in Recent Post-Myocardial Infarction Patients at Risk of Sudden Death

Principal Investigator: COL Alice M. Mascette, MC

Department: Medicine/Cardiology **Facility**: MAMC

Associate Investigator(s): MAJ Maureen A. Arendt, MC; MAJ Karen A. Hicks, MC; MAJ James P. Olson, MC; LTC James J. King, MC; MAJ David T. Schachter, MC; CPT Kenneth M. LeClerc, MC; CPT Allan B. Wicks, MC; MAJ Steven E. Miller, MC; MAJ Theresa A. Horne, AN

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/19/1997	May 99	09/30/1998

Study Objective: To evaluate the effects of 75 mg of azimilide dihydrochloride versus placebo or 100 mg of azimilide dihydrochloride versus placebo on all-cause mortality, based on longitudinal intent-to-treat observations in patients with a recent (within 6 to 21 days) acute MI, low left ventricular ejection fraction (15 to 35%), and low heart rate variability (<= 20 U). These patients are defined as "at high risk" of sudden death.

Technical Approach: This is a randomized, double-blind, placebo-controlled, multi-national study at approximately 500 study centers. A treatment regimen consisting of daily oral doses of 75 or 100 mg of azimilide dihydrochloride will be compared to a placebo group in a parallel design. Patients will be equally randomized across all 3 treatment groups. Patients who have recently experienced an acute MI and meet other study entrance and screening criteria will receive their first dose of study medication within 6-21 days of that MI. Once-daily treatment will be administered for approximately one year. No specific hospitalization is required for treatment. Screening procedures (to include a 24 hour Holter monitor) will be done to determine the group "at high risk" of sudden arrhythmic death. Evaluations during the treatment period will take place at Week 2, and at Months 1, 4, 8, and 12. Monthly serum pregnancy tests will be performed on females of childbearing potential who are not surgically sterile. Patients who complete 365 days of dosing will be followed for one month after completion of their participation in the study. Patients who withdraw from the trial early will return within 4 weeks for study exit procedures and furthermore, will be followed to assess survival status until the time at which they would have completed 365 day of dosing had they remained in the trial. Safety monitoring will include but is not limited to, clinical laboratory test results, 12-lead ECG measurements and frequency and severity of adverse events.

Progress: One patient has been entered and is in the follow-up phase of the study. Internationally, approximately 350 subjects have been enrolled. No preliminary reports are available at this time.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/073 **Status**: Terminated

Title: Aminophylline to Attenuate the Bradycardic and Hypotensive Response Observed with Intracoronary Administration of High Osmolar Contrast Agents

Principal Investigator: MAJ Steven E. Miller, MC

Department: Medicine/Cardiology **Facility**: MAMC

Associate Investigator(s): CPT Thomas M. Roe, MC; MAJ Patrick A. Cambier, MC; Jacquelline Gillet, RN; LTC Karl C. Stajduhar, MC

Start Date:	Est. Completion Date:	Periodic Review:
02/16/1996	Jun 96	09/30/1998

Study Objective: The intent of this study is to determine whether the bradycardia and hypotensive response that is commonly encountered during intracoronary injection of high osmolar contrast agents can be prevented by intravenous aminophylline administration. A secondary objective is to determine whether intracoronary injection of high osmolar contrast agents ipsilateral to the origin of the sinus nodal (SA) artery leads to an increased incidence of bradycardia and hypotension.

Technical Approach: We intend to enroll 50-200 consecutive patients undergoing an elective cardiac catheterization. Patients will be consented at the time of their standard pre-catheterization appointment by the cardiac catheterization lab nurse. Patients will have orthostatic vital signs recorded to establish that they are euvolemic prior to receiving standard pre-catheterization medications. Standard cardiac catheterization procedures will be followed. After intraarterial access is obtained, baseline hemodynamic data will be recorded. Prior to the initial injection of contrast media, the patient will be randomized in a double blind fashion to receive either aminophylline 5 mg/kg IV over 5-10 minutes or the equivalent volume of saline placebo. A 15 second strip of the ECG and blood pressure will be recorded just prior to injection of contrast in both the left and right coronary arterial systems, and for one minute post injection. The pre-contrast heart rate and blood pressure, and minimum heart rate and blood pressure during contrast injection, will be determined. A comparison will be made between the absolute and percentage change in heart rate and blood pressure during contrast injection in the treated vs. placebo group. Also reported will be the need for additional therapies to treat hypotension and bradycardia (e.g. atropine, fluid boluses, need to change contrast agents, or the need for temporary pacing) in each group. The angiograms will be studied to determine the origin of the sinoatrial (SA) artery (left or right coronary artery). The data will be analyzed to determine whether intracoronary injection ipsilateral to the origin of the SA artery will manifest greater incidence of bradycardia and hypotension.

Progress: Thirty patients were entered in this study by the original PI, Dr. Stajduhar. The current PI has terminated the study at MAMC because there is almost no difference in cost any longer, and he feels that his limited research time can be better spent on other projects. The data already collected have been sent to Dr. Stajduhar who is now at BAMC and will submit the protocol for approval to continue it at that site.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/108 **Status**: Ongoing

Title: A Comparison of Transradial versus Transfemoral Approach to Diagnostic Cardiac Catheterization: Patient Attitudes, Physician Attitudes, and Procedural Variables

Principal Investigator: MAJ Steven E. Miller, MC

Department: Medicine/Cardiology **Facility**: MAMC

Associate Investigator(s): MAJ David T. Schachter, MC; LTC James J. King, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/15/1998	Apr 99	N/A

Study Objective: (1) Comparisons of physician preferences and dislikes for two different arterial access approaches (radial artery verses femoral artery) to cardiac catheterization, (2) comparison of patient preferences and dislikes for two different arterial access approaches (radial artery verses femoral artery) to cardiac catheterization, and (3) to compare arterial access times, total case times, fluoroscopy times, volume of contrast used, number of catheters used and complication rates for both transradial and transfemoral approaches.

Technical Approach: 100 subjects, who require cardiac catheterization, will be randomized to either radial artery or femoral artery cardiac catheterization. Measures will be taken on arterial access times, contrast volumes, coronary angiography times, left ventriculography times, total fluoroscopy times and number of catheters used. Surveys on physician and patient satisfaction will be obtained.

Progress: This is a newly approved study. No patients have been entered to date.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/037 **Status**: Terminated

Title: Impact of Aorto-Coronary Bypass Graft Markers on Graft Patency: A Prospective Trial

Principal Investigator: MAJ James P. Olson, MC

Department: Medicine/Cardiology **Facility**: MAMC

Associate Investigator(s): MAJ Patrick A. Cambier, MC; MAJ Herman E. Collier III, MC; COL Alice M. Mascette, MC; LTC Blaine R. Heric, MC; Terry L. Eisenhauer; CPT Louis C. Coyle, MC; Bonnie Goodman; CPT Lisa Snyder, AN, USAR; MAJ Michael D. Eisenhauer, MC; LCDR Jeffrey Carstens, MC, USNR

Start Date:	Est. Completion Date:	Periodic Review:
12/15/1995	Jun 97	09/30/1998

Study Objective: To address the impact of aorto-coronary bypass graft marker placement on graft patency in response to the widespread opinion that they may adversely affect graft patency.

Technical Approach: A power analysis has been performed to estimate required sample size. To detect a 10% adverse effect on graft patency, we estimate that 296 patients would be required, and to detect a 15% adverse effect, 132 patients would be required. Our sample size of 200 exceeds that needed to detect a 15% difference, and approaches the sample size needed to detect a 10% difference. Options include (1) extending the protocol for 6 months (if necessary after statistical evaluation has been completed for the first 200 cases), and (2) inviting BAMC to become involved with the protocol. All data will be compiled on a Microsoft EXCEL or ACCESS spreadsheet, allowing import or export of data to available software-statistical programs, including MacIntosh programs currently in use by MAMC's Department of Clinical Investigations.

A weighted student's t-test will be performed to compare patency rates obtained from the 6-month angiography. Patient characteristics between the "marked" and "unmarked" (i.e.: experimental and control) groups will be compared with Chi-square testing. If profile characteristics are low in frequency, Fisher's Exact-testing will be substituted. P-values of <0.05 will be required to define statistical significance.

Progress: No new patients were entered in this study at MAMC in FY 98 due to a lack of sufficient time and support personnel. Therefore, MAMC participation in the study was terminated. Eighty-five patients had been enrolled at MAMC in previous years. The protocol will be continued at BAMC and Naval Hospital San Diego.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/069 **Status**: Ongoing

Title: Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)

Principal Investigator: MAJ James P. Olson, MC

Department: Medicine/Cardiology **Facility**: MAMC

Associate Investigator(s): MAJ Patrick A. Cambier, MC; COL Roger F. Chamusco, MC; COL Alice M. Mascette, MC; MAJ Herman E. Collier III, MC; LTC Karl C. Stajduhar, MC; MAJ Michael D. Eisenhauer, MC; CPT John A. McHenry, MC; MAJ Maureen A. Arendt, MC; CPT Thomas M. Roe, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/16/1996	Mar 01	02/20/1998

Study Objective: 1) To compare whether optimized antiarrhythmic drug therapy administered to attempt to maintain sinus rhythm has an impact on total mortality when compared to optimized therapy which controls the heart rate. 2) Since stroke is such an important endpoint in trials of patients with atrial fibrillation, composite endpoints will include the following: total mortality, disabling stroke or anoxic encephalopathy, major bleeding and cardiac arrest; cost; quality of life.

Technical Approach: This is a multi center trial sponsored by the National Heart, Lung, and Blood Institute. The purpose is to compare the effect on survival of two different treatment plans in patients with atrial fibrillation. One treatment is aimed at rate control and the other at maintaining a normal sinus rhythm. The primary physician will choose which drug or drugs are used to obtain each treatment objective. The physician will initially determine the treatment to convert patients to normal sinus rhythm after which the patient will be randomized to one of the treatments described above. Patients will be followed at month 2 and 4 and then at least every 4 months until the year 2001. Patients will complete a quality of life questionnaire and have an assessment of their functional status completed at various time points. Patients who fail their assigned treatment or are intolerant will continue to be followed regardless of crossover to another therapy. We anticipate enrolling 15 patients at Madigan Army Medical Center.

Progress: Five subjects were entered in this study in FY 98 for a total of 19 entries. The enrollment date has been extended to 31 Oct 99. No adverse events have occurred.

The principal investigator was changed from MAJ Maureen Arendt, MC, to LTC James P. Olson, MC, in June 1998.

Detail Summary Sheets

Endocrinology Service, Department of Medicine

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/083 **Status**: Completed

Title: The Polar T3 Syndrome: Metabolic and Cognitive Manifestations, Their Hormonal Regulation and Impact Upon Performance

Principal Investigator: LTC Homer J. Lemar Jr., MC

Department: Medicine/Endocrinology **Facility**: MAMC

Associate Investigator(s): COL H. Lester Reed, MC; CPT Nhan V. Do, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/15/1996	Oct 97	03/20/1998

Study Objective: This is a subportion of the blanket protocol "The Polar T3 Syndrome: Metabolic and Cognitive Manifestations, Their Hormonal Regulation and Impact Upon Performance". In this subportion we will: (1) Evaluate the response of central nervous system hypothyroxinemia in the development of the Polar Triiodothyronine (T3) Syndrome to thyroxine (T4) administration using the cognitive parameters of memory and mood; (2) Define the role of decreasing skeletal muscle efficiency in the increased energy requirements observed in the Polar T3 Syndrome; and (3) Evaluate the effect of thyroxine supplementation on muscle efficiency and energy utilization during development of the Polar T3 Syndrome.

Technical Approach: Sixteen military and civilian health care beneficiaries including men and women who are between 18 and 55 years old and are members of the winter-over crew in McMurdo, Antarctica will be recruited for the study. Subjects will perform monthly exercise, mood, and cognitive testing beginning one month prior to departure and continuing through their entire 11 month stay in McMurdo. The parameters that will be examined include changes in muscle oxygen utilization, changes in thyroid functions, and changes in cognitive, memory, and mood during the development of the Polar T3 Syndrome. One of the characteristics of the Polar T3 is a low T4 state in the CNS that may be responsible for the characteristic decline in mood and memory during winter seasons in circumpolar regions. It is proposed that T4 supplementation can correct the low T4 state in the CNS and thus attenuate the syndrome. All subjects will be placed on placebo for the first 6 months of the study, then one-half of the subjects will be switched from placebo to levothyroxine 50 mg per day in a double blind fashion. Thyroid functions will be monitored monthly throughout the study. Subjects will serve as their own controls for analysis of mood and cognitive data. Comparisons will also be made between levothyroxine and placebo groups for the exercise, mood, and cognitive testings.

Progress: Sixteen subjects were enrolled in this study. Previous studies showed a CNS hypothyroxinemia state represented by a 30% increase in TSH over 11 months. This study describes that L-thyroxine supplementation reverses the decline in memory encountered during extended Antarctic residence. These changes in memory may represent changes in attention, short-term memory, or both, and further study is needed.

Seasonal changes in thyroid function associated with the Polar T3 syndrome are significantly associated with changes in mood. Thyroxine supplementation offers a potential intervention to improve mood and well being during extended Antarctic residence.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/124 **Status**: Ongoing

Title: The Effect of Partial Energy Restriction on the Changes in Metabolic and Kinetic Measures of Thyroid Hormone Metabolism During Antarctic Residence

Principal Investigator: COL H. Lester Reed, MC

Department: Medicine/Endocrinology **Facility**: MAMC

Associate Investigator(s): LTC Homer J. Lemar Jr., MC; CPT Nhan V. Do, MC; Nancy S. Finney

Start Date:	Est. Completion Date:	Periodic Review:
07/18/1997	Oct 98	07/17/1998

Study Objective: 1) To evaluate the influence of circulating TSH and energy restriction upon the previously described increases in triiodothyronine (T3) plasma appearance rate and distribution volume (Vd) observed with extended Antarctic residence (AR). A reduction in serum TSH will be obtained by using 50mcg per day of thyroxine supplementation for the entire 11 month period, in contrast to our current study evaluating thyroxine supplement during the last 7 months of deployment. This dose schedule will allow an extension of our earlier findings regarding the effects of AR upon memory performance in this group. 2) To continue our previous mood and cognitive studies in the current study by contrasting placebo and thyroxine supplementation to insure the cognitive performance goal of supplementation has been achieved during the year as identified in our previous study.

Technical Approach: Sixteen military and civilian health care beneficiaries including men and women who are between 18 and 55 years old and are members of the winter-over crew in McMurdo, Antarctica will be recruited for the study. After recruitment subjects will perform monthly exercise, mood, and cognitive testing beginning one month prior to departure and continuing through their entire 11 month stay in McMurdo. The parameters that will be examined include changes in muscle oxygen utilization, changes in thyroid functions, and changes in cognitive, memory, and mood during the development of the Polar T3 Syndrome. One of the characteristics of the Polar T3 Syndrome is a low T4 state in the CNS that may be responsible for the characteristic declines in mood and memory during winter seasons in circumpolar regions. All subjects will receive either thyroxine 50mcg/day or daily placebo starting the day after October 1997 baseline studies and ending 11 months later in August 1998. Thyroid functions will be monitored monthly throughout the study. Subjects will serve as their own controls for analysis of kinetic parameters, mood and cognitive data. Comparisons will also be made between levothyroxine and placebo groups for the exercise, mood, cognitive testing, and kinetic parameters.

Progress: FY 98 began with the establishment of personnel and activities to conduct the study and collect data for this protocol in McMurdo Station, Antarctica. Community outreach, recruiting, and satisfactory subject number, as well as baseline studies were conducted on site by the team deployed in Oct 97 and the study was begun. The study team was again deployed in Jan 98 and Aug 98 for periodic studies. All planned periodic testing was completed, with the final studies done in Sep 98 with all samples shipped to MAMC and WRAMC for assays and evaluations. Interim results of the first four months of evaluation have confirmed findings of the previous year of Antarctic studies. The serum TSH values in the placebo group were elevated after four months of Antarctic residence while TSH levels in the LT4 treatment group were not increased. This preliminary finding supports the T4 supplement methodology outline in the protocol. Further assays are currently under way. A manuscript has been submitted to the Antarctic Journal for consideration for publication.

Detail Summary Sheets

Gastroenterology Service, Department of Medicine

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/005 **Status**: Ongoing

Title: Intron A + Ribavirin for Treatment of Patients with Chronic Hepatitis C not Previously Treated with Interferon

Principal Investigator: MAJ William K. Hirota, MC

Department: Medicine/Gastroenterology **Facility**: MAMC

Associate Investigator(s): COL Amy M. Tsuchida, MC; LTC Robert H. Sudduth, MC; LTC Spencer S. Root, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
10/17/1997	Dec 98	N/A

Study Objective: To provide ribavirin for use in combination with Intron A for the treatment of Hepatitis C in patients who have not previously received interferon therapy; to obtain additional safety information on the combination of Intron A and ribavirin; to obtain additional information on different regimens of Intron A and ribavirin.

Technical Approach: Subjects will be randomized to either Intron A plus ribavirin or Intron A plus placebo. Treatment for the first 12 weeks will be double-blind. At 12 weeks, blood test for HCV-RNA will be done to assess response. If the test is positive, treatment will be unblinded and those on placebo will be offered cross over to treatment with Intron A plus ribavirin. If they were on ribavirin, they will be finished with the study. If the test is negative, subjects will continue with their current blinded treatment.

Progress: Seven patients have been entered in the protocol. The drug assignment was unmasked for two patients who had persistent viremia, and both were receiving placebo. Both have elected to crossover to open-label Ribavirin plus Intron A. MAMC has experienced one major complication. The patient experienced an episode of self-limited tunnel vision which was thought to be due to migraine aura. On further assessment, the patient was found to have either a perfusion defect or a blockage (or both) of the choroidal circulation of the left eye. This lesion may be associated with Intron A. The patient was taken off protocol, and is being followed in the Ophthalmology Service without any specific visual acuity defects.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/006 **Status**: Ongoing

Title: Intron A + Ribavirin for Treatment of Patients with Interferon-Refractory or Interferon-Relapsed Chronic Hepatitis C

Principal Investigator: MAJ William K. Hirota, MC

Department: Medicine/Gastroenterology **Facility**: MAMC

Associate Investigator(s): COL Amy M. Tsuchida, MC; LTC Robert H. Sudduth, MC; LTC Spencer S. Root, MC

Start Date:	Est. Completion Date:	Periodic Review:
10/17/1997	Dec 98	N/A

Study Objective: To provide ribavirin for use in combination with Intron A for the treatment of Hepatitis C patients who failed previous interferon therapy or relapsed after treatment with interferon; to obtain additional safety information on the combination of Intron A and ribavirin; to obtain additional information on different regimens of Intron A and ribavirin.

Technical Approach: Patients will be treated throughout the study with open-label Intron A and ribavirin; dose dependent on weight. Safety and tolerance will be evaluated at weeks 1, 2, 4, 8, and then every 4 weeks during treatment and at weeks 4, 8, 12, and 24 until the end of therapy. Complete response will be defined as loss of detectable HCV-RNA by PCR.

Progress: Two patients were enrolled in this study in FY 98. One, at the three month follow-up, showed no evidence of hepatitis C virus by bDNA techniques. The patient continues on to complete the 48 week protocol. The other subject complained of new onset exertional chest pain which was relieved by rest. The suspected etiology of the chest pain is underlying ASCAD, but the sponsor elected to take the patient off study.

The FDA approved Ribavirin in June 98 for hepatitis C relapsers and it is presently being received by MAMC through a CRDA. Subject #2 is being treated with Ribavirin at a reduced dose off protocol and is doing well.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/164 **Status**: Ongoing

Title: Epidemiology of Gallbladder Sludge and Stones in Pregnancy

Principal Investigator: COL Amy M. Tsuchida, MC

Department: Medicine/Gastroenterology **Facility**: MAMC

Associate Investigator(s): Sum P. Lee, M.D., Ph.D; MAJ Kazunori Yamamoto, MC; COL Roderick F. Hume Jr., MC; LTC Byron C. Calhoun, MC; Scott J. Schulte, M.D.; Beth W. Alderman, M.D., MPH; Gerard Schallenberg, M.D.; Edward J. Boyko, M.D., Ph.D.; Gail Jarvik, M.D.; Katherine H. Moore, Ph.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/20/1996	Sep 02	09/30/1998

Study Objective: The primary objective of this NIH-funded study is to determine the incidence of gallstones and sludge during pregnancy. Other objectives are to: 1) identify behavioral and genetic risk factors for the development and regression of sludge and stones; 2) elucidate the mechanism by such risk factors may induce gallstones; and 3) predict the development and regression of sludge and stones.

Technical Approach: This cohort study will include serial ultrasound tests of the gallbladder during pregnancy and post-partum. All women presenting for prenatal care will be eligible unless they: (1) do not speak English; (2) have had gallbladder surgery; (3) are over 20 weeks pregnant; (4) do not expect to deliver at MAMC; and (5) are less than 18 years of age. Eligible women who agree to participate will complete Participation and Consent Forms and under waist and hip circumference measurements. the ultrasonographers will test participants for evidence of sludge and stones at 10, 18, and 28 weeks of gestation and 6 weeks postpartum. For each ultrasound test, the study radiologist will review selected ultrasound images saved by the ultrasonographer. Participants who have stones or sludge at 6 weeks postpartum will return in 12 year for a follow-up ultrasound. At her time of each ultrasound, participants will be asked to complete a one-hour questionnaire and interview. They will also be asked to give an extra fasting blood sample at 128 weeks of gestation. Medical data from the CIS and CHCS will be downloaded and linked to study data.

Progress: 2,420 pregnant women have been enrolled to date. There are currently 1,922 women in the study of whom 795 have completed the post-partum examination and interview. Seventy-eight women have been identified as requiring a follow-up at one year post-partum because of incident stones or sludge identified during pregnancy, About 14% of the data have been entered using ACCESS screens.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/012 **Status**: Ongoing

Title: A Pre-Clinical Research and Development Study to Evaluate Stool Specimens for Basement Membrane Fragments/Complexes and Cytoskeletal Proteins

Principal Investigator: COL Amy M. Tsuchida, MC

Department: Medicine/Gastroenterology **Facility**: MAMC

Associate Investigator(s): LTC Robert H. Sudduth, MC; MAJ Kazunori Yamamoto, MC; MAJ John G. Carrougher, MC

Start Date:	Est. Completion Date:	Periodic Review:
11/15/1996	Oct 97	11/21/1997

Study Objective: Evaluate the clinical utility potential of the CoTA test strip assay in detecting basement membrane complexes in individuals with or without colorectal cancer, respectively. And to isolate sufficient amounts of colon BMC for additional antibody production and antigen characterization using the CoTA test strip assay and other antibody tests.

Technical Approach: This is a multicenter trial with MAMC providing stool specimens only from patients diagnosed with colorectal cancer. Following colonoscopy, eligible participants will be instructed to collect a stool specimen after their stools have returned to normal and prior to any other intestinal procedures. The specimen will be shipped directly to BARD Diagnostic Sciences, Inc.

Progress: Thirteen subjects have been enrolled to date, with no problems encountered.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/004	**Status**: Ongoing

Title: Epidemiology of Barrett's Esophagus

Principal Investigator: COL Amy M. Tsuchida, MC

Department: Medicine/Gastroenterology	**Facility**: MAMC

Associate Investigator(s): Diana C. Farrow, Ph.D.; MAJ William K. Hirota, MC; LTC Spencer S. Root, MC; LTC Robert H. Sudduth, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
10/17/1997	Jun 01	N/A

Study Objective: To determine whether there are any specific environmental, dietary, or personal factors which increase the risk of developing Barrett's Esophagus.

Technical Approach: This will be a case-control study. Cases will be patients 20-79 years of age who receive a new histologically-confirmed diagnosis of Barrett's esophagus following upper endoscopy for refractory gastroesophageal reflux disease (GERD), in two large hospitals in western Washington state between 1 Oct 97 and 30 Sep 2000. They will be compared to two control groups. Population controls will be randomly selected by a modified random digit telephone dialing technique and GERD controls will consist of a random sample of patients undergoing upper gastrointestinal endoscopy for GERD symptoms who are biopsy-proven negative for Barrett's metaplasia. All cases and GERD controls will undergo upper endoscopy as part of their ongoing care. Data collection will consist of a structured in-person interview, anthropometric measurements, and a self-administered food frequency questionnaire. Blood samples will be collected from cases and both control groups for measurement of serum antioxidant levels including ascorbic acid, carotenoids, selenium, and alpha-tocopherol. Demographic characteristics, height, current weight, and weight in each decade of life, tobacco use, alcohol consumption, use of medications that reduce lower esophageal sphincter pressure, history of gastroesophageal reflux symptoms and treatment, history of other medical conditions and treatment, family history of Barrett's esophagus, cancer , and gastrointestinal disorders, and measures of access to health care, including insurance status, income, education, and health care utilization, will be compared between groups.

Progress: Forty-five subjects have been entered in this study with no adverse events.

Detail Summary Sheets

Hematology/Oncology Service, Department of Medicine

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/017 **Status**: Terminated

Title: Evaluation of Immunity to Breast Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: Medicine/Hematology & Oncology **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Patrick L. Gomez, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Mark E. Robson, MC; MAJ John R. Caton, MC; MAJ Richard F. Williams, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/04/1994	Nov 94	09/30/1998

Study Objective: To determine the significance/relationship of CD4 helper/inducer T cell response in the presence of H2N positive/negative cancers in an attempt to determine how the immune system responds to breast cancer.

Technical Approach: Patients with breast cancer will have samples of tumor tissue obtained at the time of surgery for Her-2/neu. Blood will be obtained at the same time to evaluate for an anti-Her-2/neu T-lymphocyte response. Further venipunctures will be performed monthly during the 5 year follow-up period to continue evaluation for an anti-Her-2/neu T-lymphocyte response.

Progress: This protocol has been terminated due to a PCS of the principal investigator. Forty-two subjects were entered at MAMC without any untoward events. All data have been forwarded to the University of Washington since this protocol was done in collaboration with researches at that institution.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/049 **Status**: Ongoing

Title: An Open-Label, Long-Term, Multicenter Study of Oral Transmucosal Fentanyl Citrate (OTFC) for the Treatment of Breakthrough or Incident Pain in Cancer Patients Previously Enrolled in Other OTFC Studies

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: Medicine/Hematology & Oncology **Facility**: MAMC

Associate Investigator(s): LTC Robert B. Ellis, MC; LTC Luke M. Stapleton, MC; LTC Robert D. Vallion, MC; MAJ James S. D. Hu, MC; MAJ John R. Caton, MC; LTC Robert L. Sheffler, MC; Rakesh Gaur, M.D.; MAJ Richard F. Williams, MC; MAJ Matthew P. Jones, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/19/1996	Mar 97	02/20/1998

Study Objective: To establish the long-term safety and tolerance of OTFC in cancer patients experiencing breakthrough or incident pain while taking other opioids.

Technical Approach: The study will be conducted using an open-label, uncontrolled design in cancer patients. Cancer patients successfully completing other appropriate studies of OTFC will be eligible for this study. When patients experience breakthrough pain, they may treat up to 4 episodes each day with OTFC. Patients will be given a supply of OTFC units, all the same dosage strength, to treat breakthrough or incident pain for one month. The patient will be contacted at least weekly by telephone by a study physician or nurse and will be seen by study personnel at least monthly. After each contact, the investigator will decide whether or not the patient requires a larger or smaller dose of study medication to relieve breakthrough pain using a single OTFC unit. Patients may remain in the study for up to four months if they continue to experience breakthrough pain and are able to provide complete and accurate information on the safety and efficacy of the study medication. Patients will record in a daily diary the use of OTFC and any other medications, assess the performance of the study medication in relieving breakthrough or incident pain, and report any adverse events they experience. Demographics, medical history, physical exam, and laboratory results will be summarized using descriptive statistics.

Progress: No additional subjects were entered in FY 98. Five patients were entered in previous years. Only one patient remains on study drug, The patient tolerates study medication without problems and the medication is effective.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/025 **Status**: Completed

Title: Efficacy and Tolerability of 2.5 mg Itasetron Orally and of 32 mg Ondansetron Intravenously in the Prevention of Vomiting and Nausea in Patients Undergoing Cisplatin (>=75 mg/m²) Containing Chemotherapy

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: Medicine/Hematology & Oncology **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; MAJ John R. Caton, MC; MAJ Richard F. Williams, MC; Rakesh Gaur, M.D.

Start Date:	Est. Completion Date:	Periodic Review:
11/15/1996	Nov 97	12/18/1997

Study Objective: The objectives are to evaluate the efficacy, safety, and tolerability of one-time oral administration of 2.5 mg itasetron hydrochloride and 32 mg of IV ondansetron standard therapy in the prevention of vomiting and nausea in patients undergoing high-dose cisplatin (□ 75 mg/m²) containing chemotherapy.

Technical Approach: This is a randomized, double-blind (double-dummy), actively controlled, multicenter, parallel-group comparison of 2.5 mg itasetron orally and 32 mg ondansetron intravenously in the prevention of vomiting and nausea. Before inclusion, potentially eligible patients will be screened -4 to 1 day before or on treatment day 1. Eligible patients will then be allocated to either of the two treatments. The medications will be given prior to initiation of cisplatin. Blinding of the treatment will be secured by using the double dummy technique. Patients will be monitored during the trial for changes in physical exam, vital signs, ECG and laboratory results. Efficacy will be measured by the frequency of complete responders (0 emetic episodes and no need for a rescue medication) within the first 24 hours after initiation of chemotherapy. Patients will be asked to maintain a diary of emetic episodes and adverse events. They will be seen for a post treatment visit 6 to 9 days after treatment.

Progress: This study was closed to enrollment by the sponsor on 24 Oct 97 in order to initiate a similar protocol utilizing the same patient population. No subjects were consented or randomized at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/110 **Status**: Ongoing

Title: Double Blind, Double Dummy, Randomized, Multicenter, 2-Arm, Phase III Trial Comparing Letrozole 2.5 mg versus Tamoxifen 20 mg as First Line Therapy in Postmenopausal Women with Advanced Breast Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: Medicine/Hematology & Oncology **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ Richard F. Williams, MC; Rakesh Gaur, M.D.; James H. Timmons, MD; MAJ Matthew P. Jones, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/20/1997	Aug 01	07/17/1998

Study Objective: To compare the efficacy, as evaluated by the primary variable of time to progression (TTP), and the secondary variables of objective response rate, duration of response, and time to treatment failure (TTF) between the two treatment arms (2.5 mg letrozole once daily and 20 mg tamoxifen once daily). Secondary: a) To compare the tolerability and toxicity of the two treatment arms; b) to determine the survival time in each of the two treatment arms; and c) to summarize time to progression, objective response rate, and time to treatment failure for the second-line therapy using the subset of patients in the cross-over treatment period.

Technical Approach: This is a double blind, double dummy, multicenter, randomized, 2-arm, cross-over, Phase III trial, comparing the efficacy of letrozole versus tamoxifen in first-line treatment of postmenopausal women with advanced breast cancer. Once patients have met the inclusion/exclusion criteria, they will be randomly assigned to one of the two treatment arms. The two treatments are randomly assigned according to a predetermined, computer generated randomization list using permuted blocks. Patients will be evaluated radiographically every three months for disease progression. If they remain disease free, they will be seen for an exam, laboratory tests and re-dispensing of blinded trial medication. Once disease progression has been documented, patients will be given the option of taking open label letrozole (if they were on prior treatment with tamoxifen) or open label tamoxifen (if they were on prior treatment with letrozole) and will continue to be followed every three months.

Progress: No patients have been entered in this study.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/111 **Status**: Ongoing

Title: Multicenter, Double-Blind, Crossover Study of Oral Transmucosal Fentanyl Citrate (OTFC) Compared to Immediate Release Morphine Sulfate for the Treatment of Breakthrough Pain in Cancer Patients Taking Stable Doses of Opiods, Protocol AC600/001

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: Medicine/Hematology & Oncology **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ Richard F. Williams, MC; Rakesh Gaur, M.D.; MAJ David E. McCune, MC

Start Date:	Est. Completion Date:	Periodic Review:
06/20/1997	Feb 98	07/17/1998

Study Objective: To demonstrate that ActiqTM (oral transmucosal fentanyl citrate) is more effective for the treatment of breakthrough pain than immediate release morphine sulfate in opioid tolerant cancer patients.

Technical Approach: This double-blind, double-dummy, multiple cross-over, multicenter study will be conducted in cancer patients who are currently using 60-100 mg per day of oral morphine (or morphine equivalent of another oral opioid) or 50-300 μg per hour transdermal fentanyl, on around-the-clock (ATC) schedule to control persistent pain. Patients will continue to use their ATC medication for persistent pain at a constant dose and regimen throughout the study. Patients who are currently using a stable dose of 15 mg, 30 mg, 45 mg, or 60 mg capsules of immediate release morphine sulfate (MSIR) to effectively treat breakthrough (BT) pain will be eligible for the study. In the open-label titration phase (Phase A), patients will be titrated to a dose of OTFC such that one unit of OTFC will successfully treat an episode of BT pain. Successfully titrated patients will enter the double-blind phase of the study (Phase B). In Phase B, patients will be supplied with ten sequentially numbered sets of study drug - each set containing one active OTFC unit and placebo capsule(s), or one placebo OTFC unit and immediate release morphine sulfate capsule(s). The dose of MSIR that the patient used prior to study will determine the number of capsules provided. Placebo and active drug will be prepared in a way to maintain the blind. Five of the study drug sets will contain active OTFC units, and five will contain active MSIR. The order of administration of active drug will be randomized. Patients will be instructed to take IN ORDER one set of study drug (one OTFC and capsules) for each episode of BT pain they experience until all ten sets have been administered, or until they have been in the double-blind phase for 14 days. Patients will be asked to rate their pain every 15 minutes for an hour after taking the study medication. In phase B, patients will be instructed not to use additional rescue medication within one hour of treating an episode of BT pain with study drug. Patients will also be instructed not to take study drug within 2 hours of previous rescue medication. Health changes, persistent and breakthrough pain, and use of concomitant and rescue medication will be assessed daily.

Progress: Five patients were enrolled in this study in FY 98. Three patients have completed the study. One patient reported mouth sores and thrush that resolved, and fatigue, nausea, and depression which are on-going. It was felt that these problems were due to chemotherapy rather than the study drug.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/112 **Status**: Ongoing

Title: An Open-Label, Long-Term, Multicenter Study of Oral Transmucosal Fentanyl Citrate (OTFC) for the Treatment of Breakthrough or Incident Pain in Cancer Patients Previously Enrolled in AC 600 Series Protocols, Protocol AC600/002

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: Medicine/Hematology & Oncology **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ Richard F. Williams, MC; Rakesh Gaur, M.D.; MAJ Matthew P. Jones, MC; MAJ William B. Reece, MC; CPT Brent L. Kane, MC; MAJ Mark E. Shaves, MC; MAJ David E. McCune, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/20/1997	Sep 98	07/17/1998

Study Objective: To establish the long-term safety and tolerance of Oral Transmucosal Fentanyl Citrate (OTFC) in cancer patients experiencing breakthrough pain while taking other opioids and to collect data regarding patients' preferences for OTFC versus immediate release morphine sulfate.

Technical Approach: This open-label, multicenter study will be conducted in cancer patients previously enrolled in other AC 600 series protocols. Patients who have complete an AC 600 series protocol will be eligible for this study provided that they safely tolerate OTFC and are enrolled within four weeks of completing the earlier study. Patients will choose either OTFC or IRM (immediate release morphine) for treatment of their breakthrough pain. Patients who choose to use OTFC will start therapy at a dose selected from experience in the earlier study. Patients who choose IRM will start therapy at a dose determined from their previous rescue dose. Patients must continue to take an opioid around the clock. Medication and dosage regimen can be changed at the discretion of the investigator. Contact every two weeks between the patient and study personnel will be used as the occasion to adjust the dose of study medication up or down, as needed. Dose adjustments may be made more frequently at the discretion of the investigator. In addition, patients will be asked to maintain a diary of the study drug usage. Patients will remain in the study for up to 6 months if they continue to experience breakthrough pain and are able to provide complete and accurate information on the safety and efficacy of the study medication. Eligibility will be evaluated monthly.

Progress: Three patients were enrolled in FY 98. Disease progression in one patient led to weakness and inability to continue in the protocol. The patient was withdrawn from the study and died of the disease within a month. Two patients continue in the treatment phase, with side effects of pleuritis, nausea, diarrhea, anemia, hyperglycemia, numbness in legs, occasional involuntary muscle spasms and dry mouth. Side effects remain on-going.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/123 **Status**: Terminated

Title: Efficacy and Tolerability of 2.5 mg Itasetron IV and 32 mg Ondansetron Intravenously in the Prevention of Vomiting and Nausea in Patients Undergoing Cisplatin Containing Chemotherapy. A Randomized, Double-Blind, Multicenter, Parallel-Group Comparison

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: Medicine/Hematology & Oncology **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ Richard F. Williams, MC; Rakesh Gaur, M.D.

Start Date:	Est. Completion Date:	Periodic Review:
07/18/1997	Sep 98	08/20/1998

Study Objective: To evaluate the efficacy, safety, and tolerability of one-time IV administration of 2.5 mg itasetron hydrochloride and 32 mg of IV ondansetron standard therapy in the prevention of vomiting and nausea in patients undergoing high-dose cisplatin (greater than or equal to 75 mg/m^2) containing chemotherapy.

Technical Approach: This is a randomized, double-blind (double-dummy), actively controlled, multicenter, parallel-group comparison of 2.5 mg itasetron IV and 32 mg ondansetron IV in the prevention of vomiting and nausea. Before inclusion, potentially eligible patients will be screened - 10 to 1 day before or on treatment day 1. Eligible patients will then be allocated to either of the two treatments. The medications will be given prior to initiation of cisplatin. Blinding of the treatment will be secured by using the double dummy technique. Patients will be monitored during the trial for changes in physical exam, vital signs, ECG and laboratory results. Efficacy will be measured by the frequency of complete responders (zero emetic episodes and no need for a rescue medication) within the first 24 hours after initiation of chemotherapy. Patients will be asked to maintain a dairy of emetic episodes and adverse events. They will be seen for a post treatment visit 6 to 9 days after treatment.

Progress: One patient was entered and completed the study at MAMC. The protocol was closed to enrollment at MAMC due to contract issues between the Geneva Foundation and the sponsor.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/014 **Status**: Completed

Title: Thrombotic Thrombocytopenic Purpura Response and Relapse Pattern: A Retrospective Review

Principal Investigator: Rakesh Gaur, M.D.

Department: Medicine/Hematology & Oncology **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/21/1997	Oct 97	N/A

Study Objective: To describe the pattern of treatment with apheresis in patients with TTP to include duration and frequency; to describe use of other agents to include steroids, vincristine, cryo-depleted plasma, etc. in TTP; to describe parameters used to document remission and initiate a taper of apheresis.

Technical Approach: All patients diagnosed to have TTP before November 1996 at MAMC will be included in this chart review. Patient charts will be reviewed for relapse pattern, patient characteristics and method of plasmapheresis; specifically, number of TPE procedures, tapering and amount of plasma used.

Progress: Data were collected from eight patients with thrombotic thrombocytopenic purpura (TTP), who were treated at MAMC. The data were included with that from 12 other medical centers for a total of 101 patients studied. There was no benefit to the use of a tapering schedule of therapeutic plasma exchange (TPE) following the recovery of platelet count. The use of albumin as replacement fluid was associated with no relapse and requires further investigation. End points for discontinuation of TPE in TTP are attained by 50% of patients by the eighth day following initial presentation. Ninety percent of the patients responded by 24 days. Although response time remains difficult to predict, it does not appear to influence the recurrence rate of TTP.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/026 **Status**: Ongoing

Title: A Phase II Trial of Thioplex Following Induction Chemotherapy to Decrease the Incidence of Brain Metastases in Limited Stage Small Cell Lung Cancer Patients

Principal Investigator: MAJ Matthew P. Jones, MC

Department: Medicine/Hematology & Oncology **Facility**: MAMC

Associate Investigator(s): MAJ Richard F. Williams, MC; LTC Kenneth A. Bertram, MC; LTC Robert B. Ellis, MC; MAJ James S. D. Hu, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.; LTC Robert L. Sheffler, MC; MAJ David E. McCune, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/15/1996	Jan 98	11/21/1997

Study Objective: The primary objective is to evaluate the effectiveness of Thioplex in the prevention of CNS metastases in limited stage SCLC subjects who have achieved a complete or partial remission following initial systemic chemotherapy and chest irradiation. Secondary objectives are to evaluate the treatment with respect to overall survival, incidence of systemic metastases, and safety.

Technical Approach: This is a multicenter, open label, Phase II pilot study designed to evaluate the efficacy of Thioplex following a standard Etoposide (VP-16)/platinum-based regimen for the prevention of CNS metastases in limited small cell lung cancer. Patients who have achieved a complete or partial remission following chest irradiation and four courses of standard induction chemotherapy will be eligible for the study. Subjects will receive Thioplex at a dose of 45 mg/m^2 IV each month for 3 cycles. Patients will be followed for up to 30 months for evidence of CNS metastases and survival.

Progress: One patient has been entered in this study. This patient had several adverse events that were possibly related to the study drug. These were 3 episodes of upper respiratory infections (all resolved); fatigue (resolved), and elevated blood glucose (on-going but stable). The patient has completed study drug and is now in follow-up phase. The investigators continue to screen for other eligible participants.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/138 **Status**: Terminated

Title: Phase 2/3 Placebo Controlled Trial of Targretin Capsules (LGD1069) in Patients with Advanced Non-Small Cell Lung Cancer

Principal Investigator: MAJ Matthew P. Jones, MC

Department: Medicine/Hematology & Oncology **Facility**: MAMC

Associate Investigator(s): MAJ Richard F. Williams, MC; LTC Robert L. Sheffler, MC; Rakesh Gaur, M.D.; LTC Kenneth A. Bertram, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/19/1997	Nov 98	09/15/1998

Study Objective: 1) To determine whether Targretin capsules administration at a high (600 mg/m²/day) or a moderate dose (300 mg/m²/day) is more effective than placebo in prolonging-free interval (survival) in patients with Stage IIIB with pleural effusion, Stage IV, or recurrent, non-small cell lung cancer who have previously been stable or had tumor regression following platinum-based combination chemotherapy; 2) to evaluate the safety and tolerability of Targretin capsules when administered to non-small cell lung cancer patients following platinum-based combination chemotherapy; and 3) to document objective antitumor responses to Targretin capsules that occur in patients with measurable or evaluable non-small cell lung cancer at study entry.

Technical Approach: This is a multicenter, Phase 2/3, double-blinded, randomized, placebo-controlled trial comparing two dosing levels of Targretin capsules to placebo with regards to progression free-survival in patients with Stage IIIB, Stage IV, or recurrent non-small cell lung cancer who are stable or responding to platinum-based combination chemotherapy. Patient and Investigator will be blinded to the drug assignment and will be unblinded to the dose level assignment. Eligible patients who have signed the consent form will be randomized to one of the following three arms: 1) Arm I: Targretin capsules at 600 mg/m²/day as a single daily dose; 2) Arm II: Targretin capsules at 300 mg/m²/day as a single daily dose; and 3) Arm III: Placebo capsules either 600 mg/m² day (Arm IIIA) or 300 mg/m²/day (Arm IIIB) as a single daily dose.

Therapy will continue until disease progression, patient withdraw, dose-limiting toxicity or death. Date and cause of death will be obtained on all patients. Patients will be evaluated for tumor assessment at baseline, every eight weeks during treatment, and at study termination. Patients who progress while receiving Targretin capsules or placebo will be removed from the study. The primary efficacy endpoint of the study is the progression-free interval (survival) (time from study entry to progressive disease). The secondary efficacy endpoint is overall survival (time from study entry until death). Additional efficacy parameters evaluated will include quality of life measures according to the Lung Cancer Symptom Scale.

Progress: This protocol was terminated by the sponsor because patient accrual has lagged significantly behind initial projections. The sponsor may the decision that it will take such an extended length of time to get a large enough population to obtain meaningful results that it is impossible to continue to provide the resources necessary to complete the study. No patients were entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 95/162	**Status**: Terminated

Title: The Characterization of Breast Cancer Susceptibility Genes in Males and Their Kindred

Principal Investigator: MAJ Richard F. Williams, MC

Department: Medicine/Hematology & Oncology	**Facility**: MAMC

Associate Investigator(s): LTC Robert B. Ellis, MC; Amelia Langston, M.D.; Elaine Ostrander, Ph.D.; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
08/18/1995	Sep 98	08/20/1998

Study Objective: Using male breast cancer patients as probands we will characterize the known breast cancer susceptibility genes BRCA1, BRCA2, AT and additional genes such at p53, RB and ras in the affected individuals and their families.

Technical Approach: The data obtained from a previous study of the Automated Central Tumor Registry database (ACTUR) revealed 123 total cases of male breast cancer within the Department of Defense (DOD) healthcare system. Those patients with a family history of breast cancer are currently in the process of evaluation under a previous IRB approved protocol. The next step involves collecting samples of blood from each living male breast cancer patient and family members of both living and deceased patients as deemed appropriate for study. Additionally, formalin fixed paraffin imbedded tumor blocks will be collected on as many patients as possible. Once the specimens are collected the blood will be processed at Madigan Army Medical Center. Both DNA and buffy coat cells will be extracted and frozen for storage. Aliquots of these specimens along with portions of tumor blocks will be blinded with regard to clinical information and sent to Dr. Ostrander's lab at Fred Hutchinson Cancer Research Center for analysis. This analysis will initially include screening for mutations in BRCA1, BRCA2 (when cloned) and the Ataxia-Telangiectasia gene (AT) using the patient DNA extracted from the blood sample. The tumor blocks would be tested for the loss of heterozygosity for markers on chromosomes 13q covering both the BRCA2 and Retinoblastoma (RB) genes, chromosome 11 for the AT gene and chromosome 17 regions covering the p53 and BRCA1 genes. Data collected from these studies would then be matched with the clinical information in order to derive information regarding cancer susceptibility, prognosis and basic mechanisms of carcinogenesis.

Progress: No new patients have been entered since June 1996. Approximately 50% (25) of the patients required for the study had been enrolled when the previous PI (Dr. Caton) was reassigned. Dr. Williams had only been the PI for a couple of months before he resigned from the Army. No other individuals at MAMC were interested in taking over the study. Therefore, it has been terminated. Dr. Caton hopes to revive the protocol at BAMC.

Detail Summary Sheets

Infectious Disease Service, Department of Medicine

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/057 **Status**: Completed

Title: Protocol #M/1260/0039: Linezolid vs. Clarithromycin for the Treatment of Uncomplicated Skin and Superficial Skin Structure Infections

Principal Investigator: LTC Joseph T. Morris III, MC

Department: Medicine/Infectious Disease **Facility**: MAMC

Associate Investigator(s): MAJ Kenneth S. Azarow, MC; Preston L. Carter, M.D.; LTC David C. Elliott, MC; COL William E. Eggebroten, MC; LTC Donald G. Kim, MC; MAJ Clifford A. Porter, MC; LTC David M. Watts, MC; MAJ Thomas K. Curry, MC; CPT Bret R. Hansen, MC; CPT Clinton S. Beverly, MC; CPT Tommy A. Brown, MC; CPT Ronald A. Gagliano, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/20/1998	Apr 99	N/A

Study Objective: To assess the comparative efficacy (clinical and microbiological) of Linezolid vs. clarithromycin in the treatment of adult uncomplicated skin and superficial skin infections and to assess safety and tolerance.

Study Objective: To assess the comparative efficacy (clinical and microbiological) of Linezolid vs. clarithromycin in the treatment of adult uncomplicated skin and superficial skin infections and to assess safety and tolerance.

Technical Approach: Patients with a skin or superficial skin structure infection that is considered by the physician as uncomplicated will be randomized to treatment with either the study medication (Linezolid) or the standard antibiotic (Clarithromycin). Pre-study evaluations include culture from the skin infection to identify the bacteria, blood and urine tests, a physical exam, medical history including the cause of the infection, and any other medical conditions or surgery related to the infection.

Patients who qualify for enrollment will take either Clarithromycin 250 mg BID orally for up to 14 days or Linezolid 400 mg BID orally for up to 14 days. Patients will be required to visit the clinic a minimum of four times. Extra visits will be up to the physicians discretion to monitor treatment efficacy and safety.

Progress: This study was not initiated at MAMC because the accrual goal had been met from other sites before the study completed the approval process at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/058 **Status**: Ongoing

Title: Linezolid for the Treatment of Methicillin Resistant Staphylococcus Aureus (MRSA) Infections: An Evaluator Blinded Trial Comparing Linezolid with Vancomycin Alone and Vancomycin Followed by Oral Linezolid

Principal Investigator: LTC Joseph T. Morris III, MC

Department: Medicine/Infectious Disease **Facility**: MAMC

Associate Investigator(s): CPT Eric J. Messner, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/20/1998	Nov 98	N/A

Study Objective: To assess the efficacy (clinical and microbiological), safety, and tolerance of intravenously and orally administered Linezolid when compared with vancomycin in the treatment of methicillin resistant Staphylococcus aureus (MRSA) infections.

Technical Approach: Patients with positive culture for MRSA will be randomized to receive one of three treatments: (1) Group 1 will receive IV Linezolid with optional oral Linezolid pills for follow-up, (2) Group 2 will receive IV Vancomycin, or (3) Group III will receive a combination of IV Vancomycin with oral Linezolid pills as follow-up.

Progress: This study has not been initiated at MAMC due to receipt and approval of forthcoming protocol changes from the sponsor.

Detail Summary Sheets

Internal Medicine Service
Department of Medicine

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/015 **Status**: Ongoing

Title: Use of Blood Cultures in the Evaluation of Febrile Episodes in Neutropenic Patients Receiving Broad Spectrum Antibiotics

Principal Investigator: CPT Sue E. Fitzgerald, MC

Department: Medicine/Internal Medicine **Facility**: MAMC

Associate Investigator(s): COL Ronald H. Cooper, MC; CPT Robert V. Gibbons, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/21/1997	Jul 98	N/A

Study Objective: To determine: the prevalence of positive blood cultures in febrile granulocytopenic patients who are receiving antimicrobial therapy; whether blood culture results were used to modify antimicrobial therapy; the cost of obtaining blood cultures during these episodes, and, if possible, a population of patients in whom blood cultures are likely to be positive.

Technical Approach: The charts of febrile neutropenic patients admitted to MAMC from 1989 to 1997 will be reviewed with particular attention to blood culture results and antibiotic use. The cost of these blood cultures will be estimated. Data extracted will include: demographics, diagnoses, antibiotic use, chemotherapeutic regimen currently in use, daily ANC, blood cultures and clinical data.

Progress: No records have been reviewed at this point due to time constraints on the investigator.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/016 **Status**: Ongoing

Title: A Controlled Clinical Trial to Improve Housestaff Identification of and Attitudes Toward Mental Disorders in Primary Care

Principal Investigator: CPT Robert V. Gibbons, MC

Department: Medicine/Internal Medicine **Facility**: MAMC

Associate Investigator(s): CPT Jeffrey S. Strong, MC; MAJ Richard A. Jordan, MC; MAJ Jeffrey L. Jackson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/15/1996	Feb 96	09/30/1998

Study Objective: To determine whether simple educational intervention can increase the rate of recognition of mental disorders.

Technical Approach: As at least one third of all patients seen in an outpatient setting by primary care physicians have an underlying mental disorder, and the rate of identification of such problems by this group of physicians is generally under 50%, this educational intervention will attempt to improve housestaff attitudes toward recognition and management of psychiatric disorders.

Progress: The principal investigator was changed from MAJ Jeffrey Jackson to CPT Gibbons in June 1997. After eleven staff members had completed the testing, and before further work could be done, the control groups were inadvertently contaminated so that the study had to be restarted. CPT Gibbons has entered no new patients since he took over the study. He plans to implement the study in FY 99 if time permits.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/113 **Status**: Completed

Title: Optimal Bowel Preparation for Flexible Sigmoidoscopy: Oral Magnesium Citrate with Oral Bisacodyl or with Two Hypertonic Phosphate Enemas

Principal Investigator: CPT Robert V. Gibbons, MC

Department: Medicine/Internal Medicine **Facility**: MAMC

Associate Investigator(s): CPT Jeffrey S. Strong, MC; MAJ Jeffrey L. Jackson, MC; CPT Jon D. Roebuck, MC; COL Amy M. Tsuchida, MC; LTC Robert H. Sudduth, MC; Laurie Harrell; CPT Roger K. Fincher, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/20/1997	Mar 98	09/30/1998

Study Objective: To study the differences between a single or double enema preparation, combined with magnesium citrate orally versus oral bisacodyl combined with oral magnesium citrate use.

Technical Approach: This study will compare three bowel preparation regimens: a) 296 ml of magnesium citrate taken orally the night prior to the procedure, followed by 2 hyperphosphate enemas, taken 1 and 2 hours before the procedure, respectively, b) 296 ml of magnesium citrate taken orally the night prior to the procedure followed by a single hyperphosphate enema taken 1 hour before the procedure, and c) 296 ml of magnesium citrate taken orally the night prior to the procedure, immediately followed by 20 mg of dulcolax, also taken orally.

Progress: 325 adult volunteers from 2 academic medical centers were studied. There were no statistical differences between the quality of the three bowel preparations. Composite symptom scores were similar in all groups, though patients considered oral bisacodyl more easily tolerated. This study will be continued at Walter Reed Army Medical Center where the original principal investigator (Dr. Keith Fincher) is now assigned.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/080	**Status**: Ongoing

Title: Effect of Tricuspid Regurgitation on the Accuracy of Pulse Oximetry

Principal Investigator: CPT Michael W. Quinn, MC

Department: Medicine/Internal Medicine	**Facility**: Madigan Army Medical Center

Associate Investigator(s): COL Thomas A. Dillard, MC; MAJ Maureen A. Arendt, MC; CPT Robert V. Gibbons, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/22/1998	May 00	N/A

Study Objective: To assess the effect of severe tricuspid regurgitation on the accuracy of pulse oximetric determination of SpO2 compared to values determined by co-oximetry of arterial blood and to determine if there is a correlation between the following: tricuspid regurgitant jet velocity, tricuspid regurgitant jet distance, right atrial pressure, right ventricular systolic pressure, ejection fraction, cardiac output and strike volume (as determined by echocardiography), as well as systolic blood pressure, diastolic blood pressure, mean arterial pressure, skin pigment, and pulse rhythm and any inaccuracy found between the SpO2 values obtained by pulse oximetry when compared to the oxygen saturation as determined by the co-oximetry of arterial blood.

Technical Approach: Patients referred for echocardiograms will be asked to participate. After consent is obtained, they will be asked to complete a questionnaire regarding ethnicity, medical history, and current prescription drug use. An echocardiogram will be performed to obtain the following parameters: tricuspid jet velocity, tricuspid jet distance, tricuspid jet area on apical four chamber view, the average tricuspid jet area on three views (apical four chamber, parasternal right inflow, and parasternal short axis), visual assessment of the tricuspid regurge, right atrial area, and inferior vena cava collapsibility index. After transfer to the recovery room, the patient will undergo pulse oximetry, arterial blood gas, and vital signs (temperature, pulse, and blood pressure). Comparison will be made as stated in the objective section above.

Progress: Eighteen subjects have been entered in this study.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/007 **Status**: Completed

Title: Low Molecular Weight Heparin Used for Therapeutic Perioperative Anticoagulation

Principal Investigator: MAJ Daniel C. Randall, MC

Department: Medicine/Internal Medicine **Facility**: MAMC

Associate Investigator(s): Cristine L. Anderson, R.Ph.; Matthew R. Rutledge, R.Ph.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
10/17/1997	Mar 98	N/A

Study Objective: To demonstrate the cost benefit, provider acceptance, patient acceptance, and resources needed to use low molecular weight heparin for patients needing continuous therapeutic anticoagulation and procedures with a high likelihood of bleeding complications.

Technical Approach: Subjects will have the appropriate dose of LMWH calculated and be instructed on proper timing for beginning/stopping warfarin and LMWH by the clinical pharmacist. Subjects will be instructed on proper injection technique by the APCC RN participating. Blood samples for PT/INR, CBC and creatinine determination will be required before starting LMWH and on the day prior to the planned procedure. The last LMWH injection will be given no less than 11 and no greater than 13 hours prior to the planned procedure. LMWH and coumadin will be started no earlier than 12 hours post procedure, but may be started later at the proceduralist's discretion. LMWH and coumadin will be continued until there are two subsequent INR values between 2.0 and 3.0. The subjects will continue to have blood drawn for daily INR's, with the addition of CBC's done every third day to assess for dropping hematocrit or platelet counts. Subjects will have blood drawn for INR values 2 to 3 days after discontinuing LMWH. After participation in the study is complete, subjects will be asked to complete a satisfaction survey.

Progress: The investigators coordinated low molecular weight heparin windows on 38 patients who would otherwise have been admitted for unfractionated IV heparin therapy. There were two major bleeding complications requiring ICU stays and two minor complications in the study population. Both of the patients with major complications had the incorrect dosing of either coumadin or low molecular weight heparin given to them by physicians operating outside of study parameters. There were no neurologic sequelae. Patient and provider satisfaction was very high. Cost savings to the institution were considerable.

CONCLUSION: Low molecular weight heparin is practical and well tolerated when used for perioperative anticoagulation in patients at high risk for clotting and bleeding. Its use should be restricted to multidisciplinary teams who specialize in this area until there is more familiarity with the drug.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/017	**Status**: Completed

Title: The Utility of Echocardiography in Active-Duty, Asymptomatic Service Members with Cardiac Murmur

Principal Investigator: CPT Eric A. Shry, MC

Department: Medicine/Internal Medicine	**Facility**: MAMC

Associate Investigator(s): MAJ Maureen A. Arendt, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/21/1997	Jun 98	N/A

Study Objective: To determine if physical exam features, as described in the ACC/AHA guidelines on the use of echocardiography, predict the outcome of echocardiography.

Technical Approach: This study will evaluate all active-duty referred to the Cardiology Clinic for evaluation of a cardiac murmur. All subjects will have a standard echocardiogram read by a member of Cardiology staff. If there are abnormalities requiring medical or surgical treatment, including antibiotic prophylaxis or long-term medical follow-up, the ECHO will be considered positive (the remainder being negative). Data will be recorded on a screening tool including echocardiography, referral, and history and physical exam information, which will be placed in a database.

Progress: This study has been completed. Of 66 active duty service members referred to cardiology for evaluation of heart murmur, 40 had either a benign flow murmur or a fleeting murmur (was heard by the referring provider but not appreciated at the time of cardiology consultation). All of these subjects had normal echocardiograms; 26 subjects had non-innocent murmur by examination. Of these 7 had abnormalities requiring SBE prophylaxis on echocardiography. There was a strong association between a non-innocent murmur and an abnormal echocardiogram, $p<.002$ (Fisher's exact test). History, general physical exam (other than murmur auscultation) and electrocardiography did not predict abnormal findings on echocardiogram.

Conclusion: If a cardiology staff (or senior fellow) physician determines that a heart murmur in an asymptomatic service member represents a benign flow murmur, the incidence of echocardiographic abnormalities is very low. Confirmation of this data may make echocardiography unnecessary for the majority of the healthy, active-duty service members with heart murmurs.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/046 **Status**: Completed

Title: Case-Mix and Procedures in the MAMC Ib Ambulatory Clinic; Comparison with Civilian Providers

Principal Investigator: CPT Jeffrey S. Strong, MC

Department: Medicine/Internal Medicine **Facility**: MAMC

Associate Investigator(s): MAJ Jeffrey L. Jackson, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/20/1998	Jan 98	N/A

Study Objective: (1) To determine the distribution of diagnoses seen in the MAMC General Medicine ambulatory clinic; (2) to determine the type and number of procedures done as an outpatient in the MAMC General Medicine ambulatory clinic; and (3) To compare the distribution of diagnoses and procedures in the MAMC General Medicine ambulatory clinic to those done nationally among civilian providers.

Technical Approach: One years worth of ADS data from the 1b general medicine clinic will be compared with one year of data from the National Ambulatory Medical Care Surgery (NAMS) data set to determine the comparability of the type of diagnoses and procedures done with patients in the military setting compared to the civilian population.

Progress: This protocol has been completed. 41,374 MAMC patient encounters were compared with civilian data from the National Ambulatory Medical Care Survey. The age distribution was similar, with military patients averaging 53.5 years of age, compared with civilian patients of 54.5 years. Military patients were more likely to be female (71%vs 60%) and were more ethnically diverse. There were similar rank orderings of the top 189 diagnostic groups seen in each setting. There were also no differences in type or rank order of procedures performed between military and civilian internists. The practice content of military and civilian practices appears to be more similar than different. Several manuscripts have been submitted for publication.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/109 **Status**: Terminated

Title: Coronary Artery Calcification Detected with Computed Radiography as a Marker for Obstructive Coronary Artery Disease

Principal Investigator: LT Eric B. Stuart, MC

Department: Medicine/Internal Medicine **Facility**: MAMC

Associate Investigator(s): MAJ Michael D. Eisenhauer, MC; MAJ Cristopher A. Meyer, MC; CPT Donald J. Collins, MC, USAR; CPT Jeffrey S. Strong, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/17/1996	Dec 96	07/17/1998

Study Objective: 1) To determine if chest radiography using a computed radiographic system (MDIS) can detect coronary artery calcification which correlates with significant coronary artery obstruction by cardiac catheterization. 2) To determine if non-radiologists can interpret a computed chest x-ray image for coronary artery calcification with a clinically significant level of accuracy.

Technical Approach: Approximately 200-300 patients presenting to the cardiology service who are referred for coronary catheterization will be asked to participate. All patients undergoing coronary angiography will have their screening computed chest radiograph reviewed for evidence of coronary artery calcification. During the coronary angiography procedure, just prior to the injection of radiocontrast dye into the coronary arteries, a fluoroscopic view of the heart will be recorded on film. The sensitivity and specificity of coronary artery calcification detected by computed chest radiography, by fluoroscopy, and by the combination of the two, will be compared to the detection of obstructive coronary artery disease by coronary angiography. Comparisons and likelihood ratios will be used to evaluate data and most will be presented in table format.

Progress: This protocol has been terminated due to the reassignment of the principal investigator. No abstracts were written on the data collected from 100 patients.

Detail Summary Sheets

Neurology Service, Department of Medicine

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 97/083	**Status**: Ongoing

Title: Compassionate Use of Vigabatrin in Infantile Spasms

Principal Investigator: MAJ Jodie L. Bolt, MC

Department: Medicine/Neurology	**Facility**: MAMC

Associate Investigator(s): Letitia Steigerwald

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/18/1997	Apr 02	05/22/1998

Study Objective: 1) Continuation of compassionate use IND of vigabatrin for 2 patients as an official MAMC Clinical Investigation Protocol; 2) effective control of infantile spasms; and 3) to gain experience in the use of vigabatrin, a promising drug for infantile spasms which is used regularly outside of the U.S. and is undergoing FDA review for commercial marketing in this country.

Technical Approach: Infantile spasms are a severe epileptic encephalopathy associated with significant morbidity and mortality. Vigabatrin is becoming the first line therapy for infantile spasms in countries outside of the U.S. due to its efficacy, tolerability, and decreased morbidity compared to ACTH, the current standard of care in the U.S. Vigabatrin may have even greater benefit (and therefore greater indication for use) in certain selected patients. Patients with symptomatic infantile spasms due to Tuberous Sclerosis are especially responsive to Vigabatrin. Patients with certain inborn errors of metabolism and infantile spasms might be at higher risk from conventional therapies than Vigabatrin. The purpose of this protocol, Compassionate Use of Vigabatrin in Infantile Spasms, is to continue compassionate use of vigabatrin in two patients, one in each category listed above. An FDA IND is held for these two patients and under this protocol, the medication would be continued up to 36 months after initiation, with option to continue if the patients develop seizure types for which vigabatrin could be effective.

Progress: At the beginning of FY 98, two patients were enrolled in this protocol. One patient (with tuberous sclerosis) ended the study as he reached four years of age; the age at which risk of return of infantile spasms is thought to be markedly decreased. Although the protocol as written allows for continuation of the Vigabatrin for other seizure types which might be responsive, and he continues to have occasional complex partial seizures, the parents elected to give him a trial off of the Vigabatrin. Infantile spasms have not returned and his other seizure types remain relatively well controlled on other standard anticonvulsants. The second patient (now 3 years old with congenital lactic acidosis, microencephaly, and global developmental delay) continues to do well on Vigabatrin, without evidence of infantile spasms or other seizure types, nor adverse effects of the medication.

Conclusion: Vigabatrin has been safe and effective for control of infantile spasms in two patients with symptomatic infantile spasms for whom standard therapy with ACTH was non-effective or not indicated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/137 **Status**: Completed

Title: Clinical Experience and Use of Vigabatrin (Sabril) in Patients with Infantile Spasms

Principal Investigator: MAJ Jodie L. Bolt, MC

Department: Medicine/Neurology **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
09/19/1997	Indefinite	09/30/1998

Study Objective: 1) Assess if patients with infantile spasms treated with vigabatrin become infantile spasms free within the first fourteen days of therapy; 2) assess changes in seizure frequency of infantile spasms and other seizure types prior to and during a treatment period of at least one month and up to three years; 3) assess if pretreatment with vigabatrin alters responsiveness to subsequent antiepileptic drug therapy; 4) gain medical experience using vigabatrin in a patient population and clinical setting not extensively studied in the past; 5) document the time course and resolution of any adverse events; and 6) assess the physician's and caregiver's global assessment at specified visits.

Technical Approach: Vigabatrin (Sabril) is an irreversible inhibitor of GABA-transaminase, which catalyzes the catabolism of GABA, an important central nervous system inhibitory neurotransmitter. Vigabatrin is investigational and will be used under IND #47,707 which is held by Hoechst Marion Roussel, Inc. This is a multicenter, open-label, dose-ranging, long-term study of patients with new onset infantile spasms. Up to 150 patients may be enrolled in this study. The duration of this study will be approximately three years. Patients should enroll in this study with the expectation that they will be treated with vigabatrin for a minimum of one month. Appropriate statistical comparison to baseline for seizure control and adverse events will be made.

Progress: No patients were entered at MAMC. The PI has received word that the drug will be approved for routine use in the very near future. No patients were entered at MAMC. The protocol has been terminated at MAMC.

Detail Summary Sheets

Pulmonary Disease & Critical Care Service, Department of Medicine

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/057 **Status**: Terminated

Title: The Use of Ipratropiumn Bromide (Atrovent) in COPD Exacerbation

Principal Investigator: LTC William E. Caras, MC

Department: Medicine/Pulmonary&Critical Care **Facility**: MAMC

Associate Investigator(s): COL Thomas A. Dillard, MC; Michael G. Winter, RRT

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/21/1997	Jul 97	12/18/1997

Study Objective: The objective of our protocol is to perform a head to head comparison of nebulized albuterol and ipratropium in hospitalized patients with COPD exacerbation. We plan to use the maximum recommended daily doses of each drug dosed every four hours (ipratropium bromide 350 µg unit every four hours vs albuterol 3.5 mg every four hours).

Technical Approach: Major outcomes will include the FEV-1. We will obtain repeated measures in each patient. Ultimately, we wish to determine if there is any significant change in FEV-1 at 24 and 48 hours between treatment groups. We would also like to determine if the initial FEB-1 (<40% or >40%) has any bearing on treatment response. We plan to apply a t-test with data obtained at the 24 hour study interval. If enough patients are still on the protocol at 48 hours, we will apply the ANOVA for repeated measures, but we do not know how many patients will be available for analysis after 24 hours. Clinical outcomes will include length of stay as well as change in respiratory rate, pulse oximetry, VAS, at 24 and 48 hours. The limit of statistical significance will be taken at p=0.05.

Progress: This protocol was terminated due to logistical problems. No patients were entered.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/054	**Status**: Ongoing

Title: The Use of Combined Ipratropium Bromide and Albuterol Given as Combivent MDI in COPD Exacerbation

Principal Investigator: LTC William E. Caras, MC

Department: Medicine/Pulmonary&Critical Care	**Facility**: MAMC

Associate Investigator(s): COL Thomas A. Dillard, MC; Michael G. Winter, RRT

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/20/1998	Jan 99	N/A

Study Objective: To compare the use of Combivent MDI with that of Albuterol MDI alone in patients admitted with COPD exacerbation.

Technical Approach: Once subjects are enrolled, all inhaled bronchodilators will be held for four hours. During this time, a FVC and a FEV-1 will be obtained and the subject will be randomized to one of two groups. Group 1 will receive conventional metered dose albuterol under the supervision of a respiratory therapist. Spirometry will be checked (by a second respiratory therapist who was not present during the delivery of the inhaled medication) at 60, 90, and 120 minutes, and at four hours following the bronchodilator. If the FEV-1 at four hours is within 15% of the baseline value the subject will crossover to the second treatment protocol which will consist of combivent MDI. Again spirometry will be obtained at 60, 90, and 120 minutes and 4 hours following inhalation. Group II will receive the exact same medications, but in reverse order of Group 1; combivent followed by albuterol. The major endpoint of the study is the FEV-1 response to the treatment with combivent vs albuterol. Separately, the dyspnea scale between treatment groups will be analyzed.

Progress: No patients have been entered in this study.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/029 **Status**: Ongoing

Title: A Prospective Study Using the Airway Occlusion Pressure (PO.1) To Predict the Outcome of Weaning From Mechanical Ventilation

Principal Investigator: COL Thomas A. Dillard, MC

Department: Medicine/Pulmonary&Critical Care **Facility**: MAMC

Associate Investigator(s): MAJ James D. Pike, MC; LTC George N. Giacoppe Jr., MC; MAJ Francis J. Landry, MC; CPT Jeremy R. Blanchard, MC; MAJ Lewis L. Low, MC; CPT Kurt W. A. Grathwohl, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/17/1993	May 94	09/30/1998

Study Objective: The main objective of this study is to ascertain the usefulness of the PO.1 as a weaning parameter in predicting success or failure of patients upon extubation. The secondary objective is to validate the Rapid Shallow Breathing Index as described by Yang and Tobin.

Technical Approach: Weaning parameters will be obtained and documented by a Respiratory Care Practitioner (RCP) on patients in the surgical and medical ICU at MAMC. Individual progress toward weaning and extubation will be determined by the primary physician/team. When it is determined the patient is ready for extubation, a second set of weaning parameters will be obtained immediately prior to extubation. Weaning parameters will only be collected on patients at rest and who have not been stimulated within the prior 10 minutes. The parameters will be obtained by utilizing the Respiratory Mechanics Package on the Infrasonics Adult Star as required by MAMC policy. Only the data obtained from patients on the Infrasonic Adult STAR mechanical ventilator will be used so that our results are reproducible since other available ventilators do not easily measure the PO.1. The first 50 patient's will be used to form ROC curves to develop threshold values for the prediction of success or failure of extubation which can then be prospectively applied. A successful weaning/extubation will be defined as one in which the patient does not have to be reintubated within 24 hours.

Progress: Seventy-three subjects have been enrolled. Final data extraction is in progress before data analysis can begin.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/049	**Status**: Completed

Title: International Study of Mechanical Ventilation

Principal Investigator: COL Thomas A. Dillard, MC

Department: Medicine/Pulmonary&Critical Care		**Facility**: MAMC

Associate Investigator(s): LTC George N. Giacoppe Jr., MC; Michael G. Winter, RRT

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/20/1998	Mar 98	N/A

Study Objective: To obtain a better understanding of the spectrum of use of mechanical ventilation in intensive care units (ICU's); to establish reference standards according to the use of mechanical ventilation, morbidity, ICU stay and mortality; to design a database of patients that require mechanical ventilation in order to identify objective criteria which can predict mortality, total duration of mechanical ventilation, total duration of ICU stay, weaning predictability, and outcomes.

Technical Approach: Data will be collected on study patients for 28 days after study entry or until discharge from the hospital or death. Data will be collected by means of five questionnaires. Questionnaire A is designed to collect information on the ICU under Study (only one questionnaire per ICU to be completed). Questionnaires B, C, D, and E will be used to collect data on each individual patient enrolled in the study. A Simplified Acute Physiology Score (SAPS II) will be completed at baseline and data entered in Questionnaire B. Questionnaires C (monitoring of arterial blood gas, ventilator mode and setting, and pharmacotherapy) and Questionnaire D (Ventilator monitoring) will be obtained from baseline, one hour after starting mechanical ventilation, and on days 3, 7, 14, 21, and 28 while the patient continues to receive mechanical ventilation. Data for Questionnaire E (Monitoring of Weaning) will be obtained daily while the patient is in the weaning period. Baseline demographic characteristics, mechanical ventilation parameters, monitoring parameters, weaning methods and outcome results between countries will be compared by Student's t test analysis of variance. A difference will be considered significant if the p value is <0.05.

Progress: This study has been completed. Sixty subjects were enrolled at MAMC in this multicenter study. Data were forwarded to a central committee for analysis.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/087 **Status**: Completed

Title: A Phase 2 Study to Determine the Safety, Pharmacokinetics, and Effective Dose Range and Dosing Duration for Recombinant Activated Protein C (rAPC) in Severe Sepsis

Principal Investigator: LTC George N. Giacoppe Jr., MC

Department: Medicine/Pulmonary&Critical Care **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
04/18/1997	Jul 97	12/18/1997

Study Objective: 1) To assess the safety of administration of rAPC as a function of dose and dose duration; 2) to determine the degree to which the coagulation abnormalities of severe sepsis are affected by the administration of rAPC as a function of dose and dose duration; and 3) to determine the effective dose and dose duration of rAPC administration, based on the ability of rAPC to alter the coagulation abnormalities of severe sepsis, for use in a future Phase 2 protocol.

Technical Approach: This Phase 2 study seeks to demonstrate the safety and pharmacokinetics of rAPC, as well as identify the effective dose range and dose duration of rAPC in the correction of sepsis-induced intravascular coagulation and in the prevention or improvement of sepsis-induced organ failure. rAPC will be administered as a continuous intravenous infusion. This study will be conducted in two sequential steps designated as Stage 1 and Stage 2. Both Stage 1 and 2 are double-blind, placebo-controlled, dose-ranging studies of rAPC administered as a continuous intravenous infusion over a fixed interval of 48 hours (Stage 1) and 96 hours (Stage 2). The initial rAPC dose used in Stage 1 will be based on the doses capable of correcting the coagulation abnormalities seen in hereditary protein C-deficient (HPCD) patients. The initial rAPC doses used in Stage 2 will be chosen from the safest and most efficacious dose of all doses evaluated in Stage 1. After patients are determined to meet eligibility criteria and the patient (or next of kin) has consented to participation, patients will be randomized. Dose and length of infusion will be determined by what stage the study is in. Patients will have frequent assessments and both local and central lab work. A bedside aPTT analyzer will be used to adjust the dosage of study medication. Patients will be followed throughout their hospitalization and at Day 28. All study participants will also receive standard of care treatment with antibiotics and other supportive measures.

Progress: This study was closed to enrollment by the study sponsor on 24 Nov 97 because the sponsor had met the required enrollment. No subjects were consented or randomized at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 90/099 **Status**: Ongoing

Title: Comparison of the Serum Effusion Albumin Gradient to Traditional Criteria for Transudates in Patients with Pleural Effusions Secondary to Congestive Heart Failure

Principal Investigator: CPT Jennifer E. Jorgenson, MC

Department: Medicine/Pulmonary&Critical Care **Facility**: MAMC

Associate Investigator(s): LTC William H. Cragun, MC; CPT Stephen M. Salerno, MC; CPT Donald M. Collins, MC; LTC Bernard J. Roth, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/17/1990	Jun 96	09/15/1998

Study Objective: To determine if the albumin gradient is a more effective criterion than Light's criteria to distinguish transudates from exudates in patients with congestive heart failure that have been treated with diuretics.

Technical Approach: Fifteen patients with clinically suspected congestive heart failure and chest radiograph evidence of pleural effusion will be studied. A thoracentesis to remove 50 cc of fluid will be performed and the following laboratory tests will be done on the fluid: albumin, total protein, glucose, LDH, bilirubin, cell count with cytospin differential, gram stain, and routine culture. A simultaneous sample of serum will be measured for albumin, total protein, LDH, bilirubin, and glucose. After three to five days of therapy for the congestive heart failure a repeat chest radiograph with bilateral decubitus view will be done. If pleural fluid persists, a repeat thoracentesis and laboratory tests will be done. If no fluid persists after three to five days, then the patient will be dropped from the study. Bilirubin ratio will also be assessed. The classification of the patients as exudate or transudate by serum effusion, bilirubin ratio, and Light's criteria will be compared between the two thoracentesis. McNemar's test for matched-pair data will be used to compare the albumin gradient results to Light's criteria.

Progress: No further patients were entered in FY 98 due to the departure of the PI. CPT Jennifer Jorgenson was assigned to replace CPT Douglas Collins in September 1998.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/102 **Status**: Ongoing

Title: The Effect of Saphenous Vein Versus Internal Mammary Artery Bypass on the Mortality and Morbidity of Severe Chronic Obstructive Pulmonary Disease Patients

Principal Investigator: CPT Steven W. Krause, MC

Department: Medicine/Pulmonary&Critical Care **Facility**: MAMC

Associate Investigator(s): LTC Bernard J. Roth, MC; CPT Viki J. Leefers, AN; CPT Jamia E. Howell, MC; COL Thomas A. Dillard, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/15/1998	Aug 98	N/A

Study Objective: (1) To determine the effect the type of graft used has on the morbidity and mortality of patients with severe chronic obstructive pulmonary disease who undergo coronary artery bypass, (2) to re-examine the effect confounding variables have on COPD patients under CABG.

Technical Approach: Patients within the last five years with the diagnosis of COPD undergoing CABG, and a second group of sex and age matched non-COPD patients as controls will be computer selected for this retrospective cohort study. Confounding variables which will be examined include preoperative bronchodilator usage and cardiac ejection fraction, total bypass pump time, active smoking, number of vessels bypassed, type of bypass whether left main, left anterior descending artery (LAD) or other, placement of a thoracostomy type, steroid usage, abnormal preoperative chest x-ray, higher American Society of Anesthesiologist class, and comorbid disease as defined as the preoperative existence of diabetes, hypertension, and renal disease.

Progress: Six hundred charts have been reviewed. Data analysis is in progress.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/055 **Status**: Ongoing

Title: Telomerase Activity in Bronchial Washings, Pleural Fluid, Sputum, and Cerebrospinal Fluid (CSF)

Principal Investigator: Ravi R. Ramakrishna, M.D.

Department: Medicine/Pulmonary&Critical Care **Facility**: MAMC

Associate Investigator(s): COL Thomas A. Dillard, MC; LTC William E. Caras, MC; CPT Wade K. Aldous, MS; Rakesh Gaur, M.D.; Edward Brown; LTC Jerome B. Myers, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/20/1998	Sep 98	N/A

Study Objective: To determine the sensitivity and specificity of telomerase activity as an indicator of malignancy in non-surgical pleuro-pulmonary tissue samples and CSF.

Technical Approach: All procedures will be part of the standard and accepted diagnostic workup. The specimens collected will depend on the clinical situation and the instrument being used, i.e., bronchoscopy for washings vs thoracentesis for pleural fluid vs lumbar puncture for CSF. For bronchial washing, 5-10 cc of wash will be submitted in 10 cc of RPMI. For pleural fluid, the amount of fluid remaining after aliquots sent for other analyses will be submitted in 10-50 cc of RPMI. For CSF, the amount of fluid remaining after aliquots sent for other analyses will be submitted in 10 cc of RPMI. A post- bronchoscopy sputum sample in 10 cc of RPMI will be submitted. Standard bronchial washing, sputum, and pleural fluid samples will be submitted for cytological examination. The qualitative telomerase activity will be determined using a telomerase PCR ELISA kit. In samples where there is activity, an attempt will be made to quantitate the amount of activity. The telomerase activity will be compared with cytological and histological diagnosis from samples obtained by non-surgical and surgical means. This will be done in order to determine the sensitivity, specificity, positive and negative predictive value of telomerase in non-surgical samples. The data will be analyzed to evaluate the correlation of the cytology and histology from surgical and non-surgical samples with the ability to detect telomerase activity in non-surgical samples, reporting sensitivity and specificity along with positive and negative predictive values. The sensitivity of telomerase from the bronchial washing, and/or sputum, and/or pleural fluid/ and/or CSF will be compared with the sensitivity of cytology for the same fluid.

Progress: Thus far, 114 samples from 99 patients have been analyzed. Data from the four patients from MAMC Protocol #98086 have been combined with data from this study. At this point both protocols have the same objectives except that 98086 requires a consent form for extra biopsies. Findings thus far indicate that detection of telomerase activity appears feasible from non-surgical samples. Telomerase activity in cytologically positive samples was similar in bronchoscopic and nonbronchoscopic samples. Telomerase activity from cytologically positive brushing and Wang needle aspirates had higher sensitivity than washings. Rare patients with acute inflammatory states had positive telomerase activity. Telomerase activity by gel electrophoresis was similar in small cell, non-small cell lung, and non-lung primaries. ELISA appeared less sensitive than detection of telomerase by gel. In some patients with proven cancer, telomerase activity was present when cytology from the same tissue sample was negative. Telomerase appears to be more prevalent in patients with sarcoidosis as compared with other interstitial lung diseases. An abstract has been accepted for publication by Chest and the findings have been accepted for presentation in poster form.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/138 **Status**: Ongoing

Title: Active Inspiration/Expiration versus Tidal Volume Breathing During Transbronchial Biopsy

Principal Investigator: Ravi R. Ramakrishna, M.D.

Department: Medicine/Pulmonary & Critical Care **Facility**: MAMC

Associate Investigator(s): MAJ Timothy R. Murray, MC; LTC Bernard J. Roth, MC; Suzette Gagnon-Bailey, M.D.; COL Thomas A. Dillard, MC; CPT Kurt W. A. Grathwohl, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/16/1996	Aug 97	09/15/1998

Study Objective: To compare yield, results and complications of two currently used techniques for transbronchial biopsy.

Technical Approach: All patients referred in the pulmonary clinic for bronchoscopy will be enrolled. Bronchoscopy will be performed in the usual manner. Patients will have a minimum of 6 transbronchial biopsies performed. They will be randomized to have the first three biopsies performed by either the active inspiration/expiration method or the tidal volume breathing method. After 3 biopsies are performed, the patient will be crossed over to the method not previously performed to obtain the next three biopsies. If more biopsies are needed, the attending physician can utilize any method at their discretion although the subsequent biopsy samples will not be included in data analysis. The attending pulmonologist or nurse will record the number of attempts for each and the appearance and quantity of sample grossly. Hemorrhage, pain, dyspnea, change in vital signs, and need for stopping the procedure will be recorded after each attempt. Two containers will be identified to the investigators although the examining pathologist will be blinded to the method performed. The pathologist will identify the number and size of samples in each as well as note the presence of alveolar tissue and the pathologic diagnosis if any. We will enroll 100 patients over one year. The differences between number of adequate samples and size will be compared using the paired student t-test. Other variables such as presence of alveoli and presence of complications (i.e. chest pain, bleeding, dyspnea, etc.) will be compared using the chi square test.

Progress: The principal investigator on this study was changed from MAJ Kurt Grathwohl, MC, to Dr. Ramakrishna during FY 98. Since he is still consenting patients for the same patient population (extra biopsies) for protocol #98086, he will not be enrolling any patients until that study has accrued the planned number of subjects.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/086 **Status**: Ongoing

Title: Telomerase Activity in Non-surgical Specimens Obtained at Bronchoscopy and Fine Needle Aspiration

Principal Investigator: Ravi R. Ramakrishna, M.D.

Department: Medicine/Pulmonary&Critical Care **Facility**: MAMC

Associate Investigator(s): COL Thomas A. Dillard, MC; LTC William E. Caras, MC; CPT Wade K. Aldous, MS; CPT Tommy A. Brown, MC; MAJ David P. Tracy, MC; MAJ Sean P. Murray, MC; LTC Jerome B. Myers, MC; CPT Michael C. Royer, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/19/1998	Feb 99	N/A

Study Objective: To determine the sensitivity and specificity of telomerase activity as an indicator of malignancy in non-surgical pleuro-pulmonary tissue samples.

Technical Approach: All procedures will be part of the standard and accepted diagnostic workup. The specimens collected will depend on the clinical situation and the instrument being used, i.e., brush vs transbronchial biopsy vs pleural biopsy. In patients requiring a transbronchial biopsy or endobronchial biopsy or pleural biopsy, a single 2-3 mm tissue sample will be submitted in RPMI (cell growth media). For brushing, an entire brush will be submitted soaked in RPMI. For fine needle aspiration, 0.25 - 0.5 cc of a single aspirate will be submitted. Standard brushing and fine needle aspiration samples will be submitted for cytological examination and biopsies (lung, pleural) for histological examination. The qualitative telomerase activity will be determined using a telomerase PCR ELISA kit. In samples where there is activity, an attempt will be made to quantitate the amount of activity. The telomerase activity will be compared with cytological and histological diagnosis from samples obtained by non-surgical and surgical means. This will be done in order to determine the sensitivity, specificity, positive and negative predictive value of telomerase in non-surgical samples. The data will be analyzed using statistical software to evaluate the correlation of the cytology and histology from surgical and non-surgical samples with the ability to detect telomerase activity in non-surgical samples, reporting sensitivity and specificity along with positive and negative predictive values. The sensitivity of telomerase from the Wang needle aspirates and/or trans/endo bronchial or fine needle aspirations will be compared with the sensitivity of histology for the same sample.

Progress: Four subjects have been studied. The data from this study has been combined with that from MAMC study #98055. Please see progress report for that study for preliminary results.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 91/015 **Status**: Terminated

Title: Controlled Trial of Positive Pressure Ventilation via Nasal Mask in Patients with Severe Chronic Air Flow Obstruction and Chronic Respiratory Failure

Principal Investigator: LTC Bernard J. Roth, MC

Department: Medicine/Pulmonary&Critical Care **Facility**: MAMC

Associate Investigator(s): LTC William H. Cragun, MC; MAJ Bruce S. Grover, MC

Start Date:	Est. Completion Date:	Periodic Review:
12/07/1990	Oct 91	09/30/1998

Study Objective: To determine if one eight hour period per week of ventilatory rest via nasal mask positive pressure ventilation will improve pulmonary function and exercise tolerance in patients with chronic air flow obstruction and chronic respiratory failure marked by an elevated arterial carbon dioxide.

Technical Approach: The study population will be both sexes, age >18 years, with severe COPD. The following baseline values will be obtained: age, weight, height, smoking status, medication list, chest x-ray, spirometry, formal lung volumes, MIP, MEP, DLCO, arterial blood gas measurement, pulse oximetry, end-tidal capnography, thyroid function tests, CBC, electrolytes, Karnofsky scale, dyspnea index, and 12 minutes walking distance. Spirometry, pulse oximetry, and end-tidal capnography will be repeated once weekly for four weeks. After four weeks, baseline studies will be repeated and an overnight polysomnography will be performed which includes electroencephalogram, electromyogram, electro-oculogra, airflow, chest wall and abdominal motion, pulse oximetry, and transcutaneous capnograpny. At this time the patient will be tested to determine if he tolerates intermittent positive pressure ventilation through a nose mask (nIPPV). Patients who tolerate nIPPV will be randomized to once weekly overnight nIPPV or nasal continuous positive airway pressure (nCPAP). Every 4 weeks during the 12 weeks of treatment, a repeat baseline evaluation will be done except that a transition dyspnea index rather than a baseline dyspnea index will be obtained. After 12 weeks of active therapy, the patients will be followed for an additional 12 weeks with 4 week evaluations as in the previous 12 weeks. Any change in pulmonary function, exercise tolerance, or dyspnea index will be compared between nCPAPA and nIPPV patients using Student's T test. Significantly improved exercise tolerance, subjective dyspnea, Karnofsky scale, MVV, MIP, MEP, FVC, or PaCO2 will be considered a positive result of nIPPV.

Progress: Over the seven years that this study has been open, eight patients have been entered. It has now been terminated due to inadequate staff to support this labor intensive study.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 92/024 **Status**: Ongoing

Title: Resectable Bronchogenic Carcinoma: Value of Routine Contrast - Enhanced Cranial MRI in Preoperative Staging

Principal Investigator: LTC Bernard J. Roth, MC

Department: Medicine/Pulmonary&Critical Care **Facility**: MAMC

Associate Investigator(s): MAJ Kevin L. Quinn, MC; LTC Miquel J. Rovira, MC; LTC Steven S. Wilson, MC; MAJ Frank A. Zimba, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/03/1992	Jan 93	09/30/1998

Study Objective: To determine the incidence of clinically occult brain metastasis in patients with resectable primary bronchogenic carcinoma.

Technical Approach: The subjects (100) for this protocol will be patients >18 years of age with primary bronchogenic carcinoma, Stage IIIa or less as determined by chest CT, who are neurologically intact. The patient will undergo a complete clinical neurological history and physical exam and enhanced cranial MRI to screen for brain metastasis. Patients with evidence of significant CNS pathology will be divided into four groups: (1) solitary lesion amenable to neurosurgical resection (2) significant brain pathology other than metastatic disease that would delay or preclude therapy (3) brain metastasis and (4) metastasis outside the brain. Patients in group 1 or 2 will undergo neurosurgical and/or radiation therapy evaluation for possible curative or palliative therapy. Patients in group 3 or 4 will undergo radiation therapy and/or hematology-oncology evaluation for possible palliative therapy. Patients in whom MRI revealed suspicious areas which are not definitely characteristic for metastasis will undergo brain biopsy using stereotactic localization. Patients refusing brain biopsy will be followed closely with periodic follow-up enhanced cranial MRI every three months. MRI and clinical data will be evaluated to determine the overall incidence of clinically occult brain metastases and the presence (if any) of any significant differences among primary cell types.

Progress: Two patients were entered in this study in FY 98 for a total enrollment of 36 subjects. Accrual of subjects has been very slow.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/132 **Status**: Ongoing

Title: Respiratory Care Team to Decrease the Misuse of Metered Dose Inhalers in Hospitalized Patients

Principal Investigator: LTC Bernard J. Roth, MC

Department: Medicine/Pulmonary&Critical Care **Facility**: MAMC

Associate Investigator(s): COL Thomas A. Dillard, MC; Michael G. Winter, RRT; Nora A. Regan; CPT John J. Mullon, MC; CPT Michael W. Quinn, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/19/1997	Mar 96	09/30/1998

Study Objective: To determine if a respiratory team teaching proper metered dose inhaler (MDI) use to inpatients will improve the observed rate of proper MDI use at Madigan Army Medical Center (MAMC).

Technical Approach: In this study, a pulmonologist will interview 60 inpatients prescribed an MDI and observe their MDI technique to establish a baseline rate of misuse. Then a respiratory care team will receive a daily list from Pharmacy on all patients newly prescribed an MDI. They will provide direct teaching to the patients on correct use of their MDI. After the teaching program has been in place for 2- 6 weeks the same pulmonologist will interview 60 more patients and observe their MDI technique to establish the rate of misuse after the intervention. The patient will be asked if they have received education and this will be correlated to the chart documentation of education by the Respiratory Therapist. The major endpoint will be the change in the rate of MDI misuse observed.

Progress: Thirty eight subjects were entered in this study in FY 98.

Detail Summary Sheets

Department of Nursing

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/053 **Status**: Ongoing

Title: Improving Soldier Access to Urinary Incontinence Therapy

Principal Investigator: LTC Ann M. V. Bianchi, AN

Department: Nursing **Facility**: MAMC

Associate Investigator(s): Lori A. Loan, MSN, RNC; LTC Richard A. Sherman, MS

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/16/1998	Sep 98	N/A

Study Objective: To compare access to care and patient satisfaction with care of female soldiers receiving biofeedback treatment for exercise-induced urinary incontinence in the troop medical clinic environment with those receiving similar treatments at a medical center.

Technical Approach: All subjects will be screened for evaluation of the lower urinary tract. If inclusion criteria are met, the subject will be randomized to treatment at either the TMC or Madigan Army Medical Center. Treatment visits will occur every 2 weeks for 12 weeks. During the first visit, demographic and descriptive information will be gathered and subjects will learn how to do Kegel exercises using biofeedback. Subjects will be asked to keep daily logs and to practice the Kegel exercises for twenty minutes twice a day.

Subsequent visits to the treatment center will be to encourage continuation of the Kegel exercises and the keeping of daily logs. At the final visit more demographic and descriptive information will be obtained and a Patient Satisfaction Questionnaire will be filled out by each subject. The portable biofeedback equipment will be used to evaluate Kegel performance during this final visit.

Progress: Approval from the I Corps Surgeon for distribution of the survey has been obtained. Study equipment is in the process of being ordered and study staff are being hired and trained. The survey is being prepared as an optical scannable document .

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/044	**Status**: Ongoing

Title: Physical Activity and Exercise in AD Female Soldiers

Principal Investigator: LTC Laura R. Brosch, AN

Department: Nursing	**Facility**: MAMC

Associate Investigator(s): Debra DePaul, RN; Lori A. Loan, MSN, RNC; COL Melissa A. Forsythe, AN

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/20/1998	Oct 98	N/A

Study Objective: To examine the physical activity levels and habitual exercise patterns of active duty female soldiers and to identify factors that influence those habits in hopes of producing information to be used to improve the health of female soldiers.

Technical Approach: Each subject will complete an initial survey regarding physical activity and exercise habits including family support for exercise and Annual Physical Fitness Test scores will be obtained for each subject. After completing the survey, the subjects identified as belonging to subgroups at risk for low exercise will be asked to attend a focus group session which will explore the issues related to physical activity and exercise. Data from the focus group sessions will be transcribed as narrative accounts and loaded onto a computer equipped with Ethnograph software. Data will then be subjected to a content analysis, in which key themes and phrases used by the participants will be identified and quantified by the researchers.

Progress: This study was approved for funding by the TriService Nursing Research Program and was activated in September 1998. During the first 2 months of the study, an Optical Data Entry System was purchased, the project director was hired, and the I Corps Surgeon was briefed on the details of the study. The Exercise Health Assessment is being prepared as an optical scannable document. No subjects have been entered.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/131 **Status**: Completed

Title: Risk Factors for Nosocomial Pneumonia

Principal Investigator: CPT Laura L. Feider, AN

Department: Nursing **Facility**: MAMC

Associate Investigator(s): MAJ Mary S. McCarthy, AN; MAJ Roger H. Anderson, AN

Start Date:	Est. Completion Date:	Periodic Review:
09/19/1997	Aug 98	05/22/1998

Study Objective: To determine risk factors for nosocomial pneumonia development in ICU patients; and to determine whether the variables chosen occurred more frequently in patients who developed nosocomial pneumonia than in those who did not.

Technical Approach: This study is a retrospective chart review, using a case control design, comparing records of ICU patients who develop nosocomial pneumonia to those who do not A chart review will be conducted to gather the data. Associations between the presence of the identified risk factors (physiologic and treatment variables) and the development of nosocomial pneumonia will be analyzed. The control groups will be used to determine whether the chosen variables occurred more frequently in patients who developed nosocomial pneumonia than in those who did not. The data will be recorded on the chart review tool, which includes questions related to the physiologic and treatment variables. The study endpoints include identification of variables associated with nosocomial pneumonia development for length of stay and mortality rates.

Progress: Sixty subjects with nosocomial pneumonia (NP) were matched to a control group of non-NP by age (+/- 5 years), admitting service, and length of stay until NP diagnosis. Medical records were reviewed for physiologic and treatment risk factors. The two groups were significantly different when comparing physiologic variables, self-care ability, aspiration, and bacteremia. The relative risk for NP development for aspiration was 21.3 and for bacteremia was 2.57. Of the treatment variables, differences were seen in endotracheal intubation and ventilation, performance of pulmonary exercises, respiratory treatments, and number of consults. The outcome measures were significantly different when comparing the two groups. Length of stay was 10.7 days longer and the mortality rate was 50% higher in the NP group. The number of consults was higher, the length of hospital stay increased by 60% and the mortality rate was doubled in the NP group. Nurses are key team members who can identify patients at risk using the identified risk factors. Since length of stay and mortality were higher in the NP group, more vigorous monitoring of at risk patients may also help to improve patient outcomes. A paper has been submitted and successfully defended as a requirement for a Masters degree in Biobehavioral Nursing at the University of Washington.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/052	**Status**: Terminated

Title: Domestic Violence in Women: An Army Prevalence Study

Principal Investigator: MAJ Ramona M. Fiorey, AN

Department: Nursing		**Facility**: MAMC

Associate Investigator(s): LTC Elizabeth A. Mittelstaedt, AN; Suzanne K. Wilson, MSN, RN

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/16/1998	Sep 99	N/A

Study Objective: To investigate the frequency with which women military beneficiaries voluntarily self report domestic violence in health care settings and to define barriers which prevent health care providers in the military health care system from routinely screening women for domestic violence.

Technical Approach: All women seeking acute and primary care during a 3 month period will be asked to complete the Abuse Assessment Screen (AAS). All HCPs in the acute and primary care portals will be asked to complete the Methods and Attitudes Toward Screening Patients for Abuse (MATSPA).

Progress: This protocol was not implemented because funding was not received. It has been terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/024 **Status**: Completed

Title: The Effectiveness of 5-Hydroxytryptamine Type (5-HT3) Receptor Antagonists in the Treatment of Intrathecal Narcotic-Induced Pruritus: Ondansetron versus Naloxone

Principal Investigator: 1LT Laura E. Francis, AN

Department: Nursing **Facility**: MAMC

Associate Investigator(s): CPT Richard K. Hanisch, AN; CPT Stephen R. Frietch, AN; CPT Randy J. Landry, AN

Start Date:	Est. Completion Date:	Periodic Review:
11/21/1997	Dec 98	N/A

Study Objective: To compare the effectiveness of naloxone and ondansetron HCL (5-HT3 receptor antagonist) in the treatment of pruritus associated with neuraxial opioid administration.

Technical Approach: Subjects will be randomized to either ondansetron or naloxone. Each subject will receive 0.3-0.5 mg intrathecal morphine after baseline data collection occurs. Data collection will continue post-operatively for six hours. At each data collection point, subjects will be offered medication for itch. At patient request, a study medication will be administered, either 1.0 mg naloxone or 4 mg ondansetron. The study medication can be repeated one time after 30 minutes if pruritus persists. Itch, pain, nausea and headache will be measured every hour using a self scored, closed ended, vertically oriented, 100 mm visual analogue scale.

Progress: Data collection commenced in Jan 97 and terminated in Aug 97. Forty-four (44) subjects were consented into the study. Data collection was terminated due to time constraints within the program. Difficulty attaining a sufficient number of subjects occurred for a number of reasons; primarily fewer than expected Cesarean sections, greater than expected numbers of breast feeders, and a lower than expected treatment rate (participants request for treatment). Preliminary data from this pilot study indicate that naloxone and ondansetron are equally effective in treating intrathecal narcotic-induced pruritus.

The study was presented in a poster presentation at the American Association of Nurse Anesthetists and an abstract was published in the US Army Medical Department Journal.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/043	**Status**: Completed

Title: Parenting Outcomes of Single Active Duty Postpartum Women

Principal Investigator: CAPT Annette Gomez, USAF

Department: Nursing	**Facility**: MAMC

Associate Investigator(s): Debra DePaul, RN

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/20/1998	Mar 98	N/A

Study Objective: To evaluate the impact of infant, parent, and environmental factors on parenting ability in single active duty women.

Technical Approach: This is a correlational, descriptive design with repeated measures. Subjects are single, active-duty women >18 years of age and their infants, 0-6 months at the time of the study; 11 subjects in the experimental group and 12 subjects in the control group. Subjects were asked to complete several instruments; Symptoms of Stress (SOS), Beck Depression Index (BDI), Nursing Child Assessment Sleep/Activity Record (NCASA), Community Life Skills Scale (CLSS), Visual Analog Scale-Fatigue (VAS-F), Inference Scale, Nursing Child Assessment Teaching Scale (NCATS), Infant Temperament Questionnaire (ITQ), Early Infant Temperament Questionnaire (EITQ), Difficult Life Circumstances (DLC) and Child Care Resources Questionnaire (CCRQ). Pearson Correlation will be used to assess relationships among variables, along with descriptive statistics.

Progress: This study has been completed. In a previous study, subjects were divided into a control group who received routine care and an experimental group who was cared for by an advanced practice nurse who prescribed interventions related to sleep hygiene, sleep environment regulation and sleep consolidation for both the parents and the infants. The data from that study were used for further analysis in this study to describe the impact of infant, parent, and environmental factors on parenting ability in single, active duty women. Twenty-three subjects were entered in this study. The control and experimental groups were combined for statistical analysis in this study because no differences were found in the original study . Over time the reported stress symptoms increased. Fatigue-related symptoms increased over time, depression increased over time, maternal sleep decreased postnatally, and challenges faced by this group of women increased over time. It would appear that all of these factors affect one another. Grouped scores for this set of women do not appear to be disturbing. However, some of the individual scores were quite low. Based on the mean results, being a single active duty mother was not detrimental to the parent-child interaction, but must be assessed individually. A paper has been submitted as partial fulfillment for an advanced degree at the University of Washington.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/112 **Status**: Completed

Title: Wound Healing: The Effect of Supplemental Oxygen Therapy

Principal Investigator: Stacey L. Heiner, BSN, RN

Department: Nursing **Facility**: MAMC

Associate Investigator(s): JoAnne D. Whitney, Ph.D., RN; Lori A. Loan, MSN, RNC; LTC Brenda I. Mygrant, AN

Start Date:	Est. Completion Date:	Periodic Review:
05/17/1996	Sep 97	04/17/1998

Study Objective: The aim of nursing research is to maximize positive patient outcomes through research-based nursing interventions. This study will provide a foundation of developing nursing standards based on evaluation of the independent variable, inhaled supplemental oxygen, and it's role in wound healing. Wound healing, a complex phenomenon involving modiable and non-modiable person variables, can be affected by research-based nursing interventions.

Technical Approach: The proposed pilot study utilizes a randomized, two group experimental repeated measures design. subjects are randomly assigned to either the control or the intervention group using computer generated random number blocks of 6. This assures that there are not large imbalances between groups at any point in the study. The control group will receive only room air, which is current standard therapy. The intervention group will receive supplemental oxygen at 28% in the form of 2 liter per minute via nasal cannula for 36 hours postoperatively. Subjects will be randomized upon admission to the surgical ward. Subjects will be recruited from those who undergo cervical fusion and/or excision of cervical intervertebral disc, either through the Neurosurgery or the Orthopedic Surgery Services. Based on existing data, it is hoped that 24 subjects can be recruited over the one year study period.

Progress: Twenty-four subjects having fusion of the cervical and spinal and/or excision of a cervical intervertebral disc completed the study. The treatment group (n=13) received 28% oxygen for the first 36 postoperative (PO) hours. The control group (n=11) was maintained on room air. Subcutaneous tissue oxygen and temperature were measured pretreatment and at PO hours 1-4, 18, and 36, using a tonometer/oxygen electrode system. Wound healing was evaluated by hydroxyproline content in a subcutaneous polytetrafluoroethylene tube, removed on the seventh PO day. Clinical wound complications were evaluated using the ASEPSIS Wound Scoring System and PO medical record review. Groups were similar for age, preoperative hematocrit, prealbumin, temperature, and fluid repletion. The intervention group showed a trend for increased tissue oxygen levels, with markedly higher levels at 18 and 36 hours PO. ASEPSIS scores for the groups were similar and the frequency of wound redness/incision opening was slightly higher in the control group. These preliminary results show that low level, short duration supplemental oxygen successfully increases and sustains wound tissue oxygen levels. Conclusions on improved wound healing and reduced complications cannot be made until a larger population is studied. These results were presented to the Phyllis J. Veronick Nursing Research Course in March 1998.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 97/068	**Status**: Ongoing

Title: Effects of Stress Responses on Wound Healing

Principal Investigator: Stacey L. Heiner, BSN, RN

Department: Nursing	**Facility**: MAMC

Associate Investigator(s): JoAnne D. Whitney, Ph.D., RN; Margaret M. Heitkemper, Ph.D.; Lori A. Loan, MSN, RNC; MAJ Susanne J. Clark, AN

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/21/1997	Sep 00	04/17/1998

Study Objective: Compare measures of preoperative and postoperative psychological stress, SNS and HPA activation (STAI, RIES, PSQ-III GSS, urinary norepinephrine, epinephrine and cortisol) in subjects experiencing minor (e.g., outpatient arthroscopic) and major (e.g., total knee arthroplasty) surgical procedures.

Technical Approach: The proposed study will use a prospective, correlational design to explore relationships between pre and postoperative psychologic and physiologic stress and the defined wound healing indices. The study will enroll a total of 96 subjects over a three year period from populations experiencing minor and major orthopedic knee surgery. The relationship between each preoperative and postoperative measure of stress and each wound healing measure will be evaluated with the Pearson product moment correlation coefficient. Repeated measures analysis of variance will be used to compare the stress experienced by patients undergoing major surgery to those undergoing minor surgery at the eight times of measure.

Progress: Subject recruitment began in January 1998. To date, 27 subjects have consented to participate. Of these, 23 subjects have completed the protocol, two subjects withdrew preoperatively, one subject had surgery canceled, and one subject is to be rescheduled at a later date. No data analysis has been done at this time.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/132 **Status**: Ongoing

Title: Pressure Ulcer Prevention: Comparing Support Surfaces

Principal Investigator: LTC Pamela J. Hildreth, AN

Department: Nursing **Facility**: MAMC

Associate Investigator(s): LTC Linda H. Yoder, AN; LTC Brenda I. Mygrant, AN; Gladys Cobb, BSN, MSN

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/21/1996	Sep 99	06/19/1998

Study Objective: 1) Determine the demographic characteristics that differ between patients who do and those who do not develop pressure ulcers. 2) Compare the incidence of pressure ulcers between the patients on the KinAir® bed and patients on the EHOB WAFFLE® mattress. 3) Determine the difference in length of stay and monetary expenditure for individuals within the two support surface groups who do not develop pressure ulcers. 4) Determine the difference in length of stay and monetary expenditure for individuals within the two support surface groups who do develop pressure ulcers.

Technical Approach: The proposed study is a prospective, quasi-experimental design, in which subjects who are at risk for pressure ulcer development will be randomly assigned to one of two support surfaces. Data will be collected for a period of at least one week or until the subject is discharged, expires, or is no longer considered at risk. Data to be collected will include pressure sore risk using the Braden Scale for Predicting Pressure Sore Risk, daily skin integrity assessments, and information on pressure ulcer development and subsequent ulcer progression using the Pressure Sore Status Tool, as well as data on selected demographic variables. The study will be conducted in multi-site settings. The primary site for the study will be Madigan Army Medical Center and Brooke Army Medical Center (BAMC) is the study's secondary site.

Using data obtained from the Wound Care Specialists at both MAMC and BAMC, it is anticipated that approximately 4 eligible subjects will be admitted to BAMC per week. Because the proposed study offers daily care from a research team devoted to maintaining skin integrity, a 75% consent rate is predicted. This equates to enrollment of 3 subjects per week at MAMC and 2 per week at BAMC. An attrition rate of approximately 10% is anticipated based on preliminary data from the Tri-Services Nursing Research Group funded study "Pressure Ulcers: Patient Outcomes on Kinair Bed or EHOB Mattress." Recruitment will occur for twenty-eight months and enrollment of 560 subjects is anticipated.

Progress: By the end of study year one, both sites had abandoned the Kin-Air bed as the standard surface and adopted the less costly ZoneAire bed. A total of fifty-three patients was entered in year one from BAMC and MAMC. There were no statistically significant differences between patients who did and did not develop pressure ulcers for any of the demographic variables. There was no statistically significant difference in pressure ulcer development between support surfaces. No patients had a length of stay extended due to pressure ulcer development. Patients experiencing pressure ulcers had significantly more days in the ICU. Length of hospital stay approaches statistical significance. Cost expenditures were similar for patients with and without pressure ulcers. Patients in the Kin-Air group had statistically significantly more days in the ICU, longer hospital stays, and higher cost expenditures.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/077 **Status**: Ongoing

Title: Linking Nursing Care to ANA Quality Indicators

Principal Investigator: LTC Pamela J. Hildreth, AN

Department: Nursing **Facility**: MAMC

Associate Investigator(s): Lori A. Loan, MSN, RNC; COL Bonnie M. Jennings, AN; Elizabeth Pulos, Ph.D.; COL Nancy Staggers, AN; Pamela H. Mitchell, Ph.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/18/1997	Sep 98	04/17/1998

Study Objective: 1) To gain a better understanding of our ability to collect the ANA Nursing Quality Indicator data; 2) to assess the feasibility of collecting nursing care quality data and; 3) to examine the existence and strength of relationships between nursing care and the ANA Nursing Quality Indicators.

Technical Approach: Because nurses are an integral part of the health care delivery system, both in terms of patient contact and hospital spending, the ANA has initiated an endeavor to formulate a nursing report card which will include patient-focused outcome indicators chosen for their ability to link nursing care quality to patient-focused outcomes. The links between patient outcomes and the nursing care quality identified by the ANA Nursing Quality Indicators are not well understood. However, before these relationships can be tested, more information about the feasibility of collecting nursing care data and patient outcomes data is necessary. Using a variety of methods including expert panels, chart review and questionnaires, information related to the ANA Nursing Quality Indicators and nursing care quality will be gathered and evaluated. The final goal is to statistically determine whether the ANA Nursing Quality Indicators are sensitive to documented differences in the quality of nursing care patients receive using ANOVA. Further research on indicators sensitive to changes in nursing care quality will potentially improve the quality of patient care by promoting both the science of outcomes research and the practice of nursing. In addition, identifying quality indicators will provide valuable input for balancing administrative and clinical decision making.

Progress: In the first phase of the study, using existing Nursing Standards of Care for intravascular access devices, skin care, patient safety, nursing assessment and plan of care, patient education and pain management, a panel of expert nurses identified each standard's essential and less essential elements. These elements were categorized in regard to importance to documentation as optimal (essential and less essential elements documented) , adequate (only essential elements documented), or deficit (essential elements omitted from the documentation). The second phase consisted of trialing strategies to identify patients at risk for falling or skin breakdown, experiencing pain, or having an intravascular access. Strategies were also trialed for collecting data required to asses the ten ANA Nursing Quality Indicators. In the third phase, data related to nursing care quality were collected via the computerized documentation system , the 24 hour patient report, and the daily workload management system for nursing report. In this phase, patient satisfaction data were collected via the Patient Satisfaction with Nursing Care questionnaire which was sent to all patients within 2-3 days of their discharge. Nursing satisfaction data were gathered via the McCloskey/Mueller-Satisfaction Scale. This questionnaire was distributed to nursing staff at the end of the 3 month data collection period. The study is currently in the last two phases of the study (analysis and interpretation).

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/125 **Status**: Ongoing

Title: A Survey of Access to Care in the TRICARE Environment

Principal Investigator: COL Bonnie M. Jennings, AN

Department: Nursing **Facility**: MAMC

Associate Investigator(s): COL Frances D. Anderson, AN; Lori A. Loan, MSN, RNC; Suzanne K. Wilson, MSN, RN

Start Date:	Est. Completion Date:	Periodic Review:
06/21/1996	Sep 98	06/19/1998

Study Objective: To describe access to health care in the TRICARE environment.

Technical Approach: Using a stratified sample of 7,680 military beneficiaries from the MAMC 40 mile catchment areas, this descriptive survey aims to describe access to health care in the TRICARE environment. The research questions are: 1) How do military beneficiaries (consumers) in the MAMC 40 mile catchment area evaluate access to health care? 2) How do military beneficiaries in each of the consumer groups evaluate access to health care? 3) How do members of each of the components of TRICARE evaluate access to health care? 4) Do consumer evaluations of access to care differ according to TRICARE component? Randomly selected beneficiaries from the four TRICARE components will complete and return a mailed questionnaire. Instruments selected for use in the study include the PSQ-III, the General Health Perceptions scale from the SF-36, and select sociodemographic questions from the 1994-1995 Annual Health Care Survey for DoD Beneficiaries. The instruments were chosen for their appropriateness and their high levels of reliability and validity. Data form the survey will be analyzed using descriptive statistics and one-way ANOVA.

Progress: During FY 98, a total of 3,012 randomly chosen military beneficiaries in the 40 mile Madigan Army Medical Center catchment area, who responded to the composite questionnaire entitled The 1997 Health Care Survey of DoD Beneficiaries Adult Form or Child Form, were entered in the study. Data cleaning and analysis are in progress.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/107	**Status**: Ongoing

Title: Nurses Influence on Patient Outcomes in US Army Hospitals

Principal Investigator: COL Bonnie M. Jennings, AN

Department: Nursing	**Facility**: MAMC

Associate Investigator(s): COL Barbara Jo Foley; Dr. Carolyn C. Kee; Dr. Ptlene Minick; Dr. Susan Harvey

Start Date:	**Est. Completion Date:**	**Periodic Review:**
09/15/1998	Sep 99	N/A

Study Objective: To describe patient outcomes in active duty personnel, military retirees, and military dependents, associated nursing organizational structures and processes; and hospital characteristics.

Technical Approach: Interviews, questionnaires and short answer surveys will be used to gather information on (1) patient outcomes while in the hospital to include the occurrence of adverse events such as injury-sustaining falls, length of stay, and severity-adjusted mortality; (2) outcomes following discharge from the hospital, including patient satisfaction with nursing care, satisfaction with how symptoms were managed, and functional health status. (3) nursing organizational structures include factors such as nursing practice model, nursing skill mix, and the education and experience level of registered nurses (RN);and (4) nursing organizational processes include RN job satisfaction, the degree of autonomy in nursing practice or the discretionary judgement 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.

Progress: This protocol has only recently been approved and has not been implemented.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/018 **Status**: Completed

Title: Using Progesterone to Determine an Association of Menstrual Cycle Phase with Clinically Significant Post-Operative Nausea and Vomiting Following Laparoscopic Surgery

Principal Investigator: LTC Patti A. Lederer, AN

Department: Nursing **Facility**: MAMC

Associate Investigator(s): CPT Naomi S. Childres, AN; 1LT Joel M. Ehler, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/18/1997	Aug 98	N/A

Study Objective: To investigate the influence of the menstrual cycle on clinically significant postoperative nausea, retching, and vomiting following laparoscopic gynecologic surgery using serum progesterone levels as a biological indicator of a specific phase of the menstrual cycle.

Technical Approach: Patients scheduled for laparoscopic surgery will be included in this study. Information will be obtained about the subject's menstrual cycle and about any nausea or vomiting following surgery. A blood sample will be collected to determine the menstrual cycle phase based on blood progesterone levels. Nausea and vomiting information post-op will be recorded on study data collection form.

Progress: Forty-seven subjects were enrolled. Of these, 12 were excluded secondary to breaches in the study's inclusion criteria, lab error, or having progesterone levels which placed them in the indeterminate phase of the menstrual cycle. The target sample size for the study was 52 subjects. This study investigated the use of progesterone as a biological marker to determine the phase of the menstrual cycle and its association with post-operative nausea, retching, and vomiting. Of these three factors, only retching demonstrated a statistically significant association with the menstrual cycle and gynecologic laparoscopy. Ten of the 35 subjects experienced retching. Of the 23 subjects in the follicular phase, 10 retched while none of the 12 subjects in the luteal phase experienced retching. Although statistically significant, retching did not appear to be clinically significant enough to warrant change in nursing practice. In addition, the small samples size of the study must be taken into account.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/190 **Status**: Ongoing

Title: The Effects of Thermocouple Sensor Placement on Neonatal Skin Temperature Measurement

Principal Investigator: Lori A. Loan, MSN, RNC

Department: Nursing **Facility**: MAMC

Associate Investigator(s): Lauran T. Taquino, RN, MS; Susan T. Blackburn, Ph.D., RN, FAAN; Karen A. Thomas, Ph.D., RN; Sue E. Chambers, RN

Start Date:	Est. Completion Date:	Periodic Review:
09/15/1995	Oct 96	08/20/1998

Study Objective: The objectives of this study are to compare temperature readings from probes placed on peripheral skin sites with readings of axilla temperature, and to compare temperature readings form probes placed on the abdomen and back during periods when the infant is lying -on and not lying-on the temperature probes. Also, to evaluate the effects of body size on accuracy of temperature probe measurements from selected sites, and when the infant is lying-on versus not lying-on the probe.

Technical Approach: This descriptive study is designed to objectively evaluate several common nursing practices and beliefs regarding the care of neonates and the placement of temperature probes. The study seek to provide a physiologic basis to support and validate nursing practice. Four body sites will be studied simultaneously through the use of a small thermocouple sensor and two channel continuous readout device. Data will be collected for one hour with the subject in each of two common positions, supine and prone. Environmental temperature and basic demographic data will also be collected for each subject and study period. The study period will consist of approximately 2.5 hours for each study subject and will not interfere with or alter the standard neonatal nursing and medical care of that infant. This study is sponsored by the local chapter of the national professional association for neonatal nursing and is designated to support data collection in multiple hospital sites. Data from all sites will be aggregated for the purpose of analysis and reporting. Descriptive statistics will be use initially to examine differences in temperature readings from the four sensors. Further analysis will examine clinically and statistically significant changes in temperature between the four sites and between lying-on and not lying-on the sensors. comparisons will also be made of differences in temperature values between sites and between infants of different weight groups.

Progress: Twenty subjects have been entered. Preliminary data were presented at the National Association of Neonatal Nurses Annual Conference in September 1998.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/137 **Status**: Ongoing

Title: Single Woman's Breast Cancer Program

Principal Investigator: Lori A. Loan, MSN, RNC

Department: Nursing **Facility**: MAMC

Associate Investigator(s): Nancy F. Woods, Ph.D., RN

Start Date:	Est. Completion Date:	Periodic Review:
07/19/1996	Jun 98	07/17/1998

Study Objective: There are five study purposes: to (1) test the effectiveness of a home-based counseling intervention for single women with early stage breast cancer with dependent children; (2) investigate the causal model underlying the intervention; (3) explore time related patterns of change in individual study participants; (4) develop a discriminant function that effectively categorizes women and children most able to benefit from the intervention; and (5) test the cost-effectiveness of the intervention. The goal of the intervention is to improve psychosocial adjustment and quality of life in single women with early stage breast cancer and their dependent children.

Technical Approach: This study will enroll 200 single females who have a recent diagnosis (11 months or less) of early-stage breast cancer (Stage 0, 1 or 2). Subjects will be inpatients or outpatients, from medical, surgical or radiation oncology departments. Subjects will be randomized prior to initial contact so that the woman is invited to participate in either the coached or evaluation group. When subjects have agreed to participate, an in-home appointment is made with the evaluation nurse. Consent is obtained on the first visit and questionnaires are administered. Child participation is desirable but not mandatory. Initial explanation to the child is always is left to the mother, but the nurse will provide additional information and obtain written consent from the child, if willing. All families receive 4 evaluation visits. Women randomized to the coached group receive an additional 5 in-home visits by the coach. At the end of the study, all women receive thank you a letter and those who were randomized to the evaluation group receive $20 for each visit and an informational packet about breast cancer. Data will be analyzed by 5 major methods: formal statistical tests of the effect of the intervention (MANCOVA); investigation of the explanatory model underlying the intervention (structural equation modeling); exploration of time-related patterns of change in individuals (trend analysis and latent growth model); discriminant analysis and cost-effectiveness analysis. All of these data analytic components constitute outcome analyses and there will also be a process evaluation component.

Progress: To date no subjects from MAMC have participated in this study. Although MAMC provides care to many women with breast cancer, very few are single with young children . Only two subjects have met this criteria and none have met all the inclusion criteria for the study. Likewise, there have been no participants meeting the inclusion criteria from other Northwest military health care facilities. 132 subjects have been entered from civilian sites. An additional 44 participants are needed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/076 **Status**: Ongoing

Title: Gastric/Jejunal Feeding: Nutritional Outcomes and Pneumonia

Principal Investigator: MAJ Mary S. McCarthy, AN

Department: Nursing **Facility**: MAMC

Associate Investigator(s): LTC Bernard J. Roth, MC; CPT Kurt W. A. Grathwohl, MC; 1LT Faith U. Watanabe, SP; MAJ Susanne J. Clark, AN

Start Date:	Est. Completion Date:	Periodic Review:
05/17/1996	Sep 98	04/17/1998

Study Objectives: To compare nutritional outcome between patients randomized to gastric or jejunal tube feedings; (2) To compare rates of nosocomial pneumonia between gastric and jejunal fed patients; (3) To compare two methods of jejunal tube insertion for accuracy and efficiency of placement.

Technical Approach: The proposed study is a replication effort of a randomized, prospective, quasi-experimental design in which selected nutritional and physiological parameters will be evaluated during a course of enteral nutrition therapy in a convenience sample of adult ICU patients. The independent variables will be the two routes of enteral feeding involving 3 methods of tube insertion: gastric by blind insertion, proximal jejunal feeding by bedside videoscopic placement, or jejunal feeding by bedside fluoroscopic placement. The dependent variables are nutritional outcome and nosocomial pneumonia rates. Nutritional outcome will be described in terms of daily caloric intake and tube feeding volume, subjective global assessment, biochemical parameters, and indirect calorimetry using a metabolic cart. Nosocomial pneumonia rates will be determined by standard clinical criteria. Other physiologic parameters to be monitored are gastric pH and guaiac tests for occult GI hemorrhage, diarrhea, distention, and vomiting. Data will be collected on selected demographic variables and severity of illness will be assessed using the APACHE II scoring system and the Glasgow Coma Scale.

Progress: Recruitment for this study has been the most challenging aspect because the randomization arms of the study have been difficult to implement. The jejunal placement of feeding tubes by the videoscopic method was unavailable for six months because the videoscope fiberoptics were damaged beyond repair. The substitute videoscope was unacceptable to the physicians. A new videoscope has been purchase and found to be acceptable by the ICU physicians. Twenty-two patients have been consented to date: 15 gastric and 7 jejunal with 5 crossovers to gastric. Clinical observations of note include difficulty with successful placement and subsequent maintenance of jejunal feeding tubes. Diarrhea (>300 ml of liquid stool/day) or loose stools appears to be a prevalent gastrointestinal concern in critically ill patients regardless of feeding route. Nutritional screening parameters suggest an undernourished, critically ill population with an average "prefeeding" prealbumin value of 10.8 g/dl (normal 18.45 g/dl). Astute nursing assessment and use of standardized orders have enabled study patients to achieve 85% of their goal intake. Study measurements have proven to yield valuable data for critically ill patients with complex metabolic demands.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/063 **Status**: Ongoing

Title: Improving ARDS Patient Outcomes with Metabolic Support

Principal Investigator: MAJ Mary S. McCarthy, AN

Department: Nursing **Facility**: MAMC

Associate Investigator(s): CPT Maginia S. Morales, AN; Janet C. Chilton

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/20/1998	Sep 00	09/15/1998

Study Objective: (1) To determine the differences in nutritional and physiologic responses between ARDS patients who receive a special formula (Oxepa) versus ARDS patients who receive a standard formula (Osmolite HN): (2) to determine the differences in patient outcomes between ARDS patients who receive a special formula (Oxepa) versus ARDS patients who receive a standard formula (Osmolite HN)

Technical Approach: Subjects will be randomized to receive either the immune-enhanced formula, Oxepa, or a standard stress formula, Osmolite HN, for a minimum of 4 days. Nutritional outcomes will be based on prealbumin values, nitrogen balance, and percent caloric goal achieved. Physiologic outcomes will be measured by the oxygenation ratio respiratory quotient, and plasma interleukin-6 levels.

Progress: Equipment and supplies have been received and staff education is in progress.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/038	**Status**: Completed

Title: Autonomy of Military Wives and Their Recognition of Alcoholism

Principal Investigator: CPT Tina M. McConnell, AN

Department: Nursing	**Facility**: MAMC

Associate Investigator(s): LTC Elizabeth A. Mittelstaedt, AN

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/16/1998	Jan 98	N/A

Study Objective: To obtain descriptive information of two factors that may affect the way women deal with alcoholism in a military spouse.

Technical Approach: Subjects will fill out questionnaires. Autonomy will be measured by using the Worthington Autonomy Scale. Recognition of alcoholism will be measured using six vignettes. Each vignette will be rated by the subject to indicate the level of alcohol use they think it represents; such as, drinks but no alcohol problem, problem drinker, alcoholic. Each of the vignettes includes the amount and frequency of alcohol consumption, age of the drinker, occupation of the drinker and a number of consequences of alcohol use varying.

Progress: This project studied the association between personal autonomy and recognition of spousal alcohol use severity in a pilot sample of 49 military wives at an Army OB/GYN clinic. There was no correlation between autonomy and recognition. Frequencies indicated a homogenous group with a high level of autonomy. These subjects correctly identified the severity of alcoholism 31-80% of the time in the vignettes and often chose a response which magnified the severity of the problem. These results indicate that, given a cluster of symptoms, ambivalence is not severely impairing the ability of military wives to define an alcohol problem. The responses to vignettes suggest that some symptoms are stronger indicators of a problem than others. The responses to the vignettes also suggest that these women may be better served by using their own definitions rather than the definitions developed by the medical profession. A thesis has been written as part of the requirements for an advanced degree in psychosocial and community health nursing.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/066 **Status**: Terminated

Title: Postpartum Physical Fitness in Military Women

Principal Investigator: LTC Elizabeth A. Mittelstaedt, AN

Department: Nursing **Facility**: MAMC

Associate Investigator(s): Debra DePaul, RN; Lori A. Loan, MSN, RNC; Elizabeth Pulos, Ph.D.; Marcia G. Killien, Ph.D., RN

Start Date:	Est. Completion Date:	Periodic Review:
03/21/1997	Sep 00	03/20/1998

Study Objective: 1) Describe the physical fitness of postpartum active duty military women during the first nine months (i.e., at 6 weeks, 6 months, and 9 months postpartum) following childbirth as compared to non-postpartum female soldiers. 2) Describe the health promotion behaviors (specifically exercise, diet, sleep and smoking) used by pregnant/postpartum active duty military women during pregnancy and in the first nine months following childbirth (i.e., pre-pregnancy, at 34 weeks pregnant, 2 weeks postpartum, 6 weeks postpartum, 3, 6, and 9 months postpartum) as compared to non-postpartum female soldiers. 3) Examine the extent to which health promoting behaviors (specifically exercise, diet, sleep and smoking) facilitate physical fitness in postpartum and non-postpartum female soldiers.

Technical Approach: The study will utilize a prospective, longitudinal, panel design with a two-group comparison. APFT and American College of Sports Medicine physical fitness measures and health promoting behaviors (exercise, sleep, and smoking) data will be analyzed from pregnant/postpartum (n = 80) and non-pregnant soldiers (n = 80) assigned to Fort Lewis, Washington. Data will be collected from in-person and phone interviews, daily health behaviors' recall and record review. Data will be analyzed using descriptive statistics, Chi-square, independent t-test, Pearson product-moment correlation coefficient and RM-ANOVA.

Progress: This protocol has been terminated because the grant request for funds was not approved. No patients were entered.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/106 **Status**: Ongoing

Title: Natural Killer Cell Activation and Apoptosis in Women with Early Stage Breast Cancer: Potential Measure for Nursing Research

Principal Investigator: MAJ Penny M. Moureau, AN

Department: Nursing **Facility**: MAMC

Associate Investigator(s): Betty J. Gallucci, Ph.D., RN; LTC Thomas H. Miller, AN; Genevieve M. Fuller

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/20/1997	Apr 98	06/19/1998

Study Objective: 1) To explore the whole blood assay for the measurement of activation antigens on natural killer (NK) cells. 2) For our laboratory to select and gain experience with a measure of apoptosis or programmed cell death. 3) Describe and compare expression of NK cell activation antigens in women with hyperplasia and early stage breast cancer and women without breast disease, prior to and after IL-2 incubation. Expression of activation antigens is not normally detected in peripheral NK cells of healthy women, but is present in such illness states as chronic fatigue syndrome (40) and is also present after incubation with IL-2. 4) Explore the potential mechanisms for depression of NK cell cytotoxicity seen in women with breast cancer by determining the percent of apoptotic cells across all groups of women after activation by IL-2.

Technical Approach: NK cells play an important role in immune surveillance against tumor cells and are the first line of resistance against infections. NK cell activity is increased in individuals with healthy lifestyles and is depressed in individuals who experience acute or chronic stressors of disease symptomatology such as breast cancer. Activation of NK cells leads to the expression of activation antigens on the cell surface, initiates production of cytokines, increases levels of cytotoxicity, and promotes programmed cell death. The methodologic aims of our study are to gain experience in the laboratory with the whole blood assay for activation antigens and to determine which of the apoptosis assays will be the most rapid, reliable and sensitive. For nurse researchers, measurement of natural killer cell activation has the potential to monitor an immunologic outcome of primary and tertiary prevention strategies for breast cancer.

Progress: At this time, 24 women have enrolled in the study and one woman refused to participate after discussion of the consent form. There have been no adverse reactions. Analysis on the cells is in progress; no outcome data are available at this time.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/012 **Status**: Completed

Title: Drawing Activated Partial Thromboplastin Times (aPTT) from Peripheral Venous Access Devices (Saline Lock)

Principal Investigator: MAJ Kathy K. Prue-Owens, AN

Department: Nursing **Facility**: MAMC

Associate Investigator(s): MAJ Katherine M. Kelly, AN; Lauraine K. Dunn, RN

Start Date:	Est. Completion Date:	Periodic Review:
11/21/1997	May 98	N/A

Study Objective: To determine the amount of blood that should be discarded from a peripheral venous access device on heparinized patients to obtain an accurate aPTT result.

Technical Approach: Patients receiving continuous intravenous heparin therapy will be enrolled to compare serum coagulation studies (aPTT) obtained from a venipuncture with those obtained from a peripheral venous access device (VAD when the flush solution if normal saline. The study will also try to determine how much blood must be discarded from a peripheral VAD flushed with normal saline by using different discard volumes, in order to obtain accurate aPTT results. Subjects enrolling in the study without a peripheral VAD will have one inserted according to hospital policy. Demographic information will be recorded on a data collection sheet. Blood draws will begin with the next scheduled aPTT. The order of the blood draw will be the venipuncture sample, collected consecutively with the peripheral VAD sample. The random discard volumes include deadspace volume plus 1 mL, deadspace volume plus 2 mL, and deadspace volume plus 3 mL. The aPTT value from a blood sample drawn by venipuncture will be the reference value to which the aPTT value from the peripheral VAD will be compared. By the end of the study, each subject will have had three blood collection sessions, each session consisting of one venipuncture sample and one peripheral VAD sample. The aPTT results will be used to identify the amount of discard volume needed in order for the tests to be accurate.

The data obtained from this quasi-experimental study will be analyzed using descriptive statistics. The mean values and standard deviations will be calculated to compute differences between the variables identified in Appendix A. To compare the mean scores between the venipuncture and peripheral VAD groups, paired t-tests will be computed. Calculation of confidence intervals and statistical significance testing will be computed with the $p < 0.05$ and the CI 95% for significance. Analysis of variance (ANOVA) will also be computed to test for differences in means between the three different discard volumes. ANOVA will compare the variance within each group to the variance between groups.

Progress: A convenience sample of 23 cardiac patients admitted to a critical care step-down unit participated in this study. The variables measured were activated partial thromboplastin time (aPTT) drawn from a venipuncture and a peripheral venous access device (VAD) when three randomized discard volumes consisting of deadspace + 1 ml, deadspace + 2 ml, and deadspace + 3 ml were withdrawn. The venipuncture served as the control. Results of the Pearson r correlation coefficients showed a strong positive correlation between venipuncture and peripheral VAD aPTT results. Paired t tests revealed no significant differences between the venipuncture and any of the discard volumes of deadspace . The results indicate that the minimal amount of discard volume for accurate aPTT values in this population was the catheter deadspace + 1 ml (total of 1.5 ml of blood). Based on this study, using this discard volume of deadspace + 1 ml would minimize blood loss and would ensure accurate aPTT results. A thesis has been submitted as part of the requirements for an advanced degree from the University of Washington School of Nursing.

Detail Summary Sheets

Maternal-Fetal Medicine Service
Department of Obstetrics/Gynecology

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/068 **Status**: Ongoing

Title: The Expression of Adrenomedullin and Its Receptor in the Human Placenta

Principal Investigator: MAJ Christina Apodaca, MC

Department: OB/GYN, MFM **Facility**: MAMC

Associate Investigator(s): MAJ Richard K. Wagner, MC; Katherine H. Moore, Ph.D.; LTC Byron C. Calhoun, MC; COL Roderick F. Hume Jr., MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/22/1998	Sep 98	N/A

Study Objective: To elucidate the expression of adrenomedullin (ADM) and its receptors in specific tissue components of the human placenta.

Technical Approach: Placental tissue from both uncomplicated pregnancies and pregnancies complicated by chronic hypertension or pregnancy-induced hypertension will be used. Amnion, cotyledon, umbilical artery, and umbilical vein samples will be isolated from these placentas. Western blot analysis will be used to identify the presence of the adrenomedullin protein. Reverse transcriptase-polymerase chain reaction will be used to isolate total messenger ribonucleic acid for adrenomedullin and its receptor. Histochemical staining will be used to identify adrenomedullin in the tissue samples. Categorical analysis will be performed describing the distribution of adrenomedullin and its receptor in both normal placentas and the placentas from patients with chronic hypertension and pregnancy induced hypertension.

Progress: Data have been collected on approximately 75% of the planned number of placentas.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/060 **Status**: Ongoing

Title: Random Urine Protein/Creatinine Ratio for Quantification of Proteinuria in Pregnancy: An Outcomes Based, Cost Consequences Analysis

Principal Investigator: CPT Brian T. Pierce, MC

Department: OB/GYN, MFM **Facility**: MAMC

Associate Investigator(s): CPT Jerome L. Buller, MC; MAJ Christina Apodaca, MC; MAJ Richard K. Wagner, MC; COL Howard M. Cushner, MC; MAJ Curtis L. Yeager, MS; COL Bonnie M. Jennings, AN; LTC Byron C. Calhoun, MC; COL Roderick F. Hume Jr., MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/20/1998	Apr 99	N/A

Study Objective: (1) To evaluate the use of random urine protein to creatinine ratios for accurate quantification of proteinuria in MAMC's unscreened pregnant population, (2) to determine if the random urine testing of P/C ratios yields a shorter turnaround time and therefore a shorter time to diagnosis and treatment of medical complications of pregnancy, (3) to evaluate patient compliance and satisfaction with testing are much improved by using random samples as compared with 24 hour urine collections, and (4) to determine how much both direct and indirect medical costs would be decreased.

Technical Approach: Random urine protein/creatinine ratios and 24 hour urine protein will be assessed during each trimester of pregnancy and at 6 weeks postpartum. Blood urea nitrogen and serum creatinine levels will also be drawn at the same time for assessment of overall renal function.

Progress: This study has just received final approval and no patients have been entered. The PI was changed from CPT Jerome Buller, MC, to CPT Pierce in September 1998.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/114 **Status**: Completed

Title: The Effects of Lipopolysaccharide, an Inflammatory Stimulus, on Placental Production of Interleukin 6 in the Isolated Dually Perfused Placental Cotyledon

Principal Investigator: MAJ Richard K. Wagner, MC

Department: OB/GYN, MFM **Facility**: MAMC

Associate Investigator(s): MAJ Christina Apodaca, MC; MAJ Nathan J. Hoeldtke, MC; CPT Bruce F. Arnold, MC; MAJ Roger M. Hinson, MC; LTC Byron C. Calhoun, MC; COL Roderick F. Hume Jr., MC; Katherine H. Moore, Ph.D.

Start Date:	Est. Completion Date:	Periodic Review:
07/18/1997	Dec 97	06/19/1998

Study Objective: To determine the effects of inflammatory stimuli on placental production of Interleukin 6 (IL-6). This will be investigated in the isolated, dually perfused, human placental cotyledon in two steps: 1) by determining the constitutive production of IL-6 over time, and 2) by measuring production of IL-6 over time after stimulation by lipopolysaccharide (LPS). Levels of IL-6 in the fetal compartment of the placental cotyledon will be determined by sampling effluents from the fetal venous return and utilizing commercially available assays for IL-6. This is a pilot study to investigate the utility of the placenta model as a platform for further research on inflammatory cytokines in the perinatal period.

Technical Approach: We will use cotyledons from approximately 12 placentas (24 cotyledons) obtained from uncomplicated vaginal and caesarian deliveries in MAMC's labor and delivery. A perfusate consisting of Hank's balanced salt solution, bovine albumin, heparin, and gentamicin will be used to perfuse both the maternal and fetal circulations of the cotyledons. The perfusate will be maintained at a pH of 7.35-7.45 and gassed with 95%O2/5%N2. The cotyledons will be kept at 37 degrees Celsius. After establishing perfusion of an intact fetoplacental circuit, venous effluents will be collected at regular intervals and these samples will be stored for determination of IL-6 levels. The fetoplacental vascular tone will be continuously monitored throughout the experiment. Cellular changes resulting from the perfusion and inflammatory stimulus will be evaluated histologically by grading the inflammation present in biopsies taken before and after each experiment.

Progress: This protocol has been completed. Two cotyledons from each of nine placentas were perfused. Effluents from the fetal circulations of both cotyledons were collected at regular intervals and IL-6 concentrations subsequently determined using a commercially manufactured Enzyme Linked Immunosorbant Assay. Perfusion pressures within each group were recorded at regular intervals. Data were analyzed using repeated measures analysis of variance. Interleukin-6 concentrations were identified and demonstrate a statistically significant increase over time in both the study and control groups. No statistically significant difference between the concentrations of IL-6 in the study and control groups is apparent and no dose-dependent effects of lipopolysaccharide on IL-6 production are revealed, There is no statistically significant difference in perfusion pressures between the study and control groups.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/105 **Status**: Ongoing

Title: The Effects of Magnesium Sulfate on Placental Production of Interleukin-6 in the Isolated Dually Perfused Placental Cotyledon

Principal Investigator: MAJ Richard K. Wagner, MC

Department: OB/GYN, MFM **Facility**: MAMC

Associate Investigator(s): MAJ Roger M. Hinson, MC; MAJ Christina Apodaca, MC; CPT Brian T. Pierce, MC; Katherine H. Moore, Ph.D.; COL Roderick F. Hume Jr., MC; LTC Byron C. Calhoun, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/15/1998	Nov 98	N/A

Study Objective: To determine the effects of magnesium sulfate, a commonly used tocolytic, on placental production of interleukin-6 (IL-6).

Technical Approach: Paired cotyledons from 5 placentas obtained from uncomplicated vaginal and cesarean deliveries in MAMC's labor and delivery will be used. A perfusate consisting of Hank's balanced salt solution, bovine albumin, heparin, and gentamicin will be used to perfuse both the maternal and fetal circulations of the cotyledons. The Mg2+ concentration of the base solution is approximately 1.97 mg/dl. The maternal circulation of the study cotyledon will contain additional MgSO4, with a magnesium ion concentration of 8 mg/dl. After establishing perfusion of an intact fetoplacental circuit, effluents will be collected at hourly intervals for four hours. These samples will be stored for determination of IL-6 levels by ELISA. The fetoplacental vascular tone will be continuously monitored throughout the experiment and recorded at 10-min intervals. Data will be analyzed using repeated measure analysis of variance.

Progress: All placental perfusion experiments necessary for this protocol have been completed. Effluents are currently frozen and awaiting assay for IL-6. An addendum has been submitted for this protocol recommending evaluation of PGE2 levels.

Detail Summary Sheets

Urogynecology Service
Department of Obstetrics/Gynecology

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/129 **Status**: Completed

Title: The Non-invasive Detection and Characterization of Anal Incontinence in the Parous Female Population

Principal Investigator: COL Gary D. Davis, MC

Department: OB/GYN, UG **Facility**: MAMC

Associate Investigator(s): LTC Bradley G. Bute, MC; CPT Clinton S. Beverly, MC; LTC Phillip L. Mallory II, MC

Start Date:	Est. Completion Date:	Periodic Review:
06/16/1995	Dec 95	06/19/1998

Study Objective: This study attempts to determine the frequency and nature of obstetric-related anal incontinence by using non-invasive techniques. Anal sphincter and pudendal nerve status would be assessed and correlated with patient questionnaire complaints and manometric measurement of function.

Technical Approach: Permanent anal incontinence is reported to complicate 4-6 percent of vaginal deliveries and has been blamed on pudendal nerve injury or sphincter muscle damage. A non-invasive study of 300 pregnant women during and after pregnancy is proposed to attempt to differentiate between neuronal, muscular or combination injuries which produce incontinence. Volunteer subjects would be assessed for: pudendal nerve terminal motor latency as a measure of innervation, manometric variables as an indicator of function and transanal ultrasound as a morphologic study. Comparison of results before and after delivery would help determine the cause of obstetric-related anal incontinence. Standardized anorectal physiology data would be recorded for each patient to include resting pressure, maximal squeeze pressure, presence of rectoanoinhibitory reflex, sphincter length, and sensory threshold. Statistical analysis will evaluate for differences being due to chance with less than five percent being considered significant ($p<=0.05$). Tests for ordinate and continuous variables will be employed as appropriate.

Progress: This study has been completed; 113 subjects were entered. A paper is being written for consideration for publication. Conclusion: Anal incontinence secondary to vaginal delivery is common in the active duty female soldier.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/107 **Status**: Ongoing

Title: The Effectiveness of Mechanical Devices in the Prevention of Exercise Induced Urinary Incontinence in the Female Soldier

Principal Investigator: COL Gary D. Davis, MC

Department: OB/GYN, UG **Facility**: MAMC

Associate Investigator(s): CPT Jerome L. Buller, MC; COL Milo L. Hibbert, MC; COL Lawrence A. Decker, MC; COL Romeo P. Perez, MC; LTC Richard A. Sherman, MS

Start Date:	Est. Completion Date:	Periodic Review:
06/20/1997	Nov 97	06/19/1998

Study Objective: To determine the effectiveness of mechanical devices in the prevention of exercise induced incontinence in the female soldier.

Technical Approach: Our recent study of urinary incontinence among female soldiers revealed that 30 percent use precautions of various types to help prevent urinary incontinence in the field or during exercise. We propose to study the effectiveness of four types of mechanical devices for the prevention of urinary incontinence in female soldiers by comparing perineal pad weights after exercise with and without the mechanical devices. Multichannel urodynamic parameters will also be compared with and without the mechanical devices in place. This will objectively document the effectiveness of each device in the treatment of urinary incontinence during exercise.

Progress: No patients have been entered. The investigators are attempting to get the purchase of the devices funded through their departmental budget.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/108 **Status**: Ongoing

Title: A Pilot Study for Transanal Ultrasonography (TAUS) in the Repair of Episiotomy Anal Sphincteroplasty

Principal Investigator: COL Gary D. Davis, MC

Department: OB/GYN, UG **Facility**: MAMC

Associate Investigator(s): CPT Jerome L. Buller, MC; COL Milo L. Hibbert, MC; COL Lawrence A. Decker, MC; G. McClure; LTC Frederick B. Brown, MC; COL Romeo P. Perez, MC; LTC Richard A. Sherman, MS; CPT Patrick J. Woodman, MC

Start Date:	Est. Completion Date:	Periodic Review:
06/20/1997	Nov 97	06/19/1998

Study Objective: To assess the efficiency of intra-operative transanal ultrasound (TAUS) in the repair of the anal sphincter at episiotomy.

Technical Approach: Transanal ultrasonography (TAUS) has proven to be an effective means of assessing the structure and function of both the internal and external anal sphincters. Preliminary studies at Madigan Army Medical Center have shown that the intra-operative use of TAUS provides rapid and precise identification of both the internal and external anal sphincters, as well as immediate assessment of sphincter continuity and the success of sphincteroplasty. We propose to determine if the intra-operative use of TAUS will improve the anatomical and functional outcome of (a) episiotomy repair and (b) sphincteroplasty. (a) One hundred obstetric subjects at 28 weeks gestation or greater will be evaluated by endoanal ultrasound, pudendal nerve velocity and anal manometry to obtain initial. Episiotomies will be rendered only if obstetrically indicated. Those subjects requiring episiotomies at delivery will be randomly assigned to one of two groups. Those who will receive TAUS, and those who will not receive TAUS for episiotomy repair if episiotomy is indicated at delivery. Those subjects not requiring episiotomy will be dropped from the study. (b) In addition, twenty gynecologic subjects scheduled to undergo and sphincteroplasty will receive identical pre-operative evaluations of anal manometry, pudendal nerve velocities and endoanal ultrasonography to establish pre-operative values. They will be randomly assigned to one of two groups, those having repair with the aid of TAUS, and those undergoing sphincteroplasty without the aid of TAUS. All subjects (both obstetric and gynecologic) will be evaluated six weeks after surgery with repeat and manometry, pudendal nerve velocity and endoanal ultrasound. Pudendal nerve velocities, internal and external and sphincter length and width, manometric pressures, and pelvic organ prolapse quantification (POPQ) scores will be compared.

Progress: Four subjects were entered in FY 98 for a total of 24 entries. CPT Patrick J. Woodman, MC has been added as an associate investigator in an effort to get more subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/144 **Status**: Ongoing

Title: Operative Endoscopy and Surgical Management of the Bowel and Urinary Tract Injuries in Gynecologic Surgery in the Pig (Sus scrofa)

Principal Investigator: COL Mark E. Potter, MC

Department: OB/GYN, UG **Facility**: MAMC

Associate Investigator(s): COL Lawrence A. Decker, MC; COL Gary D. Davis, MC; COL Roderick F. Hume Jr., MC; LTC Byron C. Calhoun, MC; LTC Frederick B. Brown, MC; MAJ Richard K. Wagner, MC; MAJ Martin L. Ladwig, MC; MAJ Christina Apodaca, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/19/1997	Sep 00	09/30/1998

Study Objective: To familiarize residents in OB/GYN with techniques of management of bowel and urinary tract injury with suturing or stapling techniques. To familiarize residents with techniques for colostomy, ileostomy, ureteroneocystostomy and vascular injury repair. To expand the operative endoscopy experience of OB/GYN Residents and Staff, prior to utilization in humans. Familiarity with these techniques will allow an increased margin of safety for patients in gynecologic surgery and better prepare the gynecologic surgeon to assist in general surgery patients when bowel or urinary tract procedures or repair are required. Increased operative endoscopy experience will minimize operating time and potential complications when utilized in the clinical setting.

Technical Approach: With the animal in the supine position, a midline incision will enter the abdomen and repair of lacerations and anastomosis will be performed by standard techniques. Additional surgical procedures may include ureteroneocystostomy. The abdomen will be closed. A second episode of surgery will occur 3-4 weeks later and additional procedures including colostomy, loop ileostomy, and vascular injury repair will be carried out. Following the second surgical episode, the animal will not be allowed to recover from anesthesia. In some cases an animal may be used for a single training episode. When this occurs, euthanasia will be carried out at the completion of the session. When follow-up evaluation of a surgical procedure is desired, no more than one procedure will be done on that animal during the first episode. The animal will then be allowed to recover and will be re-anesthetized and reoperated 3-4 weeks later. During the second surgical episode, more than one procedure may be performed. The animal will be euthanized at the end of the episode while still under general anesthesia. Procedures which would normally involve any postoperative care beyond normal husbandry will only be performed during the last surgical episode to which that particular animal is subjected. The animal will be euthanized while still under general anesthesia.

Progress: No training sessions have been held. The protocol has recently received its annual review, has been updated, and training sessions are planned in the near future.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/022 **Status**: Completed

Title: The Impact of A Contraceptive Options Class on Patient Satisfaction with Sterilization in A Military Teaching Hospital

Principal Investigator: CPT Jeffrey A. Rondeau, MC

Department: OB/GYN **Facility**: MAMC

Associate Investigator(s): MAJ Stephen E. Poore, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/18/1997	Dec 97	N/A

Study Objective: To analyze the impact of a recently introduced patient education seminar in the Department of Obstetrics and Gynecology on contraceptive options; designed primarily for patients who expressed a desire for sterilization (excluding hysterectomy).

Technical Approach: To assess patient satisfaction with sterilization, patient surveys will be sent to 100 patients who underwent a tubal ligation following attendance at the Patient Education Seminar on Contraceptive Options, and compared to 100 randomly selected control patients who underwent tubal ligation before the class began. Measured outcome variables included: (1) Patient's satisfaction or lack their of with permanent sterilization, (2) Patient's subjective global assessment of class value, either as a result of attendance or hypothetically; after the nature of the class is described, (3) Presence or absence of specific areas of improved contraceptive knowledge after class attendance, (4) Adequacy of alternative method counseling, (5) Presence or absence of sterilization regret, the circumstances involved and the reported willingness to act on the regret, (6) Willingness to recommend the procedure to friends, (7) Willingness to recommend the class as a valuable component of the pre-procedure tubal ligation process to friends, (8) Demographic and reproductive medical histories. Data will be analyzed using Chi-squared analysis and Student's Unpaired t-test.

Progress: This study has been completed. Approximately 200 subjects were studied. While the class did not increase the satisfaction rate, it resulted in a large number of patients who selected other options, hence potentially avoiding a larger number of regretted tubal ligations. A paper was presented to the Association of Professors of Gynecology and Obstetrics Committee on Resident Education in OB/GYN in March 1998..

Detail Summary Sheets

Department of Pathology

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/070	**Status**: Ongoing

Title: The Stability of Reagents Used in A DEPMEDS Clinical Chemistry Analyzer

Principal Investigator: CPT Arthur A. Russell, MS

Department: Pathology		**Facility**: MAMC

Associate Investigator(s): None.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/22/1998	May 99	N/A

Study Objective: To determine the stability of reagents for a clinical chemistry analyzer used by field units of the United States Army, when the reagents are not refrigerated or frozen according to the manufacturer's specifications.

Technical Approach: The performance of clinical reagents for the DT-60 clinical chemistry analyzer will be tested for stability when stored at ambient temperatures and the results compared to the performance of reagents stored according to the manufacturer's recommendations. Periodically the manufacturer's controls will be run 5 times using reagents that have been refrigerated or frozen (control group) or exposed to an ambient temperatures in a laboratory environment (experimental arm). The change in mean (bias) and precision (coefficient of variation)

Detail Summary Sheets

Department of Pediatrics

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/085 **Status**: Completed

Title: Parental Assessment of Psychologic Adjustment in Children with Asthma: A Comparison of the Child Behavior Checklist and the Behavior Assessment System for Children

Principal Investigator: CPT Veronica R. Baechler, MC

Department: Pediatrics **Facility**: MAMC

Associate Investigator(s): COL Patrick C. Kelly, MC; MAJ Robert A. Byrne, MS; MAJ Stephen E. Greefkens, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/17/1995	Jul 95	04/17/1998

Study Objective: 1) To assess the correlation between the Child Behavior Checklist (parent report) and the Behavior Assessment System for Children (parent report) in assessing the social and emotional status of a group of children and adolescents with asthma. 2) To assess the impact of disease severity on the social and emotional status of this population. 3) To assess the impact of moves or service member deployment on the social and emotional status of this population.

Technical Approach: Sixty subjects, ages from 8 to 16 years and including approximately equal number of males and females, who have chronic asthma will be identified through review of Pediatric Pulmonary Clinic files and review of upcoming appointments. After consent has been obtained the mother of these subjects will be asked to fill out both the CBCL and the Parent Report Form of the BASC. In addition, a brief questionnaire inquiring about the subjects health status, recent moves, and service member deployments will be completed by the mother. When data collection is complete, it will be analyzed as follows. Correlation between the various scales of the CBCL and BASC will be analyzed using paired t-tests. ANOVA will be used to study the relationship between disease severity and several scales on the CBCL. An unpaired t-test will be used to study the relationship between recent moves or parent deployment and several scales on the CBCL.

Progress: Sixty-eight (68) subjects were studied. The BASC and CBCL correlated in this population of school age and adolescent children with asthma similarly to the correlations between the two instruments in the normative population. Therefore, the BASC lends itself as an acceptable screening instrument for assessing internalizing and externalizing behaviors at significant levels in children with asthma and, possibly, in those with other chronic illnesses as well. In assessing whether there is higher frequency of clinically significant internalizing or externalizing behaviors in this population with asthma relative to the normative population, there is a suggested higher frequency of these behaviors in the school age but not in the adolescent group, although the number of subjects is this study is limited. In assessing whether there is higher frequency of clinically significant internalizing and externalizing behaviors between the population of children with mild asthma versus those with moderate/severe asthma, there is no difference in elevated frequency between the two groups.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/126 **Status**: Completed

Title: Long-Term Use of Every 4-8 Week Intramuscularly Administered Triamcinolone Acetonide to Treat a 13 Year-Old Who Has Severe, Life-Threatening Chronic Asthma

Principal Investigator: LTC Edward R. Carter, MC

Department: Pediatrics **Facility**: MAMC

Associate Investigator(s): MAJ Donald R. McClellan, MC; CPT Victoria W. Cartwright, MC; MAJ Robert W. Moore, MC; LTC William R. Raymond IV, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
07/18/1997	Aug 98	07/17/1998

Study Objective: To determine whether triamcinolone acetonide, a long acting corticosteroid preparation, if administered intra-muscularly on an every 4-8 week basis, can control asthma symptoms and airways obstruction without causing unacceptable adverse effects in a 13 year-old boy with severe life-threatening asthma who had complied poorly with prescribed medical regimens.

Technical Approach: After a baseline assessment the patient will receive 80 mg of triamcinolone acetonide intramuscularly. He will then continue to receive this dosage every 4-8 weeks. The dosing interval will depend upon clinical status (pulmonary function tests, signs/symptoms) and adverse effects (including the degree of adrenal suppression). The dosage and dosing interval will be altered based upon clinical response, pulmonary function tests, and the magnitude of adverse effects. The dosage and dosing interval will range from 40-80 mg and q 4-8 weeks respectively. The patient will continue to receive this steroid regimen for 12 months while being closely monitored.

Progress: The patient took the study medication for six months with a good clinical response and no adverse effects. The patient completed the one year study period and is now being followed for his asthma at Ft Hood, TX. The study objective has been completed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/111 **Status**: Ongoing

Title: Validation of the Symptom-Free Days Instrument in Children with Asthma

Principal Investigator: LTC Edward R. Carter, MC

Department: Pediatrics **Facility**: MAMC

Associate Investigator(s): COL Donald R. Moffitt, MC; Dana Winter, RCP; Jetta C. Joseph, Pharm.D.; Sean D. Sullivan, Ph.D.; David Blough, Ph.D.; Jocan Fagan, M.S.; Kevin B. Weiss, MD, MPH

Start Date:	Est. Completion Date:	Periodic Review:
09/15/1998	Feb 00	N/A

Study Objective: To determine the reliability and the validity of the Symptom-Free Days (SFD) instrument (questionnaire) as an asthma outcomes measure in children ages 6-17 years-old with mild or moderate persistent asthma and whether the responses derived on the questionnaires concerning asthma outcomes and quality of life from asthmatic children >10 years-old are similar to those obtained from their parents. We want to determine whether patient self-reporting and parental reporting of their child's symptoms are similar.

Technical Approach: Children with mild to moderate persistent asthma and their parents will be randomized to one of two groups. Group 1 will be followed two 2-week intervals and Group 2 will be assessed during two 4-week intervals. The only difference between the groups is the length of the study time intervals, two versus four weeks. During the initial visit, subjects will undergo spirometry and asthma severity assessment. They will be given a peak flow meter and diary to record peak flow measurements at home. Group 1 subjects will receive a phone call one week after the initial visit. At the second visit, asthma questionnaires will be filled out by study investigators and spirometry repeated. There is a one month hiatus, then subjects will repeat the process described above. Group 2 subjects have an initial visit, phone calls for the next three weeks and will return for their second visit at week four. At this visit, questionnaires will be filled out, concentrating on the last two weeks before the second clinic visit. (Subjects in each group will be recalling symptoms from a 2-week period). After a one month hiatus the process is repeated. Data from each of the questionnaires will be compiled, and then the results from the Symptom-Free Days instrument will be compared to those obtained from the other questionnaires. The results from the SFD will also be compared to the subjects peak flows during the study interval and spirometric values obtained at the clinic visits. The results from the SFD from the two testing periods for each child will also be compared to determine the repeatability/reliability of the tool.

Progress: Enrollment in this study has not begun as it has just been approved by the IRB.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 90/092 **Status**: Ongoing

Title: Core Project: Evaluation of Diagnostic Assays for Human Immunodeficiency Virus (HIV) in Children with Evidence of HIV Exposure or HIV Illnesses

Principal Investigator: MAJ Mary P. Fairchok, MC

Department: Pediatrics **Facility**: MAMC

Associate Investigator(s): COL James S. Rawlings, MC; MAJ Thomas A. Perkins, MC; LTC Joanna C. Beachy, MC; COL Marvin S. Krober, MC

Start Date:	Est. Completion Date:	Periodic Review:
07/20/1990	Sep 91	07/17/1998

Study Objective: To analyze laboratory assays for detection of HIV infection in children and to correlate the results with the clinical status of the child.

Technical Approach: This will be a multicenter study funded by Walter Reed Army Medical Center. The plan of this protocol is to evaluate the usefulness of new assays as they are developed, using blood from HIV-infected or high risk children. Blood will be sent to the laboratory for standard HIV testing using those tests that are most developed. Surplus will be utilized for less well developed assays or stored for future analysis. Results from the tests will be compared to conventional assays used to diagnose adult HIV infection, such as ELISA, western blot, and culture, to determine their usefulness in children. These specimens will also be used to develop improvements and new methods for HIV testing in children. This analysis will be done in 120-150 individuals at three month intervals to determine if changes in these tests correlate with changes in the patient's clinical or immunological status. Most of the data generated in this protocol will be qualitative and will be correlated to quantitative clinical data using Spearman's Rank Correlation. Logistic regression will be used for correlating the numerical data to noncontinuous clinical measures. Analysis of data from different clinical groups (patients who remain asymptomatic versus those who develop AIDS) will be compared using two-way ANOVA to determine significant differences between clinical groups.

Progress: One new patient has been entered in this study in FY 98 with no adverse events.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 90/091 **Status**: Completed

Title: A Phase III Open Protocol for a Multicenter Study for the Treatment of Central Precocious Puberty with D-Trp(6)-Des-Gly(10)-N-ethylamide-LHRH, A Long-Acting Analog of Luteinizing Hormone Releasing Factor (Deslorelin)

Principal Investigator: MAJ Donald R. McClellan, MC

Department: Pediatrics **Facility**: MAMC

Associate Investigator(s): COL Dan C. Moore, MC

Start Date:	Est. Completion Date:	Periodic Review:
07/20/1990	Nov 92	07/17/1998

Study Objective: To treat patients who have central precocious puberty with Deslorelin in order to suppress pubertal development and excess growth, to restore gonadotropin and sex hormone levels to normal prepubertal levels, and to demonstrate the safety of such treatment.

Technical Approach: Central precocious puberty will be defined as: stage 2 pubic hair or greater, stage 2 breast or genital development or greater, pubertal LH and FSH peak following GnRH stimulation, and absence of peripheral origin of precocity (lack of adrenal or ovarian mass on ultrasound and normal serum hCG). After diagnosis and standard evaluations, patients will be given Deslorelin, 4 mcg/kg SC daily. At three month intervals, patients will be re-evaluated. A physical examination with pubertal staging will be done. Serum sex hormones and gonadotropins (before and post GnRH) will be measured and bone age will be determined. Treatment will be continued until the patient reaches an age at which pubertal development is deemed appropriate (usually 10-11 years) at which time therapy will be discontinued.

Progress: The principal investigator was changed from COL Dan Moore to MAJ Donald McClellan in Sep 97. The protocol has been closed to enrollment because the study drug has been approved by the drug company. Three patients were enrolled during the time the study was open at MAMC. One patient dropped out after a few treatments because he did not want to take the required injections. The two other patients responded well to the treatment. However, one patient died in FY 94 due to her underlying disease. The third patient completed the protocol and is now off treatment.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/016 **Status**: Completed

Title: Neuromotor Development of Low-Birth-Weight Premature Infants: Results Through Age 2 Years from the Infant Health and Development Program

Principal Investigator: MAJ Robert I. Miller, MC, USAF

Department: Pediatrics **Facility**: MAMC

Associate Investigator(s): Forrest C. Bennett, M.D.; COL Patrick C. Kelly, MC; Troy H. Patience, B.S.; COL William O. Walker, Jr., MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/21/1997	Feb 98	N/A

Study Objective: To analyze the neurodevelopmental course of 299 low-birth-weight premature infants followed prospectively over 2 years as part of the Infant Health and Development Program to determine which parts of the neurodevelopmental exam may be predictive of outcome at 2 years.

Technical Approach: This study is a chart review of a select group of patients from the Infant Health and Development Project (IHDP) data set that was collected through a multi-center study. Data analyzed will involve neurodevelopmental exams from a control group during the first two years of the study. The goal is to find indicators of abnormal development in premature infants by analyzing physical exam findings that deal with posture and spontaneous motor activity, passive tone, active tone, and reflexes. Key features of the exams that lead to a particular Neuro Class assignment (normal, transiently suspect, persistently suspect, and abnormal) at age 12 and 24 months will be determined in addition to determining which parts of the exam may be predictive of Neuro Class assignment at 12 and 24 months. Comparison of Neuro class assignment with demographic data (gender and race), birth weight and cognitive test results at 36 months will also be completed to determine if any correlation is present. The overall question which will hopefully be answered involves knowing when an examiner can feel comfortable with his determination of whether a premature infant is normal versus abnormal during the process of completing serial exams over the first two years of life. In addition, the criteria which were most helpful in making this determination will need to be identified.

Progress: In this multicenter study, 324 premature infants weighing less than 2500g at birth underwent neurodevelopmental exams at a corrected age of 4, 8, 12, 18, and 24 months. Results at 12 months showed that 49 % were normal, 47 % suspect, and 4% abnormal. Of the normals, 82% had been transiently suspect as abnormal. Results at 24 months showed that 79% of the suspect infants had normalized, resulting in 83% normal, 13 % suspect, and 4% abnormal. The 12 month neurodevelopment exam correctly classified only 52% of the infants based on the 24 month Neuro Class designation. However, a classification of normal at 12 months had a 97% negative predictive value with 89% of infants predicted normal at 12 months, remaining so at 24 months. No correlation was found with Neuro Class designation and standardized cognitive tests at 3 years. Transient neuromotor abnormalities are common in preterm infants and close monitoring should continue for all premature infants through 24 months.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/056 **Status**: Ongoing

Title: Physiological, Behavioral, and Feeding Effects of Neonatal Physical Therapy Procedures on Preterm Infants in a Neonatal Intensive Care Unit Setting

Principal Investigator: Jane K. Sweeney, Ph.D., PT, PCS

Department: Pediatrics **Facility**: MAMC

Associate Investigator(s): MAJ Roger M. Hinson, MC; MAJ Wanda A. Barfield, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/21/1997	Oct 99	06/19/1998

Study Objective: 1) To study and compare the physiological tolerance of medically stable, preterm infants to three interventions: neonatal hydrotherapy, infant seat positioning with social stimulation, and a control intervention of no physical handling or social stimulation; 2) to investigate and compare the behavioral tolerance of medically stable, preterm infants to three interventions in a neonatal intensive care unit: neonatal hydrotherapy, infant seat positioning with social stimulation, and a control intervention of no physical handling or social stimulation; 3) to evaluate and compare the effects of neonatal hydrotherapy, infant seat positioning with social stimulation and a control condition of no handling or social stimulation on oral feeding performance in medically stable, preterm infants; 4) to compare the length of hospital stay among subjects in the three intervention groups.

Technical Approach: This is a prospective, quasi-experimental study of the physiological, behavioral, feeding, and cost effects of neonatal physical therapy procedures on 60 medically stable, preterm infants (31 to 35 weeks post-conception) in a neonatal intensive care unit setting. A randomized block design is used with postconceptual age as the blocking variable. After an 10 minute initial baseline phase, subjects are randomly assigned to a physical therapy intervention followed by oral feeding and concluded by a 10 minute recovery baseline phase. The intervention conditions are a 15 minute session of neonatal hydrotherapy (20 subjects), infant seat positioning with social stimulation (20 subjects), or a control condition of no handling (20 subjects). The physiological measures of heart rate, respiratory rate, mean arterial pressure, temperature, intracranial pressure, and oxygen saturation are recorded continuously and will be compared across intervention groups among the four phases of the study using a repeated measures analysis of variance. The behavioral responses of behavioral state, motor stress cues (finger splay, arm salute, trunk arch), and autonomic stress cues (hiccoughs, sneezes, yawns, regurgitation) are measured continuously by videotape and scored at two minute intervals. Between group comparisons of behavioral responses will be analyzed by analysis of variance (ANOVA). Feeding performance of volume ingested, duration of feeding, transition from gavage to oral feedings and weight gain will be reported descriptively and compared across intervention groups with ANOVA. The length of hospital stay and estimated cost of hospitalization in the NICU will be calculated and compared among all intervention groups using ANOVA.

Progress: Five patients have been entered in this study. No conclusions are available at this point due to the small number of subjects entered. Completion of data collection is estimated to be June 1999.

Detail Summary Sheets

Physical Medicine & Rehabilitation Service

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/094 **Status**: Ongoing

Title: A Prospective Randomized Trial of Controlled Compression Cryotherapy versus Institutionalized Cryotherapy in Post-Operative Anterior or Posterior Cruciate Ligament Reconstruction Patients

Principal Investigator: CPT Roger W. Dougherty, SP

Department: Physical Medicine & Rehabilitation Service **Facility**: MAMC

Associate Investigator(s): LTC Patrick St Pierre, MC; COL Joseph R. Dettori, SP; Jeffrey T. Hermsmeyer

Start Date:	Est. Completion Date:	Periodic Review:
07/17/1998	Apr 99	N/A

Study Objective: To determine if controlled compression cryotherapy (Aircast/Cryocuff) is better than standard cryotherapy care at reducing pain and edema and enhancing weight-bearing and range of motion in post-operative ACL/PCL patients.

Technical Approach: Subjects will be randomly assigned to two study groups. Group A will serve as the control group and undergo the standard post-operative care which includes an ice-bag on top of the bulky dressing while in the PACU, followed by cryotherapy at home and in PT per standard protocol. Group B will serve as the study group and will receive less post-operative dressing in order to accommodate the Cryocuff cooling system. Group B will receive the cryosystem while in the PACU and will receive a unit for home use once discharged from the hospital. All subjects will be required to apply their respective cryotherapy for twenty minutes QID for the fourteen days post surgery and to annotate their cryotherapy times each day on the compliance log. Subject data will be collected at post-operative days three, seven and fourteen.

Progress: Eight subjects (approximately 25% of target population) have been enrolled with no adverse events.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/152 **Status**: Completed

Title: Cervical and Lumbar Radiculopathies: How Many Muscles Should Be Studied?

Principal Investigator: COL Shashi J. Kumar, MC

Department: Physical Medicine & Rehabilitation Service **Facility**: MAMC

Associate Investigator(s): Timothy D. Dillingham, M.D.; Liliana E. Pezzin, M.D.; MAJ Tamara D. Lauder, MC; LTC Steve S. Shannon, MC; Michael Andary, M.D.; Andrew Gitter, M.D.; Andrew Haig, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/20/1996	Jul 97	09/15/1998

Study Objective: The primary objective of this study is to determine how many muscles must be studied in order to ensure a high rate of identification of those radiculopathies which can be electrodiagnostically confirmed. This observational, prospective study of consecutive patients will primarily involve data collection and analysis of standard electrodiagnostic studies. The electromyographic screen will be standardized for the upper limb and the lower limb. Two or three additional muscles will be studied beyond what is normally performed in the course of a clinical study.

Technical Approach: A multi-center study will be undertaken to provide approximately 700 subjects. Subjects will include all males and females on whom a cervical radiculopathy (CR) or LSR electrodiagnostic screen is performed. Data will be collected regarding the history, physical examination, and examiner assessment. All patients will have at least one motor and one sensory nerve conduction study. A standardized needle electromyography study will then be done for each extremity studied. A 10 muscle screen will be performed on the upper extremity to look for a CR and an 11 muscle screen will be performed on the lower extremity studied to look for a LSR. Any other additional nerves or muscles may be studied at the discretion of the electrodiagnostician if they are needed to make a clear diagnosis. Data analysis will be carried out similar to previous retrospective studies. In order to determine how many muscles are needed to identify the CR or LSR, various muscle screens will be combined and their identification rates will be analyzed using an SPSS database. The sensitivity of the radiculopathy screens will be evaluated relative to gold standards such as MRI, CT, or myelography on those subjects whom have such studies available. Specificity will not be evaluated as we are not recruiting normal subjects. Analysis of variance will be used to compare which head of the quadriceps and gastrocnemius is more sensitive in identifying a LSR. The relationship between the probability of paraspinal muscle abnormality and the above variables will be determined using a multi-variate probability (PROBIT) analysis. All data analysis will be done at John Hopkins University.

Progress: This study has been completed. Approximately 150 subjects were enrolled in this multicenter study. Data analysis is in progress.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/030 **Status**: Ongoing

Title: Physical Therapy Treatment Effectiveness for Osteoarthritis of the Knee: A Prospective, Randomized, Controlled Comparison of Supervised Clinical Exercise and Manual Therapy Procedures versus A Home Exercise Program

Principal Investigator: MAJ Robert L. Matekel, SP

Department: Physical Medicine & Rehabilitation Service **Facility**: MAMC

Associate Investigator(s): COL Gail Deyle, SP; COL Nancy Henderson, SP; Skyeann Allison; MAJ Jeremy Hutton, SP; CPT John Stang, SP; CPT David Gohdes, SP; CPT Mike Ryder, SP; CPT Matt Garber, SP

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/18/1997	Oct 98	N/A

Study Objective: To evaluate the effectiveness of manual physical therapy treatment for osteoarthritis of the knee compared to a home exercise program.

Technical Approach: Subjects will be randomly assigned to one of two treatment groups. Subjects will undergo a thorough clinical examination by the treating physical therapists and then turned over to a trained research assistant (tester) blinded to the group assignment. The tester will obtain measurements of the dependent variables using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and a six-minute walk test. The subjects will be returned to the treating therapist and treatment will begin as per group assignment.
Group 1 will perform an in-clinic series of closely supervised exercises. Subjects will also receive manual physical therapy as indicated by examination and do home based exercise on the days when they are not in clinic. At the end of eight sessions the subject will be retested with the tester 2 days after the last exercise session and at the same time of day as the pretest.
Group 2 will receive a home based exercise program, instructed to the subject by the treating physical therapist, and a detailed supporting handout and compliance log. Subjects will return to the clinic 2 weeks later to ensure proper execution of the exercises and compliance with the program. After completing 4 weeks the subject will be retested with the tester 2 days after the last exercise session and at the same time of day as the pretest.

Progress: A total of 32 subjects have been enrolled in the study at Madigan Army Medical Center. Twenty-three of these have completed all phases of the study. Overall, nearly 100 patients have been enrolled including the other physical therapy clinics participating in this multi-site study. Preliminary interim data analysis demonstrates a significant difference between the treatment groups on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The six-minutes walk test scores do no appear to be trending towards a difference between treatment groups.

Detail Summary Sheets

Preventive Medicine Service

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 95/011	**Status**: Completed

Title: Comparative Morbidity Study of Active Duty Women Serving in Korea and Ft Lewis by MAJ Jeffrey D. Gunzenhauser, MC

Principal Investigator: LTC Jeffrey D. Gunzenhauser, MC

Department: Preventive Medicine	**Facility**: MAMC

Associate Investigator(s): CPT Julie A. Pavlin, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/04/1994	Mar 96	09/30/1998

Study Objective: To describe the out-patient and in-patient morbidity experience of women serving in Korea and compare this to women serving at Ft. Lewis and to men at both locations and to describe behavioral risk factors of women serving in Korea.

Technical Approach: This is an epidemiologic study. Out-patient clinical events which are assessed at military clinics will be categorized into one of 14 specific morbidity categories: orthopedic/injury, respiratory, medical illness, dermatologic, bites/stings, environmental injury, diarrhea/GI, unexplained fever, sexually transmitted disease, ophthalmic, mental health, dental, substance abuse and miscellaneous. Diagnosis will be based on medical record entries (not chief complaints) and will be broken down by gender. Rates of health care usage for men will be estimated by counting all visits registered in clinic logs. One male record will be pulled for each female record pulled (the second male to visit the clinic after the index female visit.

In-patient morbidity experience of women will be studied by analyzing data from the Individual Patient Data System maintained at Ft. Sam Houston, TX. All hospitalization of men and women will be included in the analysis. Each hospitalization at the 121 General Hospital and at Madigan Army Medical Center will be classified into one of the 14 morbidity categories to allow broader comparisons with out-patient morbidity data and between genders and locations.

Health surveys will be mailed to a probability sample of female soldiers serving in Korea and at Ft. Lewis. Approximately 1000 women in Korea and 1000 women at Ft. Lewis will be targeted for this survey.

Progress: This study has been completed. Over 23,000 clinic visits were analyzed and rates of conditions estimated. Women in Korea had a 10% higher rate of visits per week than those of Ft Lewis and 2.1 times higher than men in either location. Differences were observed in many diagnostic categories and were multifactorial in nature. A health survey was mailed to 4,000 soldiers in Korea and Ft Lewis. Women in Korea reported diminished mental health and more clinic visits than women at Ft Lewis, but were comparable in other measures of health status. The health status of women was significantly worse than men in nearly all measured categories.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/045 **Status**: Completed

Title: Military Occupational Specialties at High Risk of Musculoskeletal Injuries

Principal Investigator: MAJ Hee-Choon S. Lee, MC

Department: Preventive Medicine **Facility**: MAMC

Associate Investigator(s): LTC Jeffrey D. Gunzenhauser, MC; CPT Julie A. Pavlin, MC

Start Date:	Est. Completion Date:	Periodic Review:
02/20/1998	Jun 98	N/A

Study Objective: To identify military occupational specialties (MOS) with high rates of musculoskeletal injury; to estimate crude and adjusted (for demographics) rates of injury by MOS and type of injury; and to assess whether MOS is an independent predictor of injury occurrence, accounting for demographic variables and other known behavioral determinants of injury occurrence.

Technical Approach: This study involves analyzing data from two existing databases. The first part of the study will use data previously collected in MAMC Protocol #95/011 which was an out-patient morbidity cohort study of soldiers at Ft Lewis and In Korea. The data base will be analyzed to estimate rates of initial clinic visits for injury diagnoses by MOS . All MOS's will be ranked from highest to lowest and the population will be separated into five quintiles according to MOS-specific injury rates. In the second part of the study, the out-patient morbidity data will be merged with an existing Health Risk Appraisal database (HRA). The design of this part of the study is case-control; the Odds Ratio will be the measure of association. The HRA contains information on individual behaviors known to be associated with (confound) injury occurrence. Demographic variables and each measure of individual behavior will be analyzed in a univariate mode for association with injury, along with the MOS-specific injury quintile variable. In this mode, injury occurrence will be the dependent outcome variable. The MOS-specific injury variable will be the primary independent variable of interest. Its relationship with injury occurrence will be assessed by including all significant confounders in the regression model according to standard multivariate analytic procedures.

Progress: This protocol has been completed. All visits by active duty female soldiers and a sample of visits by active duty male soldiers in select US military out-patient treatment facilities of the Republic of Korea and Ft Lewis, WA for 22 weeks from April to September 1995 were evaluated. The overall rate of new musculoskeletal injuries was 17.4 per 1000 person-weeks. Female and male soldiers were similar in their rates of injury at 17.2 and 17.4, respectively, per 1,000 person-weeks. Injury rates decreased with increasing age and increasing enlisted rank. Officers experienced a significantly lower rate of injuries (6.4) than enlisted soldiers (19.2). Injury rates by race revealed the lowest rates for Asians (10.7). Military occupational specialties with the highest rates of musculoskeletal injuries were identified.

Detail Summary Sheets

Department of Psychiatry

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/029 **Status**: Ongoing

Title: Migraine Prevention with Magnatherm Pulsing Electromagnetic Fields

Principal Investigator: COL Russell D. Hicks, MC

Department: Psychiatry **Facility**: MAMC

Associate Investigator(s): LTC (Ret) Allyn Woerman, MMSC,TP; LTC Richard A. Sherman, MS

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/18/1997	Dec 97	N/A

Study Objective: To evaluate the effectiveness of a small, light weight pulsing electromagnetic field generating device for use in patient's homes in preventing the onset of most migraine headaches.

Technical Approach: A four-step program is planed.

Step 1: Open trial study: 20 subjects will apply the Magnatherm SSP unit to their inner thigh at half power for one hour per day for ten days,. Effectiveness will be determined by comparing headache frequency reported on a month long headache log prior to treatment to the frequency reported on a month-long log post-treatment.

Step 2: Double Blind study: 20 subjects (10 per group) will be randomized to Magnatherm SSP unit treatment to the thigh once a day five days per week for two weeks or to treatment or a non-working (placebo) generator. Effectiveness will be determined by comparing headache frequencies reported on month long headache logs, both before and after treatment.

Step 3: Minimal effective dose study: To determine whether the Magnatherm SSP unit set to its minimum power is still effective in preventing headaches, ten subjects will be treated at the lowest dose setting for two weeks. Effectiveness will be determined by comparing headache frequencies reported on month long headache logs, both before and after treatment. If the lowest dose is ineffective the next larger dose would be tried in the same manner. This step will be done in order to develop a minimal size, light weight device have a simplified arm and only one head.

Step 4: Large scale, long-term effectiveness trial: 100 migraine subjects will use the minimized device developed in "3" above with the open design from "1" above but with an eight month follow-up to provide convincing evidence that (a) the device works for a significant number of patients, (b) that the decrease is maintained beyond the six month placebo period, and (c) that side effects are either minimal or non-existent.

Progress: Eight subjects have been entered. COL Hicks replaced LTC Richard Sherman as the principal investigator in Jul 98.

Detail Summary Sheets

Department of Psychology

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/091 **Status**: Ongoing

Title: Prevention of Tension Headaches with Microcurrent Electrical Stimulation: A Placebo Controlled Pilot Study

Principal Investigator: Mary Brencick, MSW

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): Nancy E. McLaughlin;

Start Date:	Est. Completion Date:	Periodic Review:
07/17/1998	Dec 98	N/A

Study Objective: To perform a double-blind, placebo controlled pilot study which will provide sufficient information to determine whether a full study is warranted to determine whether two weeks of exposure to microcurrent electrical stimulation for one hour per day can prevent at least 50% of the expected tension headaches among at least 50% of the subjects receiving actual stimulation.

Technical Approach: Twenty subjects of either sex between the ages of 18 and 70 years, diagnosed as having uncomplicated tension headaches, will keep a one month initial baseline of headache activity. They will then be randomized into real or placebo microcurrent electrical stimulation at home for one hour per day for two weeks. Subjects will keep a headache log throughout this period. This is followed by a one month follow-up during which subjects continue to keep the log every time they get a headache.

Progress: No patients entered. This protocol is awaiting approval of a CRDA before implementation.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 95/130	**Status**: Ongoing

Title: MMPI-2 Profiles in Korean Military Dependents

Principal Investigator: CPT Kathleen S. Lester, MS

Department: Psychology		**Facility**: MAMC

Associate Investigator(s): None.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/16/1995	Aug 95	08/20/1998

Study Objective: To determine the normative scores for the Minnesota Multi-phasic Personality Inventory-2 (MMPI-2) in Korean dependent wives of active duty soldiers.

Technical Approach: In order to determine the norms for the Korean female spouses of service members, the MMPI-2 will be administered to 50 subjects, age 20 to 70. Subjects will be recruited from the primary care clinics at MAMC by means of referral by their physician and through recruitment advertisements posted in community areas of Ft. Lewis. Subjects consenting to participate will be given a questionnaire, a brief, structured psychiatric interview (mini-SCID), a screening test of English proficiency and the MMPI-2. The mean and standard deviation of the clinical and validity scales will be derived for the group. These scores will be compared with existing norms and, where differences exist, t-tests of significance will be performed. Results will be examined for co-variance of factors of age, number of years in the U.S., and proficiency in English language.

Progress: No additional patients were entered in FY 98 due to commitments to the 62nd Medical Group at Ft Lewis, WA. Ten subjects were entered in previous years and patient enrollment will recommence within the next couple of months.

Detail Summary Sheets

Department of Radiology

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 93/119	**Status**: Completed

Title: Gallbladder Ejection Fractions

Principal Investigator: COL John M. Bauman, MC

Department: Radiology	**Facility**: MAMC

Associate Investigator(s): Jerome Billingsley, M.D.; MAJ Michael F. Lyons II, MC; LTC Clifford L. Simmang, MC; MAJ Richard R. Gomez, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/09/1993	Dec 94	09/15/1998

Study Objective: To determine the clinical usefulness and reproducibility of gallbladder ejection fractions.

Technical Approach: Fifty volunteers will be studied on two occasions utilizing half of the normal radiopharmaceutical dose. These studies will be separated by no more than 30 days. Subjects will be given an injection of approximately 2.6 millicuries Tc-99m-DISIDA and serial one minute computer acquired images will be obtained for a maximum of 60 minutes. Once maximal gall bladder activity is achieved by visual inspection, 0.01 micrograms/kilo-gram sincalide will be given intravenously for three minutes via infusion pump. Serial one minute computer acquired images will be obtained for 30 minutes following this infusion. The results of the studies will not be used to determine patient care. The subject will be scheduled for cholecystectomy after the second DISIDA scan is completed. The gallbladder will be submitted to pathology for pathologic evaluation. The subject will complete a questionnaire prior to, and at one and six months post cholecystectomy. Mean, range, and standard deviation for each set of data will be calculated. A repeated measures ANOVA will be calculated.

Progress: This protocol has been completed. Twenty-seven patients were enrolled. Four were unsatisfactory due to non-vision of the gall bladder and were dropped from the study; three had only one of the two exams performed; and the remaining 20 had two valid studies. The PI will attempt to correlate gallbladder ejection fractions with clinical and pathologic outcomes at a later date when he has more time to do the analysis.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/037 **Status**: Completed

Title: Comparing the Tensile Strength of Cooks Helical Coils versus Hawkins III Wires in Goat Lung

Principal Investigator: MAJ Lawrence M. Casha, MC

Department: Radiology **Facility**: MAMC

Associate Investigator(s): Freddie J. Davis; CPT Ronald A. Gagliano, MC; MAJ Sean P. Murray, MC; MAJ David P. Tracy, MC

Start Date:	Est. Completion Date:	Periodic Review:
01/16/1998	Jan 98	N/A

Study Objective: To determine if vascular coils tied to suture will cause less injury to lung, with adequate attachment strength, as compared to Hawkins III wires for nodule localization in thoracoscopic lung biopsy.

Technical Approach: The following parameters will be used to compare the coil injection to the hookwire. Force over displacement as plotted by the Instron 8500 for the coils and hookwire at 1,2,3,cm depths. There will be two forces applied; one at .5 in per minute and a second at 720 in per minute. An agarose model will also be used to see how it compares to goat lung. If the model is adequate, it will be used for a jerk type stress test at 720 in per min.

Three goat lungs will be harvested after an ATLS session. Cooks helical coils will be sutured by hand to 5-0 proline suture. The coils with suture attached will be backloaded into a 19 gauge needle. The goat lungs will be injected with Hawkins III wires as well as helical coils under fluoroscopic guidance. Three wires and three coils will be injected at 1, 2 and 3 cm deep. The lungs will be imaged with CT and fluoroscopy in order to characterize the shape and location of coils and hooks. The lungs will be harvested with coils and hookwires in place and tested on an Instron 8500, set up with a 200 lb load cell. The force required to displace both the coils and hookwires will be measured with the Instron. An unused coil and hookwire will be stressed to failure outside of the lung. Due to damage to the lung tissue during repeated injections and displacements an agarose model will also be evaluated. Agarose at approximately 4 percent will be tested and compared to the goat lung data. The Agarose model will be used to test 5 hookwires and coils at 3 cm depths with displacements of 720 in/minute. The information will be graphed and tabulated.

Progress: This study has been completed. Three goat lungs were harvested after injection with hook wires as well as modified injectable coils to depths of 1, 2, and 3 cm. The lungs were then imaged with CT and fluoroscopy in order to characterize the shape and location of the hook wires and coils. The lungs were taken to an Instron 8500, which measured the stress required to displace both the hook wires and the coils. The hook wires and coils were stressed to failure outside of the lung to better understand what occurs when the hook wires or coils are displaced. Very small forces are required to displace both the coil and the hook wire from lung tissue when a slowly increasing force is applied. For the hook wire, only 0.75 pounds of force are required to displace it from the lung. This is only 1/3 of the force needed to deform a hook wire to failure outside the lung. A coil injected into the lung tissues requires 0.29 pounds of force to displace it in lung tissue, which is a five fold increase from the force needed to deform a coil outside the lung. When a constant force is applied, a hook wire has a 2.6 fold strength advantage over an injectable coil. When a hook wire is displaced, it does so by tearing though the lung tissue, which could result in hemorrhage or pneumothorax. When a coil is displaced, it does so by uncoiling along the injection tract, therefore causing less injury to the lung tissue. An abstract has been accepted for presentation in November 1998 at a national radiological meeting.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 95/166	**Status**: Ongoing

Title: Cost Effectiveness of Early MRI in Traumatic Wrist Injury

Principal Investigator: MAJ Richard S. Makuch, MC

Department: Radiology	**Facility**: MAMC

Associate Investigator(s): Rush A. Youngberg; COL John M. Bauman, MC; CPT John D. Crocker, MC; S. P. Scheer, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/16/1997	Feb 96	09/30/1998

Study Objective: To determine the cost effectiveness and utility of scintigraphy in the management of patients with traumatic wrist injury whose initial radiographs are negative, yet who clinically are felt to have scaphoid fractures.

Technical Approach: This is a prospective blinded study to determine the cost effectiveness of a more accurate, slightly more expensive imaging modality in the management of patients with traumatic wrist injury. All patients over 18 years of age with a fall on the outstretched hand (a "FOOSH" injury) will be included. One hundred patients will be enrolled.

Those enrolled in the study will undergo a limited high resolution bone scan of each wrist (the uninjured wrist will serve as a comparison to the injured wrist) within 48-96 hours of the time of injury. When the clinician has determined that management is complete, the clinician will have access to the bone scan results, prior to the patients' discharge from care.

The radiographs will be reviewed by the chief of musculoskeletal radiology, the bone scans by a staff nuclear medicine physician, and the clinical evaluation and follow-up will be performed per usual orthopedic clinic practice at MAMC. Costs will be calculated based on the CHAMPUS allowable reimbursement for the services rendered as defined by the 1995 CPT codes of the American Medical Association. Data analysis will include determining if there is statistical significance between the costs of caring for clinically "false positive" fractures and the costs of early bone scintigraphy.

Progress: Thirteen additional patients were added in FY 98 for a total of 24 subjects entered.

The PI was changed from Dr. Richard Makuch, when he was reassigned in Jul 98, to Dr. Rush Youngberg.

Preliminary findings indicate that MR of the scaphoid is an expeditious, cost effective way of exonerating the scaphoid as justification for immobilization of the wrists.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/093 **Status**: Ongoing

Title: Magnetic Resonance Imaging of the Sternum

Principal Investigator: CPT Andrea R. Manzo, MC

Department: Radiology **Facility**: MAMC

Associate Investigator(s): Rush A. Youngberg; LTC John D. Pitcher Jr., MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
07/17/1998	May 99	N/A

Study Objective: To determine the magnetic resonance imaging characteristics of the normal sternum and anatomical variations.

Technical Approach: 25 adult patients, with no prior history of trauma, scheduled for abdomen or thorax MRI will be recruited as subjects for this study, adding an extra 15 minutes of imaging time. Using a phased array surface coil, 3 imaging sequences will be obtained: T1 weighted sagittal localizer of the sternum, T1 - weighted coronal, and STIR coronal images. The 25 subject's sternums will be described and the imaging protocol optimized. Described will be the magnetic resonance imaging characteristics, the morphology, the optimal imaging parameters, the length of time the study takes, and the number of acquisitions.

Progress: This protocol has only recently been approved. No patients have been entered.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/027 **Status**: Completed

Title: Helical Computed Tomography Oral Cholecystography (HCT-OCG) vs. Ultrasound (US) in the Detection of Cholelithiasis; Sensitivity, Specificity, and Cost

Principal Investigator: MAJ Robert E. Morgan, MC

Department: Radiology **Facility**: MAMC

Associate Investigator(s): LTC Gregory N. Bender, MC; James H. Timmons, MD; MAJ Janice C. Stracener, MC

Start Date:	Est. Completion Date:	Periodic Review:
11/15/1996	Dec 98	09/30/1998

Study Objective: To identify the best methodology (HCT-OCG vs. US) for use in screening for the presence or absence of gallstones. Best, is defined as the examination with the greatest sensitivity, specificity and lowest cost.

Technical Approach: A prospective study in the identification of gallstones is to be completed comparing two imaging modalities in a large clinical study of 103 patients. The focus of the study is to identify which modality gives radiologists the greatest sensitivity and specificity in gallstone detection at the greatest economy. Surgery or overwhelming agreement among studies will provide the standard of truth. Chi-square analysis will be used to compare the results for statistical significance between the positive and negative rates as well as the average comparative cost.

Progress: This study has been completed and an abstract presented at the American Roentgen Society Meeting in April 1998. A total of 30 subjects were entered. There was no significant difference in the sensitivity or the specificity in detecting cholelithiasis between CT-oral cholecystography and ultrasound. The length of examination time and interpretation time has been approximately the same. Therefore, CT-oral cholecystography may be employed as an alternate test for cholelithiasis that is operator independent.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/047 **Status**: Ongoing

Title: Clinical Evaluation and Diagnostic Tests for Suspected Pulmonary Embolic Disease: A Survey of Physician Attitudes and Correlation to Clinical Practice

Principal Investigator: MAJ Sean P. Murray, MC

Department: Radiology **Facility**: MAMC

Associate Investigator(s): CPT Gina J. Kim-Ahn, MC; MAJ Scott C. Williams, MC; MAJ Robert B. Gibbons, MC; LTC Bernard J. Roth, MC; MAJ Matthew P. Jones, MC; COL John M. Bauman, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/20/1998	Apr 98	N/A

Study Objective: To determine clinician attitudes regarding diagnosis and clinical decision making for pulmonary thromboembolic disease. Secondary objectives will be to determine the factors which affect work-up, and use data to educate referring clinicians.

Technical Approach: A self-administered, anonymous survey about pulmonary embolic disease will be mailed/distributed to each clinician. The clinician's satisfaction with pulmonary embolism work-up, the performance of a complete (or incomplete) pulmonary embolism work-up, and the primary reason a pulmonary arteriogram is not ordered will be evaluated. These will be compared with demographic data such as years of clinical practice, referring service and number of such evaluations during past six months. The survey will also obtain descriptive data detailing diagnosis and management of these patients.

Progress: Data collection is still in progress. A second questionnaire has been sent to nonresponders.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/106	**Status**: Ongoing

Title: Peri-Hepatic Lymphadenopathy in Patients with Chronic Hepatitis

Principal Investigator: MAJ Sean P. Murray, MC

Department: Radiology	**Facility**: MAMC

Associate Investigator(s): MAJ Daniel W. Walsh, MC; COL Amy M. Tsuchida, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/15/1998	Sep 99	N/A

Study Objective: To retrospective evaluate abdominal computed tomography (CT) for abdominal lymphadenopathy in patients with either laboratory or histologic evidence of chronic hepatitis. Correlation will be made between radiology results and subtypes of hepatitis.

Technical Approach: Patients with histologic or laboratory evidence of hepatitis over the past four years will be identified through a computer search. The radiologic records of these patients will then be examined. Patients with both hepatitis and an abdominal CT scan within one year will be included in the study. Patients with known malignancy will be excluded. The abdominal CT scan will be evaluated for the presence of enlarged peri-hepatic lymphadenopathy. The incidence, location and size of the lymphadenopathy will be correlated to hepatitis subtypes.

Progress: This protocol has only recently been approved. No data have been collected as yet.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/076 **Status**: Completed

Title: Effectiveness of Oral Dolasetron Mesylate (50 mg) versus Prochlorperazine in the Treatment of Nausea and Emesis Due to Fractionated Abdominal Radiotherapy

Principal Investigator: MAJ Mark E. Shaves, MC

Department: Radiology **Facility**: MAMC

Associate Investigator(s): LTC Steven S. Wilson, MC; LTC Kenneth A. Bertram, MC; MAJ Nyun C. Han, MC; CPT Brent L. Kane, MC

Start Date:	Est. Completion Date:	Periodic Review:
02/16/1996	Apr 97	09/30/1998

Study Objective: 1) To evaluate the effectiveness of dolasetron mesylate in the treatment of radiation-induced nausea and emesis (RINE) in patients undergoing fractionated abdominal radiotherapy. 2) To evaluate the safety and tolerability of oral dolasetron mesylate in cancer patients receiving radiotherapy. 3) To evaluate the net incremental health care resource utilization, and net incremental work productivity and family/household assistance associated with the use of dolasetron mesylate versus prochlorperazine in the treatment of RINE. 4) To evaluate the use of select quality of life domains in measuring quality of life in patients receiving treatment for RINE.

Technical Approach: This study is a randomized, double-blind, active-controlled, multi-center trial to evaluate the effectiveness and safety of oral dolasetron mesylate in patients exhibiting nausea or emesis after undergoing fractionated abdominal radiotherapy for malignant disease. Patients will be eligible for the study if they experience significant nausea requiring antiemetic medication or have had at least one emetic episode after receiving radiotherapy during the 5 day screening period. Patients will be randomized to receive either oral dolasetron mesylate 50 mg qd or prochlorperazine 10 mig tid. Study medications will be ingested on a tid schedule. Patients randomized to dolasetron mesylate will take one 50 mg dolasetron mesylate capsule (as their first dose) and two matching placebo capsules for a total of three daily doses. The first daily dose of study medications will be ingested within 1 hour prior to the start of radiotherapy. The second and third daily tid scheduled doses of study medication (placebo or prochlorperazine) will be ingested over the remaining 24 hour treatment day. For each day on which no radiotherapy is administered (eg, weekends), study drug is to be administered using the same regimen (1 capsule tid). Radiation treatment will be administered for a minimum of 5 and a maximum of 30 days during the treatment phase. Study drug may be continued for up to 3 days after completion of the last fraction of radiotherapy.

Progress: This protocol has been closed at MAMC because the accrual goal has been reached by the sponsor. Seven patients were screened at MAMC and three met the enrollment criteria. Two patients completed the study and one patient withdrew from the study.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/081 **Status**: Suspended

Title: Pulmonary Manifestations of Gastro-esophageal Reflux Disease: HRCT Findings

Principal Investigator: CPT Manish K. Varma, MC

Department: Radiology **Facility**: MAMC

Associate Investigator(s): MAJ Cristopher A. Meyer, MC; MAJ Kazunori Yamamoto, MC; CPT Matthew D. Gilman, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/15/1996	Jan 96	09/30/1998

Study Objective: To investigate the pulmonary high resolution CT findings of patients with GERD. By categorizing HRCT findings in patients with GERD, a distinction may be made between pulmonary manifestations of GERD and other entities which often have similar plain film findings. This would allow clinical decisions regarding therapy, e.g. steroid therapy in UIP versus anti-reflux measurements to be facilitated.

Technical Approach: Gastroesophageal reflux disease is very common in Western Countries and is associated with significant morbidity. Based on symptoms alone, up to 44% of adult Americans experience GERD. The Gastroenterology Department has a proven population of patients with gastroesophageal reflux disease using the gold standard - 24 hour pH probe monitoring. 25 patients will be selected from the patient population after screening out those patients with prior lung disease, smoking, pregnancy, etc. that may interfere with pulmonary findings of GERD. High Resolution Computed Tomography of the lung will be performed in an attempt to categorized findings unique to GERD that are not discernible on plain film examination. CT and CXR findings will be reviewed by a radiologist and radiology resident. A grading system will be devised on the findings of the first five patients which will consist of five normal volunteers with normal pHs and no GERD. These findings will facilitate treatment options, e.g. steroid treatment in UIP verses anti-reflux precautions in GERD, in diseases that have similar plain film findings.

Progress: No further work was done on this protocol in FY 98. It was suspended in March due to failure of the PI to respond to the Continuing Review Process. The original PI, Dr. Varma, PCS'd in Jun 98 and CPT David Keadle, MC, was appointed to be the PI. The protocol is still in a suspended status until CPT Keadle furnishes the required information for the continuing review.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/142 **Status**: Ongoing

Title: Radiologic Guided Aspiration of Intra-articular Ganglia in the Knee

Principal Investigator: Rush A. Youngberg

Department: Radiology **Facility**: MAMC

Associate Investigator(s): CPT Manish K. Varma, MC; LTC John D. Pitcher Jr., MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
07/19/1996	Mar 97	09/30/1998

Study Objective: To determine whether radiologic guided aspiration and subsequent injection of 1% Xylocaine of intra-articular ganglia in the knee is a feasible alternative to arthroscopic excision.

Technical Approach: Intra-articular ganglia in the knee are an uncommon cause of knee pain. Patients with intra-articular ganglia in the knee had good or excellent results with arthroscopic excision of the ganglia. However, 50% to 78% of these patients had no associated internal derangement. CT guided aspiration of intra-articular ganglia in the knee has been successful. Ultrasound guided aspiration of ganglion cysts is a potentially cost effective alternative to surgery. We propose to perform radiologic guided aspiration of 15 patients with intra-articular ganglia in the knee. These patients have knee pain and intra-articular ganglia in the knee demonstrated on MRI. All patients will be followed at 3 month and 6 month after the procedure. An MRI will be obtained immediately post-procedure and at 6 months follow up. Failures will be offered operative (arthroscopy) treatment. The standard treatment (arthroscopy) who do not opt for aspiration. We will determine whether the intra-articular ganglia in the knee is the cause of the patients' symptom. Also, we will show whether aspiration and injection of 1% Xylocaine will successfully remove the ganglion cysts.

Progress: Two patients were entered in this study in FY 98 for a total for 5 patients.

The PI was changed from CPT Manish Varma to Rush A. Youngberg, M.D., June 1998, due to the reassignment of CPT Varma.

Detail Summary Sheets

2nd Battalion, 75th Ranger Regiment
Fort Lewis, Washington

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/117 **Status**: Suspended

Title: Special Operations Medical NCO Sustainment Training Using the Goat Model (Capra hircus)

Principal Investigator: CPT Charles Taylor, MC

Department: Ft. Lewis Rangers **Facility**: MAMC

Associate Investigator(s): 2LT David Nieman, PA-C, MS-SP; SFC Paul Linskens

Start Date:	Est. Completion Date:	Periodic Review:
07/18/1997	Jul 00	09/30/1998

Study Objective: Ranger medical personnel will be exposed, gain experience and demonstrate proficiency in the following invasive resuscitation procedures: cricothyroidotomy (needle and surgical), endotracheal intubation, needle thoracentesis, chest tube placement, pericardiocentesis, intravenous catheterization, venous cutdown and techniques of suture placement.

Technical Approach: Anesthetized adult goats will be used to train Ranger medical personnel basic surgical and emergency resuscitation skills they are expected to perform in combat. These tasks are identified by the American College of Surgeons in the Advanced Trauma Life Saving course. Ranger medical personnel must achieve a score of 70% on the written exam at the conclusion of the didactic instruction before proceeding to the hands on portions of the exercise. This protocol does not vary from previously accepted regimens for this purpose.

Progress: This protocol has been suspended since July 1998 because the PI was reassigned and DCI has been unable to get any definite commitments from the Special Operations Unit regarding a new PI.

Detail Summary Sheets

General Surgery Service, Department of Surgery

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/078 **Status**: Ongoing

Title: Inflammatory Response Related to Tracheobronchial Distention in Pigs (Sus scrofa) Using Absorbable Tracheal Stents

Principal Investigator: MAJ Kenneth S. Azarow, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/22/1998	May 01	N/A

Study Objective: To characterize the inflammatory reaction and granulation tissue formation following absorbable stent placement in the pig airway. To achieve this long term objective, the pilot study should demonstrate any differences between in vivo and in vitro absorption of the stents.

Technical Approach: A total of 10 pigs will be utilized in this study, two pigs per group during a 5 week period of time. Group 1 will have stent insertion with sacrifice of the animals at day 7; Group 2 will be sacrificed at day 14; Group 3 will be sacrificed at day 21; Group 4 will be sacrificed at day 28 and Group 5 will be sacrificed at day 35. All animals will undergo histologic examination of their airways to include videoscopic recordings in order to more accurately measure airway lumen diameters and tissue condition and reactivity.

Progress: This protocol has not been started since the investigators are awaiting approval of a CRDA to provide the equipment and supplies.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/098 **Status**: Ongoing

Title: Gastrin Releasing Peptide Receptor: A Potential Novel Marker of Clinical Aggression in Human Neuroblastoma Cells

Principal Investigator: MAJ Kenneth S. Azarow, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): Ann O'Connor, M.D.; Robert S. Sawin, M.D.

Start Date:	Est. Completion Date:	Periodic Review:
08/20/1998	Jul 99	N/A

Study Objective: To determine whether the expression of gastrin releasing peptide receptor by human Neuroblastoma cells correlates with increased malignancy and to demonstrate that gastrin releasing peptide receptor is expressed by human neuroblastoma cells and expression of this receptor may correlate with advanced malignancy

Technical Approach: The established cell lines IMR32, SK-N-SH, SK-N-MC, SK-N-AS, SK-N-DZ, and SK-N-F1 (human neuroblastoma cells) as well as H345 (human small cell lung carcinoma) and S3T3 (murine fibroblast) will be grown to confluence. After appropriate washes, cells will be incubated with Fluo-GRP which is expected to bind specifically to the GRP receptor on those cells which express it. To visualize cell surface binding, cells will incubate for 20-60 minutes at 4 degrees C. To visualize internalization of the labeled receptor, cells will incubate for 20-60 minutes at room temperature. The H345 and S3T3 cells will serve as the positive controls, as these cells have been shown to express the GRP receptor. Following incubation, cells will be rinsed three times in buffer. Cells with then be fixed in a 4% paraformaldehyde solution for 20 minutes at room temperature and then briefly washed in buffer. The cells will be stored in darkness at 4 degrees C until visualization under a fluorescent microscope. Non-specific binding will be assessed by including 100-fold excess unlabeled GRP in parallel incubations.

Progress: This is a recent project which has not been started until other projects are completed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/083 **Status**: Ongoing

Title: Porcine Iliac Artery Injury Model for Testing of Absorbable Vascular Templates

Principal Investigator: CPT Alec C. Beekley, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Kenneth S. Azarow, MC; COL Charles A. Andersen, MC

Start Date:	Est. Completion Date:	Periodic Review:
06/19/1998	Jun 01	N/A

Study Objective: To determine if pigs can serve as an adequate living tissue model for testing the *in vivo* absorption of polyphosphasene vascular templates and to determine if the absorbable vascular templates or stents will effectively treat deliberate, non-transecting iliac artery injuries in a porcine model in a reproducible fashion.

Technical Approach: In Phase I, individual animals will undergo incision in both groins with arteriotomy in one external iliac artery and placement of an experimental vascular stent in the opposite iliac artery over an angiographic wire and balloon under manual and angiographic guidance. Impact of the stent will be assessed immediately through intraoperative arteriographic measurement of luminal diameters. Impact of the templates over time will be assessed by repeat angiography with subsequent sacrificing of the animals and tensile strength testing, routine histopathologic evaluation, and electron microscopic evaluation of the arterial segment containing the experimental stent at one, two, three, four, and five weeks after stent placement.

In phase II, individual animals will undergo incision in both groins. Each will then have controlled operative creation of a vascular injury in one iliac artery, followed by placement under manual and angiographic guidance of experimental stent through an arteriotomy of the iliac artery on the opposite leg. After removal of the angiographic equipment each animal will have a controlled operative creation of an arteriotomy on the opposite iliac artery with primary suture repair. Resulting artery and stent patency and integrity will be assessed by intraoperative arteriography. Impact over time will be assessed via repeat arteriography with subsequent sacrifice of the animals and tensile strength testing, routine histopathologic evaluation, and electron microscopic evaluation of the segments of artery containing the experimental stent at one, two, three, four, and five weeks following stent implantation. These results will be compared with the results of the same tests done on the arteriotomies that were repaired primarily with suture.

Progress: This protocol has not been implemented. The investigators are still awaiting the arrival of the absorbable stents.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 96/009	**Status**: Completed

Title: Postoperative Cisapride Therapy After Colorectal Surgery

Principal Investigator: CPT Tommy A. Brown, MC

Department: Surgery/General Surgery	**Facility**: MAMC

Associate Investigator(s): LTC William C. Williard, III, MC; CPT Jerome M. McDonald, MC; LTC Gregory N. Bender, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
10/20/1995	Oct 96	09/30/1998

Study Objective: To test the efficacy of cisapride in the postoperative period in relation to bowel motility and length of hospital stay.

Technical Approach: In this double-blind study 66 patients undergoing colorectal surgery will be randomly assigned to one of two groups. The experimental group will receive 20mg cisapride orally four times daily until discharged; the control group will receive placebo. All patients will be given an oral sitz mark radiographic marker on the first postoperative morning to follow bowel motility. A daily portable abdominal x-ray will be taken until 80% of the sitz markers have completely passed through the system. Length of hospital stay, daily progression of radiographic marker, onset of bowel movements, regular diet intake and perioperative complications will be monitored and compared for experimental and control groups.

Progress: This protocol has been completed. In this study of 35 subjects, the outcome measurements included time to first bowel movement, time to advancement of a regular diet, and time to hospital discharge. The study demonstrated a significant improvement in the study group compared to the placebo group in all outcome parameters, as well as substantial cost savings in the study group. An abstract has been accepted for presentation at the North Pacific Surgical Association Meeting and a manuscript has been accepted for publication in the American Journal of Surgery.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/064 **Status**: Ongoing

Title: Prognostic Significance of p53 Mutations in the Lymph Nodes of Dukes B Colon Cancer Patients

Principal Investigator: CPT Tommy A. Brown, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Kenneth S. Azarow, MC; CPT Wade K. Aldous, MS; LTC Jerome B. Myers, MC; LTC William C. Williard, III, MC

Start Date:	**Est. Completion Date:**	**Periodic Review:**
04/18/1997	Jun 97	07/17/1998

Study Objective: Our objective is to evaluate the relationship between p53 mutations in the lymph nodes and long term survival of patients with colon cancer.

Technical Approach: This is a retrospective pathology review and chart review. Slides of lymph nodes from 50 Dukes B colon cancer patients will be stained for p53 mutation using standard immunohistochemical stains. These results will be compared to long term tumor recurrence patterns.

Progress: Forty patients have been entered. The investigators are awaiting block cutting and staining to complete the study.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/141 **Status**: Ongoing

Title: A Prospective Multi-institutional Study to Determine the Sensitivity and Specificity of Telomerase in ERCP Brushings for Detection of Pancreatic and Biliary Cancer

Principal Investigator: CPT Tommy A. Brown, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Kenneth S. Azarow, MC; LTC William C. Williard, III, MC; CPT Wade K. Aldous, MS; COL Amy M. Tsuchida, MC; LTC Mary Maniscako-Thegerge, MC; LTC Jeffrey Kavolius, MC; LTC James North, MC; LTC Russell Martin, MC; LTC Steve Hetz, MC

Start Date:	Est. Completion Date:	Periodic Review:
09/19/1997	Nov 98	09/30/1998

Study Objective: To evaluate telomerase activity as a screening modality for the detection of pancreatic and biliary tumors.

Technical Approach: This study is designed to evaluate the efficacy of measuring telomerase activity in endoscopic retrograde cholangiopancreatography (ERCP) bushings and bile samples as a screening tool for pancreatic carcinoma and cholangiocarcinoma. The six Army medical centers involved include MAMC, WRAMC, TAMC, DDEAMC, WBAMC and BAMC. Patients with suspicious pancreatic or bile duct lesions will have lumen brushings of the lesions and bile collected to determine if telomerase activity is present in the specimens. Additionally, after surgical excision of the suspicious lesions, a sample of the primary tumor will also be evaluated for telomerase activity. The results of these tests as well as patient clinical data will be analyzed to determine the sensitivity and predictive value of telomerase as a screening tool for pancreatic and bile duct malignancy. Approximately 36 patients for each group will be studied. The data will be collected and analyzed using statistical software to evaluate surgical correlation of telomerase activity in ERCP brushings and bile fluid. Major analysis will be the correlation of the surgical results to the telomerase activity detected in FNAs, reporting sensitivity and specificity, along with positive and negative predictive value. The study will run for approximately 1 year.

Progress: Twenty-one subjects have been studied. Preliminary results were presented at the 1998 Gary Wratten Surgical Symposium.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/143 **Status**: Ongoing

Title: A Prospective Multi-institutional Study to Determine the Sensitivity and Specificity of Telomerase in Thyroid FNAs for the Detection of Thyroid Cancer

Principal Investigator: CPT Tommy A. Brown, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Kenneth S. Azarow, MC; LTC William C. Williard, III, MC; MAJ Clifford A. Porter, MC; CPT Wade K. Aldous, MS; CPT Brenda K. Bell, MC; MAJ Raymond S. Lance, MC; MAJ Janice C. Stracener, MC; LTC Mary Maniscako-Thegerge, MC; LTC Jeffrey Kavolius, MC; LTC James North, MC; MAJ Rodger K. Martin, MS; LTC Steve Hetz, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/19/1997	Nov 98	09/30/1998

Study Objective: To evaluate telomerase activity in thyroid fine needle aspirations as a screening modality for the detection of thyroid cancer.

Technical Approach: This study is designed to evaluate the efficacy of measuring telomerase activity in fine needle aspirations of thyroid nodules as a screening tool for thyroid carcinoma. The six Army medical centers involved include MAMC, WRAMC, TAMC, DDEAMC, WBAMC and BAMC. Patients with suspicious thyroid nodules requiring fine needle aspiration (FNA) will have additional FNA samples taken at the time of surgery sent to MAMC to determine if telomerase activity is present in the specimens. Additionally, after surgical excision of the thyroid, a sample of the primary tumor will also be sent to MAMC for evaluation of telomerase activity. The results of these tests as well as patient clinical data will be analyzed to determine the sensitivity and predictive value of telomerase as a screening tool for thyroid malignancy. We estimate the total number of patients needed to complete the study to be 360 utilizing a power analysis. The total number of specimens analyzed will be approximately 1000. The data will be collected and analyzed using statistical software to evaluate surgical correlation to telomerase activity in FNAs. Major analysis being the correlation of the biopsy cytology to the telomerase activity detectability, reporting sensitivity and specificity, along with positive and negative predictive value. The study will run for approximately one year. Consent is required for additional FNA passes for all patients.

Progress: Approximately 40 subjects have been studied. Preliminary results were presented at the 1998 Gary Wratten Surgical Symposium.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 97/047	**Status**: Ongoing

Title: Genetic Testing for Inherited Cancer

Principal Investigator: Preston L. Carter, M.D.

Department: Surgery	**Facility**: MAMC

Associate Investigator(s): Jamilyn L. Daniels, M.S., C.G.C.; Charlene P. Holt, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/21/1997	Sep 97	09/30/1998

Study Objective: We propose to develop a model for genetic counseling and testing for patients at risk for breast cancer. Multiple phases of a program will be developed and tested in this pilot program at Madigan. Two breast cancer susceptibility genes will be studied, BRCA1 and BRCA2. A commercial laboratory will be used to perform the actual testing. Results and interpretation of each patient's test will be sent to Madigan, and each patient enrolled in appropriate counseling and medical care.

Technical Approach: Historical data indicate that 55 of 100 patients meeting the inclusion criteria may test positive for BRCA1 or BRCA2 genetic mutations. Thus we anticipate that approximately 23 patients from the group of 50 recruited at Madigan will have a positive test result and request additional care. Informed consent will be performed at two points in the project, first before patients complete a questionnaire, perform pre-test counseling and education, and second before providing a blood sample for genetic testing. The guidelines for follow-up of individuals testing positive for BRCA1 or BRCA2 genetic mutations have been presented by Dr. Wylie Burke to the National Cancer for Human Genome Research Advisory Council. Madigan patients will be instructed and counseled on their individual test results and choices of action for the follow-up surveillance.

Progress: Fifty-eight (58) subjects were enrolled in FY 98 for a total of 105 subjects. Of these, 75 completed phase I only; 27 have completed Phases I and II, and three who completed Phase 1 are scheduled to completed phase II in FY 99.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/020 **Status**: Completed

Title: Subtotal Gastrectomy in the Treatment of Morbid Obesity

Principal Investigator: Preston L. Carter, M.D.

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Thomas K. Curry, MC; MAJ Clifford A. Porter, MC; LTC David M. Watts, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/21/1997	Oct 97	N/A

Study Objective: To review the institutional experience, and determine the efficacy of subtotal gastrectomy (resectional gastric bypass) in the surgical treatment of patients with morbid obesity.

Technical Approach: The records of patients who have undergone resectional gastric bypass will be reviewed for the following variables: basic demographics; pre-op height, weight, and body mass index; short term surgical morbidity and mortality; average weight loss over the first post-op year, and long term weight loss maintenance for patients in long term follow-up; follow-up patient satisfaction as determined by follow-up clinic visits and telephone interviews; and long-term morbidity.

Weight loss over time in the first year after surgery will be compared to the weight loss in the year before surgery with non-surgical dieting attempts. Patients will be seen in follow-up clinic at 1, 3, 6, and 12 months postoperatively, with documentation of postop weight at each visit. Patients will also be interviewed for presence of post-gastrectomy symptoms (dumping) and monitored at 6 months and one year for hemoglobin and vitamin B-12 /folate levels. Weight loss results are to be analyzed by the Student's t-test.

Progress: The records for 85 patients were studied. Twenty six patients undergoing resectional gastric bypass (RGB) for conversion of an anatomically or functionally failed prior bariatric procedure have had mean additional weight loss of 37% excess body weight (EBWL) in 18 months follow-up. Twelve patients undergoing RGB for intractable side effects of prior bariatric procedures have all had clinical improvement. Forty-seven patients undergoing RGB as a primary procedure have had EBWL of 53%, in mean follow-up of 11 months. For the entire series, major complications were one anastomotic leak, one reexploration for suspected subphrenic abscess, and one major pulmonary embolus. These patients recovered. There was no mortality in the series. Conclusions: Resectional gastric bypass is a new alternative for salvage of a failed or problematic prior bariatric procedure. It is also effective as a primary weight control operation. The results were published in the American Journal of Surgery 175:367-370, 1998.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 96/045	**Status**: Suspended

Title: The Effect of Low-Dose Dopamine on Splanchnic Blood Flow with Intra-abdominal Hypertension in Domestic Yorkshire Swine, Sus scrofa

Principal Investigator: CPT Mathew H. Chung, MC

Department: Surgery/General Surgery	**Facility**: MAMC

Associate Investigator(s): LTC Patrick J. Offner, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/19/1996	Jan 99	09/30/1998

Study Objective: To investigate the ability of low-dose dopamine to improve visceral blood flow and organ perfusion during induced intro-abdominal hypertension.

Technical Approach: We will use an established porcine model of elevated intra-abdominal pressure. The animals will be anesthetized, mechanically ventilated and instrumented. Femoral arterial and venous catheters will be placed and a Swan-Ganz pulmonary artery catheter will be placed via jugular vein. Laparatomy will performed for the placement of Doppler flow probes and gastric and ileal tonometers. Two catheters will be placed in the abdominal cavity percutaneously and a urinary catheter will be placed through a cystotomy. Following instrumentation, animals will be randomly assigned to one of four experimental groups. Group I is the negative control with no further manipulations. Group II will have elevated intra-abdominal pressure by instillation of saline solution. Group III will have the same elevated (Group II) intra-abdominal pressure established plus low dose dopamine. Group IV will have low-dose dopamine alone. There will be six animals per group. Intra-abdominal pressures of 20 and 40 mm Hg will be studied. Measurements will include the following every 20 minutes for two hours during the experiment: (1) renal, hepatic, and superior mesenteric arterial flow and portal vein flow, (2) hepatic and renal perfusion, (3) gastric and terminal ileum pHi, (4) cardiac hemodynamics, and (5) laboratory values on ABG, mixed venous blood gas and lactate levels.

Progress: This protocol was suspended in July 1997 in an effort to find a replacement for the PI who PCS'd. Currently, it is being reworked by Dr. Kenneth Azarow in an effort to get it updated for a new PI. It has never been implemented.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/067 **Status**: Completed

Title: Nasopharyngeal Teratomas and Dermoids: A Review of the Literature and Case Series

Principal Investigator: CPT George L. Coppit, III, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Jonathan A. Perkins, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/22/1998	Dec 97	N/A

Study Objective: To review the clinical differences between nasopharyngeal teratomas and dermoids and to evaluate the impact of prenatal diagnosis on the treatment and outcome of these lesions.

Technical Approach: A retrospective chart review will be conducted to identify those patients treated for nasopharyngeal dermoid or teratoma. Records pulled may include any patient medical records, operative reports, or pathology reports with this final diagnosis. Records will be carefully reviewed for age at diagnosis, presenting signs and symptoms, prenatal diagnosis and management, preoperative evaluation, surgical treatment, and outcome. Collected data will be compiled and presented in a descriptive fashion.

Progress: Records for five subjects were retrospectively reviewed. Additionally, the medical literature was reviewed to evaluate the clinical differences between nasopharyngeal teratomas and dermoids, as well as to determine if prenatal diagnosis has impacted the treatment and outcome for these lesions. Inconsistent use of a standard classification system has made differentiating between the two lesions difficult. The majority of lesions are diagnosed at birth, with teratomas having a higher incidence of maternal polyhydramnios and need for emergent airway management. Additionally, teratomas were more likely to be associated with congenital abnormalities. Total surgical extirpation remains the treatment of choice for both lesions. Recurrences were rare, occurring more commonly in cases of teratoma. The incidence of death was also rare and was attributable to associated congenital abnormalities in all but one case. Prenatal diagnosis did not significantly impact the management of these lesions, but did serve to alert the clinician to the potential need for acute airway management.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/035 **Status**: Terminated

Title: Madigan Army Medical Center Institute for Advanced Endoscopic Training Using the Pig (Sus scrofa)

Principal Investigator: COL William E. Eggebroten, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): LTC William C. Williard, III, MC; LTC Donald G. Kim, MC; MAJ Clifford A. Porter, MC; LTC David M. Watts, MC; LTC Patrick J. Offner, MC; LTC Clifford L. Simmang, MC; MAJ Timothy F. Deaconson, MC

Start Date:	Est. Completion Date:	Periodic Review:
01/23/1995	Jan 98	05/22/1998

Study Objective: To familiarize General Surgery residents, staff, and invited surgeons form our local community with techniques in the management of advanced endoscopic-laparoscopic techniques. This would familiarize surgeons with techniques for laparoscopic procedures upon the esophagus and stomach, especially for anti-reflux procedures, and the biliary tract for cholecystectomy and common bile duct exploration and for the small intestine in colon for intestinal resection, appendectomy, and colonic resection.

Technical Approach: This training protocol on laparoscopic and endoscopic surgical procedures will use a total of 10 pigs. Two to four pigs will be used per session with three sessions per year. The animals will be maintained on a nothing-by-mouth status for 12 hours prior to the procedures. General anesthesia will be used. The animals will be intubated, prepped and maintained on inhalant anesthesia. At the completion of the procedures, the pig will be euthanized. During each procedure, each animal will be used for a single training episode. Maximum teaching benefit will be obtained by repeating the procedures in order that each trainee assigned to the animal may have an opportunity to perform the procedure in rotation. Critique forms will be utilized for the training and will provide evaluation of effectiveness of the course.

Progress: This protocol was terminated in March 1998 due to expiration of the three-year limit on animal studies. No sessions were held in 1998.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/038 **Status**: Terminated

Title: Advanced Trauma Life Support Course Utilizing the Goat (Capra hircus)

Principal Investigator: COL William E. Eggebroten, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Katherine L. Bevill, MC; Preston L. Carter, M.D.; CPT Ronald J. Place, MC; LTC Clifford L. Simmang, MC; LTC Patrick J. Offner, MC

Start Date:	Est. Completion Date:	Periodic Review:
11/18/1994	Jul 97	05/22/1998

Study Objective: The objective of this training exercise is to teach physicians one safe method of performing five life-saving procedures for trauma patients.

Technical Approach: This training exercise will MAMC residents in the initial management of trauma patients. The physicians will practice the safe methods of performing the following life-saving procedures in the order listed: venous cut down, diagnostic peritoneal lavage, chest tube insertion, pericardiocentesis and cricothyroidotomy. The procedures will be performed after the animals are properly prepared and adequately anesthetized for surgery. The endpoint of this training will be completion of all procedures or evidence of excessive duress or anesthetic instability. Students will be evaluated by instructors on the direct basis of psychomotor skills and verbalization of the indications, contraindications and potential complication of each procedure.

Progress: This protocol was terminated in November 1997 due to expiration of the three year limit for animal protocols. No sessions were held in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/034 **Status**: Ongoing

Title: Computed Tomography Guided Percutaneous Placement of Injection Coils Ligated to Suture and Thoracoscopic Pulmonary Resection

Principal Investigator: CPT Ronald A. Ganglion, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Lawrence M. Casha, MC; MAJ Sean P. Murray, MC; MAJ David P. Tracy, MC; James H. Timmons, MD; MAJ Scott C. Williams, MC; LTC Maceo Braxton Jr, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/18/1997	Indefinite	N/A

Study Objective: The primary objective is to reduce the number of displaced localization devices by the use of a Cook helical coil tied to a suture line as an alternative to the hookwire for video-assisted thoracic surgery (VATS). A secondary objective is to reduce damage that occurs with displacement of wires.

Technical Approach: Twenty patients already slotted for needle localization with Hawkins III wires will have be randomized to the placement of either coils attached to suture or hookwires. The patient will be scanned radiographically to determine the success of the procedure. They will then be taken to the OR and thoracic surgery will remove the coils or hookwires with a surrounding wedge of lung tissue containing the lung nodule. The surgical specimen will be evaluated by Pathology. The degree of displacement and associated complications will be compared to our current 90% Hawkins III wire displacement rate.

Progress: Seven patients have been enrolled in this study.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/022 **Status**: Ongoing

Title: The Use of Autologous Fibrin Glue to Prevent Post-operative Seromas in Patients Undergoing modified Radical Mastectomy

Principal Investigator: CPT Bret R. Hansen, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): LTC Patrick J. Offner, MC; CPT Daniel D. Mais, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/18/1994	Dec 96	09/30/1998

Study Objective: To determine if the use of autologously donated fibrin glue can decrease the incidence of post-operative fluid collections in patients undergoing modified radical mastectomy.

Technical Approach: We plan to conduct a prospective, randomized study evaluating the effects of autologously donated fibrin glue on the flaps created during modified radical mastectomy in attempts to increase the adhesion of the flaps to the underlying tissue and prevent post-operative fluid collections. A total of 60 subjects will be recruited and randomized to a study group and a control group. All subjects will donate one unit of autologous blood pre-operatively. This blood will be used to provide the autologous fibrinogen for the study group. Surgeons will be given the fibrin preparation or saline to apply after mastectomy. The surgeons will be blinded as to whether they are applying fibrin glue or control saline. Drainage from the surgical area will be recorded by the subjects and a blinded evaluator will assess fluid accumulation at least weekly after drains are removed. Seroma fluids will be drained as necessary. Rates of seroma formation will be compared using chi-square analysis. The mean total amount of drain output and the mean length of time for the drains to be discontinued will also be analyzed using the Student's T-test or a non-parametric test should the distribution prove to be non-Gaussian.

Progress: No patients have been entered in this study. One of the residents in the General Surgery Service (CPT Sanborn) is reviewing this protocol and will take over the protocol early in FY 99.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/097 **Status**: Ongoing

Title: Telomerase Level in Neuroblastoma Tumors: Can This Be Used to Guide Prognosis and Management?

Principal Investigator: CPT Leroy J. Trombetta, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): CPT Tommy A. Brown, MC; MAJ Kenneth S. Azarow, MC; CPT Wade K. Aldous, MS; M. J. DeHart, B.S.; Robert S. Sawin, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
08/20/1998	Sep 98	N/A

Study Objective: To evaluate telomerase activity in frozen neuroblastoma specimens, while being blinded to any and all data concerning the patients from which these specimens originated.

Technical Approach: This is a cooperative study with Seattle Children's hospital, which will provide 50 tumor samples. Telomerase activity will be measured quantitatively and the results compared to the existing data in the Children's Cancer Study Group (CCSG) database for that tumor. Telomerase activity will be determined by the telomere amplification repeat protocol (TRAP) using the telomerase PCR ELISA kit from Boehringer Mannheim. Positive and negative controls will be used from the kit. In addition, RT-PCR will be used to amplify the RNA component (HTR) from the same protein extracts used for telomerase assays. B-2 microglobulin, a common housekeeping gene, will be used as a quantitation control. PCR products will be run on 1% agarose gels, transferred to a nylon membrane and then probed for B-2 microglobulin and the RNA component. Densitometric analysis correcting for B-2 microglobulin content will determine the HTR.

Progress: Twenty-one telomerase specimens have been assayed via the TRAP-ELISA kit and RT-PCR gels have been run. The study will be unblinded on 30 Oct 98, at which time an abstract will be written.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/099 **Status**: Ongoing

Title: Postoperative Cisapride Therapy After Abdominal Surgery in the Pediatric Patient

Principal Investigator: CPT Leroy J. Trombetta, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): CPT Tommy A. Brown, MC; MAJ Kenneth S. Azarow, MC; COL James M. Noel, Jr., MC; LTC David Wiechmann, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/20/1998	Jul 99	N/A

Study Objective: To compare the effects of cisapride and erythromycin on return of bowel motility and length of hospital stay in pediatric post-surgical patients.

Technical Approach: Subjects will be randomized to one of two groups. Group A will receive erythromycin at 1-3 mg/kg orally TID and Group B will receive cisapride 0.2 mg/kg orally TID. Subjects will take the study medication until time of discharge. Information will be collected concerning length of hospital stay, onset of bowel movements, regular diet and intake and perioperative complications.

Progress: One subject has completed the study. All aspects of her enrollment in the study went very well.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/100	**Status**: Ongoing

Title: Intra-abdominal Pressure in Elective Aortic Surgery Patients: A Prospective Series

Principal Investigator: CPT Leroy J. Trombetta, MC

Department: Surgery/General Surgery	**Facility**: MAMC

Associate Investigator(s): LTC Stephen B. Olsen, MC; COL David F. J. Tollefson, MC; COL Charles A. Andersen, MC; CPT Bret R. Hansen, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
08/20/1998	Aug 00	N/A

Study Objective: To determine a range of normal values of intra-abdominal pressures (IAP) in patients undergoing elective surgery of the abdominal aorta.

Technical Approach: All subjects will have the IAP measured: (1) immediately before surgery, after induction of anesthesia, before initial skin incision is made; (2) immediately post-operatively once the subject has been transferred to the intensive care unit, and all essential nursing tasks have been performed to ensure that the subject is stable; (3) four hours from reading number 2 above and (4) each morning on all subsequent post-operative days until the Foley catheter has been removed. Data recorded will include pre-operative weight, intra-operative fluid balance, length of surgery, hematocrit, pulmonary artery systolic and diastolic pressures, mean arterial pressure, overall fluid balance, peak airway pressure, serum creatinine level, use/non-use of pre-operative bowel preparation and type and use/non-use of evisceration to gain exposure at the time of surgery. Data will be recorded until subject is discharged from the hospital.

Progress: Four subjects have been entered.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/122 **Status**: Terminated

Title: Linezolid in the Treatment of Skin/Soft Tissue Infections: An Open Label, Randomized, Dose Comparative Phase II Study of Low Dose Linezolid

Principal Investigator: LTC William C. Williard, III, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Kenneth S. Azarow, MC; Preston L. Carter, M.D.; COL William E. Eggebroten, MC; MAJ Clifford A. Porter, MC; LTC David M. Watts, MC; MAJ Thomas K. Curry, MC; CPT Bret R. Hansen, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
07/18/1997	Sep 98	03/20/1998

Study Objective: 1) To assess the efficacy (clinical and microbiological) and safety of low dose linezolid in the treatment of skin/soft tissue infections; 2) to determine the minimum effective therapeutic dose of linezolid for skin/soft tissue infections. A success rate of □75% effective dose; and 3) to assess pharmacokinetic parameters and their variance, as well as the relationship between linezolid pharmacokinetics and therapeutic effects.

Technical Approach: This open label, randomized, dose comparative study will test the efficacy (clinical and microbiological) and safety of low dose linezolid, and will assess the minimum effective therapeutic dose of linezolid in adult patients with gram positive skin and soft tissue infections. For this study, low dose linezolid is defined as 600 mg/day (300 mg BID) or lower. Patients will be randomized to receive either 100 mg or 200 mg twice a day of linezolid. A third dosage group of 300 mg twice a day may be initiated during the course of the study. Depending upon the severity of the infection, patients may be hospitalized or may be treated entirely as outpatients. Patients may be treated entirely with oral linezolid. Hospitalized patients may be treated totally with intravenous linezolid, or intravenous linezolid followed by oral linezolid. Treatment duration will be 5 to 14 days (total IV plus oral treatment). Patients should be afebrile for 72 hours before cessation of study drug. Patients will have follow-up 1 to 14 days post treatment, and at 15 to 28 days post treatment. Safety labs will be drawn at end of treatment and at both follow-up visits. Pharmacokinetic blood samples will be drawn three times during the course of their participation.

Progress: This study was withdrawn by the sponsor. No patients were entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/135 **Status**: Completed

Title: Linezolid (PNU-100766) in the Treatment of Gram Positive Bacteremia: An Open Label Phase II Study of Intravenous Therapy with Optional Oral Continuation

Principal Investigator: LTC William C. Williard, III, MC

Department: Surgery/General Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Kenneth S. Azarow, MC; Preston L. Carter, M.D.; COL William E. Eggebroten, MC; MAJ Clifford A. Porter, MC; LTC David M. Watts, MC; MAJ Thomas K. Curry, MC; CPT Bret R. Hansen, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/15/1997	Oct 97	08/20/1998

Study Objective: 1) To assess the efficacy and safety of intravenously and orally administered linezolid in the treatment of bacteremia; and 2) to assess pharmacokinetic parameters and their variance in this population, as well as the relationship between linezolid pharmacokinetics and therapeutic effects.

Technical Approach: This open label trial will test the efficacy and safety of Linezolid (PNU-100766) in at least 30 hospitalized adult patients with gram bacteremia. Those with negative cultures may remain in the study if they are clinically improving. Aztreonam may be administered to patients for gram negative organism coverage. At entry patient's APACHE II scores must be no higher than 23. Patients will receive linezolid 600 mg intravenously or orally twice a day. Duration of treatment will be 5 to 21 days. Patients must start study drug via the intravenous route of administration. They may switch to oral therapy after 3 days (4 doses) of IV therapy, but they must show clinical improvement (e.g., body temperature of <37.5 c, heart rate <100 BPM) for at least 24 hours before switching. Patients should have normal body temperature for 72 hours before cessation of study drug. The Short Term Follow-up will occur at 1 to 14 days post treatment, and the Long Term Follow-up will occur at 15 to 28 days post treatment.

Progress: This study has been closed by the sponsor due to sufficient numbers and the completion of the study at all sites. No patients were enrolled at MAMC.

Detail Summary Sheets

Ophthalmology Service, Department of Surgery

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/103	**Status**: Ongoing

Title: Madigan Eye and Orbit Trauma Scale

Principal Investigator: MAJ Darryl J. Ainbinder, MC

Department: Surgery/Ophthalmology Surgery	**Facility**: MAMC

Associate Investigator(s): CPT Earle G. Sanford, MC; LTC William R. Raymond IV, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/15/1998	Aug 99	N/A

Study Objective: To provide a rapid, standardized triage trauma scale for the management of eye and orbital trauma.

Technical Approach: The Madigan Eye and Orbit Trauma Scale will consist of five index categories which include: vision, eyeball structure, proptosis, pupils, and motility. In Phase I, 50 consecutive cases of ocular and orbital trauma patients who presented to the Department of Ophthalmology for ocular and orbital trauma will be evaluated using the scale. The trauma scale score will be compared to the final diagnosis and outcome documented by the patient's medical record. Recorded data includes age, sex, rank if applicable, mechanism of injury, trauma scale index by index category, and total score. An independent observer will determine if there was a correlation between the trauma score and the severity of the final diagnosis/outcome. The results of Phase I will be presented to the MAMC Multiservice Facial Trauma Team for critical peer review to determine if the trauma scale is predictive of severity of injury and if the scale provides a common language for multiple examiners with different backgrounds.

Phase II will be expanded to include the Department of Emergency Medicine and the field medics of the 2/75 Ranger Battalion. One hundred ocular and orbital trauma cases will be evaluated. Training for supported units will be revisited at six months and upon request from a supported unit. Quarterly results of all patients evaluated with this trauma scale will provide the data for the final report at one year.

Progress: Fifty patients have been evaluated. Training has been completed for the Facial Trauma Team and has begun for the Emergency Department. This study was presented at the 12th Annual Madigan Otolaryngology Head and Neck Surgery Seminar.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/065 **Status**: Completed

Title: A Parallel, Randomized, Double-Masked, Active Controlled, Multiclinic Study Comparing the Tolerability and Efficacy of 2.0% Dorzolamide Ophthalmic Solution and Orally Administered Acetazolamide in Patients with Ocular Hypertension or Glaucoma Being Treated

Principal Investigator: COL Kevin J. Chismire, MC

Department: Surgery/Ophthalmology Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Roger K. George, MC; LTC Vernon C. Parmley, MC; LTC Rob A. Mazzoli, MC; LTC William R. Raymond IV, MC; MAJ Eugene F. May, MC; COL Anthony R. Truxal, MC; LTC Thaddeus J. Krolicki, MC; CPT Keith F. Dahlhauser, MC; COL Thomas H. Mader, MC; LTC Elizabeth A. Hansen, MC; MAJ Mary B. Grazko, MC; MAJ Mark L. Nelson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/21/1997	May 98	04/17/1998

Study Objective: Primary: To determine the incidence of systemic adverse events; including those most commonly reported with oral CAIs (e.g. headache, dizziness, nausea, paresthesia, fatigue as well as malaise, weight loss, depression, anorexia and loss of libido), in patients receiving 0.5% timolol maleate ophthalmic gel forming solution qd and acetazolamide 250 mg qid who are switched to 2.0% dorzolamide tid from acetazolamide compared to patients who remain on acetazolamide 250 mg qid. Secondary: In patients receiving 0.5% timolol maleate ophthalmic gel forming solution qd and acetazolamide 250 mg qid who are switched from acetazolamide to 2.0% dorzolamide tid compared to patients who remain on acetazolamide 250 mg qid: 1) To determine the incidence of systemic adverse experiences most commonly associated with oral CAI therapy (e.g. headache, dizziness, nausea, paresthesia, fatigue as well as malaise, eight loss, depression, anorexia and loss of libido. 2) To determine intraocular pressure.

Technical Approach: This is a parallel, randomized, double-masked, active-controlled study comparing the tolerability and efficacy of topical vs. oral carbonic anhydrase therapy added to 0.5% timolol maleate ophthalmic gel forming solution qd in patients with ocular hypertension or glaucoma. There is one open-label 3-week run-in period with Timoptic XE QD with acetazolamide 250 mg qid added on day -7. This is followed by a 12-week double-masked treatment period. The worse eye must be clinically suitable for additional IOP lowering on Day 1. Patients will be randomized at week 3 to one of 2 treatment groups. Intraocular pressure will be measured at 0900 (immediately pre-drop) and 1100 on Days 1, 15, 29, 57 and 85. Visual acuity, external ocular examination, slit lamp examination, funduscopic examination, visual field, and ocular symptoms will be evaluated on Days -21, -7, 1, 15, 29, 57 and 84. Safety laboratory tests will be done at baseline and on days 28 and 84.

Progress: This study was closed to patient accrual on 17 Mar 98 due to sufficient enrollments. Ten patients were consented at MAMC and three completed the study. Most of those who dropped out of the study did so due to inability to tolerate the study medication.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/086 **Status**: Ongoing

Title: A 6-Month, Randomized, Double-Masked Comparison of Fixed Combination of Latanoprost and Timolol with the Individual Components, Continuing into a 6-Month Open Label Safety Study of Fixed Combination in Patients with Glaucoma or Ocular Hypertension

Principal Investigator: COL Kevin J. Chismire, MC

Department: Surgery/Ophthalmology Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Roger K. George, MC; LTC Vernon C. Parmley, MC; LTC Rob A. Mazzoli, MC; LTC William R. Raymond IV, MC; MAJ Eugene F. May, MC; COL Anthony R. Truxal, MC; LTC Thaddeus J. Krolicki, MC; CPT Keith F. Dahlhauser, MC; COL Thomas H. Mader, MC; LTC Elizabeth A. Hansen, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/18/1997	Jun 98	04/17/1998

Study Objective: To demonstrate that the fixed combination has a better IOP-reducing effect than the individual monotherapies. The differences from baseline diurnal IOP reduction after six months of treatment will be tested between the fixed combination and the monotherapy groups.

Technical Approach: This is a six month, randomized, double-masked, multicenter study with three parallel groups, continuing into a six month open label study with one treatment group. After a run-in period of two to four weeks on timolol 0.5% twice daily, the patients will be randomized at baseline into one of three treatment groups:
Group I - fixed combination of latanoprost 0.005% and timolol 0.5% in the morning and placebo in the evening.
Group II - Timolol 0.5% in the morning and evening.
Group III - Placebo in the morning and latanoprost 0.005% in the evening.

After six months of masked treatment, the patients will continue into a six month open treatment period when fixed combination is given in the morning to all patients. The patients shall be checked for eligibility within four weeks prior to baseline. A medical and ocular history as well as concomitant medications will be asked for and gonioscopy, perimetry, ophthalmoscopy, visual acuity and refraction, lid and slit lamp examination and IOP measurements will be performed. The masked treatment period comprises four visits at which visual acuity will be checked, lid and slit lamp examination performed, IOP measured, adverse events asked for and other ocular findings, as well as any changes in concomitant medications, will be recorded. Furthermore, at baseline, Week 26 and 52 heart rate and blood pressure measurements will be performed and the iris photographed. In addition, at Week 26 and 52 perimetry, refraction and ophthalmoscopy will be performed. During the open treatment period, patients will be examined at three visits. In addition, a follow-up contact will be performed two to four weeks after end of treatment

Progress: Five patients have completed the initial study and have moved into the open label phase.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/060 **Status**: Ongoing

Title: Radial Keratotomy and Phototherapeutic Keratectomy: Comparison of Corneoscleral Integrity After Controlled Blunt Trauma to Post Mortem Eyes That Had Refractive Surgery

Principal Investigator: CPT Benjamin B. Chun, MC

Department: Surgery/Ophthalmology Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Mark L. Nelson, MC; COL Thomas H. Mader, MC; LTC Vernon C. Parmley, MC; Larry Rich, M.D.; MAJ Lawrence J. White, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/21/1997	Jun 97	03/20/1998

Study Objective: The goal of this study is to examine and compare corneoscleral integrity, by means of controlled blunt trauma to the corneas of cadaver eyes obtained from the Lion's Human Eye Bank. The effects of phototherapeutic keratectomy (PTK) and radial keratotomy (RK) on postmortem corneas will be compared to controls.

Technical Approach: Three groups of eyes will be compared, two in each group. One group will have RK, done by an established Cornea Specialist, and the second group will have PTK, also done by an established Cornea Specialist who also specializes in the area of PTK. The third group will serve as control and will not have surgery. The intraocular pressure of each eye will be measured by Tonopen®. Intraocular BSS will be injected with a 27g needle until the IOP is 18.0m Hg in each eye. Each eye will be placed in a container measuring 35mm X 45mm X 40mm, closely approximating the human orbit. 30 cc's of orbital volume not replaced by the eye will be filled with surgical lubricant and 4 X 4 gauze pads. The eye will be held in place by tight packing with gauze. The specimen will then be placed on the Instron where a blunt 1 cm diameter probe will descend toward the cornea at speed of 10cm/min. The computer will dynamically measure by way of graph, the breaking elongation, breaking load, yield point load, work of rupture and elastic stiffness of the globe. The data from all three groups will then be studied and compared. Total of 6 eyes will be utilized.

Progress: Fifteen eyes were studied in FY 98 for a total of 22 eyes studied. The Instron equipment was used to demonstrate the strength of the eye, comparing eyes that had RK or PTK and controls. Preliminary results indicate that less force is required to rupture eyes that had RK. There was no difference between PTK and control eyes.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/050 **Status**: Ongoing

Title: A Phase III Study of MDX-RA Compared with Placebo Administered in Patients Undergoing Phacoemulsification or Planned Extracapsular Extraction for Cataract

Principal Investigator: CPT Keith F. Dahlhauser, MC

Department: Surgery/Ophthalmology Surgery **Facility**: MAMC

Associate Investigator(s): LTC Vernon C. Parmley, MC; COL Thomas H. Mader, MC; MAJ Mark F. Torres, MC; CPT Benjamin B. Chun, MC; MAJ Mark L. Nelson, MC; CPT Keith J. Wroblewski, MC; MAJ Roger K. George, MC; COL Kevin J. Chismire, MC; LTC Dennis R. Beaudoin, MS

Start Date:	Est. Completion Date:	Periodic Review:
01/16/1998	Apr 99	N/A

Study Objective: To describe and compare the safety of a single dose of the murine immunotoxin MDX-RA to placebo over a six-month period post-randomization, and to test the efficacy of MDX-RA by comparing the proportion of patients in the treated group to the proportion of patients in the placebo group who have had a visual acuity explainable YAG laser capsulotomy by 24 months of follow-up.

Technical Approach: In Phase I, A Pre-operative screening evaluation period: Patients will be evaluated prior to eye surgery for inclusion into the study: within four weeks for ophthalmic evaluations and within 2 weeks for physical evaluation.

Phase II, Operative Procedure: subjects will undergo phacoemulsification or planned extracapsular cataract surgery and receive 100 units of MDX-RA or placebo.

Phase III, 24 Month Follow-up Period: ophthalmic examinations, concomitant medication use, and occurrence of adverse experiences will assess safety. Subjects will be monitored for the need of visual acuity explainable YAG laser capsulotomies as the primary efficacy variable.

Progress: Six patients have been studied without adverse effects.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/119 **Status**: Ongoing

Title: The Use of Photorefractive Keratectomy on Active Duty U.S. Army Personnel for the Correction of Myopia

Principal Investigator: COL Thomas H. Mader, MC

Department: Surgery/Ophthalmology Surgery **Facility**: MAMC

Associate Investigator(s): LTC Vernon C. Parmley, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
07/18/1997	Dec 99	07/17/1998

Study Objective: To determine if excimer laser photorefractive keratectomy (PRK) is a suitable procedure for use on active duty Army personnel for the correction of myopia.

Technical Approach: Refractive surgery of myopia with the excimer laser is of current command interest because of its potential to be performance enhancing in myopic active duty soldiers. Many active duty soldiers have an interest in this surgery and may elect to have it performed by civilian ophthalmologists at their own expense. There has been no prospective Army study to evaluate the effect of myopic excimer laser refractive surgery on active duty soldiers and how it affects the soldier's ability to perform his duties. This study proposes to 1) recruit a cohort of myopic active duty soldiers who voluntarily agree to participate, 2) prior to any treatment, evaluate their vision and its impact on certain basic military performance standards (such as qualifying with an M-16 rifle), 3) treat the myopia in both eyes by surface ablation of the cornea with an excimer laser, and finally 4) follow and re-evaluate vision and performance standards on these individuals for at least two years after treatment to examine the effect of the surgery on performance. One of the purposes of this study is to evaluate the potential of using this procedure to treat myopic soldiers thereby improving their ability to function in a combat environment and improve mission efficacy.

Progress: This study has not been implemented. The investigators are awaiting approval from the Command at Ft Lewis to use the soldiers, and the funding has not been received at this time.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/032 **Status**: Ongoing

Title: Study of Differential Swelling Using an ORB Scan (ORBTEK, Inc.) in Corneas Which Have Undergone Radial Keratotomy and are Exposed to Hypoxia with Resultant Corneal Edema

Principal Investigator: CPT Michael A. McMann

Department: Surgery/Ophthalmology Surgery **Facility**: MAMC

Associate Investigator(s): COL Thomas H. Mader, MC; MAJ Lawrence J. White, MC; LTC Vernon C. Parmley, MC; CPT Earle G. Sanford, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/18/1997	Feb 98	N/A

Study Objective: To determine the amount and pattern of differential swelling in edematous corneas that have undergone radial keratotomy using an Orb scan (ORBTEK, Inc) along with central and peripheral pachymetry values.

Technical Approach: Seven subjects (fourteen radial keratotomy eyes) and seven control subjects (fourteen eyes) will be recruited for the study. All subjects will be given a complete dilated ocular exam between the hours of 1300 and 1700 to establish initial baseline data. The afternoon time frame was chosen for consistency and to avoid any residual corneal edema from the prior nights sleep. Tests to be performed include: (1) Orb scan analysis, (2) measuring central and peripheral corneal pachymetry values, (3) perform computerized video keratography, and perform cycloplegic refraction. Immediately following baseline data collection, the subjects will be fitted with a swimming goggle apparatus which will bathe their corneas in a humidified nitrogen atmosphere (0% oxygen) for a period of two hours. Subjects will be instructed not to fall asleep or close their eyes except for physiologic blinking. After two hours, the apparatus will be removed and all of the initial baseline data measurements and analysis will be repeated as described above.

Repeated measures ANOVA will be used to evaluate the differences in corneal thickness (microns) from peripheral to central, computerized video keratography (diopters), and cycloplegic refraction (diopters of spherical equivalent) between baseline measurements and those obtained following exposure to the humidified nitrogen in radial keratotomy subjects and normal non radial keratotomy controls. This analysis will be used in an effort to detect a 20 micron difference between central and peripheral pachymetry values to the 0.05 level.

Progress: No patients have been entered in this study because the investigators have been awaiting the delivery of the Orb Scan. It is due to be delivered in Nov 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/121 **Status**: Ongoing

Title: Refractive Changes During Exposure to the Hyperbaric Environment Following Radial Keratotomy Surgery

Principal Investigator: MAJ Mark L. Nelson, MC

Department: Surgery/Ophthalmology Surgery **Facility**: MAMC

Associate Investigator(s): Ted Edson, M.D.; CPT Benjamin B. Chun, MC; COL Thomas H. Mader, MC; LTC Vernon C. Parmley, MC

Start Date:	Est. Completion Date:	Periodic Review:
07/18/1997	Nov 97	07/17/1998

Study Objective: Our objective is to verify significant changes in corneal shape, visual acuity, refraction and intraocular pressure that may take place in subjects within two years following radial keratotomy when these individuals are exposed to the hyperbaric environment.

Technical Approach: We will select three groups for our experiment. The first study group will consist of 13 U.S. Navy volunteers who have had bilateral radial keratotomies within two years prior to this study. (Currently RK's are disqualifying for flight status and entry into the military, but not disqualifying for retention in the military.) We will record and examine several ocular parameters, at sea level and immediately after exposure to depth equivalent to 50 feet of sea water: 1) cycloplegic refraction, 2) intraocular pressure, 3) corneal keratometry, and 4) central corneal thickness. Barometric pressure will also be recorded. Duration will be the maximum allowed at that depth for a no decompression dive (100 minutes). This depth was chosen because military divers carry out most of their missions at or above this depth, and this is an average depth for recreational diving. The second study group will also consist of 13 U.S. Navy volunteers who have had bilateral radial keratotomies within 2 years prior to the study. This group will be treated exactly the same as the first group except they will wear goggles with 100% oxygen infused into them at depth. The third study group will consist of 13 active duty volunteers with no previous ocular surgery. In these individuals, we will measure the above listed parameters at sea level and immediately after hyperbarics at 50 fsw. We will then compare data to see if a significant difference exists between the three groups. A power analysis was performed, assuming a 0.25 diopter intraobserver variability and a significant myopic shift of 0.50 diopters. The required sample size computed was 25 eyes. We will have 26 eyes in each study group.

Progress: No patients have been entered. The MAMC investigators are awaiting approval from the Navy BUMED before the study can be started.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/101	**Status**: Ongoing

Title: Refractive Changes Due to Hypoxia Following LASIK Corneal Surgery

Principal Investigator: MAJ Mark L. Nelson, MC

Department: Surgery/Ophthalmology Surgery	**Facility**: MAMC

Associate Investigator(s): COL Thomas H. Mader, MC; MAJ Lawrence J. White, MC; CPT Steven M. Brady, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
08/20/1998	Jun 99	N/A

Study Objective: To observe changes in corneal shape and visual acuity that may take place in subjects more than 1 month following LASIK when their corneas are exposed to a low oxygen tension environment.

Technical Approach: Ten subjects who have undergone LASIK in both eyes and ten myopic controls will be used for this study. Following baseline measurements, the subjects will be fitted with a pair of airtight goggles. Room air will be released into one side of the goggles and 100% nitrogen will be released into the other after being bubbled through sterile water for humidification. Following two hours of exposure to these environments, the goggles will be removed and repeat measurements will be obtained immediately and again two hours post exposure. The examiner will be blinded to the type of gas to which each eye has been exposed.

Progress: Twenty-five control patients and four LASIK patients have completed the study.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/056 **Status**: Ongoing

Title: Congenital Esotropia Observational Study (CEOS)

Principal Investigator: LTC William R. Raymond IV, MC

Department: Surgery/Ophthalmology Surgery **Facility**: MAMC

Associate Investigator(s): Avery Weiss, M.D.; CPT Benjamin B. Chun, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/20/1998	Feb 99	N/A

Study Objective: To observe the early course of congenital esotropia in order to determine the probability of spontaneous resolution and to correlate this finding with various aspects of the esotropia such as the size of the esotropia, variability, and presence of hyperopia.

Technical Approach: Medical records of children identified as being early course congenital esotropia which meet eligibility criteria will be reviewed. Data will be collected from charts on their initial exam, 2 to 4 weeks (14-28 days) after the initial examination but no later than 19 weeks (133 days) of age, and between 28 and 32 weeks (196-224 days) of age.

Progress: Records from one patient at MAMC have been studied. Thirty-three patients have been entered nationwide.

Detail Summary Sheets

Orthopedics Service
Department of Surgery

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/107 **Status**: Terminated

Title: Evaluation of Lateral Ankle Stress Testing With and Without Anesthesia

Principal Investigator: CPT George K. Bal, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Kirk Willard, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/17/1996	Jan 98	06/19/1998

Study Objective: To determine the significance of pain response/inhibition that occurs during lateral ankle stress testing.

Technical Approach: We will evaluate ankle stress radiographs (using the TELOS Device) without anesthesia, with local anesthetic, and finally with regional/general anesthesia. The sample population will be patients with chronic ankle pain and/or instability seen at Madigan Orthopedic/Podiatry Clinic. Between 50-100 subjects will be studied. The subject will have ankle stress radiographs performed, then repeated with a local anesthetic (intra-articular vs peroneal nerve block). If determined that the patient requires surgery, intra-operative stress radiographs will be performed after induction of regional/general anesthesia. Approximately 20 control subjects will be selected from orthopedic patients requiring surgery. They will have preoperative ankle stress radiographs done, and again after induction of anesthesia for their scheduled surgery. No local anesthetic injections will be used for control subjects. The data collected will be measurements of tibio-talar angle and anterior subluxation from the stress radiographs. These will be evaluated using an independent t-test, and repeated measures analysis.

Progress: No patients were entered in this study due to insufficient patients willing to participate.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 96/108	**Status**: Completed
Title: Subtalar Joint Stress Radiography		
Principal Investigator: CPT George K. Bal, MC		
Department: Surgery/Orthopedic Surgery		**Facility**: MAMC
Associate Investigator(s): MAJ Kirk Willard, MC		
Start Date: 05/17/1996	**Est. Completion Date**: Jun 97	**Periodic Review**: 07/17/1998

Study Objective: To establish the normal variation of the subtalar joint stress angle. We will also attempt to standardize the method of measurement.

Technical Approach: The normal values of talo-calcaneal angle will be looked at using the TELOS Device and stress radiographs. The sample population will come from patients seen at the Madigan Orthopedic/Podiatry Clinic. We will utilize up to 200 normal subjects with no prior history of ankle injuries. The subjects will have an ankle stress radiograph performed using the TELOS device. After the radiograph is complete, no further participation in the study will be needed. The talo-calcaneal angle will be measured off of the stress radiograph. This data will be evaluated for potential co-variants, and a normal range will be determined with confidence intervals.

Progress: This study has been completed and a paper has been presented.

Forty-two ankles were studied in 25 patients. Seventeen patients had stress views of both subtalar joints and 8 patients had only one normal ankle, so only one side had stress x-rays performed. There were 20 males (34 ankles) and 5 females (8 ankles) with an average age of 27 years with an age range of 18-45 years. With the available number of subjects there was no significant correlation with age or sex. The TELOS stress device provides a standardized, reproducible way of measuring the subtalar stress angle. The average, normal, subtalar stress angle is 8 degrees with a 95% confidence interval of 1 degree.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/094 **Status**: Terminated

Title: Autologous Cartilage Grafting for Talar Dome OCT Lesions

Principal Investigator: CPT George K. Bal, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): LTC Patrick St Pierre, MC; CPT Robert V. Williamson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/16/1997	Jun 01	06/19/1998

Study Objective: To evaluate the functional outcomes of the treatment of talar OCD lesions in a randomized, prospective trial.

Technical Approach: Will prospectively evaluate two methods of treating talar OCD lesions. Subjects will be randomized to two Groups; arthroscopic debridement and drilling of the OCD lesion, or open debridement with cartilage grafting. We will use arthroscopic harvesting techniques from the ipsilateral knee- as is currently used for OCD lesions of the knee. The post-operative rehabilitation protocols will be the same for both Groups. Subjects will have scheduled follow-up at 2 weeks, 6 weeks, 3 months, 6 months, 1 year, and 2 years. A standard outcome analysis questionnaire will be used at the 6 month, 1 year, and 2 year follow-ups.

Progress: This protocol was terminated due to the departure of the PI. No patients were entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/042	**Status**: Completed

Title: The Anterior T-Frame External Fixator: A Treatment Option for High Energy Tibia Fractures

Principal Investigator: CPT George K. Bal, MC

Department: Surgery/Orthopedic Surgery	**Facility**: MAMC

Associate Investigator(s): Jens R. Chapman, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/16/1998	Jan 97	N/A

Study Objective: To review the functional outcomes of the anterior T-frame external fixator in treating proximal tibia fractures.

Technical Approach: This is a retrospective study of all patients treated at Harborview Medical Center from July 1992 through January 1996 with the anterior T-frame external fixator. The study will review injury types, length of treatment, complications, and functional outcomes.

Progress: This protocol has been completed and a paper has been written. Records were reviewed from Jul 92 through Jan 96 and 38 fractures in 36 patients were treated with limited internal fixation and an anterior T-frame eternal fixator. Three patients died during the initial hospitalization from associated injuries and one patient required an amputation, leaving 32 patients with 34 fractures for which an anterior T-frame external fixator was the method of treatment. All 34 fractures eventually healed. The average follow-up was 26 months and average time to healing was 5 months. Time to healing was evaluated both clinically and radiographically. All patients who were working prior to injury had returned to work at latest follow-up. The most common complaint was a deep aching pain located in the proximal tibia that was intermittent and seemed unrelated to activity. Conclusion: the anterior T-frame external fixator, with percutaneous internal fixation, is a versatile, effective method for initial stabilization of high energy proximal tibia fractures. The frame is simple and inexpensive, and can be used for definitive treatment, thus avoiding some of the possible complications associated with hybrid or medial frame constructs.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/098 **Status**: Ongoing

Title: Fixation of Salter Osteotomies with Bioabsorbable Pins

Principal Investigator: CPT Christopher P. Cannon, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): Kit M. Song, M.D.; MAJ Ronald E. Nielsen, VC; Alan F. Tencer, Ph.D.; Robert Welch, D.V.M., Ph.D.; MAJ Clyde T. Carpenter, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/25/1997	Apr 00	07/17/1998

Study Objective: To review the feasibility of using bioabsorbable pins when doing pelvic osteotomies in children. We will do osteotomies on the pelvis of goats which are similar in size to a toddler.

Technical Approach: The first phase will involve an animal study. We have determined that the pelvis of a goat is near the size and orientation of a child's pelvis who might undergo a Salter pelvic osteotomy. We will perform a unilateral pelvic osteotomy, place bone graft, and insert pins to hold the pelvic osteotomy. The bone graft will be harvested from the ipsilateral iliac crest. The goat will be given antibiotics perioperatively. The second phase (which will involve another protocol and will be based on the goat studies) will be a multicenter prospective clinical trial of children undergoing Salter osteotomies for hip dysplasia. We will randomize the children on the basis of their institution so that all children treated at a given institution would be treated in a similar manner. Selection criteria would be children less than 3 years of age, neurologically and mentally normal, and requiring a Salter osteotomy for the treatment of congenital dislocation of the hip. We will seek to enroll 50 children (25 treated with Steinman pins and 25 children treated with bioabsorbable pins) in each group. We would endeavor to enroll 3 centers for each group for a total of 6 centers involved with each center treating approximately 8 children. We would use a fairly large human study because of the need for large enough numbers to address statistically the outcome.

Progress: Surgeries to harvest the pelves from six goats have been completed. The investigators are in the process of sectioning and examining the specimens. Passing the Steinman pin proved initially to be quite difficult due to the extremely long, narrow pelvis of the goat. This was a known complication at the time of surgery. On the first surgery, one of the pins penetrated the medial wall of the pelvis resulting in death. Following this complication, the operative technique was modified and no further difficulties were experienced.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/085	**Status**: Ongoing
Title: Healing of Tibial Stress Fractures Using Pulsed Electromagnetic Fields (PEMF)		
Principal Investigator: CPT Christopher P. Cannon, MC		
Department: Surgery/Orthopedic Surgery		**Facility**: MAMC
Associate Investigator(s): LTC Richard A. Sherman, MS		
Start Date: 06/19/1998	**Est. Completion Date**: Dec 99	**Periodic Review**: N/A

Study Objective: To determine whether application of non-thermal, pulsed high peak power, high frequency, electromagnetic energy (PEMF) over a tibial stress fracture, used in conjunction with standard therapeutic approaches, reduces the amount of shin pain and increases endurance on the treadmill in relation to those receiving standard treatments with placebo PEMF.

Technical Approach: Subjects who are diagnosed by bone scan as having a stress fracture and experience pain during a treadmill test will be enrolled into this study. The first treadmill test will be done prior to initiation of PEMF. The subjects will grade their pain using the visual analog scale every 2 minutes to a max of 15 minutes. Subjects will then be randomized to either machine "a" or "b" by a computer generated sequence. They will then be exposed to PEMF on the involved lower extremity for one hour per day, five days per week for four weeks. The treadmill test will be repeated at the end of the four weeks of treatment and then followed clinically for 6 months to determine if and when they return to full duty and whether the problem returns.

Progress: This study has not been implemented at MAMC. Presentation of the project to the IRB resulted in the requirement for several modifications and additions. These modifications have not been made due to a four month rotation of the PI at the University of Washington.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/081 **Status**: Ongoing

Title: A Prospective Randomized, Blinded Study, Comparing Treatment of Fifth Metacarpal Neck Fractures

Principal Investigator: CPT Tad L. Gerlinger, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): LTC Frederic L. Johnstone, MC; Mary Miklos-Essenberg

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/22/1998	Jun 00	N/A

Study Objective: To determine the effectiveness of treating fifth metacarpal neck fractures with closed reduction and casting with the metacarpal phalangeal joint in neutral and utilizing a three point mold.

Technical Approach: Patients with fifth metacarpal neck fractures will be randomized to undergo non-operative treatment, comparing closed reduction and casting with the metacarpal phalangeal joint in neutral and utilizing a three point mold, to closed reduction and casting with the metacarpal phalangeal joint approximating 90 degrees (the current standard technique). Outcome will be measured by the amount of residual angulation, grip strength compared to the contralateral hand, rotatory malalignment and range of motion at three weeks and again at three months after the injury.

Progress: No patients have been enrolled in this study due to temporary training of the investigators at other institutions.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/082 **Status**: Terminated

Title: Comparison of Sterile Isotonic Saline, Purified Water, and Dilute Hypochlorite Solution on the Rates of Infection and Tissue Response in Open Fractures of a Syrian Hamster Model

Principal Investigator: CPT Randall K. Hildebrand, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): LTC Frederic L. Johnstone, MC; MAJ Mark D. Brissette, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/24/1995	Oct 96	04/17/1998

Study Objective: 1) To compare different irrigating solutions and rates of infection in an open fracture model. 2) To compare the gross and histologic effects in wound healing of an open fracture model after different irrigation solutions.

Technical Approach: A total of 48 Syrian hamsters will be used in a 4 groups of 12. There will be 3 treatment groups and one control group. After adequate anesthesia, an incision on a hamster's leg will be made and the thighbone will be broken with a small power saw. The animals will be deliberately infected, and the treatment group animals will have the wound washed out with one of several kinds of irrigating fluids (sterile isotonic saline, purified water, or dilute hypocholrite solution). The animal will be awaked from anesthesia and returned to a recovery cage to be monitored for pain or infection. Two weeks later it will be euthanized. The rates of infection will be compared and the tissue around the wound will be examined under a microscope to determine any potential harmful effects of the infection or irrigation fluid.

Progress: This protocol was terminated in March 1998 due to the expiration of the three- year approval. The protocol had been suspended for approximately 18 months prior to that due to the loss of the PI. The protocol was never implemented.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/102 **Status**: Terminated

Title: Teaching Program for Practical Microsurgery Using A Rat (Rattus norvegicus, strain HSD) As a Teaching Model

Principal Investigator: LTC Frederic L. Johnstone, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): CPT Vermon S. Esplin, MC; COL D. E. Casey Jones, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/24/1995	Mar 98	04/17/1998

Study Objective: This teaching protocol will establish a formal training program in clinical microsurgery for orthopedic residents at MAMC. It will provide microsurgery practice in the repair of small vessels, nerves and tendons of the rat which model those of the hands, face and other body parts of humans.

Technical Approach: One rat will be used per week for 52 weeks for continuous microsurgery training for orthopedic residents. The rats will be placed under general anesthesia, used for numerous practice repairs and then humanely euthanitized at the conclusion of the surgical procedures. Specifically, the femoral artery of the rat serves as an excellent model of small human vessels and will be repeatedly cut and repaired. Residents will be tested after six weeks by oral examination and should be capable of performing extremity revascularizations.

Progress: Two training sessions were held in FY 98 in which four personnel were trained.

The protocol was terminated in March 1998 due to the expiration of the three-year approval limit.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 95/155	**Status**: Completed

Title: Establishment of the Natural History/Progression of Pediatric Fingernail Injury Outcomes

Principal Investigator: COL D. E. Casey Jones, MC

Department: Surgery/Orthopedic Surgery	**Facility**: MAMC

Associate Investigator(s): MAJ James T. Vandenberg, MC; CPT George K. Bal, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
07/21/1995	May 97	09/30/1998

Study Objective: To establish the natural history of fingernail injury outcomes in children (1-8 years of age) with and without any distal phalanx fractures treated in the MAMC Emergency Department. To determine whether there is a need for follow-up studies on treatment procedures designed to reduce permanent abnormalities in the nails.

Technical Approach: Trauma is a major cause of pediatric fingernail injuries. In children, trauma may result in hematoma formation or nail avulsion. When the nail matrix and bed are unaffected, the effects are temporary. If the matrix or nail bed is injured, permanent scarring of the nail may result. Among adults, long term effects of trauma may include scaring and dystrophy of the nail if early treatment is not initiated.

Fifty children with fingernail injuries will be studied. Parents of the children meeting the entry criteria will be asked to participate. The child's injury will be assessed and photographed at the time of injury, and at follow-up visits at six week intervals for six months. A rate of abnormal healing will be determines and associated with cause and severity of the initial injury.

Progress: Approximately 40 patients were entered in this study, which has been completed. As many children of those initially entered in the study as could be contacted by telephone were reviewed up to two years out from the injury. Those still within in the region were asked to come in for a direct examination. Of those not within the region or unwilling to come for direct examination, the parents were questioned regarding the outcomes of the initial injury and these outcomes were related to treatment. Treatment in the vast majority of cases was no treatment, and this was the group in which the investigators were most interested. Since appearance of the fingernail following injury and any functional problems associated with a persistent nail defect were the predominant outcomes, parental report seems a reasonable proxy for direct examination. The final data show that pediatric fingernail injuries have a different natural course history than adult fingernail injuries and that a pediatric fingernail injury has a benign outcome quite in contradiction of the literature for adult fingernail injures. The results of the study were presented to the North Pacific Orthopaedic Society in Sep 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/051 **Status**: Ongoing

Title: Comparison of Small Bone Cannulated Screw Systems

Principal Investigator: COL D. E. Casey Jones, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): CPT George K. Bal, MC

Start Date:	Est. Completion Date:	Periodic Review:
02/21/1997	Apr 97	09/30/1998

Study Objective: To compare compression and pull-out strengths of three different small bone cannulated screw systems - the Accumed 'Accutrak' screw, the Herbert-Whipple screw, and the Synthes 3.0mm cannulated screw.

Technical Approach: We will evaluate four different cannulated screws: an ASIF 3.5mm cannulated screw, Synthes 3.0mm cannulated screw/washer, Accumed's Accutrak screw, and Zimmer's Herbert-Whipple screw. The screws will be divided into three study groups designed to measure compression, pull-out strength, and compression holding. There will be ten screw of each type in each study group. We will use a synthetic cancellous bone material of uniform density, and a washer shaped strain gauge for collecting data. A servohydraulic testing machine will be used for measuring pull-out strength. The data will be evaluated by random-effects analysis of variance.

Progress: Implementation of this protocol has been delayed pending the acquisition of appropriate materials and electronic pressure sensors to conduct the experiments.

The original principal investigator, CPT Kelly Bal, graduated from his residency program in June 1998 and the protocol was transferred to COL Casey Jones.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/176 **Status**: Completed

Title: Computer Assisted Measurement of Scoliosis from Digitized Radiographs versus Traditional Cobb Angle Measurement

Principal Investigator: CPT Michael E. Kirk, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): LTC Richard W. Kruse, MC; MAJ Donald V. Smith, MC; MAJ John W. Dietz, MC; MAJ Clyde T. Carpenter, MC

Start Date:	Est. Completion Date:	Periodic Review:
12/17/1993	Sep 93	09/30/1998

Study Objective: The purpose of this study is to determine the interobserver and intraobserver error and accuracy of measurement in determining Cobb angle measurements of scoliosis and kyphosis using the digitized radiographs and measuring techniques available in the Medical Diagnostic Imaging System (MDIS).

Technical Approach: In the first phase fifty anterior-posterior or posterior-anterior spine radiographs will be collected in the Orthopaedic Clinic by two of the Investigators. These radiographs must demonstrate coronal plane deformity of 10 degrees or more. During this the radiographs will be modified to obscure the patients' names and copy the radiographs into the MDIS system. Each radiograph MDIS image will be assigned a random number. The MDIS image and its corresponding radiograph will have different numbers and a log will be created showing which random numbers have been assigned to corresponding images. The examiners will be blinded to this information.

The images will be measured in random order. All measurements will be made using the Cobb method. A line will be drawn along the superior end plate of the upper vertebra to the inferior end plate of the lower vertebra. Some radiographs will have 2 measurable curves. Only one curve from the thoracic and one from the lumbar area will be measured. Measurements on radiographs will be done with pencil and protractors usually employed in the Orthopaedic Clinic. Measurements on MDIS images will be done by choosing lines along end plates with the mouse and indicator. Actual measurements will be made by each of four observers. Measurements will be recorded on a data sheet.

Progress: Four observers (surgeons) examined the radiographs of 46 scoliosis patients. Each observer measured the scoliosis curves three times using the Cobb method and determined a Risser score when possible. Comments were also collected with regards to subjective quality of the images. the 95% confidence interval for intraobserver reliability ranged from 2.24 to 2.49 degrees. The 95% confidence interval for interobserver reliability was 2.28 degrees. Risser scores, when they could be determined, showed an average correlation of 0.86. The computer-assisted measurement of Cobb angles in scoliosis using the Medical Diagnostic Imaging System compares favorably in reliability to the manual measurements reported in the literature. The automatic measuring feature is simple and reproducible with excellent reliability.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/001 **Status**: Completed

Title: Duplex Sonographic Analysis of the Common Femoral Vein in Lower Extremity Casting: A Pilot Study

Principal Investigator: CPT Kurtis L. Kowalski, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): LTC John D. Pitcher Jr., MC; COL David F. J. Tollefson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
10/17/1997	Oct 97	N/A

Study Objective: To perform a pilot study with sufficient subjects to define the variables and number of subjects for a full study intended to characterize venous dimensions and flow during a variety of lower extremity cast applications, body positions, and ambulatory activities

Technical Approach: 5 study subjects will be selected of similar size and weight and same sex. Baseline supine, erect, ambulatory full weightbearing, and non-weightbearing B mode Duplex ultrasound measurements will be performed of the common femoral vein at the junction of the greater saphenous vein. A treadmill set at 2 miles/hour will be used for ambulatory readings. The two dimensions of the common femoral vein will be measured in cross section. A Doppler measurement of the venous flow will also be performed. The frequency of pumping as well as the smallest and largest cross sectional dimensions will be noted. Next, a standard below the knee lower extremity cast will be applied to the subject's right leg. The aforementioned measurements shall be performed in the following positions: supine, erect, full weightbearing, partial weightbearing, and non-weightbearing with crutches. Finally, an above the knee cast will be placed on the right leg and the measurements will be repeated in the same sequence. All measurements will be duplicated in all positions on the non-casted leg as well. Five trials will be performed for each measurement in each ambulatory status.

Progress: This study has been completed. Five patients were studied. The investigators found that the femoral vein size increased with the standing position and it increased further with non-weight bearing. When casts were put on the leg any increase was wholly dependent on whether weight bearing was allowed or not. A paper was presented to the Annual Meeting of the Hawaii Orthopaedic Association and a manuscript has been submitted for publication.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/087 **Status**: Ongoing

Title: Duplex Sonographic Analysis of the Common Femoral Vein in Non-Weight Bearing: Age Difference in Men

Principal Investigator: CPT Bryant G. Marchant, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): LTC John D. Pitcher Jr., MC; COL David F. J. Tollefson, MC; CPT Kurtis L. Kowalski, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
07/17/1998	Jun 98	N/A

Study Objective: To define venous dimensions during a variety of lower extremity cast applications, body positions, and ambulatory activities in various age groups of men.

Technical Approach: 15 subjects will be enrolled in this study; 5 patients 18-20 years of age; 5 subjects 45-50 years of age and 5 subjects 65-75 years of age, all of similar size and weight and of the same sex. Baseline measurements of the common femoral vein will be made with the subject supine, erect, ambulatory full weightbearing, ambulatory partial weightbearing, and non-weight bearing with B mode Duplex ultrasound. A treadmill will be used for the ambulatory readings. The two dimensions of the common femoral vein will be measured in cross section. The frequency of pumping as well as the smallest and largest cross sectional dimensions will be noted. Next, an ace wrap, a knee brace, Ted Hose and a standard below the knee lower extremity cast will be applied to the subject's right leg in sequence. The order of device application will be randomized. The measurements will be repeated with each device. Finally, an above the knee cast will be placed on the right leg and the measurements will be repeated in the same sequence. All measurements will be duplicated in all position on the noncasted leg as well.

Progress: This study has not been implemented. The investigators are awaiting approval of a CRDA.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/088 **Status**: Ongoing

Title: Blood Flow in the Common Femoral Vein in the Erect Patient with the Application of Compressive Devices

Principal Investigator: CPT Bryant G. Marchant, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): LTC John D. Pitcher Jr., MC; COL David F. J. Tollefson, MC; CPT Kurtis L. Kowalski, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
07/17/1998	Jun 98	N/A

Study Objective: To study the changes in blood flow velocity in the erect patient with the use of compression devices.

Technical Approach: 10 subjects will be enrolled. Using a Doppler ultrasound, the blood velocity of the common femoral vein will be measured 1 cm proximal to the entry of the greater saphenous vein. The measurement will be made 5 times in the standing position during the expiration phase of the respiration cycle for each subject. A calf pneumatic intermittent compression device (PICD), a thigh high PICD, and a foot PICD will be placed on the patient and the velocity again measured during inflation and deflation of each SCD. Each measurement will be taken five times.
The order in which the devices are placed on the leg will be randomized.

Progress: This study has not been implemented. The investigators are awaiting approval of a CRDA.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/013	**Status**: Completed

Title: Comparison of Four "Universal Kit" External Fixators for Use in the Military Battlefield

Principal Investigator: CPT Marc J. Michaud, MC

Department: Surgery/Orthopedic Surgery	**Facility**: MAMC

Associate Investigator(s): LTC Frederic L. Johnstone, MC; CPT Brendon Connolly, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/21/1997	Dec 97	N/A

Study Objective: To compare the biomechanical properties, as well as the ease of application and adjustment of four external fixation frames available in single use sterile packages. This study will determine the best device available to American military surgeons for the treatment of high-energy open fractures in battlefield situations.

Technical Approach: Junior residents unfamiliar with any of the external fixation systems will be given a tutorial session on external fixation application. They will then be asked to apply each of the fixators to plastic bone models called "saw bones". Each saw bone will be cut with an identical unstable fracture pattern. Residents will be asked to numerically evaluate the ease of application and to subjectively rate the devices for stability and user-friendliness. The reductions will then be numerically evaluated for alignment, stability, and the ability to easily adjust poor reductions by the senior investigators. In particular, the ability to adjust reductions in rotational and sagittal planes after the initial application will be evaluated.

The Instron Testing Machine will be used to test five of each of the units for stiffness in axial, lateral and anterior-posterior loads and in torsion. An unstable fracture pattern will be simulated in a mechanical test model. Identical aluminum cylinders will be used to standardize the pin/bone interface as well as cortical diameter and thickness.

Progress: Seven residents applied each brand of fixator to synthetic osteotomized human tibia and then subjectively evaluated the ease of application. The Synthes Trauma Fix and the Richards fixators performed adequately in all facets of biomechanical testing. The Synthes device required predrilling, the handle/wrench provided was difficult to use, and it is unable to make multi-planar adjustments, yet it is slightly stronger, lighter, and least expensive. The Richards device was easier to apply and allowed for multi-planar realignment, even though it is more expensive. The Howmedica Hoffman II is the best design for ease of application; however, the unique clamp design which makes this possible leaves the device weak in certain planes of force, notably torsion. The Biomet product was not competitive. Currently, no fixator meets all of the prerequisites for the Armed Forces, however, the Synthes Trauma-Fix and the Richards Universal-in-a-Box fixators are the best choices currently available.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/125 **Status**: Ongoing

Title: External Fixation of Displaced Clavicle Fractures

Principal Investigator: CPT Greer E. Noonburg, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): LTCR Clayton E. Turner, MC; LTC Patrick St Pierre, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
07/18/1997	Aug 99	09/15/1998

Study Objective: Determine the efficacy of external fixation in the treatment of clavicle fractures with greater than 100% displacement.

Technical Approach: Patients will be drawn from males and nonpregnant females over age 18, with acute traumatic clavicle fractures having greater than 100% displacement on radiographs. The study population will range from 10 to 20 subjects. After inclusion in the study, and a pre-operative examination, the subjects will be taken to the operating room for placement of threaded pins through four 1-cm incision sites over the clavicle. An Orthofix Pennig II External Fixator will be attached to the pins and the fracture reduced to as close as possible to anatomic alignment. After surgery, the patient will be given pain medications, instructed in pin site care, and sent home. The patient will be evaluated weekly by an orthopaedic surgeon (4-8 weeks) and usually will receive clavicle x-rays with each appointment. The external fixator will be removed in the clinic in four to eight weeks, depending upon healing of the fracture as evident on x-ray. Subsequent post-operative exams at 3, 6, and 12 months will be conducted. Outcome variables will be evaluated for functional outcomes (motor strength, range of motion, tenderness at the fracture site, residual displacement/deformity, time of healing, ability to perform occupation and activities of daily living).

Progress: Ten subjects were entered in the study in FY 98 for a total of 12 subjects entered. The consent form was modified in order to make it more easily understood. There were no adverse results or complications.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/141 **Status**: Terminated

Title: Development of a Pig Model to Produce a Growing Fused Limb by Transferring Half of the Open Growth Plate From the Lower End of the Femur to the Upper End of the Tibia When the Tibia's Growth Plate Is Removed for Cancer

Principal Investigator: LTC John D. Pitcher Jr., MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): CPT Richard C. Rooney, MC; LCDR Dave Sitler, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/26/1995	Jun 96	06/19/1998

Study Objective: Our primary objective is to determine the feasibility of maintaining open physeal plates in an autogenous, vascularized bone graft that has been traumatized by operative relocation. We will use a pig as our model for the human system in this pilot study.

Technical Approach: Research has indicated that it is possible to split the lower end of the adult femur (thigh bone), leave its vascular (blood) supply intact, and flip it upside down in order to use it as a replacement for the upper end of the tibia. We intend to develop a similar procedure in skeletally immature pigs to permit the limb to continue its normal growth while in a fused position. The technique is illustrated in the protocol. The total amount to limb growth should be normal because the growth plate is still functional at both ends of the femur. Before the procedure, the pigs will be weighed, have arteriograms and X-rays of limbs taken for status and measurement, establishing a baseline limb length. The some procedures will be performed at one, six and eleven months to assess bone growth. The animal will then be euthanitized and histologically examined. Radiographs, arteriograms, an limb length measurements will be evaluated by standard clinical means. Lengths of limbs will be measured and contralateral joints will be examined and compared to the surgical plates. The operative and non-operative limbs will be compared for parallel slopes.

Progress: This protocol was terminated in May 98 due to the expiration of the 3-year approval. It was not implemented at MAMC due to the reassignment of the original PI and the failure to find a resident of staff member who had the time and expertise to perform this study.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/082 **Status**: Ongoing

Title: A Dose-Ranging, Multicenter, Randomized, Subcutaneous, Low-Dose, Heparin-Controlled, Double-Blind Clinical Trial to Assess the Safety and Efficacy of Orally Administered Heparin With A Novel Carrier System (SNAC) in the Prevention of Major Venous Thromboembolic Events Following Elective Total Hip Arthroplasty

Principal Investigator: LTC John D. Pitcher Jr., MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): CPT John T. Steedman, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/22/1998	Jun 99	N/A

Study Objective: To assess and compare the safety and efficacy of postoperative 12 dose regimens of two different doses of oral SNAC/heparin combinations in preventing venous thromboembolism in patients who have undergone total hip arthroplasty, compared to low-dose heparin administered subcutaneously for 12 doses.

Technical Approach: Patients scheduled for total hip arthroplasty who sign informed consent will be randomized into one of three different treatment groups. Group A will take syrup with 1.5 gram SNAC and 60,000 units heparin, and an injection of saline; Group B will take syrup with 2.25 grams SNAC and 90,000 units heparin, and an injection of saline; and Group 3 will take SNAC syrup with no heparin, and an injection of saline. Treatment begins 10 hours after surgery, patients will receive a dose every 8 hours for a total of 12 doses. Examinations during the study period include blood and urine tests, echocardiogram, physical examinations and a bilateral venous ultrasonography of the legs to detect any blood clots that may be forming.

Progress: Two patients have been entered in this study, with no adverse reactions reported.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/086 **Status**: Ongoing

Title: A Prospectively Randomized Trial of Rotator Cuff Repair to Cortical Bone versus A Cancellous Trough

Principal Investigator: LTC Patrick St Pierre, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): Hollis Potter, M.D.; CPT Roger W. Dougherty, SP

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/15/1996	Apr 99	04/17/1998

Study Objective: To determine if tendon repair to a cancellous trough is necessary for rotator cuff repair in humans.

Technical Approach: Forty patients with proven rotator cuff tears will be randomized to two surgical groups. Group A will have their rotator cuff tendon repaired to the greater tuberosity after a trough is made in the greater tuberosity of the humerus. Group B will have their rotator cuff repaired to the cortical bone of the greater tuberosity of the humerus without the creation of a trough. A thorough debridement of soft tissue to include bursa and scar will be performed in both groups. Postoperative treatment will be the same for each group. Clinical evaluations and physical exams to include range-of-motion, shoulder impingement signs and tenderness will be performed at one, six, twelve and twenty-four month follow-ups by the physical therapist department. The modified Hospital for Special Surgery (HSS) Score as well as an analog pain, function, and satisfaction score will be used for clinical evaluation. A significant difference in the assessment of strength scores would indicate superiority of one method over the other. MRI evaluations will be performed at six, twelve and twenty-four months. The MRI will be evaluated by an MRI radiologist at the HSS in New York City, New York, who will be blinded to the method of treatment for each patient. Criteria for success by MRI has been established by a recent study performed at the HSS by the radiologist and the principle investigator.

Progress: One subject has been entered in FY 98 for a total of eight subjects enrolled. All patients have had satisfactory or better repair of rotator cuff.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/092 **Status**: Ongoing

Title: A Prospectively Randomized Study on the Effectiveness of Post-Operative Knee Bracing for Anterior Cruciate Ligament Reconstruction

Principal Investigator: LTC Patrick St Pierre, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): CPT Michael E. Kirk, MC

Start Date:	Est. Completion Date:	Periodic Review:
04/19/1996	May 99	06/19/1998

Study Objective: The objective of this study is to compare the effect of different post-operative brace patterns on the final outcome of an anterior cruciate ligament reconstruction. This bill be performed by prospectively randomizing patients into two different bracing groups and comparing them with subjective and objective testing during their rehabilitation period.

Technical Approach: In summary, the present knowledge on post-operative bracing for ACL reconstruction is limited. This study is designed to determine if post-operative bracing has an effect on the outcome of an ACL reconstructed patient. A total of 80 patients will participate in the study. After arthroscopically assisted ACL reconstruction patients will be randomized to two study groups. Group A will wear a knee immobilizer for three weeks after surgery followed by no protective bracing for the remainder of their rehabilitation. Group B will wear a Don-Joy IROM brace locked at 0Ý for three weeks followed by three weeks in the brace with flexion set to 10Ý less than maximum flexion. At six weeks, the patient will a Don-Joy off-the-shelf functional knee brace daily for six months and for vigorous activities after that for at least the first year. Data collected at one, two, six, twelve, and 24 months will include range-of -motion, Lachman, anterior drawer and pivot shift tests, as well as thigh circumference measurements. In addition at the six, twelve and 24 month follow-up visits, KT-100, LIDO, Lysholm and IKDC tests will be administered. A significant difference in the stability or functional assessment scores would indicate superiority of one method over the other regardless of cost. If both treatment groups are found to be equivalent, the most cost effective treatment method would be without bracing.

Progress: Three subjects were entered in FY 98 for a total subject enrollment of 53. Patient enrollment is completed and patients are now in the two-year follow-up period. No significant differences noted except in patients whose knees hyperextend and they are reconstructed with hamstring tendons.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/095 **Status**: Ongoing

Title: Delayed versus Immediate Open Repair of Achilles Tendon Rupture; A Randomized Prospective Trial

Principal Investigator: CPT Robert V. Williamson, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): CPT George K. Bal, MC; LTC John D. Pitcher Jr., MC

Start Date:	Est. Completion Date:	Periodic Review:
05/16/1997	Jun 01	07/17/1998

Study Objective: To evaluate the differences in surgically repairing Achilles tendon ruptures immediately, or waiting 10-14 days to perform the repair.

Technical Approach: All patients identified with acute Achilles tendon ruptures, who are being considered for surgical repair, will be presented the option of enrolling in this study. The subjects will be randomized to one of two Groups: Group I - Immediate surgical repair (within 72 hours) of the Achilles tendon, or Group II - delayed (between 10 and 14 days) surgical repair of the tendon rupture. The patients will be randomized using a computer generated randomization table. We will initially randomize the first ten patients, and a subsequent power analysis will be performed at 6 month follow-up to insure that enough patients are enrolled to make our results significant. The next 20 patients will be randomized using a second computer generated table. The post-operative course for both Groups will be the same. The patients will be followed up at 2 week, 6 week, 9 week, 6 month, 12 month, and 24 month intervals. They will be evaluated for post-operative complications and functional outcome.

Progress: Approximately 16 subjects have been entered in this study in FY 98 for a total enrollment of 18 subjects. No difference to date has been noted between the two groups. One patient in the delayed group has reruptured but this was due to patient non-compliance.

The PI was changed from CPT George Bal to CPT Robert Williamson in June 1998 due to the reassignment of CPT Bal.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/099 **Status**: Ongoing

Title: Tendon-Healing to Cortical Bone After Tendon Reattachment Using Suture Anchors. A Biomechanical and Histological Evaluation in Goats

Principal Investigator: CPT Robert V. Williamson, MC

Department: Surgery/Orthopedic Surgery **Facility**: MAMC

Associate Investigator(s): LTC Patrick St Pierre, MC; MAJ Ronald E. Nielsen, VC; CPT Jason L. Blaser, MS; CPT Tad L. Gerlinger, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/25/1997	Apr 00	07/17/1998

Study Objective: To examine the biomechanical properties and histological appearance of the bone-tendon interface after rotator cuff tendon repair of the shoulder in goats. The tendon will be reattached directly to the outer surface of the bone (i.e. cortical bone) using four different types of commercially available suture anchors for fixation. This will test if the anchor properties have any effect on healing of tendon to bone after surgical repair.

Technical Approach: An experimental model using the infraspinatus tendon in goats for evaluation of tendon repair has been established. 36 adult (3-5 years old) goats, Capra hircus, will be treated with bilateral tenotomy and subsequent reattachment of the infraspinatus tendon. Each test goat will have different types of suture anchors used on contralateral shoulders. The study endpoint will be at six and twenty-six weeks following operative repair. A total of 40 animals will be assigned by randomized block design to the timing and sequence of the operative techniques, the types of fixation, and for biomechanical, histological or control testing. (e.g. The first animal may be randomized to have anchor #1 used in the left shoulder and anchor #4 used in the right. It may be randomized to the histological group. The second animal may be randomized to have anchor #2 used in the left shoulder and anchor #3 used in the right. It may be randomized to the biomechanical testing at 26 weeks). Thirty-six animals will be used for biomechanical testing and four for histological analysis. By performing bilateral procedures in the same animal, we will be able to use pairing to compare different methods of fixation. This increases the statistical power of the study and reduces the number of animals needed.

Progress: This study has not been started due to a change in the participating companies and the accompanying paperwork.

The PI was changed from CPT George Bal to CPT Robert Williamson in June 1998 due to the reassignment of CPT Bal.

Detail Summary Sheets

Otolaryngology Service, Department of Surgery

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/003 **Status**: Ongoing

Title: Modification and Control of Wound Healing in Tracheobronchial Injuries Using Minimally Invasive Surgical Techniques and Biological Growth Regulators

Principal Investigator: CPT George L. Coppit, III, MC

Department: Surgery/Otolaryngology **Facility**: MAMC

Associate Investigator(s): MAJ Kenneth S. Azarow, MC; LCDR Keith Ulnick, MC, USN; MAJ Jonathan A. Perkins, MC; MAJ Larry K. O'Bryant, MC; MAJ Ronald E. Nielsen, VC

Start Date:	Est. Completion Date:	Periodic Review:
10/17/1997	Oct 00	N/A

Study Objective: To determine if the topical application of a fibroblastic inhibitor to a surgical airway site will enhance epithelialization, inhibit granulation tissue formation and fibrosis.

Technical Approach: Phase I: Wound healing in the airway with stenting alone; 28 pigs will undergo proximal tracheal stenting. Stents will be removed at 1 week, from animals in the 14 and 21 day groups. Evaluation of the healing process will consist of gross histologic examination and compared with a control pig euthanized at each of the same time periods.

Phase II: Wound Healing in the airway with augmentative reconstructive procedures using auricular cartilage; 18 pigs will undergo anterior tracheoplasty with auricular cartilage. Three pigs will be euthanized at 3 and 7 days to describe the healing process. The remaining pigs will be randomized into two groups; one will have no application of biologic modulators and the other will receive topical application of a fibrinoblast inhibitor. The harvested airways will then be assessed grossly and histologically for the degree of inflammation, healing, and stenosis.

Phase III: Wound healing in the airway with augmentative reconstructive procedures using auricular perichondrium; 18 pigs will undergo anterior tracheoplasty with auricular perichondrium used for graft material. Three pigs will be euthanized at 3 and 7 days to describe the healing process. The remaining 12 animals will be randomized into two groups; one will have no application of biologic modulators and the other will receive topical application of a fibrinoblast inhibitor. The harvested airways will be assessed grossly and histologically for the degree of inflammation, healing and stenosis.

Progress: Eighteen pigs were studied as stated above. Two-thirds of the animals demonstrated some degree of stent collapse on endoscopy. Granulation tissue formation was seen in all animals and resolved with stent removal. MTC did not affect the acute inflammatory response, nor reepithelization of the graft site. Airway diameter was smaller in the MTC treated animals; however, they demonstrated better graft incorporation with fibrocartilage proliferation of the graft. Untreated animals demonstrated liquefactive necrosis of the graft. MTC seems to prevent the liquefactive necrosis of SS-LTP grafts, allowing improved graft incorporation. While the airway diameter was smaller in treated animals, this may reflect improved structural integrity seen with the better graft incorporation. Further studies are planned.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 96/157	**Status**: Terminated

Title: Clinical Investigation of Viewpoint in Image-Assisted Surgery

Principal Investigator: MAJ Charles V. Edmond Jr., MC

Department: Surgery/Otolaryngology	**Facility**: MAMC

Associate Investigator(s): LTC Richard F. Debo, MC; LTC Dianna Chooljian, MC; Michael McFarland

Start Date:	**Est. Completion Date**:	**Periodic Review**:
08/16/1996	Sep 97	09/30/1998

Study Objective: The objective of this study, to be conducted pursuant to this protocol, is to assess the spatial accuracy and reproducibility of fiduciary and anatomic registration in patients who are undergoing functional endoscopic sinus surgery, with the Viewpoint workstation.

Technical Approach: The viewpoint workstation is a computer assisting device designed to aid the surgeon in navigation and localization in 3 dimensions. The overall registration accuracy in representing real time surgical anatomy will be evaluated. Fifteen study patients will be enlisted from the Otolaryngology Clinic who demonstrate a clinical need for sinus surgery. During the patient preparation and operative procedure, the patient will undergo 3 separate measurements using the Viewpoint probe in order to assess fiducial registration accuracy and reproducibility. In addition, anatomic registration accuracy will be assessed and compared with the accuracy of fiducial registration. The data will be evaluated using the average standard deviation with 95% confidence intervals for the registration accuracy over the course of surgery.

Progress: After numerous attempts, the device would not work for the ENT staff. Therefore, the protocol was terminated. No subjects were entered.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/177 **Status**: Ongoing

Title: ENT Surgical Simulator Project

Principal Investigator: CPT Glen J. Mesaros, MC

Department: Surgery/Otolaryngology **Facility**: MAMC

Associate Investigator(s): Dale Fawcett; Doug Sluis, Ph.D.; Suzanne Weghorst; Bill Winn, Ph.D.; Blake Hanaford, Ph.D.; Don Stredney; Roni Yagel, Ph.D.; Gregory J. Wiet, MD; Bill Bolger, MD; MAJ Charles V. Edmond Jr., MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/02/1994	Jun 96	09/30/1998

Study Objective: To develop and evaluate a minimally invasive prototype surgical simulator to establish real time fidelity requirements for tactile feedback and computer image synthesis.

Technical Approach: This project is a two phase program with the goal of Phase I to construct a simulator prototype to serve as a platform for further enhancement and evaluation. This includes the development of the geometric and virtual database of the human sinus anatomy, the development of a system to track the surgical instruments, and the system software to implement sinuscope camera emulation and tissue dissection. The prototype will provide the novice with the ability to perform a limited sinus surgery procedure on a virtual patient using sinuscope and surgical tools similar to those used in the operating room. Visual recognition skills and psychomotor skills specific to the surgical context are improved through the experience of the simulated surgery.

In Phase II, development will continue by enhancing the simulator to include changes and enhancements suggested by surgeons in the Phase I evaluation. Additional features such as tactile feedback and tissue deformation will be integrated into the prototype as time and budget permit. During Phase II further analysis will determine the simulators training effectiveness in operation.

Progress: Eight individuals were run on the simulator in all three levels of difficulty and scores were tabulated. Video recordings of actual surgeries were obtained from all levels of training, including staff. These videos were then graded by the staff in a blinded fashion. The project is now in the data analyzation phase with the final report pending.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/044 **Status**: Ongoing

Title: Pediatric Brochoesophagology Laboratory Using Swine (Sus scrofa)

Principal Investigator: MAJ Andrew B. Silva

Department: Surgery/Otolaryngology **Facility**: MAMC

Associate Investigator(s): Andrew Inglis, M.D.; MAJ Jonathan A. Perkins, MC

Start Date:	Est. Completion Date:	Periodic Review:
01/19/1996	Jan 99	07/17/1998

Study Objective: To familiarize the junior Otolaryngology residents at MAMC and the UW and the Pediatric surgery fellow at CHMC, with endoscopic instrumentation and techniques required to evaluate and treat the tracheobronchial tree and esophagus in children.

Technical Approach: This is a 3-4 hour afternoon laboratory session. During this time, three pigs will be anesthetized under general anesthesia and rigid and flexible bronchoscopy and esophaoscopy will be performed by the course participants under the supervision of an attending endoscopist. Three separate stations will be used so a maximal number of procedures can be performed in the allotted time and the length of anesthesia is shortened. The first station will be for diagnostic flexible and rigid endoscopy. The second will be for tracheobronchial foreign body removal. The third will be for esophageal foreign body removal. A separate station will be used to teach endoscopic lasing techniques on prosected animal tracheal specimens. A morning lecture will be held on pediatric endoscopy prior to the laboratory and a quiz will be given over selected readings in pediatric endoscopy.

Progress: One session was held in FY 98 utilizing 3 pigs. Approximately 30 health care personnel were trained.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/059 **Status**: Terminated

Title: Prospective, Uncontrolled, Non-Blind Clinical Trial of the Safety and Efficacy of Bay 12-8039, 400 mg PO QD in the Treatment of Patients with Acute Bacterial Maxillary Sinusitis

Principal Investigator: MAJ Andrew B. Silva

Department: Surgery/Otolaryngology **Facility**: MAMC

Associate Investigator(s): CPT Timothy M. Cupero, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/20/1998	May 99	N/A

Study Objective: To study the safety and efficacy of oral BAY 12-8039 400 mg QD (once daily) for 7 days in the treatment of adult patients with documented acute bacterial maxillary sinusitis.

Technical Approach: Prestudy evaluation will include a medical history and physical exam, with sinus x-rays, blood and urine tests and a sinus aspiration. Subjects will return for evaluation 3 to 5 days following start of treatment for blood and urine tests. Post treatment evaluations will be at 2 to 4 days after finishing the medication and will include sinus x-rays and blood and urine tests. The last visit will be 27 to 31 days following completion of treatment and will include a repeat of the sinus aspiration and sinus x-rays if the physician feels these are necessary.

Progress: This study was withdrawn by the sponsor before it could be implemented due to the lengthy approval process (CRDA). No patients were enrolled.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/035	**Status**: Completed

Title: Pilomatrixoma of the Head and Neck

Principal Investigator: MAJ Richard W. Thomas, MC

Department: Surgery/Otolaryngology	**Facility**: MAMC

Associate Investigator(s): CPT Joseph A. Munaretto, MC; MAJ Jonathan A. Perkins, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/16/1998	Dec 97	N/A

Study Objective: To review the relative incidence, common presentation and recommended treatments of pilomatrixoma at MAMC.

Technical Approach: A retrospective chart review will be conducted to identify those patients treated for a histologically confirmed pilomatrixoma involving the head and neck region. This study will describe the experience with patients treated for a head and/or neck pilomatrixoma at MAMC during the past five years. Medical records will be reviewed for presenting signs and symptoms, lesion characteristics, treatment rendered and outcome of therapy. Information on any tumor recurrences will be sought and an attempt to determine the most beneficial mode of treatment will be made. These data will be compiled and presented in a descriptive fashion. Comparison of these findings will be made to previously published results.

Progress: A five-year retrospective medical chart review was conducted to identify patients treated for a histologically confirmed pilomatrixoma involving the head and neck region. Twenty-six patients met the criteria and were included in the study. All patients were treated for solitary tumors by simple surgical excision and primary closure. There were no reported adverse outcomes and no recurrences of tumors at the surgical sites. The results support simple surgical excision with primary closure as the treatment of choice of these unusual neoplasms. A paper has been accepted for publication and an abstract was presented at a national scientific meeting.

Detail Summary Sheets

Urology Service, Department of Surgery

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/158 **Status**: Ongoing

Title: Multi-center Prospective Cohort Study to Evaluate the Safety and Effectiveness of the American Medical Systems (AMS) Ambicor Inflatable Penile Prosthesis

Principal Investigator: MAJ Sunil K. Ahuja, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC; CPT Douglas W. Soderdahl, MC; MAJ John B. Ellsworth, MC; MAJ Henry E. Ruiz, MC; MAJ Raymond S. Lance, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/16/1996	Oct 02	09/15/1998

Study Objective: The primary effectiveness objective is to evaluate the ability of the AMS Ambicor inflatable penile prosthesis to provide an erection suitable for sexual intercourse (device function) as determined by physical examination and patient self-report. Secondary effectiveness objectives include estimating the effects of the prosthesis on patient sexual function and satisfaction, self-esteem, quality of life, and psychological well-being. The study will also evaluate levels of patient satisfaction with various aspects of the prosthesis including rigidity, length, girth and flaccidity. Safety will be evaluated by measuring rates of post implant complications (including device malfunction) and the occurrence of medical conditions.

Technical Approach: This is a multi-center, prospective, cohort study with the pre-implant experience of patients serving as the comparison for the evaluation of effectiveness and safety. The study sample will be derived from patients who present to the clinic with the diagnosis of erectile dysfunction. After an eligible patient makes an informed decision to be implanted with an AMS Ambicor penile prosthesis and signs the surgical consent he will be asked to participate in the study. A total of 250 patients will be recruited nationwide (12-20 being from MAMC) and will be implanted with the Ambicor inflatable penile prosthesis. The primary measure of effectiveness (sexual function, self-esteem, and psychological well-being), will be monitored for 2 years with visits at 6 weeks post-surgery, 6 months, 1 year, 18 months and 2 years. Follow-up for complications, associated medical conditions and other adverse device effects will be followed for 5 years with phone contact at 3 and 4 years, and a visit at 5 years.

Progress: Nine patients were entered in FY 98 for a total of 17 subjects. The principal investigator was changed from Dr. Ruiz to Dr. Raymond Lance in Jul 98 and then to Dr. Sunil Ahuja in Sep 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/136 **Status**: Terminated

Title: The Protegen Sling for the Treatment of Female Stress Urinary Incontinence: A Pilot Study

Principal Investigator: MAJ Sunil K. Ahuja, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC; LTC Leland D. Ronningen, MC; COL John C. Norbeck, MC; COL Gary D. Davis, MC; MAJ Henry E. Ruiz, MC; CPT Jerome L. Buller, MC; MAJ John B. Ellsworth, MC; CPT Keith J. O'Reilly, MC; CPT Karen C. Evans, MC; Kerry Meyers, Ph.D.; MAJ Raymond S. Lance, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/15/1997	Aug 99	08/20/1998

Study Objective: 1) To determine the safety, efficacy and cost effectiveness of the Protegen sling; and 2) to determine the feasibility of using a minimally invasive technique to place the sling.

Technical Approach: Patients from the Urology and Gynecology Clinics with stress urinary incontinence who decide to have surgical treatment of their condition will be asked to participate in the study. All patients will undergo standard preoperative evaluation as previously described. The Protegen will be placed under spinal or general anesthesia, using a minimally invasive approach. Antibiotics will be used peri-operatively and post-operatively for one week. Follow-up will be scheduled at one week, 1,3,6,12 months, and yearly thereafter for a total of two years. At each visit the patient will have a history and physical examination, urinalysis and urine culture, number of pads used will be determined, urodynamics with leak point pressure measurement, uroflow and post void residuals will be done if clinically indicated. Safety, efficacy, and cost effectiveness will be assessed as previously described.

Progress: No patients were entered in this study. However, the Protegen sling which is available commercially was implanted in some patients at MAMC with erosions of the protegen slings in two patients. With these poor outcomes, the investigators felt that it would not be in the patients' best interests to enter patients in a protocol with a significant risk of erosion.

The original principal investigator on this study was MAJ Henry Ruiz, MC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/023 **Status**: Ongoing

Title: Quality of Life of Female Patients After Anti-incontinence Surgery

Principal Investigator: MAJ Sunil K. Ahuja, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC; LTC Leland D. Ronningen, MC; COL John C. Norbeck, MC; COL Gary D. Davis, MC; Kerry Meyers, Ph.D.; MAJ Henry E. Ruiz, MC; CPT Jerome L. Buller, MC; MAJ John B. Ellsworth, MC; CPT Keith J. O'Reilly, MC; CPT Karen C. Evans, MC; MAJ Raymond S. Lance, MC

Start Date:	Est. Completion Date:	Periodic Review:
12/18/1997	Aug 01	N/A

Study Objective: To determine if the quality of life of female patients suffering from stress urinary incontinence is improved after anti-incontinent surgery and which of the two most commonly performed procedures, Raz urethropexy or sling procedures, has the greatest improvement in quality of life of female patients with stress urinary incontinence.

Technical Approach: Forty patients, scheduled to undergo anti-incontinence surgery, will be randomized to have either sling procedures or the Raz urethropexy. All patients will be evaluated in the standard fashion with history and physical examination, urinalysis and urine culture, cystoscopy, pad test, urodynamics with measurement of valsalva leak point pressures, uroflow and post void residuals as deemed necessary by the attending physician. A Quality of Life Questionnaire will be administered pre-operatively as well as post-operatively at each follow-up visit at 1, 3, 6,, and 12 months and then yearly for four years. The post-operative questionnaire will have two questions added to determine if, given the opportunity to start treatment again, the patient have the surgery performed and would the patient recommend it to a relative or friend. At each follow-up visit, the patients will have a history and physical examination, the number of pads used will be assessed, and a uroflow and post void residual assessment. The incidence of blood transfusion, urinary tract infections, would infections, acute and chronic urinary retention, bladder instability, and urethral erosions will also be assessed. The quality of life score post-operatively at each follow-up visit will be compared to the pre-operative score to asses the impact on quality of live by each surgical procedure. The quality of life scores will also be compared between groups one and two.

Progress: No patients have been entered in this study, due to the PCS of the principal investigator. The PI was changed to MAJ Raymond Lance in Jul 98 and then to Dr. Sunil Ahuja in Sep 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/031 **Status**: Ongoing

Title: Dose Escalation Study with Tolterodine in Patients with Overactive Bladder. A Single-Blind Study in Patients with Symptoms of Overactive Bladder Including Urinary Urgency and Frequency With or Without Urge Incontinence

Principal Investigator: MAJ Sunil K. Ahuja, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC; COL John C. Norbeck, MC; LTC Leland D. Ronningen, MC; CPT Keith J. O'Reilly, MC; MAJ John B. Ellsworth, MC; MAJ Henry E. Ruiz, MC; MAJ Bryon D. Joyner, MC; CPT Karen C. Evans, MC; MAJ Raymond S. Lance, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/18/1997	Feb 99	N/A

Study Objective: (1) To ascertain in a 16 week study the percentage of patients with overactive bladder who will require a dose reduction or escalation of tolterodine when the initial treatment dose will be 1 mg bid; (2) to investigate the incremental clinical improvement in efficacy in those patients who increase tolterodine dose to 2 mg bid; and (3) to identify factors which predict response to tolterodine without urodynamic evidence of detrusor instability.

Technical Approach: This is a single-blind study with 16 weeks of treatment, plus an optional open-label extension for up to 8 months. Approximately 20 patients at MAMC and 1300 nation-wide will participate. A wash out and run in period of 10 days will precede the start of tolterodine treatment. All patients will start treatment at a dose of 1 mg b.i.d. After two weeks of treatment, adverse events and patient compliance will be assessed. Patients will be reassessed at weeks 4 and 8 to determine the efficacy and safety and whether the dose should be modified. If at all possible, the patient will remain on the dose given at the 8-week period for the next 8 weeks (through week 16). If the patient decides to go into the open-label study, there will be a two-week wash-out period and then the patient will continued the medication at the dose that was given at week 16. The open-label segment will last for 8 months. Assessment of efficacy and safety will be continued during this phase of the study.

Progress: Seventeen patients were entered in this study with no adverse events reported at MAMC. The study has been closed to enrollment; however patients will continue on treatment for several months.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 97/036	**Status**: Terminated

Title: Experience with the Dornier U50 Lithotriptor

Principal Investigator: MAJ John B. Ellsworth, MC

Department: Surgery/Urology		**Facility**: MAMC

Associate Investigator(s): MAJ Henry E. Ruiz, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/21/1997	Mar 97	09/30/1998

Study Objective: To determine the effectiveness (stone-free rate) and retreatment rate of the first Dornier U50 lithotriptor in North America.

Technical Approach: The Department of Urology utilizes, via TRICARE contract, the newest lithotriptor introduced into North America, at Allenmore Hospital, in Tacoma. All lithotriptors are compared to the Dornier HM3, water-immersed lithotriptor, as the accepted gold standard. This new lithotriptor is the Dornier U50, which provides an easy, tabletop approach to lithotripsy, utilizing a easily positioned treatment head which is coupled to a powerful shock-wave generator. Our goal is to determine the efficacy of this new lithotriptor. We will review the procedure logbook at Allenmore Hospital and determine patients' inclusion or exclusion into this study. We then propose to review all reports of post-ESWL radiographs to determine the stone-free and retreatment rates of this machine.

Progress: Initial data were collected on approximately 80 charts in collaboration with a civilian institution. Due to logistical factors, it was impossible to retrieve the information on the 90 day post ESWL x-rays. It was decided to terminate the protocol at MAMC because the Dornier U50 lithotriptor is no longer used at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/077 **Status**: Ongoing

Title: Depo-Provera Therapy for Hot Flushes Associated with Hormonal Treatment of Advanced Carcinoma of the Prostate

Principal Investigator: MAJ John B. Ellsworth, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): CPT Keith J. O'Reilly, MC; LTC Leland D. Ronningen, MC; MAJ J. Brantley Thrasher, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/19/1998	Apr 98	N/A

Study Objective: To determine response rates to Depo-provera for the treatment of hot flushes in hormonally treated males with advanced carcinoma of the prostate and compare these rates to published rates of alternative monotherapy regimens.

Technical Approach: The depo-provera treatment is not part of this research study. Patients will be contacted during regularly scheduled clinic visits, or by phone, at 1, 3, 6 and 12 months after treatment has been initiated to assess frequency and severity of hot flushes. Retrospective information on frequency and severity of hot flushes prior to therapy initiation will be pulled from patient chart review.

Progress: Two subjects have been entered with no adverse events.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/104 **Status**: Ongoing

Title: Telomere Length and Telomerase Activity in Human Testicular Cancer

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): CPT Wade K. Aldous, MS; MAJ J. Brantley Thrasher, MC; MAJ Kenneth W. Westphal, MC; CPT Keith J. O'Reilly, MC; Troy H. Patience, B.S.

Start Date:	Est. Completion Date:	Periodic Review:
06/16/1995	Jul 97	07/17/1998

Study Objective: This study encompasses four objectives. To determine the presence or absence of telomerase activity in tumorous testicular tissue and normal tissue. To observe the average telomeric length of both tissue types to compare differences in length, hypothesizing that tumor tissue would have shorter telomeres. To quantify telomerase activity in tissues with an active enzyme. To determine the relationship, if any, between activity of telomerase and the stage and grade of testicular cancer.

Technical Approach: Tissue samples will be taken from 40 male patients undergoing surgical resection for testicular cancer. All malignant and benign tumor types resected during surgery will be investigated. Tissue from the tumor and from surrounding histologically normal areas will be transferred from the Dept. of Pathology to the Dept. of Clinical Investigation. Genomic DNA will be extracted from the tissues and subjected to Rsa1 and Hinf1 restriction digestion. The fragments will then be separated by agarose gel electrophoresis, Southern blotted, and detected by chemiluminescence using a digoxigenin-labeled telomere probe. These will be visualized by x-ray film exposure and will provide the composite lengths of all telomeres in a cell population. Actual telomerase activity in tumorous and normal tissue will also be measured by extracting the enzyme from tissues and assaying for activity. The positive control is an immortalized cell line. Activity is measured by the successful incorporation of radio-labeled dGTP nucleotide into the telomere repeats on a known DNA primer. These will be separated on a polyacrylamide gel and quantified by densitography. The differences in telomere length will be tested by a non-parametric T-test. Chi-square analysis will be used to test for telomerase activity assuming normal tissue has inactive enzyme and tumor tissue has active enzyme. The paired T-test will be used to quantify telomerase activity compared to positive controls and a non-parametric ANOVA will be used to determine the correlation between the amount of activity and the stages and grades of tumors.

Progress: Three additional subjects were entered in FY 98 for a total of six. The investigators are still in the process of accruing subjects. It is too early for data analysis.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/134 **Status**: Ongoing

Title: Comparative Study of the Clinical Efficacy of Two Dosing Regimens of Eulexin: 250 mg Q8h vs 500 mg QD

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): LTC Kurt L. Hansberry, MC; COL John N. Wettlaufer, MC; CPT Douglas W. Soderdahl, MC; MAJ Henry E. Ruiz, MC; COL John C. Norbeck, MC; MAJ J. Brantley Thrasher, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/19/1995	Jul 96	04/17/1998

Study Objective: To compare the clinical effectiveness of a new dosing regimen (500mg QD) for administering flutamide to the currently indicated dosing regimen of 250 mg QD according to (1) the percent of patients normalizing PSA and (2) quality of life differences between the two regimens.

Technical Approach: This phase IV, multi-center, open label, prospective randomization study will include 400 patients (10 from MAMC), ages 40 to 85, with clinically proven and histologically confirmed adenocarcinoma of the prostate gland. The subjects will be randomized to one of two treatment groups, Flutamide 250mg QD or Flutamide 500 mg QD, at Time 0. Time 0 is the day of surgical or medical castration. The study treatments will be continued for three months. The two variables to be evaluated are normalized PSA values as determined by standard laboratory PSA test, and quality of life as determined by questionnaire. Laboratory tests will be taken at clinic visits at Time 0, and weeks 4, 8, and 12. PSA normalization will be performed on 12 weeks data after the last patient accrued has reached the 12 week point. In order to achieve the conventional 80% power for showing equivalence, 200 patients per arm will be required based on a threshold criterion of 15%. Evaluation of the Quality of Life modules will involve multivariate analysis of variance for repeated measures for HQL domains and symptoms. Treatment by time interaction effect will be assessed under the repeated measures model to identify HQL domains that are significantly different between the two treatment arms using a two-sided 5% level test.

Progress: Nineteen additional subjects were enrolled in FY 98 for a total of 52 subjects. There was one patient with multiple other serious medical problems who experienced 5 adverse events over a period of several months. He recovered from all, and it is believed that these adverse events were not related to the study drug.

MAJ Lance was named principal investigator of this study upon the departure of MAJ J. Brantley Thrasher, the original principal investigator.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 97/069	**Status**: Completed

Title: Vibratory Stimulated Bladder Cell Exfoliation in Voided Urine

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology	**Facility**: MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC; Nan W. Kim

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/21/1997	Mar 97	05/22/1998

Study Objective: To determine the difference in the total RNA and cell count in voided urine specimens after 5 minutes of high frequency vibration to the suprapubic area compared to routine voided urine specimens.

Technical Approach: Freshly voided urine specimens will be obtained from 20 normal male and female volunteers and again collected after application of the bladder vibrator to the suprapubic area for 5 min. Additionally, we will evaluate 10 patients with micro or gross hematuria and 10 patients with known bladder tumors prior to transurethral resection. rRNA measurements before and after application of the vibrator will be compared to determine the difference in the total RNA as well as cell count.

Progress: Forty-five subjects were entered in this study. This technique failed to show an increase in viable cell harvest.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/097 **Status**: Ongoing

Title: Telomerase Activity in Voided Urine and Bladder Washings As A Diagnostic and Surveillance Marker for Transitional Cell Carcinoma

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC; CPT Wade K. Aldous, MS; CPT Jason L. Blaser, MS; Nan W. Kim; Judd W. Moul, M.D.; MAJ Steven Lynch, MC; LTC James P. Foley, CH; LCDR Christopher Kane, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/16/1997	May 97	04/17/1998

Study Objective: The objective of this study is to determine the sensitivity and specificity of telomerase activity in the voided urine and bladder washings of patients with bladder cancer as a diagnostic and surveillance marker. This will be compared to traditional cystoscopic examination.

Technical Approach: Bladder cancer remains a significant cause of cancer among both men and women in this country. Diagnosis and surveillance require invasive and often painful testing. Telomerase activity in the voided urine appears to be a promising non-invasive marker of bladder cancer. We seek to determine telomerase activity or its absence in the voided urine of 100 patients with newly diagnosed bladder cancer as well as approximately 200 patients at high risk for recurrence. We will compare these results to the telomerase activity in voided urine from 100 age matched, mixed gender subjects undergoing cystoscopy and found not to have bladder cancer. Data collected will include percentage of telomerase positive urine in the newly diagnosed bladder cancer group compared to the non-cancer control group. Furthermore the number of telomerase positive urine in patients with recurrent TCC in the group of patients at high risk for recurrent bladder cancer. Data will be analyzed to determine sensitivity, specificity, and positive predictive values.

Progress: Twenty-three controls, 73 patients with new cancer, and 125 patients with recurrence have been entered. The first part of the study showed a problem with the specimen processing methods. No telomerase activity was detected with accuracy in the urine. The processing methods have been revised and the protocol has been restarted.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/120 **Status**: Ongoing

Title: A Randomized, Double-Blind Study (With Open-Label Treatment Extension) to Evaluate the Efficacy and Safety of VIAGRA (Sildenafil) in Erectile Dysfunction

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): COL John C. Norbeck, MC; LTC Leland D. Ronningen, MC; MAJ Henry E. Ruiz, MC; CPT Douglas W. Soderdahl, MC; MAJ J. Brantley Thrasher, MC; MAJ John B. Ellsworth, MC; CPT Keith J. O'Reilly, MC; MAJ Bryon D. Joyner, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
07/18/1997	Feb 97	07/17/1998

Study Objective: To assess the efficacy, safety, quality of life, and patient and partner satisfaction over a 3 month period of oral administration of VIAGRA™(Sildenafil), as required, approximately one hour prior to sexual activity in male outpatients with erectile dysfunction.

Technical Approach: The study population will be male outpatients, 18 years of age and older, with well-documented history (>6 months) of erectile dysfunction of broad-spectrum etiology. The study design is a randomized, double-blind, placebo-controlled, parallel group, multicenter, flexible dose study. Patients will be randomized equally into either a placebo treatment group or a VIAGRA™ treatment group. All patients will commence at a dose of 50 mg of VIAGRA™(or corresponding placebo) and depending on efficacy, safety, and toleration, the dose may be increased to 100 mg or decrease to 25 mg, if necessary. Doses will be taken as required (not more than once daily) approximately 1 hour prior to anticipated sexual activity. The study will last 16 weeks for each patient (4 week run-in period and 12 weeks double-blind treatment). Patients who complete the 16 week study protocol will be eligible to receive open label supplies of VIAGRA™ for 48 weeks or until the time that VIAGRA™ becomes commercially available, whichever comes first.

Progress: This study is closed to patient enrollment. Thirteen patients were entered. The last two patients are in the follow-up stage, expected to be completed in December 1998. One patient had a fainting episode, which was felt to be related to his underlying heart problem. He recovered without incident.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/147 **Status**: Ongoing

Title: Comparison of Quality of Life (QOL) Differences Between Radical Retropubic (RRP) and Radical Perineal Prostatectomy (RPP) for Clinically Localized Prostate Cancer

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC

Start Date:	Est. Completion Date:	Periodic Review:
10/17/1997	Sep 99	09/30/1998

Study Objective: To determine QOL differences between patients undergoing RRP and those undergoing RPP for clinically localized prostate cancer.

Technical Approach: This study will prospectively evaluate and compare the QOL of male patients 30-80 years of age who undergo RRP and RPP for clinically localized carcinoma of the prostate. The study will utilize a validated questionnaire, the UCLA-RAND Prostate Cancer Index, administered to the patients (alone and without interruption) at least one week prior to the procedure and then at 1 month, 3 months, 6 months and 1 year postoperatively. This instrument will allow us to compare the effects of the 2 procedures on the patients' health-related QOL and eventually aid the urologist in choosing the appropriate approach for each patient.

Progress: A total of 134 of 184 prostatectomy patients completed the QOL questionnaires. This instrument identified an overall incontinence rate of 35-40% and an impotence rate of 50-75%. There were no differences, however, between patients regarding surgical approach (RRP vs RPP). Overall, patients seemed to expect and tolerate these quality of life factors well. When asked about satisfaction with choice of surgery for prostate cancer in light of complications, 76% after RRP and 85% after RPP were very satisfied. The results are to be presented at the Kimbrough Urologic Seminar in October 1998. The principal investigator was changed to MAJ Lance in September 1998. MAJ J. Brantley Thrasher was the original principal investigator.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/040	**Status**: Completed

Title: Comparison of Radical Retropubic to perineal Prostatectomy for Clinically Localized Prostate Cancer: Clinical Outcomes and Quality of Life Analysis

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology	**Facility**: MAMC

Associate Investigator(s): None.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/16/1998	Jul 97	N/A

Study Objective: To retrospectively compare the clinical outcome of patients undergoing either radical retropubic (RRP) or radical perineal prostatectomy (RPP) for clinically localized prostatic adenocarcinoma to determine if the procedures offer comparable cancer control and morbidity.

Technical Approach: An extensive retrospective review of medical records of patients identified as undergoing radical prostatectomy for clinically localized prostate cancer will be accomplished. Data points collected will include age, clinical & pathologic stage and grade, short term complications, long term complications, margin positive rate, PSA level perioperatively, disease recurrence, and QOL questionnaire results.

Progress: A retrospective review was done of the USURG prostatectomy database from 9/84 - 5/97. Complete and partial data were available on 1341 men ages 30-86 years (mean 63.1) undergoing radical prostatectomy performed at six institutions. Complete data were available on 1055 men undergoing radical retropubic prostatectomy (RRP) and 215 undergoing radical perineal prostatectomy (RPP). Positive margin was defined as capsular penetration (pathologic stage >T3a) as well as involvement of inked margins. Organ confined cancer was defined as pathologic stage T_{1}-$T_{2c}N_{o}M_{o}$. The initial comparison data demonstrate a statistically lower blood loss for the RPP and no significant difference in margin positive rates when patients are matched by preoperative PSA, clinical stage, and grade.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/092 **Status**: Ongoing

Title: Multicenter Prostate Cancer Database for the Center for Prostate Disease Research (CPDR) with Patterns of Care, Outcomes, and Prognostic Analysis

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
07/17/1998	Jan 13	N/A

Study Objective: To collect standardized data on all treated prostate cancer patients during the period 1960 to present; to maintain an accurate, reliable, secure database of these patients that meets IRB patient confidentiality guidelines; and to analyze patterns of care, prognostic factors and intermediate and long-term outcomes for prostate cancer patients entered in this multicenter database.

Technical Approach: Standardized data collection instruments will be used at ten military medical centers by clinical research personnel and physicians to collect comprehensive prospective and retrospective information from men with prostate cancer. Patients will be followed proactively at a minimum of every twelve months until death. Data will be entered and maintained securely at USUHS in a relational database designed exclusively for this purpose. Standard statistical analysis will include survival analysis and univariate and multivariate analysis for prognostic factors.

Progress: This study has only recently been approved. No subjects have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/114 **Status**: Ongoing

Title: A Uniformed Services Comprehensive Database and Tissue Repository for the Study of Epidemiological, Detection, Natural history, and New Management Strategies for Prostate Cancer

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): LTC Stephen C. Groo, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/15/1998	Jun 03	N/A

Study Objective: To establish a prostate cancer serum and tissue repository that will focus on pathology data and contain supportive clinical data for the study of the etiology of prostate cancer and will incorporate a demonstration project to illustrate the utility of the repository by examining interracial differences among men with prostate cancer.

Technical Approach: Active duty and retired servicemen and their dependents with prostate cancer will be recruited for this multicenter Department of Defense study. Subjects will be asked to allow the intraoperative collection and use of a blood sample and tissue biopsies of the excised organ, as well as the retrieval and use of their original archival biopsy tissue. This enhanced infrastructure serum and tissue repository will be used for carcinogenesis, etiology, and tumor biology studies; genetics and molecular biology studies; evaluation of techniques to improve detection and prevention; and behavioral and natural history studies. The goal is to make this national resource available to the entire research community for the study of prostate cancer.

Progress: This study has only recently been approved. No subjects have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/129 **Status**: Completed

Title: Oral Ciprofloxacin for Acute Prostatitis

Principal Investigator: CPT Keith J. O'Reilly, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): CPT Rayford A. Petroski, MC; CPT Bradley F. Schwartz, MC; MAJ J. Brantley Thrasher, MC; CPT Douglas W. Soderdahl, MC

Start Date:	Est. Completion Date:	Periodic Review:
06/21/1996	Apr 97	09/15/1998

Study Objective: To evaluate the efficacy of oral Ciprofloxacin (Cipro) in the treatment of acute prostatitis in comparison to traditional I.V. Ampicillin (Amp) and Gentamicin (Gent).

Technical Approach: The study population will consist of 50 men eligible for MAMC care who present with signs and symptoms consistent with acute prostatitis and meet entry criteria for inpatient treatment with either Cipro or IV Amp/Gent. Patients will be randomized to treatment with Cipro 500mg PO BID for 30 days or IV Amp (1gm q 6hrs)/Gent (5mg/Kg) followed by Trimethoprim/Sulfamethoxazole (Septra DS), one tablet PO BID, for a combined total of 30 days. Efficacy of treatment will be based on length of hospital stay, time to resolution of symptoms, time to defervescence and evaluation of complications. Patients will be followed up in 6-8 weeks after completion of outpatient therapy an will receive exams and laboratory tests according to the Stamey technique. Additional follow-up will be done at 6 and 12 months for recurrence or chronic states. Analysis of data will include chi-square, student t-test and ANOVA.

Progress: Four additional patients were entered in this study in FY 98 for a total of 23 subjects. The study has been closed by Bayer Pharmaceutical. The number of subjects enrolled was too small to reach any conclusions.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/129 **Status**: Ongoing

Title: The Correlation Between Free and Total PSA, Prostate Specific Membrane Antigen and Sex Hormone Binding Globulin Across the Spectrum of Prostate Disease

Principal Investigator: CPT Keith J. O'Reilly, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): MAJ Raymond S. Lance, MC; MAJ J. Brantley Thrasher, MC; Gerald P. Murphy, M.D.; Katherine H. Moore, Ph.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/19/1997	Jul 98	09/30/1998

Study Objective: To examine across the spectrum of prostate disease (normal to prostate cancer) whether there is a statistically significant correlation between the serum levels of the free and bound fractions of Prostate Specific Antigen (PSA), sex hormone binding globulin (SHBG), Prostate Specific Membrane Antigen (PSMA) and serum androgens.

Technical Approach: This study will evaluate men aged 45-80 and examine the serum levels of free and bound Prostate-specific antigen (PSA), sex hormone binding globulin (SHBG), Prostate-specific membrane antigen and serum androgens. The subjects will be divided into one of two arms: those with no evidence of prostate cancer and those with histologically proven adenocarcinoma of the prostate. All subjects will be patients who present to the urology clinic for urologic evaluation and will have one extra vial of serum drawn. The levels of these proteins will be examined for statistically significant correlation. By proving or disproving a relationship among these proteins and its variation across the spectrum of prostate disease a greater knowledge of the biochemistry of the prostate will be apparent and hopefully improve current diagnostic methods for detecting the presence or absence of prostate cancer.

Progress: Ninety additional patients were entered in FY 98 for a total of 220 subjects entered with no adverse reactions.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/051 **Status**: Ongoing

Title: Immunohistochemical Localization of Insulin-Like Growth Factor (IGF) Binding Proteins in Prostate Cancer

Principal Investigator: MAJ J. Brantley Thrasher, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): Stephen R. Plymate, M.D.; MAJ Richard R. Gomez, MC; CPT Michael D. Bagg, MC; CPT Patrick A. Twomey, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/01/1994	Jan 95	04/17/1998

Study Objective: The purpose of this study is to localize IGFBP's -2.-3,-4, and -6 in regions of histologically proven prostate cancer. Additionally, these same techniques will be used to identify these binding proteins in areas of prostatic intraepithelial neoplasia (PIN) and benign prostatic hyperplasia (BPH). The information gleaned from this study will help better understand IGFBP expression in both malignant, premalignant, and benign prostatic tissue.

Technical Approach: Radical prostatectomy specimens will be obtained by the Urology Service and taken to Pathology for histologic sectioning. Prostate adenocarcinoma will be identified in sections (as well as areas of PIN or BPH) with an adjacent section taken for immunohistochemical staining. Immunohistochemical staining will be performed for identification of IGFBP's-4, -2, -3, and -6 in regions of associated neoplasms, PIN or BPH. Approximately 10 patients will be studied with comparisons to be made between neoplastic premalignant, and benign prostatic tissue.

Progress: Eighteen additional specimens were entered in FY 98. Approximately 158 specimens have been studied.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/113 **Status**: Completed

Title: Relief Strategies for Initiative Bladder Symptoms Associated with Intravesical BCG - A Pilot Study

Principal Investigator: MAJ J. Brantley Thrasher, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): Donna L. Berry, Ph.D., RN; William J. Ellis, M.D.

Start Date:	Est. Completion Date:	Periodic Review:
05/17/1996	May 97	05/22/1998

Study Objective: The purpose of this pilot intervention study is to evaluate an oral hydration regimen and dietary supplementation with potassium/sodium citrate as relief strategies for irritative bladder symptoms associated with BCG intravesical therapy.

Technical Approach: This randomized, 2 X 2 pilot study is designed to investigate an oral hydration regimen and urinary alkalinization with potassium/sodium citrate. Forty subjects, experiencing irritative bladder symptoms associated with intravesical bacillus Calmette-Guerin, will be randomized to either an oral hydration regimen, urinary alkalinization with potassium citrate, a combination of the oral hydration regimen and urinary alkalinization with potassium citrate, or usual clinical practices. The intervention will be applied for one week during week 4 of the intravesical treatment course. Urine pH will be monitored and symptoms will be measured using the Irritative Bladder Symptom Inventory. Symptom data will be analyzed using a two-way analysis of variance with a test for interaction.

Progress: This study has been completed. A total of 30 subjects was entered from all sites. The data have all been collected and will be analyzed as soon as Dr. Donna Berry has time to enter it in the computer and then analyze it.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/039 **Status**: Completed

Title: A Multicenter, Phase II, Placebo-Controlled Pilot Study of SNX-111 Administered Intrathecally to Patients with Acute Postoperative Pain

Principal Investigator: MAJ J. Brantley Thrasher, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): CPT John T. Steedman, MC; CPT Michael J. Decker, MC

Start Date:	Est. Completion Date:	Periodic Review:
12/19/1996	Aug 97	12/18/1997

Study Objective: The objective of this pilot study is to assess the safety and effectiveness of SNX-111 administered intrathecally to patients with acute, post-operative pain.

Technical Approach: This is a Phase II, multicenter randomized, double-blind, placebo-controlled pilot study to assess the safety and effectiveness of SNX-111 in patients with acute, post-operative pain. All patients will have intrathecal catheters in place for surgical anesthesia. Patients in each of the operative populations will be randomly assigned to receive a placebo, 0.7 µg/hr SNX-111 or 7.0 µg/hr SNX-111 for 48-72 hours. Infusions will begin intraoperatively, after the administration of the intrathecal anesthesia, and continue post-operatively. Drug will be delivered via an external pump and a temporary intrathecal screening catheter. Patients will have a physical exam, labs, ECT and a mini-mental status exam at baseline. During the study, routine pain assessments will be performed every 4 hours while awake and every 8-10 hours during sleep time for the 48-72 hour treatment period. Systemic morphine administered by PCA for pain post surgery. At discharge patients will again have labs and a neuro exam and will return at 2 weeks to assess for adverse events.

Progress: This study was closed to enrollment at MAMC on 20 Nov 97. The sponsor notified this site that the study was closed due to sufficient patient enrollment. Eight subjects were enrolled at MAMC. Only one patient completed the study. Of the seven not completing the study, one patient returned to the clinic for only one visit after entry in the study, there was one pump malfunction, one cath could not be placed, two caths fell out, one cath occluded, one syringe disconnected from the tubing causing contamination, and one patient had severe nystagmus.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/130 **Status**: Completed

Title: Immunity in Prostate Diseases

Principal Investigator: MAJ J. Brantley Thrasher, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): Martin A. Cheever, M.D.; Mary Lenora Disis, M.D.; MAJ Raymond S. Lance, MC

Start Date:	Est. Completion Date:	Periodic Review:
09/19/1997	Jun 99	09/30/1998

Study Objective: To determine whether patients with prostatitis have immunity to prostatic proteins.

Technical Approach: This study will be done as a cooperative effort with the University of Washington. Serum on patients with presumptive autoimmune prostatitis will be examined for antibody immunity and T cell immunity to prostate proteins. If serum antibody responses to prostate proteins are detected, additional blood will be drawn to examine for T cell responses to prostate proteins. All patients with presumptive autoimmune prostatitis or patients with prostatitis of unknown origin will be eligible. Up to 100 patients will be studied, 50 with prostatitis and 50 controls. The presence or absence of serum antibody to prostate proteins will be determined by standard immunoblot methods. If antibody to prostate proteins is detected, the protein targets of autoimmune prostatitis will be identified by expression cloning, using standard methods.

Progress: Three patients were enrolled in this study at MAMC. The study has accrued sufficient patients between the two sites and has been closed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/095 **Status**: Completed

Title: Evaluation of the BTA stat Test in the Hands of Intended Home Users

Principal Investigator: MAJ J. Brantley Thrasher, MC

Department: Surgery/Urology **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
08/20/1998	Aug 98	N/A

Study Objective: (1) To demonstrate the accuracy of the use of the BTA stat Test by subjects following the package insert instructions, (2) to evaluate the safety of the procedure demonstrated by subjects performing the BTA stat Test and (3) to evaluate the technique in the performance of the BTA stat Test by lay persons.

Technical Approach: Subjects will be required to read the test instructions, perform the test two times with two urine samples prepared in the laboratory, and answer a questionnaire with questions relating to the test instructions.

Progress: This study has been completed. Thirty-two patients participated in this test at MAMC. The evaluation turned out to be positive and the results have been submitted to the FDA for approval of the BTA stat Test.

Detail Summary Sheets

Vascular Surgery, Department of Surgery

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/163 **Status**: Ongoing

Title: Clinical Evaluation of the Handling and Performance of the HEMASHIELD Knitted Double Velour Fabric and Polytetrafluoroethylene (PTFE) Patched for Carotid Endarterectomy Patch Procedures in Patients

Principal Investigator: COL Charles A. Andersen, MC

Department: Surgery/Vascular Surgery **Facility**: MAMC

Associate Investigator(s): COL David F. J. Tollefson, MC; LTC Stephen B. Olsen, MC; Edmund A. Kanar; George J. Collins, Jr.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/20/1996	Nov 98	09/30/1998

Study Objective: The objective of this randomized, parallel group, multi-center study is to evaluate the performance of the test product, the HEMASHIELD® Knitted Double Velour patch in comparison to the control product, the Gore-Tex patch, for use as a carotid artery patch following carotid endarterectomy in patients.

Technical Approach: This is a prospectively randomized, multi-center clinical trial in which a maximum of 40 patients will be enrolled, with approximately equal numbers of patients in each of the 2 treatment groups, Hemashield patch vs. the Gore-Tex patch. Anticipated MAMC enrollment is approximately 20 patients. Patients included in this study will be evaluated preoperatively, intraoperatively, at discharge from the hospital, and at 3 months, 6 months, 12 months and up to a total of 24 months postoperatively. Follow-up evaluations will include a medical history and physical exam at 3, 6, 12 and 24 months and duplex ultrasound testing at 6 and 12 months (with optional duplex scan at 24 months) for assessment of patch repair. Completion of follow-up assessment and final report is anticipated about one and one half years after the first patient enrollment.

Progress: Five subjects were entered in FY 98 with no serious adverse events. A total of 20 patients have entered the study with no serious adverse events.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/097 **Status**: Ongoing

Title: Abdominal Aortic Aneurysm (AAA) and Chronic Obstructive Pulmonary Disease (COPD); Is There a Relationship

Principal Investigator: CPT Chatt A. Johnson

Department: Surgery/Vascular Surgery **Facility**: MAMC

Associate Investigator(s): CPT Peter J. Armstrong, MC; LTC William H. Cragun, MC; COL Charles A. Andersen, MC; COL Thomas A. Dillard, MC; LTC Stephen B. Olsen, MC; COL David F. J. Tollefson, MC; CPT Eric A. Shry, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/21/1995	Mar 96	05/22/1998

Study Objective: To determine the association, if any, of AAA and COPD as well as potential pathophysiologic explanation.

Technical Approach: A comparison will be made between patients with and without COPD and the incidence of AAA. Patients 50 years and older will be selected from those followed in the pulmonary, family practice or adult primary care clinics who have been determined to have COPD by screening history, spirometry and carbon monoxide diffusing capacity (DLCO). Controls will be age/sex matched without COPD. Selected participants will be evaluated by pulmonary function tests (spirometry, DLCO), serum alpha 1 anti-trypsin levels, serum elastase levels, serum cholesterol levels, ankle-brachial indices and abdominal aortic duplex. The incidence in the control and study groups will be compared through Chi-squared analysis and individual variables wills be determined through student T-test. A $p<0.05$ will be determined to be statistically significant. Patients and primary care physicians will be notified of the presence or absence of AAA, abnormal ankle-brachial indices, COPD, or hypercholesterolemia.

Progress: In May 98, the principal investigator was changed from COL David Tollefson to CPT Chad Johnson.

Seven patients were enrolled in FY 98 for a total enrollment of 27 subjects. A new system has been put in place that should increase the referral rate and entry rate. Controls will not be enrolled until the target of 50 study patients has been reached.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/033 **Status**: Terminated

Title: Multicenter, Double-Blind, Parallel Group, Phase III Study Comparing to Placebo the Efficacy and the Safety of Mivazerol Given as a 72-H Continuous Infusion According to 2 Dose Regimens, in Patients with Coronary Artery Disease Undergoing Major Vascular Surgery

Principal Investigator: COL David F. J. Tollefson, MC

Department: Surgery/Vascular Surgery **Facility**: MAMC

Associate Investigator(s): MAJ Stephen L. Bolt, MC; LTC Stephen B. Olsen, MC

Start Date:	Est. Completion Date:	Periodic Review:
12/18/1997	Dec 00	N/A

Study Objective: To determine the efficacy of mivazerol on the incidence of acute MI and death, during the intra- and postoperative hospitalization period until discharge (with a maximum of 30 days after surgery), in patients with definite CAD undergoing major vascular surgery; Mivazerol will be given as a continuous intraoperative and 72 hour postoperative intravenous infusion at two different dose regimens and in comparison with placebo.

Technical Approach: Prestudy physical and laboratory values will be required two weeks prior to the surgery and randomization. Study drug administration will be started at least 20 minutes prior to anesthesia induction with the rapid intravenous infusion lasting 10 minutes. The slow rate intravenous infusion will start at the end of the 10 minute rapid intravenous infusion. The study drug infusion will continue throughout the intraoperative period. Data will be collected throughout the post operative period until discharge. Any technical procedure relevant for the diagnosis or treatment of a MI will be recorded. Follow-up will conclude with a subject visit taking place 30 days after surgery where the following procedures will be performed: a complete cardio-pulmonary examination, information about medications recorded, 12-lead ECG, blood sampling, and complete information about any readmission.

Progress: This drug was studied in Europe with very positive and encouraging results. The study of the drug in the United States was to be based on the results of the European study. During the performance of the European study, it was discovered that the protocol needed various design changes. Therefore, the protocol was withdrawn for consideration until design flaws can be worked out.

Detail Summary Sheets

Social Work Service

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/100 **Status**: Completed

Title: Comparison and Prediction of Completers and Non-completers of A Domestic Violence Program

Principal Investigator: George T. Mitchell

Department: Social Work Service **Facility**: MAMC

Associate Investigator(s): April A. Gerlock, Ph.D., RN, CS

Start Date:	Est. Completion Date:	Periodic Review:
06/20/1997	Oct 98	06/19/1998

Study Objective: 1) To compare program completers and non-completers on the study variables; and 2) to determine if program completion and non-completion can be predicted.

Technical Approach: The following data will be collected, from the male batterer, during the initial interview: demographics; health consequences of domestic violence (DV); early exposure to violence (CTS); substance abuse history (MAST & DAST); legal history; level of battering behaviors (ABI); attitudes about relationship mutuality (MDPQ); physiological/affective response to stress (SOS); self-esteem (SERS); post-traumatic stress (PTSD) threshold (PCL); and court-ordered/probationary status. Certain data will also be collected from the victim/partner, as well, during the initial contact and includes: patterns of his violence (ABI); health consequences of domestic violence; and attitudes about relationship mutuality (MDPQ). Men who have completed the intensive rehabilitation phase and who have moved to the once-a-month maintenance phase will be considered the rehabilitation completers. Non-completers consists of those who either choose to remove themselves from the program or those who are removed because of non-compliance with rehabilitation. Those men who leave the program because of deployment or relocation are dropped from the study because the potential outcome is unknown due to external circumstances. Statistical analyses will include a comparison of the completers and non-completers on the study variables. In addition, the study variables that reveal the greatest difference between completers and noncompleters based on the one-way ANOVA will be entered into a multiple regression analysis to determine which ones account for the greatest variance. A discriminant function analysis will be conducted to determine which variables are best able to predict completion vs. non-completion of DV rehabilitation. Where appropriate, comparison between the reports of the batterers and their victim/partners will be investigated for consistency.

Progress: Sixty-two male batterers and 31 female victim/partners were recruited from Jun 97 through Dec 97 from an existing batterers' rehabilitation program. Forty-eight men were veterans and 14 were active duty. Of the 62 men, one man transferred to another duty station, 38 dropped out of the program, and 23 made the transition from the rehabilitation to maintenance phase of the program. Using the t-test and Chi -squire analysis, comparisons were made between completers and non-completers on the descriptive variables and the research tools. A logistical regression was performed to predict completion/non-completion status. The results of the logistical regression was a Model Chi-square statistic of 31.08. The model predicted 88.89% of the non-completers, 78.26% of the completers, and had an over-all predictive ability of 84.75%. Completers were found to be more likely to be young, court/probation monitored, have lower levels of stress, and post-traumatic stress, and have higher levels of mutuality in their relationships than non-completers.

Detail Summary Sheets

United States Department of Agriculture

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 92/001 **Status**: Terminated

Title: Methods for Assessing Vitamin A Status in Healthy Adults

Principal Investigator: Betty Jo Burri, Ph.D.

Department: U.S. Dept. of Agriculture **Facility**: MAMC

Associate Investigator(s): Andrew J. Clifford, Ph.D.

Start Date:	Est. Completion Date:	Periodic Review:
10/04/1991	Jul 92	09/30/1998

Study Objective: To determine vitamin A status in healthy free-living adults in the San Francisco area.

Technical Approach: This protocol will consist of studies focusing on three groups of people: (1) women aged 55-60 (2) men aged 55-60 and (3) men aged 18-24. Each group will consist of 30 healthy nonsmokers. These age and sex groups have been selected to include adults with divergent ages and because vitamin A and its analogs can be tetratogenic, making it potentially hazardous to administer analogs to young women. Subjects will be prescreened for serum retinol and holo-retinol binding protein (RBP) in an effort to get at least 15 people in each group with low vitamin A serum concentrations. Subjects will fill out a questionnaire in order to estimate their usual intake of high vitamin A foods over the past year. Body weights and blood pressures will be measured on the first and last days of the study. The vitamin A analogs are to be given on days one (didehydroretinol) and eight (tetradeuterated retinyl acetate) of the study. In a pilot study to test the time course of equilibration and elimination of the analogs, three volunteers from each group will be given the cocktails as stated and blood samples taken a 5, 8, and 30 hr, and at 2, 3, 4, 5, 15 days and every 30 days thereafter. This blood would be collected in addition to the blood required for the regular study (preingestion, 5 hr, and days 8, 29, and 30). The study will compare three promising new methods for assessing vitamin A status to serum retinol, and to vitamin A liver stores measured by deuterated analogs and by vitamin A2. The new methods tested will be free- and transthyretin-bound holo-retinol binding protein as determined by HPLC, erythrocyte transglutaminase levels, and goblet cell abnormalities. Addendum (Oct 91): All of the testing was done except for tests of the vitamin A2. Vitamin A2 proved to be very difficult to purify, so it was never actually given to the subjects. Then two significant things happened a supply of high quality vitamin A2, approved for human use, was obtained, and it was found that the tetradeuterated analog may interfere with the vitamin A2 test, even when these analogs are given 8 days apart. It is now recommended that the doses of vitamin A2 and other analogs be separated by at least 30 days. Therefore in this study, the vitamin cocktails will be given on day 1 and day 30, with blood draws added as appropriate.

Progress: This was a longitudinal study in which 54 patients were entered. The follow-up was planned for late 1997 or early 1998. The PI, who worked for the Department of Agriculture, was moved to a new location and was unable to perform the follow-up.

Detail Summary Sheets

Weed Army Community Hospital, Anesthesia Service

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/084 **Status**: Ongoing

Title: Confirmation of Endotracheal Tube Placement by Special Operations Combat Corpsmen and Medics

Principal Investigator: MAJ Charles Price, AN

Department: Weed AMC/Anesthesia Service **Facility**: MAMC

Associate Investigator(s): MAJ Mark D. Calkins, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/19/1998	Jul 99	N/A

Study Objective: To evaluate the effectiveness of several techniques in determining endotracheal tube placement when used by combat corpsmen and medics.

Technical Approach: This will be a randomized, blinded, pilot study of 60 patients, ages 18-65 years. The trachea and esophagus will be intubated with identical tubes. Randomization will determine which ETT will be checked by individually corps (either the tracheally or esophageally placed ETT) and as well as the order in which each technique will be used to determine whether the ETT is in the esophagus or trachea. Techniques used will include observation only with ventilation of randomized ETT, stethoscope, esophageal detector device, colorimetric end-tidal CO2 detector, stethoscope and EDD, and stethoscope and ETCO2. Prior to the evaluation, patients will receive 100% oxygen for 5 minutes and general anesthesia deepened to surgical levels. Hyperventilation will take place prior to evaluation. The medic will be allowed up to 6 breaths via an adult ambu bag and not to exceed 30 seconds to assess proper ETT placement. They will then leave the operating room and report their findings on an assessment form. Three evaluations per patient are likely, but dependent on the clinical/surgical situation.

Progress: No patients have been entered. The protocol just recently received final approval.

Detail Summary Sheets

Department of Clinical Investigation

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/025 **Status**: Ongoing

Title: The Department of Clinical Investigation's Molecular Biology Short Course for Physicians

Principal Investigator: CPT Wade K. Aldous, MS

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): MAJ Rodger K. Martin, MS; Katherine H. Moore, Ph.D.; CPT Aziz N. Qabar, MS

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/20/1995	Jun 96	09/30/1998

Study Objective: To familiarize MAMC residents, fellows, and staff physicians with the research capabilities and resources of the Department of Clinical Investigation. To support MAMC Graduate Medical Education through instruction and research. To foster an appreciation of molecular biology concepts in residents, fellows, and staff physicians and to augment their understanding of the scientific literature. To encourage residents, fellows and staff physicians to develop research protocols incorporating these technologies.

Technical Approach: This course is designed to familiarize physicians with the most commonly encountered molecular approaches in the scientific and clinical literature. It is hoped that this will foster more critical reading of the literature as well as encouraging the development of research protocols employing these technologies. Although six weeks in duration, students will be required to attend two hours of lecture per week in addition to approximately seven hours of laboratory exercises. Topics addressed and used in the course range from DNA isolation to cloning and sequencing of PCR products.

Progress: The course was offered to 12 physicians at MAMC and offered as a workshop at SAFMLS in 1998. A change to a four hour workshop format from a longer lecture format was implemented. The shorter format functions as an introductory workshop, and follow-up instruction is arranged as investigators have specific projects.

Detail Summary Sheet

Date: 30 Sep 98 | **Number**: 96/058 | **Status**: Completed

Title: Detection of Telomerase Activity from Plasmodium falciparum

Principal Investigator: CPT Wade K. Aldous, MS

Department: Clinical Investigation | **Facility**: MAMC

Associate Investigator(s): MAJ Rodger K. Martin, MS; MAJ Curtis L. Yeager, MS; MAJ Dennis E. Kyle, MS

Start Date:	Est. Completion Date:	Periodic Review:
02/16/1996	Jan 97	09/30/1998

Study Objective: (1) To modify and to optimize the telomerase repeat amplification protocol (TRAP) employing nonradioactive methods for detection of telomerase activity from the human parasite, P. falciparum. (2) To develop DNA primers specific for P. falciparum telomerase. (3) To detect and to identify by the modified TRAP assay P. falciparum telomerase activity.

Technical Approach: Total protein extractions from normal human testis tissue, erythrocytes, and Plasmodium falciparum will be performed. Parasites will be harvested from in vitro cultures and protein concentrations will be measured. TRAP assays will be performed as described with modifications. PCR amplification of the TRAP assay will be performed. Standard TRAP assays will also be performed. TRAP PCR products will be analyzed on 10% non-denaturing gels. TRAP assays will be performed with a fluorescein-labeled forward TS primer for P. falciparum. Data will be generated in fluoregram and chromatogram forms. TRAP assay products will be amplified using the GeneAmp PCR Reagent Kit and will be visualized by ethidium staining in 12% Tris-Glycine acrylamide gels. Standard procedures for DNA hybridization will be performed using the amplified TRAP products. TRAP amplification products will be analyzed by electrophoresis on a 4% agarose gel, visualized by ethidium bromide and UV irradiation. Bands representative of telomeric repeats will be excised from the gel. Purified DNA will be cloned and ligation mixes will be used for transformation into competent cells. Sequencing of repeats will be accomplished and detected with ALF DNA analysis.

Progress: Telomerase activity in crude extracts of in vitro derived plasmodium falciparum was detected using the telomeric repeat amplification protocol (TRAP). Telomerase activity was observed in all erythrocytic stages examined with the greatest activity present during the ring-trophozoite stages. Nucleoside analogs AZT, ddI, 7-deaza-dGTP, and 7-deaza-dATP were evaluated for their ability to inhibit telomerase activity in these stage-specific extracts. Of these nucleoside analogues, 7-deaza-dGTP was observed to have the most significant inhibition in all stages.

A paper was presented to the American Society of Tropical Medicine and Hygiene in 1997 and a manuscript is in press in Molecular and Biochemical Parasitology. This abstract from this protocol was awarded the 1997 MG Kenyon Joyce Award.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/019 **Status**: Completed

Title: Expression and Regulation of Telomerase Related Genes in Breast Cancer Cell Lines

Principal Investigator: CPT Wade K. Aldous, MS

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): CPT Aziz N. Qabar, MS; Katherine H. Moore, Ph.D.; Louis A. Matej, B.S.; M. J. DeHart, B.S.; Amber Marean, B.S.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/18/1997	Nov 98	N/A

Study Objective: To determine the level of expression of three different telomerase related genes in breast cell lines via PCR and RT-PCR and the effects of chemotherapeutic agents and other effectors in cultured cells as a factor of time, by measuring gene expression via Northern analysis, telomerase activity, telomere length, and apoptosis in these drug-treated cells.

Technical Approach: The study will begin by using PCR and RT-PCR on three breast cancer cell lines, two of which have no detectable telomerase activity and one cell line with high levels of telomerase activity. The PCR products should show similar sizes for the telomerase genes in the cell lines unless there has been a deletion or deletions of the gene sequences. RT-PCR should detect all three expected gene products in the cell line with telomerase activity, but may also detect different products in the cell lines with no telomerase activity.

All cell lines will be subjected to a peptide nucleic acid, cyclophosphamide, and tamoxifen in order to see if these agents have any effect on telomerase activity. A Northern blot will be performed on products detected by RT-PCR to determine if there is differential expression of any RNAs. The overall effects of the proposed reagents will be measured through TRAP assays (to measure telomerase activity), telomere restriction fragment measurements (measures the effects of the loss of telomerase activity), and apoptosis assays (mechanism of determining the effects of telomere loss).

Progress: Total cell counts and telomerase activity levels of both cell lines with 10-8M tamoxifen treatment were lower than control cells and other tamoxifen treatments. Changes in expression of individual telomerase components correlated with telomerase activity. Estrogen receptor status did not correlate with telomerase activity. Tamoxifen strongly affected both cell counts and telomerase activities within the 10-8M concentration for both cells lines. Cells were able to overcome drug inhibition at all other doses after four days. Telomerase activity and cell proliferation correlated in both cell lines and were dependent on drug concentration. Tamoxifen showed long term effects on cell proliferation with the MCF-7 cells.

This study generated a manuscript and two presentations; one at a local meeting and one at an international meeting.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/041	**Status**: Completed

Title: The Infection Risk of Re-using Orthopedic Instruments

Principal Investigator: CPT Wade K. Aldous, MS

Department: Clinical Investigation	**Facility**: MAMC

Associate Investigator(s): CPT George K. Bal, MC; MAJ Clyde T. Carpenter, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/20/1998	Mar 98	N/A

Study Objective: To determine the risk of infectious transmission from re-use of contaminated orthopedic instruments.

Technical Approach: Three different organisms will be studied, *S. aureus, E. coli,* and *Bacillis subtilis*. Harvested bone will be infected with each organism. A cannulated screw will then be placed through the infected material. This will be sterilized in the usual fashion, then placed in culture. Twenty controls and 100 samples will be used for each organism. The endpoint data will be to determine if any organisms are cultured from the sterilized implants. If an organism is cultured, it will be genetically identified for correlation with the original infectious agent.

Progress: A total of 400 assorted size bone screws were tested looking at the re-infection rate following sterilization. There were 300 in the test group (100 for each organism tested), and 100 each were positive and negative controls. The reinfection rate following sterilization was less than 2% for each organism. There was some contamination found in some of the culture tubes, but the organisms identified did not match the original organism. Identified organisms were normal skin flora likely due to handling errors.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/069 **Status**: Ongoing

Title: Use of Alternative Medicine Therapies for Treatment of Cancer

Principal Investigator: CPT Wade K. Aldous, MS

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): CPT Aziz N. Qabar, MS; Katherine H. Moore, Ph.D.; Louis A. Matej, B.S.; M. J. DeHart, B.S.; Amber Marean, B.S.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/22/1998	Nov 98	N/A

Study Objective: To determine the effects of common therapies used in alternative medicine on cell viability and to determine the effects of the same therapies on telomerase activity.

Technical Approach: A variety of "compounds" will be tested to determine their efficacy against cancer cells *in vitro*. We will subject the MCF cell line to a variety of the agents from local health food stores, including mistletoe extract, ginseng root, melatonin, and selenium, in order to see if these agents have any effect on cell growth and telomerase activity. The same drugs purchased commercially will be tested to determine the effect of purified agents. A Northern blot assay will be performed on cells treated with "promising" agents to determine if there is differential expression of any RNAs. The overall effects of the proposed reagents will be measured through TRAP assays (to measure telomerase activity) and total cell counts (to measure cell viability).

Progress: The combined effects of tamoxifen and melatonin were tested using the breast cancer cell line MCF-7. Cells were cultured for 10 days in the presence of tamoxifen, melatonin, or the two drugs combined. Flasks were harvested daily, the number of cells counted, and protein extracted for determination of telomerase activity. Tamoxifen alone at a dose of 10-8 reduced cell proliferation, and melatonin alone also reduced cell proliferation. However, the combination of tamoxifen and melatonin did not produce the expected additive suppressive effect on cell growth. Instead, cell growth in the presence of both drugs was better than growth with each drug used individually, but did not return to the proliferation seen with culture media and vehicle alone.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/126 **Status**: Completed

Title: Sex Hormone Binding Globulin and Prostate Cancer - Characterization of Alternate mRNA Transcripts

Principal Investigator: Katherine H. Moore, Ph.D.

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): CPT Wade K. Aldous, MS; Louis A. Matej, B.S.; M. J. DeHart, B.S.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/19/1995	Jul 97	06/19/1998

Study Objective: 1) To characterize the sex hormone binding globulin (SHBG) mRNA produced by prostate cancer cells. This will be accomplished by characterizing the SHBG products amplified by PCR, and ultimately the full length transcripts. 2) To determine if SHBG mRNA is translated into protein. This will be accomplished by metabolically labeling the proteins in the cells and detecting by immunoprecipitation. A long range objective is to develop an antibody against the protein product of an altered SHBG mRNA, and use this antibody to determine if the proposed altered transcript is translated into functional protein.

Technical Approach: We will examine prostate cancer cell lines for the presence of SHBG mRNA. In addition, we will construct a cDNA library to fully characterize the SHBG transcripts produced by prostate cancer cells. We plan to examine the proteins manufactured by prostate cancer cell using immunoprecipitation to determine if the cells are producing SHBG protein. This study will thus characterize a potential oncogene for prostate cancer and lead to a greater understanding of the mechanism of cancer formation. This is a descriptive study. The DNA sequences will be compared with known sequences using MacVector.

Progress: Reverse transcriptase-polymerase chain reaction (rtPCR) analysis of total RNA revealed two PCR products, which were cloned and sequenced. The smaller band was found to be the product of alternate processing of the mRNA, with exon seven removed and a single base deletion at the start of the exon eight. This modification is predicted to produce an altered amino acid sequence in the carboxy tail of the protein, removing the glycosylation sites and producing a truncated protein. The investigators also found that both prostate fibroblasts and epithelial cells produce SHBG mRNA.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/138 **Status**: Suspended

Title: The Effect of Tamoxifen and Ionizing Radiation on Expression of Bcl-2, Bcl-x, and p53 in Breast Cancer Cells In Vitro

Principal Investigator: Katherine H. Moore, Ph.D.

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): LTC Robert B. Ellis, MC; MAJ Nyun C. Han, MC; MAJ Mark D. Brissette, MC; MAJ Richard F. Williams, MC

Start Date:	Est. Completion Date:	Periodic Review:
06/16/1995	Mar 96	07/17/1998

Study Objective: The objective of this study is to define the molecular mechanism by which antitumor agents such as estrogen receptor antagonists and ionizing radiation initiate programmed cell death (apoptosis) in cultured breast cancer cells. Specific objectives are to examine the treated breast cancer culture cells for morphologic and biochemical evidence of apoptosis and to determine the time course for apoptotic death as well as that for changes in the level of bcl2 and p53 in the cells. Thereby, we will determine if changes in the level of these factors precede the onset of apoptotic death and provide evidence for the importance of modulation of the expression of these proteins as antitumor effects of these agents. Also, changes in other bcl2-related factors such as bax and bcl-x will be examined.

Technical Approach: Three breast cancer cell lines will be used MCF-7, MDA-MB-231, and ZR-75. Cells form each of these lines will be grown in the presence of estrogen for 24 hours, after which the medium will be treated with either tamoxifen or 4-hydroxytamoxifen, at 0.1 and 1.0 micromolar for six days. For the effects of radiation, cell will be grown in estrogen for 24 hours and then irradiated. At 24 hour intervals, cells from each experimental condition will be harvested and examine for apoptosis and for the level of expression of bcl2, bcl-x and p53. Morphologic and biochemical evidence for apoptosis in these cultures will be obtained by light microscopy and DNA agarose gel electrophoresis. Flow cytometry will be used to determine the fraction of apoptotic cells. Expression of the protein products of the three oncogenes will be determined by quantitative Western blot electrophoresis. The mean and standard deviations for three separate cultures with each treatment at each time point will be determined. Statistical analysis will be performed using two way analysis of variance methods.

Progress: In previous years, the investigators found that megesterol acetate had no effect on apoptosis in either cell line. It was also demonstrated that tamoxifen increases the rate of apoptosis in ER positive breast cancer cells and that this effect may be mediated through a decrease in the level of expression of the apoptotic inhibitory factor BCL-2. This effect was also noted in an ER negative cell line, but only at much higher doses. It is unknown if this represents a direct effect on BCL-2 gene regulation or an indirect effect through an estrogen receptor-mediated pathway.

The principal investigator was changed from MAJ Richard Williams (who resigned from the Army) to Katherine Moore, Ph.D., in Jul 98. The protocol has been suspended while discussions are taking place as to whether it will be possible for Dr. Williams and Dr. Moore to continue working on this protocol jointly to determine if further information can be obtained to elucidate the findings of the protocol thus far.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/033 **Status**: Ongoing

Title: Is BRCA1 Loss of Expression Found in Tumors Others Than Breast and Ovarian Cancer

Principal Investigator: Katherine H. Moore, Ph.D.

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): MAJ Richard F. Williams, MC; CPT Jerome M. McDonald, MC; MAJ Thomas P. Baker, MC; CPT Sandra L. Carter, MC; James R. Wright, M.T.

Start Date:	Est. Completion Date:	Periodic Review:
02/21/1997	Nov 97	09/30/1998

Study Objective: 1) To determine the prevalence of loss of expression of BRCA1 protein in tumors. We will examine tumors that are linked to increased risk of breast cancer (prostate, breast, ovarian and endometrial cancers) in families as well as tumors that are not associated with an increased risk (lung and kidney). We also will examine colon cancer samples, as this tumor may also be linked to BRCA1 associated cancer. 2) Through the use of two antibodies against BRCA1, we can determine if normal protein is being expressed in the tumors and surrounding normal tissue, or if a truncated protein that may be a product of a mutant BRCA1 allele is being expressed.

Technical Approach: This study will lead to an increased understanding of the role of BRCA1 protein in tumorigenesis. BRCA1 is associated with familial breast and ovarian cancer. The gene was identified by loss of heterozygosity studies in families with a high incidence of breast and ovarian cancer. In these families, it has been found that members with a mutant allele for BRCA1 have a much greater risk for developing cancer than the unaffected population. The presumed mechanism of action of BRCA1 in the development of cancer involves the loss of the normal allele which was producing a normal, functional protein. The mutant alleles contain a mutation in the BRCA1 gene, of which 85% produce a truncated protein. It is assumed that the truncated protein is not functional. It also is presumed that the function of BRCA1 is as a DNA binding protein. The basis of this assumption is the presence of a zinc ring domain near the amino terminal end of the protein. The zinc ring domain was identified through amino acid sequence homology and molecular modeling. The zinc ring is a common component of DNA binding proteins. This structure in BRCA1 may be functionally important, as a common mutation that is associated with increased risk, 185delAG, deletes two nucleotides in this region.

The presence of an inherited BRCA1 mutation, which may lead to the production of non-functional protein, is becoming a well accepted risk factor for the development of familial breast and ovarian cancer. However, the role of BRCA1 in tumors other than breast and ovarian is not well understood. We will determine if the loss of BRCA1 protein expression occurs in tumors other than breast and ovarian. If BRCA1 loss can be documented in a variety of tumors, this will add to the importance of BRCA1 loss in the progression of a normal cell to a cancerous one.

Progress: The investigators have begun evaluating antibodies directed against BRCA1 and BRCA2. Antibodies are being checked for specific labeling of intracellular proteins. Different tissue pretreatments are also being tested, including trypsin digestion and pressure treatment.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/128 **Status**: Ongoing

Title: Enhancing the Effectiveness of Tamoxifen Therapy in Breast Cancer

Principal Investigator: Katherine H. Moore, Ph.D.

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): MAJ Richard F. Williams, MC; Maryls J.M. Nesset, Ph.D.

Start Date:	Est. Completion Date:	Periodic Review:
08/15/1997	Oct 00	08/20/1998

Study Objective: 1) Investigate the mechanism by which SHBG and tamoxifen mediate a reduction in cell number in MCF-7 breast cancer cells in-vitro by measuring their effect on both G1 cell cycle arrest and apoptosis, as well as level of expression of factors which mediate apoptosis such as Bc1-2 and Bax; 2) study the regulation of production of endogenous SHBG by estrogen and tamoxifen, as well as agents reported to affect SHBG levels on other systems, such as insulin, prolactin, androgen, and cAMP; and 3) determine the effect of simultaneous treatment of MCF-7 cells with exogenous SHBG and tamoxifen on cell growth and apoptosis.

Technical Approach: We will be exploring the novel idea that interaction occurs between two effectors of steroid response in breast cancer cells, tamoxifen and sex hormone binding globulin (SHBG), resulting in a reduction of the rate of cell growth and increasing the rate of cell death. This study may provide the foundation to developing more effective treatment of breast cancer. The inhibitory effect of tamoxifen, a partial antagonist of estrogen action, on cell growth has been well documented. Evidence for an effect of tamoxifen on programmed cell death (apoptosis) has been reported recently. In preliminary studies in our laboratory, tamoxifen decreases the level of the anti-apoptosis factor Bc1-2, and this effect appears to depend on the level of estrogen to which cells are exposed prior to treatment. An inhibitory effect of cAMP on cell growth in response to estrogen has been recently shown by others and confirmed in our laboratory. Additionally, treatment with exogenous SHBG has been shown to increase cAMP levels and inhibit response to estrogen. Our group has demonstrated that SHBG is produced endogenously by MCF-7 breast cancer cells. Interestingly, recent data suggest that serum SHBG levels increase in patients treated with estrogen antagonists, suggesting that antiestrogen agents may regulate SHBG production. A potentially important aspect of this study would be the discovery of a means to increase the inhibitory effect of antiestrogens on breast cancer cell growth and/or cell death by modulation of SHBG levels as addressed in objective 2. If one of these agents is found to modulate SHBG levels, and if SHBG is shown to modulate the inhibitory effect of tamoxifen, a potential means of biologically increasing the effectiveness of breast cancer treatment with antiestrogens could be identified.

Progress: Phase I of this multipart project is currently in progress. The breast cancer cell lines, MCF7 and MDA-MB-231, are being used as the models for tamoxifen treatment. The MCF7 cell line contains estrogen receptor type alpha and the MDA-MB-231 contains estrogen receptor type beta. Each estrogen receptor has different activities at the different response elements, estrogen receptor response elements, or AP1 sites. The investigators will determine the effect tamoxifen treatment has on sex hormone binding-globulin expression in these cell lines. The tool being used is quantitative PCR. Two methods of quantitative PCR are being developed. One uses an internal standard of a shortened piece of SHBG RNA that can be added to samples. The other method is semiquantitative and utilizes an external standard of a second mRNA target (beta 2 microglobulin) to estimate the levels of SHBG expression. An abstract was presented to the DoD Breast Cancer Research Program Meeting "Era of Hope."

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/036 **Status**: Completed

Title: Gastrin Releasing Peptide: A Potential Autocrine Growth Factor in Human Neuroblastoma Cells

Principal Investigator: Katherine H. Moore, Ph.D.

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): Ann O'Connor, M.D.; Robert S. Sawin, M.D.

Start Date:	Est. Completion Date:	Periodic Review:
01/16/1998	Jun 98	N/A

Study Objective: To determine whether gastrin releasing peptide is an autocrine growth factor in human neuroblastoma cells, and to determine whether expression of gastrin releasing peptide is linked to more aggressive clinical disease.

Technical Approach: The established cell lines IMR32, SK-N-SH, SK-N-MC, SK-N-AS, and SK-N-DZ as well as the H345 (human small cell lung carcinoma) and the S3T3 (murine fibroblast) cells lines will be maintained in cell culture. When the cells become confluent, the total RNA will be harvested for each cell line. H345 cell RNA will serve as the positive control, as these cells are known to produce both GRP and GRP-receptor (GRP-R). The S3T3 cell RNA will serve as the negative control, as it is known that these cells do not produce GRP, but do express the receptor for GRP. The technique of reverse transcription polymerase chain reaction (RT-PCR) will be used to first synthesize GRP cDNA from the total RNA, and then amplify the GRP cDNA product. The same technique will be used to synthesize and amplify GRP-R cDNA. Specific primers for these experiments will be obtained from the published GRP and GRP-R gene sequences. This technique is of great value, as it allows detection of very small amount of RNA.

In addition to proving that GRP and GRP-R mRNA are present in neuroblastoma cells, it can also be determined whether there is a difference between production of GRP or GRP-R in N-myc amplified cells (IMR32) and non-N-myc amplified cells (SK-N-SH). Finally, using similar techniques, probes for both GRP and GRP-R will be synthesized from bacterial phagemids containing the complete GRP and GRP-R cDNA. If this is successful, the probes can be used to detect the presence and distribution of GRP and GRP-R mRNA in neuroblastoma tumors.

Progress: Human neuroblastoma cells (IMR32, SK-N-MC, SK-N-SH, SK-N-AS, SK-N-DZ), human small cell lung carcinoma cells (H345), and murine Swiss 3T3 fibroblasts were grown in culture. When they reached confluence, total RNA was extracted, Reverse-Transcription Polymerase Chain Reaction (RT-PCR) was utilized to see whether these cells expressed gastrin releasing peptide (GRP), mRNA. Not only did these human neuroblastoma cell lines express GRP mRNA, but some also expressed the GRP-receptor (GRP-R) mRNA. Additionally, the expression of the GRP and GRP-R genes appears to be via an alternative splicing mechanism. All the fragments obtained were proven to be GRP or GRP-R by Southern blot using specific probes which the investigators created and purified. This is a novel discovery and a portion of this data is pending acceptance to the journal Surgery. Future projects will include sequencing of these gene fragments to better elucidate the mechanism of alternative splicing and fluorescence microscopy with fluorescene-labeled GRP to visualize GRP receptor binding. A paper was presented at the Medical College of Wisconsin and also submitted for the Condon Residents Research Competition at that institution.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/096 **Status**: Ongoing

Title: Gastrin Releasing Peptide: A Potential Growth Factor Expressed in Human Neuroblastoma Tumors

Principal Investigator: Katherine H. Moore, Ph.D.

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): Ann O'Connor, M.D.; Robert S. Sawin, M.D.; Jeff M. Bullock, M.S.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
08/20/1998	Dec 98	N/A

Study Objective: To determine whether the gastrin releasing peptide and gastrin releasing peptide receptor genes are expressed in human neuroblastoma tumors, and to determine whether expression of these genes is associated with more aggressive tumor histology.

Technical Approach: Total RNA will be harvested from each tumor (per standard protocols). The technique of reverse transcription polymerase chain reaction (RT-PCR) will be used to first synthesize GRP cDNA from the total RNA, and then amplify the GRP cDNA product (per standard protocols). The same technique will be used to synthesize and amplify GRP-R cDNA. Specific primers for these experiments have been obtained from the published GRP and GRP-R gene sequences, and have been used successfully in neuroblastoma cell culture models. Results will be confirmed by Southern Blot analysis (per standard protocol), using digoxigenin labeled probes previously generated through PCR.

Progress: This project will build on a previous study that examined gastrin releasing peptide in neuroblastoma cell lines. We will use rtPCR to determine if the mRNA for gastrin releasing peptide is present in tumor tissue. Tissue has been obtained.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/013 **Status**: Ongoing

Title: The Role of Thrombospondin in Macrophage-Mediated Wound Healing. A Structural/Functional Dissection of Thrombospondin

Principal Investigator: CPT Aziz N. Qabar, MS

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
11/15/1996	Oct 98	11/21/1997

Study Objective: To delineate the role of macrophage thrombospondin in the process of wound healing; to determine the mechanism(s) by which angiogenisis, associated with wound healing is controlled; and to analyze the functional and structural domain of thrombospondin.

Technical Approach: This study will examine the role of macrophages in wound healing. The profile of thrombospondin 1 and 3 secreted by activated macrophages will be tested in an in vitro system consisting of circulating monocytes (human monocytic cell lines, THP-1 and HL-60) which are activated with a phorbol ester or retinoic acid. Assays will consist of Western blots, metabolic labeling and immunoprecipitation, and Northern blots. The level of expression of each molecule will be determined quantitatively from developed autoradiographs. The level of regulation will be determined from the corresponding Northern blot, by comparing the profiles of the protein expression with that of its mRNA expression. A human TSP1/murine TSP3 chimera will be constructed using recombinant DNA techniques and PCR technology, resulting in a cDNA encoding the NH2-terminal of murine TSP3 and the COOH-terminal of human TSP1. A mutant form of the chimera will also be constructed, such that the two cysteine residues involved in S_S bridging in mTSP3 (Cys245 and Cys248) will be mutated into serine residues. The two chimeric proteins will be expressed in mammalian cells and their role on cell growth and differentiation will be investigated.

Progress: Thrombospondin (TSP1) was reported to have both angiogenic and angiostatic activities. To investigate this dual function, TSP1 expression profiles in solid tumor cell lines were examined. The expression of TSP1 , but not TSP3, was found in three cell lines, ZR-75, MDA, and MCF-7. MCF-7 cells were pro-angiogenic although they expressed low levels of TSP1, whereas MCF-7 stably transfected with TSP1 cDNA expressed 5 times more TSP than untransfected cells and were antiangiogenic. These observations imply that solid tumors may partially control their angiogenesis through the regulation of TSP1 but not TSP3 expression. Additionally, the effect of oligomerization on human TSP1 function was investigated. Stable cell lines expressing recombinant truncated, mutated, or full length TSP1 and/or TSP3 cDNAs were initiated. Two chimeric molecules were constructed either by replacing the trimer-forming amino terminus, heparin-binding domain of TSP1 with the pentamer-forming amino terminus domain of mTSP3 (TSP1/TSP3 chimera) or by fusing the trimer-forming heparin-binding domain and Type 1 repeats of TSP1 with the dimer-forming Fc portion of human immunoglobulin G (TSP1-Ig chimera). It was found that overexpresssed recombinant trimeric TSP1 or its trimeric Type 1 repeats were the only constructs that were capable of inhibiting angiogenesis of endothelial cells *in vitro*. Taken together, these results indicate that the three-dimensional structure of the Type 1 repeats of TSP1 is crucial for its antiangiogenic activity. The results of this study were presented at the 12th Symposium of the Protein Society in July 1998 and the 22nd Annual Meeting of the Society of Armed Forces Medical Laboratory Scientists in April 1998.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/104 **Status**: Ongoing

Title: Expression of Angiostatin and TSP1 in Human Microvascular Endothelial Cells and Breast Cancer Cells: In Vitro Study of a Potentially Superior Antiangiogenic Activity

Principal Investigator: CPT Aziz N. Qabar, MS

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): Katherine H. Moore, Ph.D.; Jeff M. Bullock, M.S.; James R. Wright, M.T.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/15/1998	Aug 99	N/A

Study Objective: (1) To establish the profile of plasminogen and TSP1 expression in quiescent and proliferating human microvascular endothelial cells and two breast cancer cell lines, MCF-7 and MDA-431 and (2) to compare the antiangiogenic phenotype of angiostatin, TSP1, and type I repeat truncations on the proliferation of human microvascular endothelial cells (HMVEC) *in vitro*.

Technical Approach: This study is designed to examine the possibility of a combinatorial antiangiogenic activity *in vitro*, where the effectiveness of two or more antiangiogenic molecules against proliferating human microvascular endothelial cells (HMVEC) is evaluated. The expression of an angiostatin, a proteolytic fragment of pasmino (gen), in the non-invasive breast cancer cell lines MCF-7, the invasive breast cancer cells line MDA-431, and HMVEC will be evaluated using Western blots, Northern blots, and polymerase chain reaction (PCR). A profile of TSP1 and angiostatin expression in these cells will be established, as a function of time in culture and following bFGF-induced proliferation. Moreover, the inhibitory effect of truncated forms of TSP1 on HMVEC angiogenesis will be determined and compared to that of both TSP1 and angiostatin, separately. Finally, a combination of two or more of the antiangiogenic molecules will be tested to determine the most potent inhibitory activity.

Progress: This protocol has just been approved and has not been implemented.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/118 **Status**: Completed

Title: Role of Human Steroidogenic Factor-1 (hSF-1) in Human Breast Cancer

Principal Investigator: Meera S. Ramayya, M.D.

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): COL Dan C. Moore, MC; George P. Chrousos, M.D.

Start Date:	Est. Completion Date:	Periodic Review:
08/15/1997	Jul 98	08/20/1998

Study Objective: 1) To determine the expression of hSF-1 in normal breast tissue, various types of human breast cancers, estrogen receptor (ER) negative breast cancer cells, ER positive native human breast cancer MCF-7 cells and MCF-7 cells treated with estradiol or tamoxifen using RT-PCR analysis; and 2) to determine the effect of transfection of hSF-1 on the growth of estrogen receptor positive and negative human breast cancer cells in the presence and absence of estradiol, tamoxifen or cAMP.

Technical Approach: Steroidogenic Factor -1 (SF-1), a tissue-specific orphan nuclear receptor, regulates the genes encoding several steroidogenic enzymes, Mullerian inhibiting substance, gonadotropins and StAR. In addition, SF-1 is crucial to hypothalamic, adrenal and gonadal organogenesis. StAR, a nonenzymatic protein, enhances the movement of cholesterol from the outer to the inner mitochondrial membrane. The human StAR (hStAR) has two hSF-1 response elements (SFRE's), which are essential for cAMP-dependent activation of the StAR gene. These response elements are identical to estrogen receptor response element (ERE) half sites. We will study the co-regulation of hStAR promoter-driven luciferase construct by hSF-1 and estrogen receptor a (ERa). We will perform co-transfection studies in HeLa cells to examine hSF-1's role as a regulator of the hStAR promoter through these SFREs. In addition we will examine the role of hSF-1 in the regulation of the ERE promoter of the oxytocin gene. We will study the co-regulation of oxytocin promoter-driven lucerferase construct by hSF-1 and ERa. Finally we will perform gel-retardation studies with MCF-7 nuclear extracts to determine if ER derived from these breast cancer cells can bind to wild type and mutated SFRE's.

Progress: This study has been completed. The investigators performed co-transfection studies in HeLa cells to examine hSF1's role as a regulator of the h StAR promoter through these SF-1 response elements (SFREs). The hSF-1 expression vector generated functional protein, which increased luciferase activity by 4-fold in the absence of and up to 7-fold in the presence of cAMP. Interestingly, co-transfection of ERa with wild type StAR promoter, in the presence of hSF-1, down regulated this SF-1 stimulated luciferase activity to 2-fold over the baseline. Gel-retardation studies showed that ERa derived from MCF-7 nuclear extracts bound to both the wild type and mutated 32P labeled-SFREs. However, co-transfection studies revealed that ERa was unable to stimulate StAR promoter-driven luciferase activity through these mutated SFREs. Taken together, these data suggest that in this transient transfection system, hSF-1 stimulated StAR promoter activity is further enhanced in the presence of cAMP and inhibited in the presence of ERa. An abstract of this work was presented at the Endocrine Society Meeting.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/139 **Status**: Terminated

Title: Pilot Study for: Wound Healing Using Pulsed Electromagnetic Field Therapy

Principal Investigator: LTC Richard A. Sherman, MS

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): MAJ Thomas K. Curry, MC; LTC John B. Whittemore, AN

Start Date:	Est. Completion Date:	Periodic Review:
04/21/1995	Sep 95	06/19/1998

Study Objective: The overall objective is to determine whether pulsing electromagnetic fields (PEMFs) can potentiate post operative recovery by increasing the rate of incisional wound healing and decreasing pain management requirements in patients undergoing abdominal and vascular surgery whose wounds are left open for secondary closure. The objective of this particular study is to perform a pilot which will provide trained staff and practiced methodologies for a larger study.

Technical Approach: This project is designed as a pilot to test the objectives as described and to prepare personnel and methods for a larger study with more subjects. The study is designed as a semi-double blind, randomized, two-group experimental repeated measures design. Ten subjects will be randomly assigned to two groups of five each. One group will receive PEMF treatment and the other will receive placebo treatment. The study will be double-blinded for the PEMF technician as well as the evaluators. Subjects will be males or females, over 18 years of age, who have undergone abdominal or vascular surgery at MAMC and who have incisions healing by secondary intention. Patient information will be collected pertaining to pre-existing disorders that may act as confounding variables to normal wound healing. All eligible subjects will be sequentially entered into the study until the groups are full. Wound healing will be assessed by ASEPSIS (a wound healing and infection assessment), videothermography, photography, and plenography (a computer program used to trace and compare wound outlines). Post operative incisional pain will be assessed by a Visual Analog Scale and post-operative analgesic usage. Each variable will be initially analyzed separately. The non-parametric variables will be analyzed using a two-way, repeated measures, non-parametric analysis of variance. The parametric variables will be analyzed with a parametric repeated measures ANOVA.

Progress: This study was terminated due to inadequate staffing to provide personnel to conduct and support the study.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/158 **Status**: Terminated

Title: Pilot Study For: Environmental-Temporal Relationships Between Changes in (a) Paraspinal Muscle Tension and Low Back Pain and (b) Trapezius Muscle Tension and Migraine and Tension Headache Intensity

Principal Investigator: LTC Richard A. Sherman, MS

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): Melissa Wong, BA; Christie Hill; Linda Robson, BA; Estelle Hamblen, BA, MHA; Kimberly A. Hermann-Do, BS, MHA; Antje F. W. Goeken, Psy.D.

Start Date:	Est. Completion Date:	Periodic Review:
06/16/1995	Feb 97	07/17/1998

Study Objective: 1) To determine whether there is a temporal relationship between changes in paraspinal muscle tension and changes in musculoskeletal low back pain in patients' normal environments. 2) To determine whether there is a temporal relationship between changes in trapezius muscle tension and changes in intensity of migraine and tension headaches in patients' normal environments. 3) To determine whether environmental - temporal relationships between (a) musculoskeletal low back pain and paraspinal muscle tension pain and (b) trapezius muscle tension and migraine and tension headache change after successful biofeedback therapy.

Technical Approach: There will be ten subjects in each group with the groups consisting of patients diagnosed as having tension headaches, musculoskeletal low back pain, migraine headaches, or mixed migraine-tension headaches (a total of 40 patients). Ten subjects per group are likely to be needed to detect consistent temporal relationships between pain and muscle tension reliably because the previous data were highly variable and idiosyncratic. Assignment to groups will be by diagnosis only as there are no controls, etc. The subjects will all be patients referred from the TMC's at Ft. Lewis or the Neurology and Family Practice clinics at Madigan AMC who meet the diagnostic criteria for entrance into the study. They will be between 18 and 55 years of age, be otherwise healthy, and of either sex. Each subject will have four consecutive days of ambulatory recordings during all waking hours before and after standard muscle tension awareness and control treatment which will take approximately six weeks. Headache patients will have their bilateral trapezius muscled tension recorded while low back pain patients will have their paraspinal muscles recorded. The motion sensor will be placed in the center of the back between the shoulder blades for all patients. The recorded will beep every hour to remind the subjects to record their pain levels and type of activity being engaged in. the beeper does not stop until a pain rating is entered on the keyboard. The intervention/treatment is not experimental and will be performed (and its success rated) according the Surgical Research Service SOPs.

Progress: This protocol was terminated due to the inability to get students or residents interested in performing the project.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/019 **Status**: Completed

Title: Treatment of Aura-Inaugurated Migraine Headache (Classic Migraine) with Pulsing Electromagnetic Fields: A Pilot Efficacy Study

Principal Investigator: LTC Richard A. Sherman, MS

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): MAJ Linda A. Marden, MC; Linda Robson, BA

Start Date:	Est. Completion Date:	Periodic Review:
11/17/1995	Sep 96	07/17/1998

Study Objective: To determine whether classic migraine headaches can be treated with pulsing electromagnetic field (PEMF) therapy. This pilot will only determine whether the application of PEMF appears to have a clinically important effect. If it appears to have such an effect, larger, controlled studies will be proposed which will determine the extent and duration of the effect.

Technical Approach: We propose to have ten patients of either sex between the ages of 18 and 70 with at least a two year history of having classic migraines at least once per week keep a daily log of the frequency and intensity of headaches as well as medication use for two weeks. They will then be exposed to PEMF on the thigh at a power/frequency setting 6/600 for one hour per day, five days per week for three weeks. Analysis of headache activity will be performed by making a composite rating for each subject for each of the three rated periods (before, during, and after intervention). Activity for each period will be calculated for each variable by simply adding up the ratings (e.g. total hours of pain for the period) and by constructing a composite score equal to frequency times intensity for each period. The parametric measures (e.g. hours of pain) will be compared using a parametric, one way, repeated measures analysis of variance while non-parametric measures (e.g. pain intensity) will be evaluated using the non-parametric equivalent.

Progress: Twenty-three subjects were studied. The number of headaches per week decreased from 4.03 during the baseline period to 0.43 during the initial two week follow-up period and then to 0.14 during the extended follow-up which averaged 8.1 months. Large controlled studies should be performed to determine whether this intervention is actually effective.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/085 **Status**: Completed

Title: Treatment of Headaches with Pulsing Electromagnetic Fields: A Multigroup, Double-Blind, Placebo-Controlled Study

Principal Investigator: LTC Richard A. Sherman, MS

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): MAJ Linda A. Marden, MC; Linda Robson, BA; CPT Amy J. Asato, MC; LTC John B. Powell, MS

Start Date:	Est. Completion Date:	Periodic Review:
03/15/1996	Mar 97	04/17/1998

Study Objective: To determine the duration and impact of pulsing electromagnetic field (PEMF) therapy on migraine and tension headache activity.

Technical Approach: We propose to have adult patients of either sex between the ages of 18 and 70 with at least a two year history of having headaches at least once per week keep a daily log of the frequency and intensity of headaches as well as medication use for two weeks. They will be stratified by type of headache (either migraine with aura, migraine without aura, migraine associated with the menstrual cycle, tension headache, and mixed migraine - tension headache) and randomized into actual or placebo PEMF therapy. They will then be exposed to PEMF (real or placebo) on the thigh at a power/frequency setting of 6/600 for one hour per day, five days per week for two weeks. Neither the therapist nor the patient will know which group they are in. A two week stabilization period will follow the two weeks of real or placebo therapy. Patients will keep a headache log during this period. The next stage will cross-over the subjects. At the end of this period, patients will keep a two week follow-up log and be followed-up by phone at one month, three months, and six months after the end of therapy. Patients will be instructed to call us when their headaches have returned to pre-treatment levels. Standard treatment will be offered at that time. Success is usually defined as at least a 50% decrease in headache activity as calculated from a composite score based on frequency, duration, and intensity with a commensurate decrease in medication use. We will perform a power analysis after the first five patients complete the post-treatment log to determine the number which will probably be required. We will request permission to increase our number of subjects if more than a total of 100 subjects are required to differentiate between groups if the differences are such that differentiating between groups would be worthwhile.

Progress: This study has been completed. Twenty-eight subjects were studied. Exposure of the inner thighs to pulsing electromagnetic fields is an effective intervention for migraine but not for tension type headaches at least in the short term. It is crucial to give a minimum of three weeks of exposure as two weeks exposure is not sufficient to produce an optimal effect. A manuscript has been submitted to Headache for publication.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/126 **Status**: Terminated

Title: Incidence and Impact of Headaches Among Users of Medical and Dental Facilities at Fort Lewis

Principal Investigator: LTC Richard A. Sherman, MS

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): MAJ Linda A. Marden, MC; MAJ Richard T. Dombroski, MC; LTC Ann M. V. Bianchi, AN; Steven A. Pace, MD; CDR Brian J. Kelly, MC; 1LT Jan L. Sprague, AN; Linda Robson, BA; Melissa Wong, BA

Start Date:	Est. Completion Date:	Periodic Review:
05/17/1996	Oct 96	06/19/1998

Study Objective: To determine the incidence and impact of headaches and low back pain among people eligible for care at military medical facilities. To estimate the utilization of medical facilities at Fort Lewis for treatment of headaches and low back pain. To estimate the cost of treating headaches and low back pain to the medical facilities at Fort Lewis.

Technical Approach: The proposed study had three parts: 1) distribute a two page survey of headache and low back pain activity and impact to a representative sample of people eligible for care at Ft. Lewis medical facilities. It will be distributed to people waiting in the Pharmacy, Pediatrics, Family Practice, Dental Clinics, Adult Primary Care Clinic, and the TMCs, as well as during annual physical exams in OB/GYN and Physical Exam. Additionally, it will be offered to over 2,000 ROTC Cadets in the summer. A power analysis of the response variability will be conducted after 1,000 responses and used to guide continued distribution. 2) Daily patient records from the ER, the TMCs, Family Practice and the Adult Primary Care Clinic will be prospectively reviewed for two months to identify patients with non-trauma headaches and their record will be reviewed for the history of treatment over the last two years. 3) A list of medications primarily prescribed for headaches will be compiled and the pharmacy will prepare (a) a record of how much of these prescriptions have been dispensed over the last two years and their costs and (b) a list of the people receiving these medicines. Every fifth name on a random sample of 500 people receiving those medications will be evaluated to insure that the medications are used for headaches.

Progress: This study was terminated due to a lack of personnel to perform the study.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/058 **Status**: Completed

Title: Determination of whether a Pronation-Controlling Insole Reduces the Occurrence of Lower Limb Pain Among Overpronating Soldiers During Basic Training

Principal Investigator: LTC Richard A. Sherman, MS

Department: Clinical Investigation **Facility**: MAMC

Associate Investigator(s): MAJ Leanne Marie Vonasek, RPT; Laura Crane, Ph.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/21/1997	Oct 97	09/30/1998

Study Objective: To determine whether a pronation-controlling insole reduces the occurrence or extent of overpronation-related lower limb pain and injuries among overpronating U.S. Army recruits in basic training compared with similar overpronating trainees who do not use the insoles. Because pain and some minor injuries may not be reported, we will measure parameters such as PT test scores which are likely to be effected by these problems. We will also factor out reports of pre training lower limb pain and injuries as well as changes in exercise.

Technical Approach: During basic training the enrolled trainees will be monitored for 1) raw-physical fitness test scores, 2) number of trainees graduating on time, 3) number of visits to the clinic for lower limb pain, 4) number and severity of lower limb injuries. The physical fitness test, which consists of a timed 2-mile run and timed push-ups and sit-ups, is given for record at the beginning and at the end of basic training. For purposes of this protocol, minor lower limb pain injuries are rated as 1) pain with no change in activities, 2) pain with decreased activities 3) pain with rest. After four weeks of training, the inserts will be replaced with new ones and the used ones will be returned to the sponsor for evaluation. This is necessary so trainees will not be using worn inserts. Subjects will rate their pain on a colored visual analog scale that shows a continuous gradation of colors from white, indicating no pain, to bright red, indicating the maximum pain. The continuous scale is marked with 0 through 10 with zero indicating no pain and 10 indicating maximal pain. At the completion of this basic training the enrollees will complete a questionnaire that asks about overall frequency of use of inserts, use during physical training, use during road marches, use during class time, lower limb pain during basic training, and injuries during training. This information was successfully gathered from this population at the proposed test site without significant problem.

Progress: 3,557 subjects were evaluated for degree of overpronation just before they entered basic training. Twelve percent (431) demonstrated hyperpronation in one or both feet. Forty-nine of these declined to participate or were not going to remain at the training facility for basic training. The remaining 382 soldiers filled out the questionnaire and were issued the inserts to wear throughout the eight weeks of training. After completion of training, soldiers were questioned about their insert use and pain during training. This information was correlated with changes in their physical training test results and with their medical records. When pain at the start of training was controlled for, significantly ($p<0.04$) fewer trainees wearing the overpronation correcting insoles reported lower limb pain than those not wearing them.

Detail Summary Sheets

Gynecology Oncology Group

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 82/073 **Status**: Terminated

Title: GOG 0026A: Master Protocol for Phase II Drug Studies in Treatment of Advanced Recurrent Pelvic Malignancies

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC

Start Date:	Est. Completion Date:	Periodic Review:
11/20/1981	Indefinite	02/20/1998

Study Objective: To implement a master protocol to screen for activity and efficacy of new agents or combinations in patients with advanced or recurrent pelvic malignancies, resistant to higher priority methods of treatment.

Technical Approach: A "rejection" type design will be used with a fixed sample size of 25 eligible patients/disease site/drug or combination studied. The design allows replacement of ineffective regimens by newer agents or combinations. Sections relating to specific agents will be sequentially incorporated into this protocol as these agents are studied. Continuing review will be done for each separate protocol. To be eligible, patients must have histologically confirmed, advanced, recurrent, persistent, metastatic, or local gynecologic cancer with documented disease progression; lesions that are measurable and can be followed for tumor response; abdominal, pelvic, or other masses which can be defined in at least two dimensions by palpation or by x-ray; a GOG performance Grade 0, 1, or 2 (Karnofsky scale 30-100); free of clinically significant infection; off previous chemotherapy for at least 3 weeks; recovered from effects of recent surgery, radiotherapy, or chemotherapy; passed the nadir blood counts from previous therapy and a granulocyte count >1500/mm3, platelet count >100,000/mm3, BUN <25 mg%, creatinine <1.5 mg%, bilirubin <1.1 mg, SGOT <5 IU. Patients receiving myelosuppressive agents will have adequate bone marrow function as described above. Exception to the general requirement for normal liver function will be secondary to documented metastatic tumor to the liver or as noted in the section dealing with that particular agent. Patients with all primary disease sites of gynecologic malignancies are eligible. Each disease site will be accumulated as a separate study sample. For a particular drug study, the allowable disease site(s) may be further qualified. Ascites and pleural effusion alone are not considered measurable for purposes of the study. A steady rise in the titers of alpha-fetoprotein and beta-HCG will be taken as evidence of disease progression in germ cell tumors of the ovary.

Progress: One patient being followed in the 26 series expired in FY 98. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 82/007 **Status**: Terminated

Title: GOG 0026C: A Phase II Trial of Cis-Platinum Diamminedichloride in Treatment of Advanced Pelvic Malignancies

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/20/1981	Indefinite	02/20/1998

Study Objective: To determine the efficacy of cisplatinum diamminedichloride in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

Technical Approach: All patients with measurable gynecological cancer, who have failed higher priority therapies, will be offered cisplatinum as a Phase II drug to determine its efficacy. The drug is given at 50 mg/m^2 intravenously every three weeks as toxicity permits. Patients who respond or who demonstrate disease will continue to receive the agent until progression has occurred.

Progress: No patients have been entered in this study. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 91/008 **Status**: Terminated

Title: GOG 0026II: Trial of 5-Fluorouracil and High Dose Leucovorin in Advanced Metastatic or Recurrent Pelvic Malignancies

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
10/19/1990	Indefinite	02/20/1998

Study Objective: To implement a protocol to screen for activity and efficacy of new agents or combinations in patients with advanced or recurrent pelvic malignancies, resistant to higher priority methods of treatment. In this case, the agents are 5-FU and high dose Leucovorin.

Technical Approach: Patients who have received prior 5-FU are ineligible. Leucovorin will be administered in a dose of 200 mg/m^2 daily for 5 days and repeated at four and eight weeks and thereafter every five weeks. 5-FU will be administered in a dose of 370 mg/m^2/day for 5 days, infused immediately after the Leucovorin has been given. An adequate trial will be defined as receiving one course of treatment and living four weeks for additional tumor assessment, provided death is not due to tumor progression. All patients entered on the study will be evaluated for toxicity. Patients will remain on study and continue receiving chemotherapy until disease progression or until toxicity prevents further treatment.

Progress: No patients have been entered in this study at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/153 **Status**: Completed

Title: GOG 0026LL: A Phase II Trial of Prolonged Oral Etoposide (VP-16) in Patients With Advanced Pelvic Malignancies

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
08/06/1993	Dec 93	02/20/1998

Study Objective: 1. To determine if low dose oral VP-16 given on a daily basis for 21 days out of the month yields significant clinical response in patients who have previously been treated with platinum containing compounds. 2. To evaluate the relative side effects of such low dose therapy.

Technical Approach: Patients with recurrent pelvic malignancies not amenable to curative therapy are eligible. The treatment regimen will consist of oral VP-16 given at 50 mg/m²/d on the 1st to the 24th of the month. This will be cycled every four weeks until disease progression or adverse effects prohibit further therapy. Patients will be followed by clinical examinations or if applicable chest x-rays prior to the initiation of each cycle.

Progress: This study was closed to patient entry, 1 Dec 95. Two patients were entered. Both have died of disease progression. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 81/035	**Status**: Ongoing

Title: GOG 0041: Surgical Staging of Ovarian Carcinoma

Principal Investigator: COL Mark E. Potter, MC

Department: GOG	**Facility**: MAMC

Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/16/1981	Jan 86	02/20/1998

Study Objective: To determine the spread of ovarian carcinoma to intraperitoneal structures and retroperitoneal lymph nodes by direct examination, cytologic sampling, and biopsy; to establish a surgical protocol for patients entered into GOG ovarian cancer treatments protocols; to determine the complication rate of the procedures.

Technical Approach: This protocol is being performed as a statistical protocol on patients who have surgery as standard treatment. Eligible patients will be those who have Stages I, II, or III ovarian carcinoma. Patients undergoing total abdominal hysterectomy, bilateral or unilateral salpingo-oophorectomy, bivalving of the ovary, selective pelvic and para-aortic lymphadenectomy, omental biopsy, or peritoneal cytology sampling will be studied. They will not be given any preoperative treatment, but will be subjected to a completed and thorough evaluation before surgery. All patients will be explored and the steps for surgery will be as standard surgery dictates. Specific observations will be made as to the findings. If fluid is not present, washings will be taken from the inside of the abdomen to study cells. A thorough examination of all structures from the diaphragm to the pelvic floor will be carried out. After surgical staging, patients will be transferred to the appropriate treatment protocol or to standard treatment if no protocol is available.

Progress: This study was closed to patient entry, 12 Feb 87. Thirteen patients were enrolled. One patient expired due to Alzheimer's/empyema during the past year and eight persons are currently being followed who remain disease free at least 10 years after therapy.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 81/105 **Status**: Ongoing

Title: GOG 0052: A Phase III Randomized Study of Cyclophosphamide Plus Adriamycin Plus Platinol Versus Cyclophosphamide Plus Platinol in Patients with Optimal Stage II Ovarian Adenocarcinoma

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): COL William L. Benson, MC; COL Roger B. Lee, MC; LTC Gordon O. Downey, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/21/1981	Mar 98	02/20/1998

Study Objective: To determine, in optimal Stage III ovarian adenocarcinoma, if the addition of adriamycin to cyclophosphamide plus cis-platinum improves progression-free interval, frequency of negative second-look laparotomy and survival. This protocol replaces GOG 0025.

Technical Approach: Eligible patients are those more than six weeks post-operative with proven primary Stage III ovarian adenocarcinoma confined to the abdominal cavity and its peritoneal surfaces with residual tumor masses after surgery no larger than 1 cm in diameter. Patients with prior chemo or radiotherapy are ineligible. Patients will be randomized to cyclophosphamide plus Platinol every three weeks for eight courses or to cyclophosphamide and Platinol plus adriamycin every three weeks for eight courses. After eight courses those with less than clinically complete response will go off study and be followed for survival; those with clinically complete response will have second-look surgery to validate the complete response or to remove residual tumor masses. Patients will then be followed for approximately five years for survival rates.

Progress: This study was closed to patient entry, 20 Jul 85. Six patients were enrolled. One patient, disease free 16 years after completing therapy, is being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 84/033 **Status**: Ongoing

Title: GOG 0072: Ovarian Tumors of Low Malignant Potential: A Study of the Natural History and a Phase II Trial of Melphalan and Secondary Treatment with Cisplatin in Patients with Progressive Disease

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC

Start Date:	Est. Completion Date:	Periodic Review:
02/17/1984	Dec 88	02/20/1998

Study Objective: To evaluate the biologic behavior of ovarian tumors of low malignant potential; to evaluate the effectiveness of chemotherapy against this disease (initially, a Phase II study of melphalan); and to evaluate the response rate to cisplatin in melphalan failures.

Technical Approach: Patients without prior chemotherapy of radiotherapy who have had adequate surgical staging will be eligible. Patients with no grossly visible residual disease will receive no treatment and be followed for five years if there is no subsequent disease. If there is no grossly visible clinically apparent residual for 12 months, the patients will have second look surgery and then proceed to melphalan treatment (5 days every four weeks) or follow-up (complete response). With progression after melphalan, patients will proceed to third look and cisplatin treatment (once every three weeks for eight weeks) or follow-up. If there is no evidence of response after three courses of cisplatin, the treatment will be discontinued. Patients who have progression during the first 12 months will be treated as above except they will proceed directly to melphalan treatment without second look surgery. Follow-up will be for a minimum of five years with clinical examination every three months for the first two years, then every six months thereafter.

Progress: This study was closed to patient entry 25 Feb 92. Ten patients were enrolled; of these, 7 patients are being followed, two have been lost to follow-up, and one has died.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 84/074 **Status**: Ongoing

Title: GOG 0078: Evaluation of Adjuvant VP-16, Bleomycin, and Cisplatin (BEP) Therapy in Totally Resected Choriocarcinoma, Endodermal Sinus Tumor, Embryonal Carcinoma and Grade 3 Immature Teratoma of the Ovary, Pure and Mixed with Other Elements

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
08/17/1984	Jul 89	02/20/1998

Study Objective: To evaluate the effect of adjuvant vinblastine, bleomycin, and cisplatin (VBP) chemotherapy in patients with endodermal sinus tumor and choriocarcinoma of the ovary (pure and mixed) after removal of all gross tumor; to evaluate the role of serum markers, especially alpha fetoprotein and HCG, in predicting recurrence; to evaluate the role of reassessment laparotomy in determining response, detecting early relapse, and planning further therapy; and to compare the biologic behavior of pure endodermal sinus tumors with mixed germ cell tumors containing endodermal sinus elements. Per addendum of Jan. 87: to evaluate the acute and chronic toxicity of this chemotherapy on gonadal and reproductive function.

Technical Approach: Patients with totally resected Stage I choriocarcinoma, endodermal sinus tumor, or embryonal carcinoma of the ovary with negative peritoneal washings, normal (or falling at a rate that does not suggest residual disease) serum AFP and beta-HCG levels, and adequate bone marrow, renal, and hepatic function will be studied. Stages II and III will also be eligible if all gross tumor is resected. After recovery from surgery, patients will receive 3 cycles of VBP therapy. Patients who show evidence of progression while on VBP therapy will be candidates for GOG Protocol 26. Patients completing three cycles of treatment clinically free of disease will undergo reassessment laparotomy. Patients with recurrent disease at reassessment laparotomy will be candidates for GOG Protocol 26. To be eligible a patient will receive at least one week of chemotherapy and live another two weeks. Each patient will remain on study until adverse effects prohibit further therapy or until evidence of progression is noted. Per addendum of Jan. 86: the title has been changed as shown above; vinblastine has been replaced by VP-16; Grade 3 immature teratoma has been added for entry and evaluation.

Progress: This study was closed to patient entry, 10 Feb 92. One patient , enrolled in FY 92, is being followed and remains disease-free.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 86/089 **Status**: Ongoing

Title: GOG 0085: A Randomized Comparison of Hydroxyurea versus 5-FU Infusion and Bolus Cisplatin as an Adjuvant to Radiation Therapy in Patients with Stages II-B, III, and IV-A Carcinoma of the Cervix and Negative Para-Aortic Nodes

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): COL William L. Benson, MC; COL Roger B. Lee, MC; LTC Gordon O. Downey, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/15/1986	Feb 94	02/20/1998

Study Objective: To determine whether hydroxyurea or the combination of 5-FU and cisplatin is superior as a potentiator of radiation therapy in advanced cervical carcinoma and to determine the relative toxicities of hydroxyurea versus the combination of 5-FU and cisplatin when given concurrently with radiation therapy.

Technical Approach: Patients with invasive squamous cell, adenocarcinoma, or adenosquamous carcinoma of the cervix, Stages II-B, III, and IV-A, who meet the eligibility requirements as listed in the protocol, will undergo clinical staging as permitted by FIGO rules. All patients will undergo surgical staging to include extraperitoneal sampling of the para-aortic lymph nodes, peritoneal cytology, and intraperitoneal exploration. Patients with cancer confined to the pelvis will receive pelvic irradiation and will be randomly assigned to receive either concomitant 5-FU and cisplatin or hydroxyurea. Patients with disease outside the pelvis are not eligible for this protocol. The study will continue as long as treatment protocols remain activated. The patients will be followed for two years and then every six months for three additional years.

Progress: This study was closed to patient entry, 3 Dec 90. Two patients, disease free nine years after completion of therapy, are being followed at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/025 **Status**: Terminated

Title: GOG 0087-I: Evaluation of Mitomycin, Doxorubicin, and Cisplatin in the Treatment of Recurrent or Advanced Leiomyosarcomas of the Uterus

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
11/21/1997	Aug 00	02/20/1998

Study Objective: To estimate the antitumor activity of the combination of mitomycin, doxorubicin, and cisplatin in patients with recurrent or advanced leiomyosarcoma of the uterus and to determine the nature and degree of toxicity of the above combination in this cohort of patients.

Technical Approach: Therapy is administered intravenously over three hours, every three weeks for six courses and will be discontinued for progressive disease or unacceptable side effects.

Progress: No patients were enrolled in this protocol at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 87/013 **Status**: Terminated

Title: GOG 0090: Evaluation of Cisplatin, Etoposide, and Bleomycin (BEP) Induction Followed by Vincristine, Dactinomycin, and Cyclophosphamide (VAC) Consolidation in Advanced Ovarian Germ Cell Tumors

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
10/17/1986	Indefinite	02/20/1998

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: After adequate recovery from surgery (if done) previously untreated patients will be treated by three courses of BEP followed by three courses of VAC. Patients exhibiting disease progression on either phase will be taken off study. Patients who had previous VAC or similar regimens will be treated with four courses of BEP. After recovery from BEP therapy, reassessment laparotomy will be performed in patients with negative markers who are clinically free of disease. Progressing patients will be removed from the study. Patients with no evidence of disease at second look will be followed. Patients with persistent disease at second look will be removed from the study. An adequate trial is defined as receiving two courses of the drug and living at least six weeks. Each patient will remain on study until adverse effects prohibit further therapy or until evidence of progression of disease.

Progress: No patients have been enrolled in this study. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 87/104 **Status**: Ongoing

Title: GOG 0092: Treatment of Selected Patients with Stage 1B Carcinoma of the Cervix After Radical Hysterectomy and Pelvic Lymphadenectomy: Pelvic Radiation Therapy versus No Further Therapy

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC; COL Donald H. Kull, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/21/1987	Indefinite	02/20/1998

Study Objective: To determine the value of adjunctive pelvic radiation in the treatment of Stage 1B carcinoma of the cervix but with selected high-risk factors; to determine the recurrence-free interval, survival and patterns of failure in those patients; and to determine the morbidity of adjunctive pelvic radiation following radical hysterectomy.

Technical Approach: All patients with Stage 1B cancer of the cervix who have been treated by radical hysterectomy and pelvic node dissection and found to have cancer confined to the cervix and who have a large tumor and/or lymph or blood vessel invasion in the cervix will be eligible to enter the study. Patients will be randomized to one of two groups. One group will receive external radiation therapy to the pelvis and the other group will receive no further therapy. Patients assigned to receive the radiation therapy will receive the therapy daily for 4 to 6 weeks. Both groups of patients will be required to have check-ups every three months for three years and then every six months for two more years.

Progress: This study was closed to patient entry, 18 Dec 95. One patient, enrolled in FY 88, remains disease free.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 87/028 **Status**: Ongoing

Title: GOG 0095: Randomized Clinical Trial for the Treatment of Women with Selected Stage IC and II (A,B,C) and Selected IAi, IBi, IAii, and IBii Ovarian Cancer, Phase III

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC

Start Date:	Est. Completion Date:	Periodic Review:
11/21/1986	Indefinite	02/20/1998

Study Objective: In definitively staged patients who have tumor involving one or both ovaries with pelvic extension and/or malignant ascites and/or positive peritoneal washings and in those Stage IAi and IBi patients with poorly differentiated tumors and stage IAii and IBii (all grades) to: compare the progression-free interval and overall survival of the two treatment regimens; determine the patterns of relapse for each form of therapy; and define the relative toxicities of the two treatment approaches.

Technical Approach: The study design will be a randomized comparison between the standard adjuvant treatment (P32) and an experimental arm of short term intensive adjuvant combination chemotherapy with cyclophosphamide/cisplatin in patients with ovarian cancer. One to two weeks following surgery, P32 therapy will be started. Fifteen millicuries of chromic phosphate suspension mixed in 500 cc of normal saline will be infused into the peritoneal cavity via the peritoneal dialysis catheter after a technetium scan or abdominal x-rays with contrast material has demonstrated adequate distribution. In order to facilitate distribution of the P32, the patient will be turned every 15 minutes to the left side, onto the back, in Trendelenburg and reverse Trendelenburg positions, onto the right side and so on for two hours following the infusion. Chemotherapy will consist of cyclophosphamide, 1 mg/m^2 I.V., on day 1 plus cisplatin, 100 mg/m IV, on day 1 administered one hour after cyclophosphamide. Cycles of combination chemotherapy will be repeated every three weeks depending upon the time to recovery of the blood counts to pretreatment level. Cycles of chemotherapy will be repeated for a total of three cycles. Patient follow-up will continue until death, loss of follow-up, or termination of the study. Patients will remain on study until disease progression or adverse effects dictate otherwise. An adequate trial is defined as receipt of at least one course of therapy and one follow-up visit.

Progress: This study was closed to patient entry, 14 Mar 94. Five patients were enrolled. One patient, who remains disease free, is currently being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 87/091 **Status**: Ongoing

Title: GOG 0099: A Phase III Randomized Study of Adjunctive Radiation Therapy in Intermediate Risk Endometrial Adenocarcinoma

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/19/1987	Indefinite	02/20/1998

Study Objective: To determine if patients with intermediate risk endometrial adenocarcinoma who have no spread of disease to the lymph nodes benefit from postoperative pelvic radiotherapy and to 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 Grade 2 or 3 endometrial adenocarcinoma (endometrioid, villoglandular, mucinous and adenosquamous) and clear cell carcinoma will be eligible. Patients must have had a total abdominal hysterectomy, bilateral salpingo-oophorectomy, selective pelvic and para-aortic node sampling, pelvic washings and found to be surgical Stage 1 with myometrial invasion. Following surgery, patients will be randomized to no additional treatment of pelvic radiation therapy to begin no later than eight weeks after surgery. Those randomized to radiation therapy will be treated with AP and PA parallel ports with each port being treated each day. A daily tumor dose of 180 cGy will be given to a total dose of 5040 cGY in approximately six weeks. Each patient will be followed with regular visits occurring every three months for the first two years, every six months for the third, fourth and fifth years, and yearly thereafter.

Progress: This study was closed to patient entry, 3 Jul 95. Three patients were enrolled. All are currently clinically disease free.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 89/052 **Status**: Terminated

Title: GOG 0108: Ifosfamide (NSC #109724) and the Uroprotector Mesna (NSC #113891) with or without Cisplatin (NSC #119875) in Patients with Advanced or Recurrent Mixed Mesodermal Tumors of the Uterus

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
04/21/1989	Indefinite	02/20/1998

Study Objective: To determine: whether the addition of cisplatin to doxorubicin offers significant improvement in the frequency of objective response; the duration of progression-free interval; and the length of survival as compared to doxorubicin alone in patients with advanced or precurrent mixed mesodermal tumors of the uterus

Technical Approach: Patients will be randomized to either Regimen I or Regimen II. Regimen I: doxorubicin 60 mg/m^2 IV every three weeks to a maximum total dose of no greater than 500 mg/m^2. Regimen II: doxorubicin 60 mg/m^2 IV every three weeks plus cisplatin, 50 mg/m^2 IV, every three weeks, to be continued to a maximum total dose of doxorubicin of 500 mg/m^2. Each regimen will require both dose escalation and dose reduction in accordance with adverse effects observed on the previous course of therapy. Patients who reach maximum doxorubicin dose will undergo a complete re-evaluation. All therapy will then be stopped and the patient followed on no further therapy until progression of disease is documented. Further therapy at that point will be at the discretion of the investigator. Patients on no further treatment will be followed every three months for the first two years, then every six months for three years, and annually thereafter.

Progress: No patients have been entered in this study at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 91/086 **Status**: Ongoing

Title: GOG 0109 (SWOG 8797): A Randomized Comparison of 5-FU Infusion and Bolus Cisplatin as an Adjunct to Radiation Therapy versus 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

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
08/02/1991	Sep 94	02/20/1998

Study Objective: To determine whether the combination of 5-fluorouracil (5-FU) 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 pelvic lymph nodes, positive parametrial involvement, or positive surgical margins following radical hysterectomy and lymph node dissection for Stages I-A2, I-B, and II-A carcinoma of the cervix and to determine the increase in toxicities due to 5-FU and cisplatin as an adjunct to radiation therapy versus radiation therapy alone.

Technical Approach: Patients must have primary, histologically confirmed, invasive squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix, clinical stages I-A2, I-B, or II-A and must have had a radical hysterectomy with total pelvic lymphadenectomy and para-aortic sampling. Patients must have, at surgical evaluation, either histologically confirmed positive pelvic lymph nodes, positive parametrial involvement, or positive surgical margins. Patients with confirmed positive para-aortic lymph nodes are not eligible. Patients must not have received prior chemotherapy, immunotherapy (including biologics), hormonal therapy, or pelvic irradiation. Patients will be randomly assigned to receive either 5-FU and cisplatin plus pelvic irradiation or pelvic irradiation alone. Patients with positive high common iliac lymph nodes will receive extended field para-aortic irradiation. Irradiation and chemotherapy will begin simultaneously within six weeks after surgery. Chemotherapy will be given once a week every three weeks for four cycles. Radiation therapy will be given for six weeks. After completion of therapy, patients will be followed every 3 months for two years and every 6 months thereafter. Formal analysis of progression-free and overall survival will be performed at 2 1/2 years after the start of patient accrual to determine if consideration should be given to early termination of either treatment arm.

Progress: This study was closed to patient entry, 20 May 94. One patient, enrolled in 1991, remains without evidence of recurrence of disease.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 91/074 **Status**: Ongoing

Title: GOG 0115: Bleomycin (NSC #125066), Etoposide (NSC #141540) and Cisplatin (NSC #119875) (BEP) as First-Line Therapy of Malignant Tumors of the Ovarian Stroma (Granulosa Cell, Sertoli-Leydig Tumor, and Unclassified Sex Cord Stromal Tumor)

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
07/12/1991	Indefinite	02/20/1998

Study Objective: To assess the efficacy of bleomycin, etoposide (VP-16), and cisplatin (BEP) chemotherapy in patients with malignant tumors of the ovarian stroma as a first-line regimen.

Technical Approach: Eligible patients will be those with histologically confirmed primary Stages II, III, or IV with incompletely resected disease, recurrent or persistent tumor of the ovarian stroma (granulosa cell tumor, granulosatheca cell tumor, Sertoli-Leydig cell tumor, androblastoma, gynandroblastoma, unclassified sex cord stromal tumor, or sex cord tumor with annular tubules). Patients will undergo, where appropriate, a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Omentectomy, cytologic washings, and other surgical staging such as pelvic and peri-aortic node sampling, multiple pelvic and diaphragmatic node biopsies are optional. Within 8 weeks of surgery, patients will be placed on BEP therapy: bleomycin IV push weekly for nine weeks, etoposide IV daily times five every three weeks for four courses, cisplatin IV daily times five, every three weeks for four courses. Complete responders or patients with nonmeasurable disease will undergo reassessment laparotomy not later than eight weeks following final course of therapy. To be evaluable for response, a patient will receive at least one course of chemotherapy. The efficacy of the three-drug combination will be evaluated by frequency of negative second-look and frequency and severity of acute toxicity.

Progress: This study was closed to patient entry, April 1997. One patient had disease detected at second look laparotomy in Sep 98. However, she still has no clinical evidence of disease.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/061 **Status**: Terminated

Title: GOG 0120: A Randomized Comparison of Hydroxyurea vs Hydroxyurea, 5-FU Infusion and Bolus Cisplatin vs Weekly Cisplatin as Adjunct to Radiation Therapy in Patients with Stages IIB, III, IV-A Carcinoma of the Cervix and Negative Para-Aortic Nodes

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
03/05/1993	Oct 97	02/20/1998

Study Objective: 1) To compare the relative efficacy of radiation sensitization of hydroxyurea alone or in combination with 5-Fluorouracil and Cisplatin versus Cisplatin alone in the treatment of Stages II-B through IV-A carcinoma of the cervix. 2) To determine the relative toxicities of these three different radiation sensitization schemes.

Technical Approach: Patients with locally advanced carcinoma of the cervix who have histologically confirmed negative para-aortic lymph nodes will be eligible for this study. Patients who consent will be randomized to three different treatment regimens. All treatment regimens will include the same radiation therapy technique given as standard therapy. Randomization will be between 1) Cisplatin 40 mg/m^2 IV q week X 6, (2) Cisplatin 50 mg/m^2 IV on days 1 & 29 with continuous infusion of 5-FU 1000 mg/m^2 on days 2 - 5 and 30 - 33 and hydroxyurea PO 2 mg/m^2 Mon/Thurs every week during radiation therapy (3) hydroxyurea PO 3 gm/m^2 Mon/Thurs every week during radiation therapy. Following therapy, patients will be monitored every 3 months for first 2 years and then every 6 months for the next 3 years.

To determine the efficacy of cisplatin, the principle parameters to be collected, analyzed and reported are: a) outcome variables (recurrence-free interval and survival) b) tumor characteristics c) host characteristics d) adverse effects (frequency and severity e) therapy administered.

Interim analyses will be conducted at approximately the 2nd, 3rd, 4th and 5th years using a global log-rank test. The goal will be to identify large differences in the recurrence free interval among the three treatment regimens. The interim log-rank test will be adjusted for important prognostic factors.

Progress: No patients have been enrolled at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/014 **Status**: Terminated

Title: GOG 0122: Whole Abdominal Radiotherapy Versus Combination Doxorubicin-Cisplatin Chemotherapy in Advanced Endometrial Carcinoma

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
10/01/1993	Jan 97	02/20/1998

Study Objective: 1) To compare the effectiveness of chemotherapy to whole abdominal radiation therapy in patients with advanced endometrial cancer which has been resected to less than 2 cm residual tumor. 2) To compare the relative toxicity of these two treatment strategies.

Technical Approach: Patients who have had surgical intervention for advanced (Stage III or IV) endometrial carcinoma confined to the abdominal cavity will be randomized either to whole abdominal radiation therapy or chemotherapy utilizing Doxorubicin at 60 mg/m^2 and Cisplatin at 50 mg/m^2 given every three weeks for eight cycles. After the completion of therapy patients will be seen and evaluated every three months for two years and six months thereafter for five years after treatment. Nationally 240 patients will be enrolled over 4 years. Patients will be evaluated for length of survival, disease-free survival and toxicity.

Progress: No patients have been enrolled in this study at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/063 **Status**: Ongoing

Title: GOG 0123: A Randomized Comparison of Radiation Therapy & Adjuvant Hysterectomy vs Radiation Therapy & Weekly Cisplatin & Adjuvant Hysterectomy in Patients with Bulky Stage IB Carcinoma of the Cervix

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
03/05/1993	Oct 97	02/20/1998

Study Objective: To evaluate the addition of weekly chemotherapy with Cisplatin during radiation therapy in patients with bulky Stage IB carcinoma of the cervix.

Technical Approach: This study randomizes patients to two different treatment regimens. Both regimens include radiation therapy followed by hysterectomy. Regimen I - Radiation Therapy Plus Adjuvant Hysterectomy - Patients will undergo combined external and intracavitary radiation therapy followed by extrafascial hysterectomy (total doses of 13000 cGy). Regimen II - Radiation Therapy Plus Weekly Cisplatin Infusion Plus Extrafascial Hysterectomy. Patient will undergo radiation therapy to receive a total dose of 13000 cGy using a combination of external and intracavitary radiation therapy. Each week during external radiation therapy and during the intracavitary applications the patient will receive an infusion of cisplatin 40 mg/m^2 not to exceed 70 mg maximum in any single infusion, up to a maximum of 6 doses of cisplatin. Extrafascial hysterectomy will be carried out no later than six weeks following the last day of treatment in both regimens.

The principal parameters to determine the efficacy of weekly cisplatin during radiotherapy are: 1) Outcome variables (recurrence-free interval (RF), survival and local control rate); 2) Tumor characteristics; 3) Host characteristics; 4) Adverse effects; 5) Therapy administered.

Progress: This study was closed to patient entry, April 1997 One patient was enrolled who remains without evidence of recurrence of disease.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/072 **Status**: Terminated

Title: GOG 0126-G: Evaluation of CI-958 in Recurrent, Platinum Resistant, and Refractory Ovarian Cancer

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
03/21/1997	Mar 98	02/20/1998

Study Objective: 1) To estimate the antitumor activity of CI-958 in patients with recurrent or refractory ovarian cancer who have failed on higher priority treatment protocols. 2) To determine the nature and degree of toxicity of CI-958 in this cohort of patients.

Technical Approach: Patients with histologically determined recurrent platinum-resistant epithelial ovarian cancer who agree to participate in this study will be treated with a two hour infusion of CI-958 administered at 21 day intervals. All patients require the placement of a central venous access device because of significant phlebitis resulting from the administration of CI-958. Treatment will continue until the disease progression or unexceptable side effects develop or two cycles pasted a clinical complete response. Initial treatment modification are listed page 11 and 12 of the treatment protocol. Standard hematologic support with granulocyte colony stimulating factor may be utilized at the discretion of the investigator. While on therapy, patients will be evaluated by physical examination and tumor measurements prior to every cycle if the tumor measurements are obtained by physical examination. For those patients requiring radiographic assessment to determine response, tumor measurements will be obtained after every second cycle. All patients will undergo pretreatment assessment by history, physical examination, tumor measurements, CBC with differential and platelets, serum electrolytes, bun, creatinine, Ca, Mg, Phosphate, urinalysis, bilirubin, SOOT, Alkaline Phosphatase, chest x-ray, EKG, CA-125, and Muga Scan. The Muga scan will be repeated after six cycles and then every three thereafter or more frequently if dictated by the patients clinical condition. The patients will be followed subsequent to treatment until death.

Progress: No patients have been entered at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/073 **Status**: Terminated

Title: GOG 0126-H: Evaluation of 24-Hour Continuous Infusion Topotecan in Recurrent, Platinum-Resistant and Refractory Ovarian Cancer

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
03/21/1997	Mar 98	02/20/1998

Study Objective: To evaluate the efficacy of 24 Hour continuous infusion topotecan in the treatment of patients with recurrent epithelial ovarian cancer.

Technical Approach: This study will evaluate the safety and efficacy of a 24 hour continuous infusion of intravenous topotecan in patients with histologically documented recurrent epithelial ovarian cancer who have been determined to be platinum-resistant. Platinum-resistance is determined by lack of response to platinum based chemotherapy or recurrence within six months of completion of platinum based chemotherapy. Topotecan will be administered by a 24-hour continuous intravenous infusion at three week intervals. In the event of significant hematologic toxicity, a dose reduction will be accomplished. Hematologic toxicity will be evaluated with weekly CBC's. Prior to patients will be treated at three week intervals. Prior to each treatment cycle a history and physical examination will be performed and the following laboratory evaluation: PT/PTT, BUN/creatinine, bilirubin, total/direct, SGOT/SGPT, alkaline phosphatase, Na, K, Cl, CO2, P, glucose, and urine analysis. In the event that tumor measurements are obtained by imaging studies such as a CT scan or MRI imaging studies will be performed every six weeks for tumor measurement. Chest x-ray and EKG will be obtained prior to every treatment cycle as clinically indicated. Patients will continue treatment until disease progression for the development of unexceptable side effects.

Progress: No patients have been entered at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/064 **Status**: Terminated

Title: GOG 0126C: A Phase II Evaluation of Altretamine (Hexamethylmelamine) in Recurrent, Platinum-Resistant and Refractory Ovarian Cancer

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
01/20/1995	Aug 95	02/20/1998

Study Objective: To evaluate the use of altretamine as second-line chemotherapy in patients resistant to platinum containing compounds and taxol.

Technical Approach: Patients with epithelial ovarian cancer refractory to platinum containing compounds and taxol will be eligible for participation in this study. Participants in this study will be treated with altretamine at a dose of 260 mg/m^2 daily for 14 days. Treatment cycles will be repeated at 28 day intervals, providing serious side effects or tumor progression do not interfere. During the course of therapy weekly CBC's and liver function tests will be obtained. Should disease progression or severe side effects occur, therapy will be discontinued. Patients will be continued to be followed for life.

Progress: This protocol was suspended by GOG in August 1996 until data could be analyzed to determine if enough patients have been accrued. No patients have been enrolled at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/066 **Status**: Terminated

Title: GOG 0126D: Evaluation of Pyrazoloacridine (PZA) (NSC #366140) in Recurrent, Platinum-Resistant and Refractory Ovarian Cancer

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
02/16/1996	Jul 96	02/20/1998

Study Objective: To evaluate the safety and efficacy of Pyrazoloacridine in the treatment of platinum-resistant and refractory epithelial ovarian carcinoma.

Technical Approach: Patients with recurrent epithelial ovarian cancer who are resistant to platinum containing compounds will be eligible for this study. Subjects will be treated with Pyrazoloacridine, administered intravenously over three hours. Treatment cycles will be repeated every three weeks.

During the course of therapy, patients will have weekly CBC's and platelet counts. Prior to each course of treatment a history and physical examination will be performed and routine liver function test will be obtained. Additionally, routine blood chemistries will be obtained. Tumor measurements will be obtained every three weeks if measurable on physical examination, however, if measured by CT, ultrasound or chest x-ray it will be evaluated every six weeks. Patients will continue to receive chemotherapy every three weeks until tumor progression or severe toxicity intervenes. If complete tumor resolution occurs treatment will continue at least three cycles, but may continue indefinitely at the discretion of the patient and investigator. Patients who develop febrile neutropenia or a granulocyte count less than 500 will have dose reductions as outlined in the protocol. Patients who develop febrile neutropenia or develop neutropenia long enough to result in repetitive delays may be supported with Granulocyte-Colony Stimulating Factor (G-CSF). Patients entered into this protocol will be followed for life.

Progress: This protocol was suspended in Feb 96 until data could be analyzed to determine if more subjects were needed. No patients have been entered at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/091 **Status**: Terminated

Title: GOG 0127-J: Evaluation of 9-Cis Retinoic Acid (9-CRA, NSC #659772) in Persistent or Recurrent Squamous Cell Carcinoma of the Cervix Previously Treated by Chemotherapy

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
04/18/1997	Mar 98	02/20/1998

Study Objective: 1) To estimate the anti tumor activity of 9-Cis Retinoic Acid in patients with persistent or recurrent squamous cell carcinoma of the cervix who have failed previous chemotherapy. 2) To determine the nature and degree of toxicity of 9-Cis Retinoic Acid in this cohort of patients.

Technical Approach: Patients with recurrent squamous cell carcinoma of the cervix who have failed previous chemotherapy are eligible for entry into this study. All eligible patients who consent to therapy will be treated with continuos oral 9-Cis Retinoic Acid until disease progresses or adverse effects prohibit further therapy. If tumor measurements are determined on physical examination, tumor measurements will be part of the physical examination prior to each four week course of chemotherapy. In the event of radiologic determination of tumor measurements other than chest x-ray, imaging studies will be performed every two courses. While undergoing therapy a weekly CBC with differential and platelet count will be obtained. Prior to each course of chemotherapy a creatine, bilirubin, SOOT, alkaline phosphatase, triglycerides, calcium, LDH and urinalysis will be obtained. Treatment modifications based of toxicity are outlined in pages 12-15 of the study protocol. All patients will be followed after treatment until death.

Progress: No patients have been enrolled at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/171 **Status**: Terminated

Title: GOG 0127H: Evaluation of Prolonged Oral Etoposide (VP-16) in Persistent or Recurrent Squamous Cell Carcinoma of the Cervix

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
07/21/1995	Sep 96	02/20/1998

Study Objective: To evaluate the safety and efficacy of prolonged oral VP-16 in the treatment of recurrent or metastatic squamous cell carcinoma of the cervix.

Technical Approach: Patients with historically proven or metastatic squamous cell carcinoma of the cervix will be treated with oral VP-16 for 21 consecutive days out of a 28 day cycle. Treatment will be reviewed on day 29 after a one week break. Patients who have received previous radiation therapy will be started at a lower dose initially. Dose modification with either dose reduction or dose intensification is possible depending on marrow rescue. Clinical management, including physical examination and chest x-ray will be obtained prior to each cycle. If additional imaging studies, such as CT ultrasound or MR are required, tumor measurements will be repeated after every other cycle. Treatment will be discontinued should severe toxicity or tumor progression result. There are no treatment comparisons involved and no known historical controls available. The study design will be primarily based on prior GOG experience in this disease entity. This will insure consistency in evaluation of response. Therapy plans demonstrating activity will later be compared and investigated in ensuing phase III studies

Progress: No patients have been enrolled at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/009 **Status**: Terminated

Title: GOG 0127K: Evaluation of Gemcitabine in Persistent or Recurrent Squamous Cell Carcinoma of the Cervix

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
10/17/1997	Dec 98	02/20/1998

Study Objective: To evaluate the safety and efficacy of Gemcitabine in the treatment of patients with recurrent or metastatic squamous cell carcinoma unresponsive to traditional therapy.

Technical Approach: Patients will receive weekly infusions of Gemcitabine over 30 minutes, for 3 weeks followed by one week rest prior to starting the next course. Treatment may be continued until disease progression or until severe toxicity limits further treatment.

Progress: No patients were enrolled in this protocol at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/102 **Status**: Terminated

Title: GOG 0128B: Evaluation of Paclitaxel (Taxol) in Persistent or Recurrent Non-Squamous Cell Carcinoma of the Cervix and Vagina

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
05/06/1994	May 95	02/20/1998

Study Objective: To evaluate efficacy of Paclitaxel (Taxol) in the treatment of patients with persistent or recurrent non-squamous cell carcinoma of the cervix or vagina.

Technical Approach: Patients with incurable recurrent or persistent non-squamous cell carcinoma of the cervix and vagina are eligible to participate in this study. All patients will receive a 24 hour infusion of Paclitaxel at 170 mg/m^2 every three weeks. Patients who have received previous radiation therapy to the pelvis will be treated at a dose of 135 mg/m^2 every three weeks. Routine weekly CBCs will be obtained to monitor for significant neutropenia. Should significant neutropenia develop resulting in fever or prolonged neutropenia, dose reduction will occur. If a dose of 110 mg/m^2 still results in significant neutropenia, granulocyte colony stimulating factor (G-CSF) will be used. On subsequent treatment cycles, 5 microgram/kg will be administered subcutaneously starting 24 hours after therapy and continuing until absolute granulocyte count is sufficient. Patients will continue to receive Taxol every three weeks until tumor progression occurs or severe side effects prevent further therapy. Tumor measurements will be obtained prior to every cycle if detectable on physical examination. Measurements determined by x-rays or imaging studies will be obtained every 6 weeks.

Progress: This study was closed to enrollment in Dec 94 to review data collection. It was reactivated in May 95. No patients have been enrolled at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 97/029	**Status**: Terminated

Title: GOG 0128D: Evaluation of Tamoxifen in Persistent or Recurrent Non-squamous Cell Carcinoma of the Cervix

Principal Investigator: COL Mark E. Potter, MC

Department: GOG	**Facility**: MAMC

Associate Investigator(s): None.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/15/1996	Jan 98	02/20/1998

Study Objective: 1) To evaluate the efficacy of tamoxifen citrate in the treatment of non-squamous cell carcinoma of the cervix. 2) To evaluate the influence of hormonal manipulation on the expression of Human Papilloma Virus (HPV) viral protein products (E6 & E7).

Technical Approach: This study will assess the relative efficacy of tamoxifen citrate in the treatment of advanced recurrent non-squamous cell carcinoma of the cervix. Patients with histologically proven recurrent non-squamous cell carcinoma of the cervix will be eligible for treatment. All patients entered into this study will have a pre-treatment biopsy specimen submitted for the evaluation of the expression of the E6 & E7 protein of the Human Papilloma Virus. Patients will be treated with tamoxifen citrate at 10 mg orally bid. Treatment will continue until there is evidence of disease progression or adverse effects prohibit further therapy. Upon withdrawal of tamoxifen therapy, a further tissue sample will be obtained to re-evaluate the HPV E6 & E7 protein expression. Physical examination, routine CBC will be obtained prior to initiation of therapy and monthly thereafter. Tumor measurements will be obtained on a monthly basis.

Progress: No patients have been enrolled at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/026 **Status**: Terminated

Title: GOG 0129-I: Evaluation of Pyrazoloacridine (PZA) (NSC#366140) in the Treatment of Recurrent or Persistent Endometrial Carcinoma

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
11/21/1997	Dec 98	02/20/1998

Study Objective: To determine if PZA has significant activity with an acceptable level of toxicity in patients with advanced or recurrent endometrial carcinoma who have failed standard therapy.

Technical Approach: PZA will be given intravenously over three hours every three weeks. Treatment will continue until disease progression or significant toxicity precludes further therapy.

Progress: No patients were enrolled in this protocol at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 96/068	**Status**: Terminated

Title: GOG 0129E: Evaluation of Dactinomycin (Cosmegen) in the Treatment of Recurrent or Persistent Endometrial Carcinoma

Principal Investigator: COL Mark E. Potter, MC

Department: GOG		**Facility**: MAMC

Associate Investigator(s): None.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/16/1996	Feb 97	02/20/1998

Study Objective: To determine if the Dactinomycin has significant activity with an acceptable level of toxicity in patients with advanced or recurrent endometrial carcinoma who have failed standard therapy.

Technical Approach: This study will assess the relative efficacy as well as toxicity of intravenous Dactinomycin in patients with histologically documented recurrent or advanced endometrial carcinoma with clinically measurable disease who have failed standard therapy and are not curable by surgery or radiation therapy. Dactinomycin will be given intravenously over 15 minutes every four weeks. Treatment will continue until disease progression or significant toxicity precludes further therapy. In the absence of severe toxicity or tumor progression, the patient may remain on therapy indefinitely at the discretion of the investigator.

Progress: No patients have been enrolled at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/010 **Status**: Terminated

Title: GOG 0129H: Evaluation of Doxil in the Treatment of Recurrent or Persistent Endometrial Carcinoma

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
10/17/1997	Dec 98	02/20/1998

Study Objective: To determine if the Doxil has significant activity with an acceptable level of toxicity in patients with advanced or recurrent endometrial carcinoma who have failed standard therapy.

Technical Approach: Patients will receive Doxil intravenously over one hour every four weeks. Treatment may be continued until disease progression or significant toxicity precludes further therapy.

Progress: No patients were enrolled in this protocol at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/074 **Status**: Terminated

Title: GOG 0130-C: Evaluation of Trimetrexate in the Treatment of Persistent or Recurrent Mixed Mesodermal Tumors of the Uterus

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
03/21/1997	Mar 98	02/20/1998

Study Objective: 1) To estimate the objective response rate of trimetrexate in patients with advanced, persistent, or recurrent mixed mesodermal tumors of the uterus who have failed standard therapy. 2) To determine the nature and degree of toxicity of trimetrexate in this cohort of patients.

Technical Approach: Patients with advanced or recurrent mixed mesodermal tumors of the uterus who have failed higher GOG priority treatment protocols will be eligible for this study. Eligible patients will be treated with oral trimetrexate twice a day for five days every fourteen days until disease progression or unexceptable toxicity develops. Leucovorin support will be administered for grade IV toxicity. Prior to the study patients will have a physical examination and undergo tumor measurements by either physical examination or imaging studies. Laboratory including CBC with differential and platelets, creatine, alkaline phosphatase, SOOT, bilirubin, and serum albumin will be obtained at it's baseline. While on therapy a weekly CBC with platelets and differential will be obtained. Tumor measurements by physical examination or imaging will be repeated every four weeks. Serum bilirubin, albumin, creatine, SOOT, alkaline phosphatase will also be repeated at four week intervals. Subsequent to the completion of treatment, patients will be followed until their death.

Progress: No patients have been enrolled at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/062 **Status**: Terminated

Title: GOG 0131-B: Evaluation of Prolonged Oral Etoposide (VP-16) in the Treatment of Recurrent or Advanced Leiomyosarcoma of the Uterus

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
02/04/1994	Jun 95	02/20/1998

Study Objective: To determine if the utilization of semi-continuous low dose oral etoposide has significant activity with an acceptable level of toxicity in patients with advanced or recurrent leiomyosarcoma of the uterus who have failed standard therapy.

Technical Approach: Patients with histologically confirmed recurrent or metastatic leiomyosarcoma that have failed local therapeutic measures and have adequate bone marrow, renal, and hepatic function will be invited to participate in this study. Etoposide (VP-16) will be administered at a dosage of 50 mng/m²/day, day 1-21 every 4 weeks. If side effects are not severe, a patient may remain on the study agent indefinitely at the investigator's discretion. Likewise, patients with evidence of progressive disease or those with significant side effects or deterioration of performance status may be removed from study at the investigator's discretion. All patients will be followed until death.

Progress: No patients have been entered at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/011 **Status**: Terminated

Title: GOG 0131-C: Evaluation of Paclitaxel (TAXOL) in the Treatment of Recurrent or Advanced Leiomyosarcoma of the Uterus

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
10/17/1997	Jun 99	02/20/1998

Study Objective: To estimate the antitumor activity of paclitaxel in patients with recurrent or persistent leiomyosarcoma of the uterus who have failed on higher priority treatment protocols and to determine the nature and degree of toxicity of paclitaxel in this cohort of patients.

Technical Approach: Paclitaxel will be administered as a 3 hour continuous infusion at an initial dose of 175 mg/m^2 every 3 weeks. The starting dose should be reduced to 135 mg/m^2 for patients who have had prior pelvic radiation therapy. The minimum treatment period will be one course. Patients who have complete response, partial response, or stable disease will continue for at least 3 courses.

Progress: No patients were enrolled in this protocol at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/075 **Status**: Terminated

Title: GOG 0131-D: Evaluation of Trimetrexate in the Treatment of Recurrent or Advanced Leiomyosarcoma of the Uterus

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
03/21/1997	Mar 98	02/20/1998

Study Objective: 1) To estimate the objective response rate of trimetrexate in patients with advanced, persistent, or recurrent Leiomyosarcomas of the uterus who have failed standard therapy. 2) To determine the nature and degree of toxicity of trimetrexate in this cohort of patients.

Technical Approach: Patients with advanced or recurrent Leiomyosarcomas of the uterus who have failed higher GOG priority treatment protocols will be eligible for this study. Eligible patients will be treated with oral trimetrexate twice a day for five days every fourteen days until disease progression or unexceptable toxicity develops. Leucovorin support will be administered for grade IV toxicity. Prior to the study patients will have a physical examination and undergo tumor measurements by either physical examination or imaging studies. Laboratory including CBC with differential and platelets, creatine, alkaline phosphatase, SOOT, bilirubin, and serum albumin will be obtained at it's baseline. While on therapy a weekly CBC with platelets and differential will be obtained. Tumor measurements by physical examination or imaging will be repeated every four weeks. Serum bilirubin, albumin, creatine, SOOT, alkaline phosphatase will also be repeated at four week intervals. After completion of treatment, patients will be followed until death.

Progress: This study met its first stage accrual goal and was suspended to patient entry, 2 Sep 97. No patients were entered at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 97/146	**Status**: Terminated

Title: GOG 0137: A Randomized Double-Blinded Trial of Estrogen Replacement Therapy versus Placebo in Women with Stage I or II Endometrial Adenocarcinoma

Principal Investigator: COL Mark E. Potter, MC

Department: GOG	**Facility**: MAMC

Associate Investigator(s): None.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/19/1997	Jun 04	02/20/1998

Study Objective: To determine if the use of estrogen replacement therapy significantly increased the risks of developing recurrence of endometrial cancer after primary treatment.

Technical Approach: Patients entered into this randomized, placebo controlled study will be patients with endometrial cancer without evidence of metastatic disease beyond the uterus or cervix. Some patients may have been simultaneously entered into a protocol randomizing them to receive chemotherapy or no chemotherapy. Other patients will have received treatment with or without radiation as recommended by their primary physician and/or by choice. Patients who are randomized to estrogen replacement therapy will be taking estrogen on a daily basis for the duration of the study. Starting at .625 per day and increasing to a maximum of 1.25 per day as needed for hot flashes for three years. Patient compliance is assets by turning in the empty prescription and a medication log. All patients will receive yearly mammograms because of an increased risk of breast cancer in patients with endometrial cancer and to evaluate the potential confounding risk afforded by estrogen replacement in this group of high risk patients. All other follow-up is in a standard fashion.

Progress: No patients have been entered at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/087 **Status**: Terminated

Title: GOG 0139: A Randomized Study of Doxorubicin Plus Cisplatin versus Circadian-Timed Doxorubicin Plus Cisplatin in Patients with Primary Stages III and IV, Recurrent Endometrial Adenocarcinoma

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
04/02/1993	Mar 96	02/20/1998

Study Objective: 1) To evaluate the potential benefit of the administration of Circadian-timed, chemotherapy versus standard administration of chemotherapy utilizing Doxorubicin and Cisplatin. 2) To evaluate the relative toxicities of these two techniques of administration.

Technical Approach: This study will assess the relative benefit either in improved response rate or decreased toxicity by changing the method of delivery of the chemotherapeutic agents from an arbitrarily administered event to a timed delivery method. Patients will be randomized to receive either standard Doxorubicin/Cisplatin infusions given at a dose of Doxorubicin 60 mg per meter squared, IV Push followed by Cisplatin 60 mg per meter squared over 30 minutes immediately following the Doxorubicin in one treatment regimen as opposed to Doxorubicin at the same dose given IV Push over 30 minutes at 6 a.m. with the Cisplatin at 60 mg per meter squared delivered over 30 minutes at 6 p.m. Both chemotherapeutic regimen would be delivered every 3 weeks for a maximum of eight treatments. Dose reduction would occur initially because of advanced age or previous pelvic radiation therapy. Only patients with advanced or recurrent measurable Adenocarcinoma, Adenoacantheoma, Adenosquamous carcinomas, whose potential for cure by radiation therapy or surgery, alone or in combination is very poor. Prior to each cycle of chemotherapy, patients will be evaluated by history, physical examination, and the usual radiologic test required for monitoring tumor response. The treatment will continue for a maximum of eight treatments or until the tumor progresses.

Progress: No patients have entered this study at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/092 **Status**: Terminated

Title: GOG 0141: 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

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/18/1997	Nov 02	02/20/1998

Study Objective: To evaluate the efficacy of neoadjuvant chemotherapy preceding surgical therapy of bulky stage IB cervical cancers.

Technical Approach: This study will assess the value of neoadjuvant chemotherapy utilizing vincristine and cisplatin prior to definitive therapy of stage IB (bulky) cervical cancer by radical hysterectomy, pelvic and para-aortic lymphadenectomy. All patients will be treated with radical hysterectomy, pelvic and para-aortic lymphadenectomy unless histologically documented para-aortic lymph node involvement, parametrial extension, or unresectable pelvic lymph nodes are present. Said involvement must be histologically confirmed. Prior to surgery all patients will be randomized to receive neoadjuvant therapy with vincristine at 1 mg/m^2 IV and cisplatin at 50 mg/m^2 IV administered every ten days for three treatments or no chemotherapy. Patients who randomize to chemotherapy will undergo radical hysterectomy, pelvic and paraaortic lymphadenectomy two to four weeks following completion of chemotherapy, unless progression beyond the cervix occurs during chemotherapy. If progression beyond the cervix occurs during chemotherapy they will be treated with radiation therapy. After radical hysterectomy, pelvic and para-aortic lymphadenectomy patients with surgical margins or positive pelvic lymph nodes will receive radiation to the pelvis post-operatively. Patients who have unsuspected para-aortic metastases will be treated with extended field radiation to the para-aortic lymph nodes.

Subsequent to therapy, all patients will be seen every three months times eight and every six months times six and then yearly thereafter.

Prior to treatment and each course of chemotherapy all patients will undergo a physical examination and tumor measurements.

Additionally, tumor measurements will be obtained each week for those patients who require radiation therapy because of extra cervical progression while receiving chemotherapy. Prior to each course of chemotherapy as well as prior to surgery all patients will have a CBC with differential and platelet, creatinine, SGOT alkaline phosphatase, and bilirubin. Patients who receive radiation therapy will have a CBC with differential and platelets obtained weekly during radiation therapy.

Progress: No patients have been entered at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/149 **Status**: Terminated

Title: GOG 0143: Familial and Reproductive Factors in Ovarian Cancer

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
08/06/1993	Aug 95	02/20/1998

Study Objective: 1. To further define the epidemiologic pattern of patients with invasive ovarian carcinoma. 2. To store genetic material for comparison should a genetic marker be identified in the future utilizing risk factors for the development of ovarian cancer to target a patient population suitable for screening.

Technical Approach: Patients identified with invasive ovarian carcinoma will be asked to complete a questionnaire. Additionally, two tubes of blood will be obtained and forwarded for storage, for potential DNA analysis. This is an epidemiologic study and requires no follow-up of the patients.

Progress: No patients entered this study at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/140 **Status**: Terminated

Title: GOG 0145: A Randomized Study of Surgery vs Surgery + Vulvar Radiation in the Management of Poor Prognosis Primary Vulvar Cancer and of Radiation vs Radiation & Chemotherapy for Positive Inguinal Node

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
08/05/1994	Aug 99	02/20/1998

Study Objective: 1. To determine whether he additional radiation therapy to the area of vulvar resection decreases the risk of recurrent cancer in high risk patients. 2. Whether the addition of chemotherapy along with radiation improves the effect of radiation therapy in decreasing the risk of tumor recurrence in the areas treated by radiation therapy. 3. To evaluate the impact of these therapeutic interventions on the overall quality of life both during and subsequent to treatment. 4. To determine if HPV status alters the risk of local recurrence and/or survival.

Technical Approach: Patients with invasive squamous cell carcinoma of the vulva who meet the eligibility criteria will have initial surgery on the vulva and groins. After pathological examination of the specimen, patients will be eligible for randomization to observation or to additional therapy to the vulva. Patients with positive nodes will be randomized to receive radiation alone or radiation and chemotherapy to the inguinal and pelvic nodes. Patient treated with chemotherapy will receive Cisplatin day one, followed by four days of continuous infusion of 5 FU. In addition, patients will complete quality of life questionnaires prior to receiving radiation or chemotherapy, then at three, six, twelve, eighteen, and twenty-four months. All patients will be followed in the OB-GYN Oncology Clinic subsequent to treatment. Initial frequency of follow-up will be at three month intervals for one year, followed by four month intervals for one additional year and then every six months for an additional three years. The patient's disease status will be correlated with the presence or absence of HPV in the tumor and surrounding tissue.

Progress: No patients have been enrolled in this study at MAMC. The study was suspended to patient entry 11 Aug 97 due to inadequate accrual; the study was terminated 27 Oct 97 due to insufficient patient accrual.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/090 **Status**: Terminated

Title: GOG 0146-C: Evaluation of Topotecan (SKF 104864-A) (NSC#609699) in Recurrent, Platinum, Sensitive Ovarian Cancer

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
03/17/1995	Dec 95	02/20/1998

Study Objective: To evaluate the safety and efficacy of Topotecan in the treatment of platinum-sensitive epithelial ovarian carcinoma.

Technical Approach: Patients with recurrent epithelial ovarian cancer who have previously responded in a favorable fashion to platinum containing compounds will be eligible for this study. Patients who choose to participate will be treated with Topotecan, administered intravenously over thirty minutes daily for five consecutive days. Treatment cycles will be repeated every three weeks from the first day of chemotherapy. During the course of therapy, patients will have weekly CBC's and platelet counts. Prior to each course of treatment a history and physical examination will be preformed and routine liver function test (i.e., PT and PTT) will be obtained. Additionally, routine blood chemistries will be obtained. Tumor measurements will be obtained every three weeks if measurable on physical examination or routine chest radiography, however, if measured by CT or ultrasound it will be evaluated every six weeks. Patients will continue to receive chemotherapy every three weeks until tumor progression or severe toxicity intervenes. Patients who develop febrile neutropenia or develop neutropenia long enough to result in repetitive delays will be supported with Granulocyte-Colony Stimulating Factor (G-CSF) at 5 mcg/kg/day subcutaneously. G-CSF support will be administered the day after the last dose of Topotecan and continued through day 18 or until hematopoietic recovery. No G-CSF will be administered when the white blood cell count is greater than or equal to 15,000/mcL. Patients entered into this protocol will be followed for life.

Progress: This study was closed to patient entry, 16 Feb 96, to review the data. It was reactivated, 21 Apr 96. No patients have been enrolled at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/065 **Status**: Terminated

Title: GOG 0146-D: Evaluation of Pyrazoloacridine (PZA) (NSC #366140) in Recurrent, Platinum-Sensitive Ovarian Cancer

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/16/1996	Jul 96	02/20/1998

Study Objective: To evaluate the safety and efficacy of Pyrazoloacridine in the treatment of platinum-sensitive epithelial ovarian carcinoma.

Technical Approach: Patients with recurrent epithelial ovarian cancer who have previously responded in a favorable fashion to platinum containing compounds will be eligible for this study. Subjects will be treated with Pyrazoloacridine, administered intravenously over three hours. Treatment cycles will be repeated every three weeks.

During the course of therapy, patients will have weekly CBC's and platelet counts. Prior to each treatment, a history, physical examination and routine liver function test will be performed. Additionally, routine blood chemistries will be obtained. Tumor measurements will be obtained every three weeks if measurable on physical examination, however, if measured by CT, ultrasound or chest x-ray it will be evaluated every six weeks. Patients will continue to receive chemotherapy every three weeks until tumor progression or severe toxicity intervenes. If complete tumor resolution occurs treatment will continue at least three cycles, but may continue indefinitely at the discretion of the patient and investigator. Patients who develop febrile neutropenia or a granulocyte count less than 500 will have dose reductions as outlined in the protocol. Patients who develop febrile neutropenia or develop neutropenia long enough to result in repetitive delays may be supported with Granulocyte-Colony Stimulating Factor (G-CSF). Patients entered into this protocol will be followed for life.

Progress: This study was suspended, 4 Jun 96, to review the data. No patients have been entered at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/102 **Status**: Terminated

Title: GOG 0146-E: Evaluation of CI-958 in Recurrent, Platinum-Sensitive Ovarian Cancer

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
05/16/1997	Feb 98	02/20/1998

Study Objective: To evaluate the safety and efficacy of the investigational drug CI-958 in the treatment of recurrent platinum-sensitive ovarian cancer.

Technical Approach: Patients with measurable recurrent platinum-sensitive ovarian cancer entered into this protocol will receive CI-958 at 560 mg/m^2 over two hours every 21 days until disease progression, or two cycles beyond complete clinical response, or until adverse effects prohibit further therapy. All patients will have placement of a permanent central venous access devise prior to initiation of the first dose of chemotherapy. Routine laboratory tests will be obtained.

Progress: No patients have been entered at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/104 **Status**: Terminated

Title: GOG 0146-F: Evaluation of 24-Hour Continuous Infusion Topotecan in Recurrent and Platinum-Sensitive, or Metastatic Ovarian Cancer

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
05/16/1997	Mar 98	02/20/1998

Study Objective: To evaluate the efficacy of 24-Hour continuous infusion topotecan in the treatment of patients with recurrent epithelial ovarian cancer.

Technical Approach: Patients with histologically documented recurrent epithelial ovarian cancer who have been determined to be platinum-sensitive by a recurrence greater than six months after the initial treatment of platinum containing compounds will be treated with the 24-Hour continuous infusion of intravenous topotecan. In the event of significant hematologic toxicity, a dose reduction will be accomplished. Hematologic toxicity will be evaluated with weekly CBC's. Prior to patients will be treated at three week intervals. Prior to each treatment cycle a history and physical examination will be performed and the following laboratory evaluation: PT/PTT, BUN/creatinine, bilirubin, total/direct, SGOT/SGPT, alkaline phosphatase, NA, K, CL, CO2, P, Glucose, and urine analysis. In the event that tumor measurements are obtained by imaging studies such as a CT scan or MRI imaging studies will be performed every six weeks for tumor measurement. Chest x-ray and EKG will be obtained prior to every treatment cycle as clinically indicated. Patients will continue treatment until disease progression for the development of unexceptable side effects.

Progress: No patients have been entered at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/094 **Status**: Terminated

Title: GOG 0148: The Clinical Utility of Soluble TNF/LT Membrane Receptors in the Serum of Patients With All Stages of Primary Epithelial Ovarian Cancer

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
04/01/1994	May 95	02/20/1998

Study Objective: To evaluate the clinical utility of TNF/LT membrane receptor levels in the serum of patients with epithelial ovarian cancers as both a screening test and marker of therapeutic effect.

Technical Approach: This investigation will follow serum TNF/LT membrane receptors in the serum of patients who are undergoing treatment for primary epithelial ovarian cancer under other GOG protocols. Serum will be obtained prior to the first cycle of chemotherapy and then every other cycle thereafter. After the completion of chemotherapy, serum will be obtained every six months for two additional years. In the event that recurrent disease is suspected, serum will be obtained for investigation. The serum samples will be obtained at the time of routine laboratory studies utilized in the monitoring of ovarian cancer patients. No additional phlebotomy is therefore required.

Progress: No patients have been enrolled at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/061 **Status**: Terminated

Title: GOG 0150: A Phase III Randomized Study of Accelerated Hyperfractionated Whole Abdominal Radiotherapy (AHWAR) vs Combination Ifosfamide-Mesna With Cisplatin in Optimally Debulked Stage I, II, III, or IV Carcinosarcoma (CS) of the Uterus

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
02/04/1994	Feb 00	02/20/1998

Study Objective: To compare the use of combination Ifosfamide with Mesna and Cisplatin to hyperfractionated whole abdomen radiation therapy with regard to tolerance and efficacy in patients with carcinosarcomas of the uterus.

Technical Approach: Patients entering this study will have undergone surgical staging, TAH/BSO, and resection of gross intra-abdominal/pelvic disease. They will then be randomized to receive either radiation therapy (given as a hyperfractionated technique) or chemotherapy (utilizing ifosfamide with mesna and cisplatin). The chemotherapy will be administered over a four day period, at three week intervals. Patients treated with radiation therapy will receive twice a day treatments of 3000 cGy to the whole abdomen with a boost to the pelvis to 5000 cGy. Subsequent to therapy, patients will be seen in the clinic at three month intervals for two years and then six month intervals for the remainder of their follow-up, until completion of their analysis. Routine blood work evaluating renal and hepatic status will be obtained throughout therapy and in post-treatment follow-up.

Progress: There was one patient entered in this study in FY 96 who expired from liver failure resulting from treatment of an entero-entero fistula . This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/150 **Status**: Terminated

Title: GOG 0152: A Phase III Randomized Study of Cisplatin & Taxol (Paclitaxel) With Interval Secondary Cytoreduction vs Cisplatin and Paclitaxel in Patients with Suboptimal Stage III & IV Epithelial Ovarian Carcinoma

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
07/01/1994	Mar 96	02/20/1998

Study Objective: To determine the impact of interval cytoreductive surgery on the progression free interval, survival and quality of life of patients with Suboptimal debulked Stage III & IV epithelial ovarian cancer.

Technical Approach: All patients will have undergone maximal cytoreductive surgery for their cancer prior to entrance into the study. Subsequently, all patients will receive three treatments at three week intervals of Paclitaxel and Cisplatin by intravenous infusion. After three treatment cycles, patients will be re-evaluated to determine tumor response. Patients with stable disease or tumor response will then be randomized to secondary cytoreductive surgery followed by or three more courses of chemotherapy. Those receiving secondary cytoreductive surgery will receive three more courses of chemotherapy after surgery. Quality of life questionnaire will be completed at intervals during and after therapy.

Progress: No patients have been enrolled at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 95/095	**Status**: Terminated

Title: GOG 0156: Randomized Trial of Pelvic Radiation versus Doxorubicin Plus Cisplatin in Stage IB, Stage IC, IIA, and IIB Endometrial Carcinoma

Principal Investigator: COL Mark E. Potter, MC

Department: GOG	**Facility**: MAMC

Associate Investigator(s): None.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/21/1995	Jun 00	02/20/1998

Study Objective: To compare radiation therapy versus chemotherapy in an adjuvant setting for high risk, early stage endometrial cancer.

Technical Approach: Patients with high risk Stage IB, IC, IIA, or IIB endometrial cancer will be randomized to receive either post operative radiation therapy or post operative chemotherapy. Radiation therapy will be given in standard pelvic fields to a total dose of 5040 cGy. Patients who are randomized to receive chemotherapy will receive Doxorubicin and Cisplatin therapy given at a dose of 60 mg/m^2 and 50 mg/m^2 respectively. Chemotherapy will be given at three week intervals for a total of six treatment cycles. While receiving therapy, patients randomized to radiation therapy will have weekly CBCs drawn and patients randomized to chemotherapy will have CBCs, liver function test, and creatine obtained immediately prior to the next cycle of chemotherapy. Subsequent to treatment, all patients will be followed at three to four month intervals for two years. Standard follow-up in the Gyn Oncology Clinic involves six month follow-up thereafter until five years from treatment. However, the protocol requires a less liberal follow-up of yearly evaluations after the two year anniversary date of therapy. Patients will be followed for evidence of progressive disease and survival.

Progress: No patients have been enrolled at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increase the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/096 **Status**: Terminated

Title: GOG 0157: A Randomized Phase III Trial of Carboplatin (AUC 7.5) and Paclitaxel 175 mg/m^2 q 21 Days x 3 Courses Versus the Same Regimen x 6 Courses in Patients With Selected Stage IC and II (A,B,C) and Selected IA and IB Ovarian Cancer

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/21/1995	May 01	02/20/1998

Study Objective: 1. To evaluate the role of Taxol in the treatment of early stage high risk epithelial ovarian cancers. 2. To determine the optimal number of treatment cycles for the treatment of high risk early stage epithelial ovarian cancer.

Technical Approach: Patients entered into this study will be treated with intravenous Carboplatin at an area under the curve of 7.5. Taxol at 175 mg/m^2 will also be administered. Treatments will be provided intravenously at three week intervals. During the course of chemotherapy, weekly CBCs will be obtained to evaluate toxicity. Prior to each treatment cycle, a history and physical examination will be performed as well as creatine, CA-125 and urinalysis. Other investigative tests will be ordered as needed only. Patients will be randomized prior to the initiation of therapy to receive three or six cycles of chemotherapy. Dose reduction or the addition of G-CSF to reduce myelosuppressive side effects are outlined in the protocol. The primary modality to reduce toxicity will be dose reduction followed by the administration of G-CSF for repeated episodes or for febrile neutropenia. After the completion of therapy, patients will be followed in the GYN Oncology clinic on a monthly basis for six months and then every three months for four follow-up visits. Thereafter, they will be followed on a yearly basis for life.

Progress: No patients have been enrolled at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increase the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/072 **Status**: Terminated

Title: GOG 0158: A Phase III Randomized Study of A Platinum Compound and Paclitaxel in Optimal Stage III Epithelial Ovarian Carcinoma: Cisplatin vs Carboplatin and 3-Hour vs 96-Hour Infusions of Paclitaxel

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
01/20/1995	Mar 98	02/20/1998

Study Objective: To compare the relative efficacy and toxicity of two different platinum compounds when utilized with taxol in two different infusions schemes for the treatment of patients with optimally debulked epithelial ovarian cancer.

Technical Approach: Patients with optimally debulked Stage III epithelial ovarian cancer who agree to participate in this study will be randomized to four different treatment regimens. The treatment regimens will have two different variables (platinum compound selected - cisplatin or carboplatin and duration of infusion - 3 hours or 96 hours). All patients will be treated at three week intervals. Treatment will consist of six treatments followed by a second-look (reassessment laparotomy). Patients with progressive disease or obviously elevated CA-125's (> 100) will not be required to undergo a second-look laparotomy. After the completion of reassessment laparotomy, patients will be followed at monthly intervals for six months followed by three month intervals for additional 36 months and then every six months thereafter. Physical examinations and CA-125s will be obtained during follow-up.

Progress: No patients have been enrolled at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/093 **Status**: Terminated

Title: GOG 0160: Evaluation of Anti-HER2 Antibody in Recurrent or Refractory Ovarian Cancer

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
04/18/1997	Nov 98	02/20/1998

Study Objective: To evaluate the safety and efficacy of recombinant anti-HER2 antibody in the treatment of recurrent or refractory ovarian cancer.

Technical Approach: Patients with measurable HER2 antigen positive recurrent ovarian cancer will be treated with weekly 90 minutes intravenous infusions of rhuMAb HER2 until disease progression. The initial dose will be delivered at 4mg/kg with subsequent doses at 2mg/kg. Patients will be measured for disease status by standard physical examination or radiologic studies. Weekly laboratory tests will be obtained. Subsequently, patients will be seen every eight weeks or three visits then every twelve weeks until termination of the study.

Patients who respond and subsequently progress are eligible for retreatment at an increased dose level of 4mg/kg weekly.

Progress: No patients have been entered at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/114 **Status**: Terminated

Title: GOG 0162: A Phase III Randomized Trial of Cisplatin with Paclitaxel Administered by Either 24 Hour Infusion or 96 Hour Infusion in Patients with Selected Stage III & Stage IV Epithelial Ovarian Cancer

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
05/17/1996	May 01	02/20/1998

Study Objective: To compare the safety and efficacy of 24-hour infusion versus a 96-hour infusion of paclitaxel in the treatment of advanced ovarian cancer. To correlate pharmacokinetics of paclitaxel with clinical outcome.

Technical Approach: This study will assess the relative safety and efficacy of 24-hour versus 96-hour infusion times for the administration of paclitaxel in the treatment of ovarian cancer. Patients with selected Stage III ovarian cancer who are not eligible for other GOG studies may participate in this study. Patients are randomized to receive either of the two study treatments. The 96-hour infusion may be administered as an inpatient or as an outpatient utilizing a standard chemotherapy pump. All patient will receive the administration of paclitaxel followed by cisplatin. Treatment will be administered at three week intervals form the beginning of the previous cycle for a total of six cycles. Grade IV myelosuppression will be modified by dose reduction. GCSF may be utilized for acute febrile episodes. In the event of persistent Grade IV myelosuppression, patients will be removed from the study. Patients with measurable disease will be followed with CT-scans after every other cycle. All patients will have a pre-chemotherapy CT as well as a CT-scan at the completion of therapy. CA-1125 levels will also be followed at regular intervals. Subsequent to treatment, patients will be followed at three month intervals for at least the first year for study and points as well as standard follow-up for ovarian cancer patients. Correlation between pharmacokinetics and clinical outcomes will be made at the conclusion of the study. All patients will receive four samples for pharmacologic studies.

Progress: No patients have been enrolled in this study at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/030 **Status**: Terminated

Title: GOG 0163: A Randomized Study of Doxorubicin Plus Cisplatin Versus Doxorubicin Plus 24-Hour Paclitaxel Plus G-CSF in Patients with Primary Stage III & IV or Recurrent Endometrial Carcinoma

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
11/15/1996	Feb 99	02/20/1998

Study Objective: To compare the efficacy of doxorubicin plus cisplatin versus doxorubicin plus 24-Hour paclitaxel in the treatment of patients with advanced or recurrent endometrial cancer.

Technical Approach: Patients eligible for this protocol will be randomized to receive doxorubicin with either cisplatin or paclitaxel with G-CSF support. Treatment will occur at every three week intervals for a total of seven treatments unless disease progression occurs. Dose reduction and/or the administration of G-CSF will be utilized to reduce the impact of myelosuppression. Cardiac toxicity will be monitored with ejection fractions prior to the initiation of therapy and after three and six cycles. The cumulative dose of doxorubicin will be limited to 420 mg/m^2 in regimen I and 350 mg/m^2 in regimen II.

Progress: No patients have been enrolled in this study at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/103 **Status**: Terminated

Title: GOG 0164: A Randomized, Controlled Intergroup Trial of Salvage Therapy with Paclitaxel and Carboplatin versus Salvage Therapy with Stem Cell Supported High-Dose Carboplatin, Mitoxantrone, and Cyclophosphamide in Patients with Persistent Low Volume Disease and Response to Primary Therapy

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
05/16/1997	Jan 02	02/20/1998

Study Objective: To compare the efficacy of standard salvage chemotherapy to high-dose chemotherapy with stem cell support in improving overall survival, disease survival, or improved quality of life.

Technical Approach: Patients will be evaluated regularly for disease status every three weeks for three months, then every three months from two years from the start of treatment. In addition to physical examination laboratory perimeters and quality of life assessments will be obtained as per the master protocol. Details of the plan of management and baseline eligibility can be obtained from the master protocol.

Patients randomized to standard chemotherapy will be treated as outpatients at Madigan Army Medical Center. Patients randomizing to the high-dose chemotherapy arm with support will be treated at Brook Army Medical Center, an approved SWOG transplant center.

Progress: No patients have been enrolled in this study at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/027 **Status**: Terminated

Title: GOG 0165: A Randomized Comparison of Radiation vs Radiation + Weekly Cisplatin vs Radiation + PVI (Protracted Venous Infusion) 5-FU in Patients with Stage II-B, III-B, and IV-A Carcinoma of the Cervix

Principal Investigator: COL Mark E. Potter, MC

Department: GOG **Facility**: MAMC

Associate Investigator(s): None.

Start Date:	Est. Completion Date:	Periodic Review:
11/21/1997	Feb 05	02/20/1998

Study Objective: 1) To compare the progression free survival and survival of patients with locally advanced cervical cancer receiving radiation therapy only with radiation plus weekly cisplatin; 2) To compare the progression free survival and survival of patients with locally advanced cervical cancer receiving radiation plus prolonged venous infusion (PVI) 5-FU with radiation plus weekly cisplatin; 3) To compare the relative toxicities of radiation plus chemotherapy to radiation alone; 4) To compare the progression free survival and survival of patients with locally advanced cervical cancer and smokers versus non smokers and smokers who quit versus those who do not quit.

Technical Approach: Patients will be randomized to one of three treatment regimens. Regimen I consists of "modern" radiation therapy plus weekly cisplatin; Regimen II consists of "modern" radiation therapy alone; Regimen III consists of "modern" radiation plus PVI 5-FU. The effect of smoking on therapeutic outcome will be assessed by a pre-treatment questionnaire and urine samples for nicotine analysis. Urine samples will be obtained prior to treatment and 2 to 4 weeks of treatment. After completion of protocol therapy, follow-up will be once every 3 months for two years and once every 6 months for the next 3 years, then annually thereafter.

Progress: No patients were enrolled in this protocol at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/008	**Status**: Terminated

Title: GOG 0169: A Randomized Phase III Study of Cisplatin Versus Cisplatin Plus Paclitaxel in Stage IVB, Recurrent or Persistent Squamous Cell Carcinoma of the Cervix

Principal Investigator: COL Mark E. Potter, MC

Department: GOG	**Facility**: MAMC

Associate Investigator(s): None.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
10/17/1997	Nov 99	02/20/1998

Study Objective: To assess the impact of adding Paclitaxel to Cisplatin on 1) response rate, 2) progression free interval, 3) overall survival, and 4) quality of life for patients with advanced or recurrent squamous cell carcinoma of the cervix.

Technical Approach: Patients will be randomized to one of two treatment regimens; intravenous cisplatin with or without Paclitaxel. Treatment will continue at three week intervals for six courses, or until disease progression, or unacceptable toxicity develops. After therapy, patients will follow-up every 3 months for two years then every 6 months for three years.

Progress: No patients were enrolled in this protocol at MAMC. This protocol has been terminated. The GOG program at MAMC was closed because of insufficient patients entered in protocols at MAMC. The NIH increased the number of audits which increased the costs for GOG. In turn, institutions with minimal accrual were dropped from the program as a cost cutting measure. Therefore, all GOG protocols with no patients entered or being followed at MAMC were terminated.

Detail Summary Sheets

National Surgical Adjuvant Breast and Bowel Project (NSABP)

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/147 **Status**: Ongoing

Title: NSABP R-03: A Clinical Trial to Evaluate the Worth of Preoperative Multimodality Therapy (5-FU-LV and RTX) in Patients with Operable Carcinoma of the Rectum

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: NSAB **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Timothy P. Rearden, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ John R. Caton, MC; MAJ Richard F. Williams, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
08/06/1993	Jul 98	09/30/1998

Study Objective: 1). To determine whether the administration of chemotherapy (chemo) with radiotherapy (RTX) preoperatively is more effective than administration of chemo and RTX (C&R) postoperatively in improving disease-free survival and survival in patients with operable carcinoma of the rectum. 2). To determine if the administration of the above C&R preoperatively results in improvement local recurrence rates when compared with the regimen administered post-operatively in this population of patients. 3). To evaluate the response of rectal tumors to preoperative C&R and to correlate that response with disease-free survival and survival. 4). To assess the downstaging effect of preoperative C&R on the tumor size and pathologic status of regional lymph nodes. 5). To estimate the proportion of patients who can be converted to sphincter-saving surgical procedures from abdomino-perineal resection and local excision alone.

Technical Approach: Patients with operable adenocarcinoma of the rectum will receive seven cycles of 5-FU (FU) + leucovorin (LV) and radiotherapy (RTX), where the first three cycles are given preoperatively and the remaining four postoperatively, to seven cycles of FU-LV and RTX given postoperatively. The patients will be randomized into 2 groups. Group 1 patients, in cycle 1, will receive LV 500 mg/m^2 by IV infusion and FU 500 mg/m^2 will be started 1 hr later. Treatment will be given weekly for 6 weeks followed by a rest period. Treatment will be restarted 21 days after the date of administration of the sixth dose of the previous cycle. RTX will begin after completion of cycle 1. FU 325 mg/m^2/day and LV 20 mg/m^2/day will be given for 5 days during the first and fifth weeks of RTX (cycles 2 and 3). Surgery will be performed after completion of radiation therapy. After recovery from surgery, four more cycles of FU with LV, as in cycle 1, will be given for a total of seven cycles. Groups 2 patients should have surgery performed no later than 3 weeks after randomization. Chemo will begin after recovery from surgery is complete but no later than 4 weeks postoperatively. LV and FU will be administered as in Group 1. RTX will begin after completion of cycle 1. Cycle 4 should begin after completion of RTX when counts allow, but no later than 5 weeks. Four more cycles of FU with LV will be given for a total of seven cycles.

Progress: No patients have been enrolled in this study at MAMC.

Detail Summary Sheets

Pediatric Oncology Group

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 95/015	**Status**: Completed

Title: POG 9150/CCSG 6901 - Intergroup Rhabdomyosarcoma Study-IV for Stage I Disease.

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG	**Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/18/1994	Jun 97	11/17/1998

Study Objective: To compare the progression-free survival rates of patients receiving vincristine-actinomycin-D-cytoxan (VAC vs patients receiving vincristine-actinomycin-D-ifosfamide (VAI) vs those receiving vincristine-ifosfamide-etoposide (VIE) for treatment of rhabdomyosarcoma and undifferentiated sarcoma. To compare hyperfractionated radiation therapy (RT) to conventional RT in regard to: a) local relapse rates, and b) early/acute toxicity and late effects. To investigate the relationship between immunohistochemical pattern of tumor and prognosis, and to evaluate newly identified immunohistochemical markers in diagnosis. To correlate clinical features of disease and prognosis with tumor cytogenetics, DNA index and amplification or rearrangement of specific cellular proto-oncogenes. To provide a bank of frozen tumor tissue for use in tumor biology studies. To evaluate the use of recombinant G-CS as a supportive measure for ameliorating hematopoietic toxicity.

Technical Approach: This is a randomized 3-arm study with an internal control consisting of a modified repetitive pulse VAC regimen for Stage 1 disease, excluding Clinical Group I paratesticular and Groups I and II orbit/eyelid patients, in IRS-IV. The modifications of VAC involve maximizing its intensity: cytoxan is delivered in a single high dose rather than at a lower dose daily x 3, actinomycin-D is delivered more frequently in induction, and VCR more frequently during continuation. The two experimental arms differ from the control in that ifosfamide is substituted for cytoxan in one (VAI) and ifosfamide + VP-16 are substituted for actinomycin-D + cytoxan in the other (VIE). The comparison then, is VAC vs VAI vs VIE. Clinical Group I paratesticular and orbit/eyelid patients will be treated separately with VA alone. The second major comparison and randomization in IRS-IV will be between conventional RT and hyperfractionated RT (Hyperfx-RT) in stages 1, 2, and 3 patients with gross residual disease after surgery (clinical group III). Within each stage, except for stage 4 radiotherapy will be randomized or assigned by Clinical Group. Participation in the corresponding tumor study (PO #9153) us required.

Progress: Protocol closed to patient entry 1 January 1998 due to adequate patient accrual. No patients were enrolled in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/016 **Status**: Completed

Title: POG 9151/CCSG 6902 - Intergroup Rhabdomyosarcoma Study-IV for Stage II and Stage III Diseases.

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/18/1994	Jun 97	11/21/1997

Study Objective: To compare the progression-free survival rates of patients receiving vincristine-actinomycin-D-cytoxan (VAC) vs patients receiving vincristine-actinomycin-D-ifosfamide (VAI) vs those receiving vincristine-ifosfamide-etoposide (VIE) for treatment of rhabdomyosarcoma and undifferentiated sarcoma. To compare hyperfractionated radiation therapy (RT) to conventional RT in regard to a) local relapse rates, and b) early/acute toxicity and late effects. To investigate the relationship between immunohistochemical pattern of tumor and prognosis, and to evaluate newly identified immunohistochemical markers in diagnosis. To correlate clinical features of disease and prognosis with tumor cytogenetics, DNA index and amplification or rearrangement of specific cellular proto-oncogenes. To provide a bank of frozen tumor tissue for use in tumor biology studies. To evaluate the use of recombinant G-CSF as a supportive measure for ameliorating hematopoietic toxicity.

Technical Approach: This study is designed to determine whether an ifosfamide-based combination (VAI) is superior to a cyclophosphamide-based combination (VAC) in previously untreated patients. Therefore, a randomized 3-arm study with an internal control consisting of a modified repetitive pulse VAC regimen is the study to be undertaken for stages 2 and 3 disease in IRS-IV. The two experimental arms (VAI and VIE) differ from the control arm as follows: ifosfamide is substituted for cyclophosphamide in one cyclophosphamide in the other (VIE). The comparison then, is VAC vs VAI vs VIE in IRS-IV. The second major comparison and randomization in IRS-IV will be between conventional RT and hyperfractionated RT (Hyperfx-RT) in stages 1, 2 and 3 patients with gross residual disease after surgery (clinical group III). The goal is to try to improve the local control rate in these Group III patients with Hyperfx-RT, whereas Group II patients in these stages have an acceptable local control rate of 90% with conventional RT and will continue to receive conventional RT in IRS-IV.

Progress: Protocol closed to patient entry 1 January 1998 due to adequate patient accrual. No patients were enrolled in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/145 **Status**: Completed

Title: POG 0942: A Study of Minimally Invasive Surgery of the Chest in Children with Solid Tumors, A Phase III Intergroup Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Stephen R. Palmer, MC; MAJ Randall M. Holland, MC; LTC Shirley E. Reddoch, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
07/19/1996	Jul 98	12/18/1997

Study Objective: 1) To compare the morbidity and mortality rates of open surgical procedures with that of MIS; 2) to compare MIS with conventional surgery in obtaining adequate pathologic material for diagnostic and special biological studies; 3) to compare MIS with conventional open surgery in the assessment of tumor resectability; 4) to assess the impact of MIS and open surgery on short-term quality of life (QOL). Several domains of QOL will be examined including surgery-related pain, physical, social and emotional functioning, and global ratings of health and overall QOL; 5) to compare post-procedure recovery time of MIS with conventional surgical techniques in children with cancer; 6) to evaluate and compare post-procedure pain in MIS with conventional surgical techniques; 7) to compare MIS with standard open surgical techniques in regards to the economic costs; and 8) to provide pilot data on a new instrument for assessing QOL in a pediatric population.

Technical Approach: This study proposes to determine the role of MIS in the management of pediatric cancer. This Phase III randomized study will test whether MIS is as efficacious as standard open surgical operations for the diagnosis and assessment of resectability of pediatric solid tumors, and whether MIS improves recovery and convalescence in addition to decreasing the cost of care for children with cancer. Eligible patients are those who require surgical intervention for diagnosis and staging, evaluation for disease progression or response to therapy, or for supportive or medical management issues during the course of cancer treatment.

Progress: Protocol was closed to patient entry 25 November 1997, due to poor patient accrual. No patients were enrolled at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/072 **Status**: Ongoing

Title: POG 7837: Evaluation of Systemic Therapy for Children with Lymphoblastic Lymphoma Including T-Cell Disease

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/22/1998	Indefinite	N/A

Study Objective: (1) To evaluate a program of intensified CNS therapy for patients with lymphoblastic lymphoma, including T-cell leukemia, treated with the Pediatric Oncology Group's most successful systemic therapy schedule for these patients. This protocol will serve as the control arm for a randomized study, (2) to assess the toxicity and rate of complications encountered by patients receiving POG modified LSA2L2 Therapy in comparison with patient who received therapy using POG 7839 Treatment Arm 1 or POG 7615, (3) to assess the value of cranial radiation therapy plus 3-drug intrathecal chemotherapy in treating occult T-cell leukemia of the central nervous system, using the rate of CNS relapse and the rate of CNS complications for comparison with responses achieved using POG 7837 Treatment Arm 1 and POG 7615 therapy in pediatric patients with T-cell acute lymphocytic leukemia, (4) to assess the therapeutic effectiveness as measured by disease-free survival of POG Modified LSA2L2 Therapy (POG 7837 Treatment Arm 2) compared with responses achieved with POG 7837 Treatment Arm 1 and POG 7615 in pediatric patients with lymphoblastic lymphoma and T-cell leukemia, (5) to provide uniform therapy for patients with lymphoblastic lymphoma, including T-cell leukemia, so as to examine the response of immunologically defined subgroups of T-cell patients to this therapy, and in those patients for whom marker studies have been obtained, to correlate response with histopathology and serologic markers, (6) to provide a common protocol for the treatment of patients with widespread T-cell malignancy, offering the opportunity for comparison of response rates among patients who have differing extent of disease.

Technical Approach: Subjects will be treated with a four week induction therapy consisting of cyclophosphamide, vincristine, prednisone, daunorubicin and intrathecal methotrexate, Ara-C and hydrocortisone. Following a bone marrow exam, subjects achieving remission will begin CNS consolidation therapy consisting of intrathecals twice weekly for 4 doses at the same time as the start of radiation therapy (12 treatments). Systemic consolidation chemotherapy will begin one week after CNS consolidation therapy. This therapy consists of Ara-C, 6-TG, L-ASP and BCNU, and last about 4 weeks. Maintenance therapy will begin 7-10 days following completion of consolidation therapy and consists of four treatment cycles lasting 5 days each with each new cycle beginning every 14 days or longer depending on blood counts. Cycle 1: 6-TG/cyclophosphamide; Cycle 2: hydroxyurea/daunorubicin; Cycle 3: methotrexate/BCNU and Cycle 4: Ara-C/Vincristine. Cycle 1 will be repeated 14 days after beginning cycle 4 or when blood counts return to normal.

Progress: This study has been closed to patient accrual; however HHS guidelines has required IRB approval of closed studies when patients are being followed for survival information. Madigan currently has 1 patient accepted in transfer from Tripler AMC who was consented on an IRB approved POG 7837 study. Follow-up information on this patient will need to be sent to the POG Statistical Office per protocol requirements.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/073 **Status**: Ongoing

Title: POG 8602: Evaluation of Treatment Regimens in Acute Lymphoid Leukemia of Childhood (ALinC #14)

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/22/1998	Indefinite	N/A

Study Objective: (1) To test the concept that intensive asparaginase (ASP) therapy, designed to maintain low asparagine levels for the first six months of maintenance will improve the outcome for patients with standard risk acute lymphocytic leukemia (ALL) when added to pulses of intermediate dose methotrexate (IDM), as compared to intensification with IDM alone, (2) to study the effectiveness in standard risk patients of intensification with a potentially synergistic or additive drug pair, i.e., IDM plus arabinosyl cytosine (AraC), as compared to that of intensification with IDM pulses alone, (3) to determine if administering a pulse of IDM + AraC at three week intervals (early intensification) during the first 4 months of complete remission in children with ALL is superior to administering the same number of IDM + AraC pulses at 12 week intervals (late intensification) during the first two years of complete remission in children with ALL with either "lower" or "higher" risk of relapse, (4) to obtain further information on the immediate and delayed toxicity of the continuation chemotherapy program that incorporates these combinations of methotrexate (MTX) and AraC or MTX and ASP in moderately high doses, (5) to continue to characterize the biological features of ALL of childhood, and their independence and interaction (with therapy and each other) as prognostic factors for attaining and maintaining remission, in order to assess the effectiveness of these regimens for the early pre-B (non-T, non-B, non-pre-B) and pre-B immunophenotypes of ALL, respectively and to investigate the hypothesis that ploidy and/or the presence of structural chromosome abnormalities predicts prognosis, (6) to learn whether outcome is related to individual patient differences in MTX availability as measured by sequential determinations of red blood cell (RBC) MTX and folate levels.

Technical Approach:. All subjects will receive identical remission induction therapy consisting of oral prednisone, IV vincristine, IM Asparaginase, intrathecal therapy with Ara-C, Methotrexate and Hydrocortisone, and oral 6-Mercaptopurine (6-MP); followed by continuation therapy. The four regimens are similar in that all subjects will receive moderately high-dose IV MTX every 3 or 12 (6 times); intrathecals every 8 weeks (13 times); prednisone/vincristine pulses every 16 weeks for a week at a time (oral prednisone daily (7 days) and IV vincristine, days 1 and 5), and IM MTX and oral 6-MP taken for long periods of time. Subjects will be randomized into one of four continuation regimens. Regimen A consists of the above therapy with the moderately high-dose MTX given every 3 weeks for 6 courses and the 6-MP and IM MTX given continuously from week 25 until the end of 3 years. Regimen B consists of the Regimen A therapy plus weekly IM ASP for 24 weeks. Regimen C consists of Regimen A therapy plus moderately high-dose Ara-C. Regimen D consists of moderately high-dose Ara-C with IV MTX every 12 weeks (6 times) and IM MTX and oral 6-MP given almost continuously from the beginning of continuation therapy (week 10) until the end of three years.

Progress: This study has been closed to patient accrual; however HHS guidelines has required IRB approval of closed studies when patients are being followed for survival information. Madigan currently follows 3 patients accepted as transfers from other POG institutions, who were consented on an IRB approved POG 8602 study. Follow-up information on these patients will be sent to the POG Statistical Office per protocol requirements.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/076 **Status**: Ongoing

Title: POG 8615: A Phase III Study of Large Cell Lymphomas in Children and Adolescents: A Comparison of Two Treatment Regimens - ACOP+ versus APO

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/22/1998	Indefinite	N/A

Study Objective: (1) To determine the influence of alkylating agent (cyclophosphamide) therapy in advanced-stage large cell lymphomas in children and adolescents, by comparing in a randomized prospective study the efficacy and toxicity of a modified ACOP+ versus a modified APO regimen, (2) to reduce the adverse effects of treatments by elimination of involved field and cranial radiation in the treatment of large cell lymphomas, (3) to evaluate the adequacy of one year of total therapy for advanced large cell Non-Hodgkin's lymphoma (NHL), (4) to study clinical pathologic patterns and biologic characteristics of large cell lymphomas in children and adolescents, (5) to assess the feasibility of the total dose of adriamycin of 300 mg/m^2 the APO arm (post closure of randomization).

Technical Approach: Subjects will be randomized into one of two treatment regimens. Regimen A, Induction therapy consists of IV vincristine once a week for 5 weeks, IV push cyclophosphamide and IV push adriamycin (days 1 and 22) and oral prednisone daily (40 days). Intrathecal MTX is given on days 1, 8 and 22. After day 42, a clinical restaging will be performed. All subjects in remission will proceed to maintenance therapy. Subjects will receive IV vincristine (days 1, 22, 36, 57), IV cyclophosphamide (days 1, 36), oral prednisone each day for 5 days (starting days 1, 22, 36, 57), oral 6-MP each day for 5 days (starting days 22, 57) and intrathecal MTX on day 1. This cycle will be repeated 3 times for a total therapy of one year.

Regimen B, Induction therapy consists of IV vincristine once a week for 5 weeks, IV push adriamycin (days 1, 22), oral prednisone daily (40 days). Intrathecal MTX is given on days 1, 8 and 22. After day 42, a clinical restaging will be performed. All subjects in remission will proceed to maintenance therapy. All subjects in remission will proceed to maintenance therapy. Subjects will receive IV vincristine (days 1, 22, 43), IV adriamycin (days 1, 22, 43), oral prednisone each day for 5 days (starting days 1, 22, 43), oral 6-MP each day for 5 days (starting days 1, 22, 43) and intrathecal MTX on day 1. This cycle will be repeated 3 times for a total therapy of one year.

Subjects who do not achieve remission after induction will require radiation therapy which will begin during the second week of maintenance therapy, 5 days a week for about 5 weeks.

Progress: This study has been closed to patient accrual; however HHS guidelines has required IRB approval of closed studies when patients are being followed for survival information. Madigan currently has 1 patient accepted in transfer from Stamford who was consented on an IRB approved 8615 study. Follow-up information on this patient will be sent to the POG Statistical Office per protocol requirements.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 93/141	**Status**: Ongoing

Title: POG 8650: Intergroup National Wilms' Tumor Study - 4

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG	**Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/09/1993	Oct 97	09/30/1998

Study Objective: To compare 1) the relapse-free and overall survival percentages of patients with: Stage I and II favorable histology (FH) and Stage I anaplastic Wilms' tumor (Ana), using conventional versus pulse intensive (P/I) chemotherapy with vincristine and actinomycin D; 2) Stages 3 and 4 FH, and Stages 1-4 clear cell sarcoma of the kidney using conventional versus P/I vincristine, actinomycin D, and Adriamycin plus radiation therapy; 3) Stages 2-4 Ana treated with vincristine, actinomycin D, and Adriamycin versus the same 3 drugs plus cyclophosphamide, and radiation therapy; and 4) Stages 2-4 FH and Stage 1-4 clear cell sarcoma of the kidney treated for 6 versus 14 months after nephrectomy.

Technical Approach: All patients will be <16 years of age, have had no prior chemo-radiation therapy, will have undergone nephrectomy, and will meet other criteria as stated in the protocol. Patients will be randomized as follows: Stage II/FH & Stage I Ana receive A + V (24 wks) or P/I A + V (18 wks), Stage II/FH receive A + V (22 vs 65 wks) or P/I A + V (60 wks), Stages III & IV FH & clear cell (I-IV) receive A + V + D (26 vs 65 wks) plus RT or P/I A + V + D (24 vs 54 wks) plus RT, and Stages II-IV Ana receive A + V + D + C (65 wks) plus RT or A + V + D + C (65 wks) plus RT. Legend: A = actinomycin D, V = vincristine, D = doxorubicin (Adriamycin), C = cyclophosphamide, and RT = radiation therapy.

Progress: This protocol was closed to patient entry, 1 Sep 94. One patient was enrolled at MAMC in FY 93 and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/074 **Status**: Ongoing

Title: POG 8823/34: Recombinant Alpha-Interferon in Childhood Chronic Myelogenous Leukemia

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/22/1998	Indefinite	N/A

Study Objective: (1) To determine toxicity, response rate and duration of response to therapy with recombinant alpha interferon for newly diagnosed "adult" chronic myelogenous leukemia (ACML) in chronic phase, and for "juvenile" chronic myelogenous leukemia (JCML) occurring within the first two decades. (2) to obtain prospective clinical, laboratory, and genetic data on cases of ACML and JCML treated with recombinant alpha interferon.

Technical Approach: Initial therapy (days 1- 14) the subject will receive daily SQ injection of recombinant alpha interferon. Acetaminophen is taken one hour prior to the injection. Blood pressure, temperature, pulse and respiration are to be checked after taking acetaminophen. Temperature and blood pressure continue to be checked at 1, 2, and 3 hours after receiving the interferon injection. Weight is to be noted each day.

Consolidation therapy (days 15-90) the subject will receive SQ injections of interferon 3 times a week (Monday, Wednesday, Friday). Provided that unacceptable toxicities, recurrent disease or progressive disease do not develop, the subject can begin Continuation therapy (days 91-726, 24 months).

Progress: This study has been closed to patient accrual; however HHS guidelines has required IRB approval of closed studies when patients are being followed for survival information. Madigan currently has 3 patients accepted as transfers from Walter Reed AMC who were consented on IRB approved POG 8823 studies. Follow-up information on these patients will need to be sent to the POG Statistical Office per protocol requirements.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 95/052	**Status**: Ongoing

Title: POG 8930: A Comprehensive Genetic Analysis of Brain Tumors

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG		**Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/16/1994	Nov 97	11/21/1997

Study Objective: 1) To determine prospectively the clinical significance of abnormalities of cellular DNA content, as measured by flow cytometry in pediatric brain tumors. 2) To determine the clinical implications of cytogenetic abnormalities found in pediatric brain tumors at diagnosis. 3) To determine the clinical significance of amplification or rearrangement of specific cellular proto-oncogenes or allelic loss of recessively-acting loci in DNA extracted from pediatric brain tumors. 4) To attempt to derive tumor cell lines and to provide a bank of frozen brain tumor tissue for use in further studies, especially molecular genetic studies.

Technical Approach: This is a non-therapeutic study intended to prospectively collect tissue from newly diagnosed patients with brain tumors. Flow cytometry, cytogenetics, and molecular studies will be used to characterize abnormalities of the DNA and correlate their findings with type of disease/diagnoses, tumor grade, and prognostic indicators.

Progress: No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/075 **Status**: Ongoing

Title: POG 9005: ALinC #15 - Dose Intensification of Methotrexate and 6-Mercaptopurine for ALL in Childhood - A Randomized Phase III Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/22/1998	Indefinite	N/A

Study Objective: (1) To determine, in a randomized trial, whether intensification with intermediate-dose methotrexate (ID MTX), and intravenous 6-mercaptopurine (IV 6-MP) is superior or inferior to repeated low-dose, oral methotrexate (LD MTX) and IV 6-MP for prevention of relapse in children with ALL in first remission and at lower risk for relapse, (2) To compare, in a randomized trial, intensification with ID MTX alone versus ID MTX and IV 6-MP for prevention of relapse in children with lower risk ALL in first remission, (3) To determine if RBC MTX/folate levels can be correlated with event free survival.

Technical Approach: The four week induction treatment will be the same for all regimens; consists of prednisone, vincristine, l-asparaginase and triple intrathecal therapy of methotrexate, Ara-C and hydrocortisone. Following a bone marrow aspirate to assess remission, subjects will be randomized into one of three treatment regimens. Regimen A, Intensive Phase, week 1 consists of a 2 day course of IV MTX/IV 6-MP; week 2 consists of IM MTX and 7 days of oral 6-MP. This cycle is repeated 12 times. The Continuation Phase, which begins at week 25 and continues to week 130, consists of weekly IM MTX and daily oral 6-MP with intrathecal therapy every 12 weeks.

Regimen B, Intensive Phase, week 1, consists of oral MTX every 6 hours for 6 doses, last dose to be given during or at the end of a 6 hour IV 6-MP infusion; leucovorin to be given 48 hours after the MTX is started, if necessary. Week 2 consists of IM MTX and 7 days of oral 6-MP. This cycle is repeated 12 times. The Continuation Phase, which begins at week 25 and continues to week 130, consists of weekly IM MTX and daily oral 6-MP with intrathecal therapy every 12 weeks.

Regimen C, Intensive Phase, week 1 consists of IV MTX over 24 hours and leucovorin leucovorin to be given 48 hours after the MTX is started, if necessary. Week 2 consists of IM MTX and 7 days of oral 6-MP. This cycle is repeated 12 times. The Continuation Phase, which begins at week 25 and continues to week 130, consists of weekly IM MTX and daily oral 6-MP with intrathecal therapy every 12 weeks.

Progress: This study has been closed to patient accrual; however HHS guidelines has required IRB approval of closed studies when patients are being followed for survival information. Madigan currently has 5 patients accepted as transfers from other POG institutions (3 military, 2 civilian) who were consented on IRB approved POG 9005 studies. Follow-up information on these patients will need to be sent to the POG Statistical Office per protocol requirements.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/018 **Status**: Ongoing

Title: POG 9031: Treatment of Children with High Stage Medulloblastoma: Cisplatin/VP-16 Pre vs Post-Irradiation

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	Est. Completion Date:	Periodic Review:
11/18/1994	Nov 94	09/30/1998

Study Objective: To compare the 2-year event-free survival (EFS) of children with newly-diagnosed high-risk medulloblastoma who are treated with cisplatin and VP-16 pre-irradiation vs post-irradiation. To define the toxicity and activity of pre-irradiation cisplatin/VP-16 in patients with newly-diagnosed high-risk medulloblastoma. To determine whether achievement of a measurable tumor response (PR and CR) to pre-irradiation cisplatin/VP-16 has prognostic significance for children with high-risk medulloblastoma, compared with failure to achieve a measurable response (SD or PD). To define the toxicity and activity of post-irradiation cisplatin/VP-16 in patients with newly-diagnosed high-risk medulloblastoma. To determine if c-myc amplification in medulloblastoma is associated with an adverse prognosis.

Technical Approach: Studies in children and adults have demonstrated the ability to deliver pre-radiotherapy chemotherapy for patients with newly-diagnosed brain tumors without increasing neurotoxicity in association with the subsequent radiotherapy. This approach creates a phase II "window" allowing evaluation of response in these patients who are previously untreated except for surgery. The theoretical anti-neoplastic advantage of this approach is the potentially enhanced efficacy of the radiotherapy when given to "chemically debulked" patients. Half of the children diagnosed with medulloblastoma are now being successfully treated and are surviving for prolonged periods. Until recently, the survival of this group of patients was limited so that long-term effects of therapy were not a concern. As survival increases, one would expect to observe an increase in frequency of certain treatment-related toxicities. There are now a variety of long-term effects which need to be considered in this cohort of patients. Specific evaluations will be made on all patients entered onto this study, so that treatment-related problems may be detected in their early stages and intervention taken. This approach should ultimately improve the quality of life for children diagnosed and treated for brain tumors.

Progress: Protocol was closed to patient entry 26 March 96. One patient was enrolled in this study at MAMC in FY 95 and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/164 **Status**: Ongoing

Title: POG 9047: Neuroblastoma Biology Protocol

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): COL Stephen R. Stephenson, MC; LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/03/1993	Feb 96	04/17/1998

Study Objective: 1) To obtain tissue for the analysis of DNA content of neuroblastoma cells by flow cytometry. 2) To characterize neuroblastoma tumor DNA from POG patients genetically by analysis of N-myc amplification and LOH for chromosome 1p. 3) To develop a reference bank of genetically characterized tumor tissue and DNA that would be available for other studies.

Technical Approach: This is a non-therapeutic study intended to collect tissue from newly-diagnosed neuroblastoma patients = 21 years. Viable tumor tissue, frozen tumor tissue (or marrow) and serum will be collected and forwarded to a designated study site.

Progress: No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 95/008	**Status**: Ongoing

Title: POG 9153: Intergroup Rhabdomyosarcoma Study/Laboratory Evaluation of Tumor Tissue

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG	**Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/04/1994	Jun 97	11/21/1997

Study Objective: 1) To prospectively correlate clinical features and outcome of newly diagnosed children with rhabdomyosarcoma with cytogenetic abnormalities of their tumors, 2) to measure cellular DNA content by flow cytometry of tumor cells and correlate the DNA index of tumor stem lines with clinical features and treatment response, 3) to determine prospectively the clinical significance of amplification or rearrangement of specific cellular proto-oncogenes or allelic loss of recessively acting loci in DNA extracted from pediatric rhabdomyosarcomas, 4) to attempt to derive tumor cell lines and to provide a bank of frozen rhabdomyosarcoma tumor tissue for use in further studies, especially molecular genetic studies, and 5) to determine the degree of specificity of monoclonal antibody probes, 4.2A8, 5.1Hll, and 3.1G11, for childhood rhabdomyosarcoma.

Technical Approach: This is a non-therapeutic study intended to collect tissue from newly-diagnosed rhabdomyosarcoma and undifferentiated sarcoma patients < 21 years. Viable tumor tissue, frozen tumor tissue and involved marrow samples will be collected and forwarded to a designated study site.

Progress: One patient enrolled in this study at MAMC in FY 96 and continues to be followed. No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/084 **Status**: Ongoing

Title: POG 9182: HIV/Malignancy Biology Protocol

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	Est. Completion Date:	Periodic Review:
02/20/1998	Apr 97	02/20/1998

Study Objective: 1) To establish a national registry of pediatric AIDS-associated lymphomas and other malignancies and a repository of well-characterized tumor tissue, cells and sera from affected patients. 2) To conduct prospective Phase I-III clinical trials of anti-cancer and anti-retroviral therapies aimed at improving outcomes and identifying critical determinants of risk. 3) To identify the presence and quantify the viral burden of human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), Human Herpes virus 6 (HHV6), and Herpes Simplex virus (HSV) in the tumor tissue, peripheral blood cells, plasma, and cerebrospinal fluid of pediatric patients with lymphomas and other malignancies; and to characterize the effect of anti-cancer and antiviral chemotherapy with regard to lymphoma stage, disease progression, host response, and toxicity. 4) To conduct the first large-scale molecular epidemiologic study of risk factors related to development of HIV-related NHL in children by means of a case-control analysis of HIV-infection characteristics such as co-infection with EBV, CMV, HHV6, Mycoplasma, the quantitative host viral burden, level of immunodeficiency, and other host characteristics. 5) For HIV+ and HIV- children, to characterize differences in NHL tumor tissue in terms of immuno-phenotype, immunoglobulin gene rearrangements and oncogene (c-myc) activation.

Technical Approach: Three groups of children are eligible for this protocol. The first, a "case" group, consists of children with a newly-diagnosed malignancy who are HIV positive. The second, a "malignancy control' group, consists of children with a newly-diagnosed malignancy who do NOT have HIV infection. The third group, a "non-malignancy control" group, consists of children with no evidence of malignancy, but who have a documented HIV infection. A total of 150, 150, and 300 patients, respectively is expected. The subject will be seen in the clinic at least every two months for up to two years, then every 6 months up to 3 years. At each visit blood will be drawn for testing. In addition, a small piece of tumor tissue or other body fluids (including spinal fluid and bone marrow), already obtained as part of routing clinical management bay be examined. We will establish a database as a repository for characteristics of pediatric patients with HIV infection and malignancies. The database will include all appropriate clinical parameters, laboratory measures, and results of molecular and virologic studies. Descriptive analyses of clinical and laboratory data will use various criteria to characterize the study population and to correlate variation in infectious virus and total viral burden with clinical course and other laboratory measurements. Primary endpoints, which may include tumor response, disease-free survival and episodes of grade 3-4 toxicities, will be confined to those specified in POG therapeutic protocols. Contingency tables relating the laboratory variables with stage, age, primary tumor site, histopathology, and clinical response will be produced. Conditional logistic regression will be used to compare biological data for cases to matched controls. Frequency matching will be performed at the Statistics Office at the time of analysis. Kaplan-Meier life tables, log rank tests, and Cox regression will be used to explore the relationship of laboratory variables to outcome.

Progress: No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/056 **Status**: Ongoing

Title: POG 9201: ALINC #16 Treatment for Patients with Lesser Risk Acute Lymphoblastic Leukemia, A Pediatric Oncology Group Phase III Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	Est. Completion Date:	Periodic Review:
12/16/1994	Dec 99	11/21/1997

Study Objective: 1) To confirm the outstanding results in patients with lesser risk not-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) To study laboratory correlates from POG 9400 and clinical correlates with outcome in pooling studies 9201, 9405, and 9406.

Technical Approach: Patients on this study will be treated with a 3-drug induction regimen (vincristine, prednisone, and L-asparaginase) to bring about remission (a state of no apparent disease) in four weeks.

This will be followed by a consolidation phase including (6) six courses of intravenous (into vein) intermediate-dose methotrexate (each will require hospital stay) at 3-week intervals. After week 5, daily 6-mercastosurine will be given by mouth until the end of planned treatment. Methotrexate will be given intramuscularly (into muscle) weekly. Periodic "pulses" (infrequent administration) of vincristine and prednisone will be given throughout the first two years of therapy. Additionally, triple intrathecal (into spinal fluid) therapy (TIT) consisting of methotrexate, hydrocortisone, cytosine arabinoside will be given at the start of treatment and periodically through the first two years of therapy to prevent the spread of leukemia to the central nervous system (CNS). The vitamin Leucovorin will be given to prevent methotrexate toxicity. After week 25, during the continuation phase, all medications will be on an outpatient basis.

The total duration of therapy is planned to be 2 1/2 years from initial diagnosis. If tests at that time indicate no evidence of leukemia, then all medications will be stopped and you (your child) will be followed closely to be sure that there is no evidence of return of the disease.

Progress: One patient enrolled in this study at MAMC in FY 96 and another patient was accepted in transfer. Both continue to be followed. No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/033 **Status**: Ongoing

Title: POG 9219: Treatment of Localized Non-Hodgkin's Lymphoma, A POG Phase IV Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): COL Stephen R. Stephenson, MC; LTC Stephen R. Palmer, MC; COL Bruce A. Cook, MC

Start Date:	Est. Completion Date:	Periodic Review:
11/05/1993	Jun 96	04/17/1998

Study Objective: 1. To maintain a high cure rate with minimum toxicity for children with localized non-Hodgkin's lymphoma in favorable sites.

2. To analyze in a large group of patients with localized non-Hodgkin's lymphoma (by pooling data from POG #83314, #8719 and the current study) prognostic factors which may predict subgroups of patients with a poor prognosis within the subgroup of patients with localized NHL.

Technical Approach: After staging, subjects that qualify will receive Vincristine 1.5 mg/m^2 (max 2 mg) IV q wk x 6 weeks, prednisone 40 mg/m^2/day in 3 divided doses x 28 days, Adriamycin 40 mg/m^2/day IV days 1 & 22, and Cyclophosphamide 750 mg/m^2/day IV days 1 & 22. Fluid intake is to be > 3000 ml/m^2 on day of treatment. Triple intrathecal chemotherapy (TIT) will be given on days 1, 8, and 22 to those with head and neck primaries.

On day 43, or when blood counts recover, the patient will receive Adriamycin 40 mg/m^2 IV, Cyclophosphamide 750 mg/m^2 IV, Vincristine 1.5 mg/m^2 (max 2 mg) IV, and Prednisone 50 mg/m^2 in 3 divided doses x 5 days.

On day 64 and when blood counts have returned to normal following the prescribed induction and consolidation regimen, the patient will be assessed for remission status.

Progress: Two patients were enrolled in this study at MAMC in FY 97. Both patients completed treatment and continue to be followed. No new patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/148 **Status**: Completed

Title: POG 9233/34: A Phase III Randomized Trial of standard vs Dose-Intensified Chemotherapy for Children Less Than 3 Years of Age With A CNS Malignancy Treated With or Without Radiation Therapy

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): COL Stephen R. Stephenson, MC; LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/06/1993	Jun 95	04/17/1998

Study Objective: To develop effective methods of treatment for very young children with malignant brain tumors that will minimize late toxicities affecting immature and rapidly developing central nervous systems.

Technical Approach: Patients < 3 yrs of age with a primary intracranial malignancy will be randomized to one of two regimens. Patients assigned to Regimen A will receive six 12-week courses of chemotherapy, given over a total of 72 weeks. Each course consist of 3 drug cycles. Cycle A; vincristine and cyclophosphamide and Mesna will be given on weeks 1, 13, 25, 37, 49 and 61. Vincristine will be repeated on day 8 of this cycle. During Cycle B, patients will receive cisplatin on day 1 and VP-16 on days 3 and 4. Patients on Regimen B will receive eight 9-week courses of chemotherapy. Each course will consist of 2 consecutive cycles of one drug combination (Cycle X) followed by a cycle of another combination (Cycle Y). On Cycle X, vincristine, and Mesna will be given on day 1 of weeks 1, 4, 10, 13, 19, 22, 28, 31, 27, 40, 49, 55, 58, 64, and 67. On day 2 patients will receive cyclophosphamide and Mesna. On days 3-15 patients will receive G-CSF. On Days 8 and 15, vincristine will be given. Cycle Y will be given on weeks 7, 16, 25, 34, 43, 52, 61 and 70. On Day 1 of Cycle Y, cisplatin will be given. VP-16 will be given on days 3 and 4. On days 5-14 G-CSF will be administered.

Patients experiencing progression or recurrence of disease at any time during or within 12 months of chemotherapy will be encouraged to begin radiation therapy immediately. If disease recurs later than 12 months after completing chemotherapy, patients will be discontinued from the study.

Progress: No patients were enrolled in FY 98. One patient was enrolled in July 94 , completed treatment and was transferred to WRAMC Aug 96. Protocol closed to patient entry 8 May 1998 due to adequate patient accrual in all stratas.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/096 **Status**: Ongoing

Title: POG 9315: A Phase III Study of Large Cell Lymphomas in Children and Adolescents; Comparison of APO vs. APO + IDMTX/HDARA-C and Continuous vs. Bolus Infusion of Doxorubicin

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC

Start Date:	Est. Completion Date:	Periodic Review:
04/19/1996	Jun 99	04/17/1998

Study Objective: 1) To study whether intermediate-dose methotrexate/high dose ARA-C (ID MTX/HRAra-C), administered during the maintenance phase can improve the event-free survival (EFS) of patients with advanced-stage large cell lymphoma (LCL); 2) to further characterize the immunophenotypic and morphologic correlates of pediatric LCL; and 3) to compare efficacy and cardiotoxicity of doxorubicin given by continuous versus bolus infusion.

Technical Approach: Patients will be randomized at registration to Regimen A or B. Patients who present with CNS disease will go after induction directly to Regimen B. Induction for both regimens will be the same, with additional intrathecals for patients with CNS disease. Maintenance A consists of 8 cycles of ID MTX/HD Ara-C alternating with 5 cycles of VCR/6-MP/ADR/Pred and 2 cycles of VCR/6-MP/MTX/Pred; a total of 15 cycles given at 3 week intervals. Maintenance B consists of 5 cycles of ADR/V/6-MP/Pred followed by 10 cycles of MTX substitution for ADR; a total of 15 cycles will be given at 3 week intervals. Following completion of therapy, examinations will be every month for the first 6 months; thereafter every 3 months until year 2 off therapy and then every 6 months until 5 years off therapy, then annually. Cardiac exams after completion of therapy will be required during first, third and fifty years off treatment.

Progress: One patient was enrolled in this study at MAMC in FY 97; however, she was transferred to a civilian hospital prior to her sponsor's separation from the military. This study remains open for patient accrual. No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/072 **Status**: Ongoing

Title: POG 9317: Chemotherapy for Children with Advanced Stage (III/IV) Diffuse Undifferentiated Burkitt's Lymphoma and B Cell ALL

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/04/1994	May 99	04/17/1998

Study Objective: 1) To evaluate the efficacy of adding VP-16/Ifosfamide intensification to the treatment of patients with advanced-stage B-cell malignancies: Stage III & IV DU NHL and B-cell acute lymphoblastic leukemia (B-ALL). 2) To compare the toxicity and efficacy of high-dose Ara-C given by intermittent bolus (q 12 hour x 4) vs bolus/continuous infusion over 48 hours.

Technical Approach: In this groupwide protocol, we propose to add, in a randomized study, two agents active in the treatment of aggressive NHL: Ifosfamide 2.8 g/m^2 with VP-16 100 mg/m^2 qd x 5. All patients in this study will be randomized at diagnosis to receive, throughout therapy, high-dose Ara-C by continuous infusion (CI) or by bolus (actually a 3 hour infusion). The CI Ara-C dose is base on the POG pilot study #9190 with a starting dose of 3.8 g/m^2/48 hours (80 mg/m^2/hr) following 9.5 g/m^2 bolus. The bolus Ara-C dose is taken from POG #8617: 3 g/m^2 q 12 hr X 4 doses.

All patients will receive therapy based on POG #8617/8616, with a reduction in duration. After a common induction with fractionated cyclophosphamide, vincristine, Adriamycin, methotrexate by 24-hour infusion, and Ara-C, patients with Stage III disease will receive these drugs without Adriamycin and patients with Stage IV/B-ALLL will receive these 5 drugs including Adriamycin during consolidation.

Patients will also be randomized to receive or not to receive VP-16/ifosfamide intensification, except for patients with CNS involvement who will be assigned to receive VP/16 ifosfamide. The study question is being posed in a randomized 2 X 2 factorial design.

Progress: No patients were enrolled in this study in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/168 **Status**: Ongoing

Title: POG 9323: Interferon-Alpha 2b Plus Hydroxyurea and Ara-C for Chronic Phase ACML in Children, A POG Pilot Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; LTC Kelly J. Faucette, MC

Start Date:	Est. Completion Date:	Periodic Review:
07/21/1995	Jul 99	06/19/1998

Study Objective: (1) To assess the toxicity of the combination of Hydroxyurea (HU) and Ara-C combined sequentially with interferon-alpha 2b (IFN) in children with adult type chronic myelogenous leukemia (ACML); and (2) To determine the frequency and duration of hematologic and cytogenetic response, and the length of time needed to achieve response during two years of such treatment.

Technical Approach: Induction, Phase 1: Therapy will begin with two, or possibly three, weekly courses of hydroxyurea and Ara-C. Each course will consist of hydroxyurea by mouth , followed two hours later by Ara-C IV over 15 minutes. This will be repeated on the second and third day of each course. Subjects will receive at least two courses, beginning days 1 and 8. If blood counts are still above certain values on day 15, a third course will be given. Induction Phase 2: Once blood counts have adequately recovered from the above chemotherapy, IFN treatment will begin, given as a subcutaneous injection daily for 14 days. Consolidation: IFN will then be continued at this dosage three times a week. IFN therapy will be interrupted for at least one week, approximately every 6 weeks, for a three day course of hydroxyurea/Ara-C. This six-week cycle (IFN three times weekly for five weeks followed by a course of hydroxyurea/Ara-C), will be repeated for a total treatment time of two years, assuming a good response to treatment. All patients who have signs of progressive disease within the first 90 days will be evaluated for possible discontinuation of this therapy. All other patients will continue on treatment for a total of 24 months. Treatment will be discontinued (prior to 24 months) if there are signs of progressive disease at any time; if there is no evidence of any improvement by six months or if side effects develop which cannot be tolerated even with reduction in the drug dosages. Therapy may also be stopped at any time if a suitable marrow donor has been found and the physician decides that bone marrow transplantation would be in the patient's best interest. If the patient is still on therapy and responding well after 24 months, then the physician may offer to continue therapy with IFN alone, but it will not be part of this study. Routine blood tests will be done during the first 4 to 6 weeks of therapy, and then every 1-2 weeks while on therapy. A bone marrow aspirate and biopsy will be done prior to start of induction therapy, then twice more at about three month intervals, and then every six months thereafter as long as on study. A Chromosomal analysis will be completed on each bone marrow aspirate to find out if the Philadelphia chromosome is present. Each bone marrow aspirate will be followed by an ultrasound study of the spleen in order to determine the size of the spleen.

Progress: One patient was enrolled in this study at MAMC in FY95. She was taken off study July 97 to pursue bone marrow transplant and continues to be followed. No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/092 **Status**: Ongoing

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

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	Est. Completion Date:	Periodic Review:
04/01/1994	Jun 99	09/30/1998

Study Objective: 1) To improve the survival of patients with osteogenic sarcoma.
2) To compare the results of a prospective, randomized trial of two chemotherapeutic regimens in the treatment of osteogenic sarcoma.
3) To compare the results of a combined chemotherapeutic regimen (high-dose methotrexate, cisplatin, and doxorubicin) given pre-operatively and post-operatively to a similar regimen using the same drugs and adding ifosfamide.
4) To test whether the early introduction of ifosfamide results in a higher rate of good histologic response at the time of definitive surgery.
5) To determine whether histologic response assessed after longer pre-operative chemotherapy with more drugs predicts disease-free survival with the same power as observed in CCG-782 which used a shorter period of pre-operative chemotherapy and fewer drugs.
6) To determine whether liposomal muramyl tripeptide-phosphatidyl ethanolamine (MTP-PE, CGP 19835a), a stimulator of macrophage function, can improve disease-free survival for patients with osteogenic sarcoma.
7) To determine whether multiple drug resistance gene-encoded P-glycoprotein expression is useful for determine prognosis or assigning therapy.

Technical Approach: This study is a phase III, prospective, 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 the primary tumor and any metastatic disease (CCG patients). Patients also are randomly assigned either to receive muramyl tripeptide (MTP-PE) with maintenance chemotherapy or to receive maintenance chemotherapy alone.

Progress: Protocol was closed to patient accrual 25 November 1997 due to adequate patient accrual. Two patients were enrolled in this study at MAMC in FY 96. One patient chose to discontinue treatment early. The other patient completed therapy. Both patients continue to be followed. No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/086 **Status**: Completed

Title: POG 9354: A Randomized 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

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	Est. Completion Date:	Periodic Review:
02/20/1998	Jun 99	02/20/1998

Study Objective: 1) To compare the event-free survival (EFS) and survival of newly diagnosed patients with Ewing's sarcoma and primitive neuroectodermal tumor (PNET) of bone or soft tissue receiving a 48 week standard regimen of vincristine, cyclophosphamide and doxorubicin alternating with ifosfamide and etoposide with G-CSF to those receiving a 30 week dose intensified regimen of the same chemotherapeutic agents. 2) To assess the diagnostic value and prognostic significance of histologic subtype as defined by routine histology, immunochemistry, electron microscopy, and MIC-2 gene expression. 3) To estimate the frequency of occurrence of serious toxicities and adverse orthopedic outcomes associated with the disease and therapy employed, and to compare them between the regimens. 4) To estimate the occurrence of second malignant tumors in these patients. 5) To determine if event free survival and survival differs between patients with PNET and Ewing's sarcoma, and between PNE and Ewing's sarcoma of bone compared to PNET and Ewing's sarcoma of soft tissue.

Technical Approach: Subjects will be assigned to one of the two regimens. Regimen A will use drugs according to the standard treatment for Ewing's Sarcoma. Regimen B will utilize the same drugs, in higher doses, over a shorter time period. It is not clear at the present time which of the treatment regimens is better. Whether randomized to Regimen A or Regimen B, the drugs listed below will be given as follows: Vincristine will be given IV push (into vein, quickly). Cyclophosphamide will be given by IV infusion over 30 minutes, (Regimen A); or 6 hours (Regimen B). MESNA will be given to prevent bleeding from the bladder which can be caused by ifosfamide or cyclophosphamide. It will be given intravenous infusion simultaneously with the cyclophosphamide or ifosfamide and will continue to be infused for 3 hours following the end of the cyclophosphamide or ifosfamide dose. Three additional doses of MESNA will be administered by IV over 15 minutes at 3, 6 and 9 hours following the end of the cyclophosphamide dose. Doxorubicin will be given by continuous infusion over 2 days. G-CSF will be given subcutaneous (SC, into the skin) or IV over 2 hours. Etoposide (VP-16) will be given IV over 1 hour. Ifosfamide will be given IV over 1-3 hours.

Progress: Protocol closed to patient entry 15 September 1998 due to adequate patient accrual. One patient was accepted in transfer from WRAMC in FY 96, relapsed shortly following completion of protocol treatment and died of the disease. Another patient enrolled in this study at MAMC in FY 97, and transferred to IWK Children's Hospital, Hallifax, Nova Scotia a few weeks after beginning treatment. No new patients were enrolled at MAMC in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/087 **Status**: Ongoing

Title: POG 9362: A Phase II Study of Alpha Interferon in HIV-Related Malignancies

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/17/1995	Jun 99	03/20/1998

Study Objective: 1) To estimate the complete response rate for HIV related malignancies treated with interferon (aIFN). 2) The secondary objectives are to estimate the one year disease free survival and to evaluate the toxicity of aIFN alone or in combination with anti-retroviral therapy.

Technical Approach: This study will require all patients to be enrolled in POG 9182 and compliance with all specimen submission requirements of that protocol. The study will minimize additional tissue, CSF or blood sampling except as required for monitoring for toxicity and tumor response. This study will take advantage of the demonstrated antitumor and antiviral activity of aIFN alone or in combination with other antiretroviral agents to treat HIV positive children with refractory or newly diagnosed malignancies. As the duration of response is one of the goals of this study, responders will continue on therapy indefinitely. Patients on this study will be treated using a interferon by subcutaneous injection every day for 14 days; then if your child's/adolescent's evaluation allows further treatment he/she will receive a interferon three times a week. This treatment will need to be monitored by a treating physician and blood tests will be performed in order to insure that the treatment is well tolerated and that the dose is appropriate. For that purpose 10cc of blood will be taken once a week. The physician and/or staff will be checking closely to see if any of these side effects are occurring. Routine physical exams, laboratory tests and tests such as biopsy or bone marrow aspiration may be necessary to monitor the effect of the treatment. Side effects usually disappear after the treatment is stopped. In the meantime, the doctor may prescribe medication to keep these side effects under control.

Progress: No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/088 **Status**: Terminated

Title: POG 9382: Molecular Studies of t(11;22) Translocation in Ewing's Sarcoma and Peripheral PNET of the Bone

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/17/1995	Jun 99	03/20/1998

Study Objective: 1) To determine if the presence of minimal metastatic disease as measured by PCR imparts a poor prognosis in patients with localized disease at diagnosis. 2) To determine the prevalence of minimal residual and metastatic disease in the bone marrow and peripheral blood of patients with Ewing's Sarcoma or PPNET as measured by PCR amplification of the t(11;22) chromosomal translocation. 3) To correlate the presence of minimal residual or metastatic disease at diagnosis with other clinical parameters. 4) To determine the types and frequency of chromosomal breakpoints and fusion transcripts and to identify whether certain chromosomal breakpoints correlate with clinical outcome. 5) To determine at what rate patients with clinically documented metastatic disease (at diagnosis or relapse) have evidence of circulating cells with the t(11;22) translocation in peripheral blood, bone marrow, or other body fluids (e.g. CSF, pleural fluid, etc.).

Technical Approach: For those subjects who are consented, will have their tumor, blood, and bone marrow looked at for residual disease. An additional blood sample will be obtained just prior to the 2nd course of chemotherapy, and at the completion of the study. Molecular studies will then be performed on these items. Statistical inference will be applied to the primary objective (#1), with descriptive measures being utilized to address the remaining objectives, which are viewed as hypothesis generating. Because of the difficulty in obtaining prior information regarding the PCR measurements, no a prior power calculations can be done. Based on POG 8850, accrual of 45 patients/year could potentially be achieved, for a total of 180 In 4 years. To test whether the presence of minimal metastatic disease as measured by PCR defines a poor risk group, we will conduct three one-sided log-rank tests on event-free survival, using a Bonferroni correction (i.e., each test will use alpha=0.05/beta=0.0167). The tests will be done at diagnosis, end of cycle 2, and end of therapy, with the two EFS curves at each time point being defined according to whether the PCR is positive or negative.

Progress: Protocol terminated. MEDCOM directed protocol could not be activated at MAMC due to inability to assess a direct, personal benefit to children from submission of their tumor tissue for molecular studies.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 95/058	**Status**: Ongoing

Title: POG 9400: ALinC 16 Classification (C) Protocol

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG	**Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/16/1994	Dec 99	11/21/1997

Study Objective: 1) To continue to characterize the biologic findings of the acute lymphoblastic and undifferentiated leukemias (immunologic markers, ploidy (DNA index), karyotyping, morphology) and their relationship, as prognostic factors for attaining and maintaining remission.

2) To apply to therapy selection, the determination that ploidy and certain structural chromosomal abnormalities predict poor prognosis.

3) To evaluate the usefulness of PCR technique in detecting minimal residual disease in patients with disease demonstrating t (9; 2 2) or t (1; 19) chromosomal abnormalities. (optional)

4) To apply to therapy selection molecular testing for 11q23 translocation in infants < 12 months of age with acute lymphocytic leukemia.

5) To determine the roll of p53 and pl6 tumor suppressor genes in T-ALL. (optional)

6) Individual patient outcome will be compared with the leukemia cell proliferation response to ask if proliferation in response to a myeloid growth factor is associated with an increased risk of developing AML. (optional)

7) To determine risk group assessment using Fluorescent In-Situ Hybridization (FISH) screening for Trisomies 4 and 10 in Non-T, Non B ALL.

8) To determine if drug sensitivity profiles of blast cells for three commonly used chemotherapeutic agents - Adriamycin, Methotrexate, and Cytarabine correlate with a) initial response b) subsequent development of relapse.

Technical Approach: A bone marrow aspirate (a needle stick in hip bone to draw marrow into syringe) will be done to prove or disprove diagnosis of leukemia. If leukemia is present, it is important to identity the exact type and subtype of leukemia, in order to plan treatment. This typing requires that several laboratory tests be run on the leukemia cells in the bone marrow. As we perform the bone marrow aspiration we will be removing enough bone marrow (about 2-1/2 teaspoons) to run the laboratory tests. We may also need to draw some blood (about 2-1/2 teaspoons) from a vein to send for studies. Some of these tests will be done here and some will be sent to reference laboratories in other Pediatric Oncology Group institutions for different kinds of special tests to identify the characteristics of the leukemia cells.

Progress: Two patients enrolled in this study at MAMC in FY95, one patient enrolled in FY 96 and one patient in FY 97 for a total enrollment of four. No new patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/144 **Status**: Ongoing

Title: POG 9404: T-Cell #4 Intensive Treatment for T-Cell Acute Lymphoblastic Leukemia and Advanced Stage Lymphoblastic Non-Hodgkin's Lymphoma

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC

Start Date:	Est. Completion Date:	Periodic Review:
07/19/1996	Aug 04	07/17/1998

Study Objective: 1) To determine, in a randomized trial, the effectiveness of high dose methotrexate (HD MTX) when added to a multi-agent chemotherapy backbone (DFCI 87-0001) proven effective in T-Cell acute lymphoblastic leukemias (T-ALL) and advanced stage non-Hodgkin's lymphoma (Lymphoblastic NHL); 2) to determine, in a randomized trial, the role of the cardioprotectant Zinecard (DZR) in preventing cardiotoxicity in children with T-ALL and advanced stage Lymphoblastic NHL receiving an anthracycline based regimen; 3) to study the biology of T-Cell lymphoid malignancies by accumulating data on the concurrent ALL classification study (POG 9400) and analyzing the data relative to outcome; 4) to evaluate the correlation of minimal residual disease with event-free survival utilizing the TAL 1 proto-oncogene; 5) to determine the role of p53 and p16 tumor suppressor genes in T-ALL; and 6) to determine if drug sensitivity profiles of blasts cells to Doxorubicin, methotrexate and cytarabine correlate with initial response and subsequent development of relapse.

Technical Approach: Patients will receive induction therapy (weeks 1-6), vincristine every week for 4 weeks, prednisone for 21 days starting day 1 and doxorubicin on days 1, 2, and 22, with or without ZINECARD. During this phase, the drug methotrexate will be given on day 2. Patients will be randomized to receive high dose methotrexate on day 22. Intrathecal methotrexate, Ara-C and hydrocortisone will be given to prevent central nervous system disease throughout the entire three phases of treatment. Once remission has been achieved, patients will receive consolidation therapy (weeks 7-33). Drugs will be given in three week cycles (6-mercaptopurine for 14 days, vincristine and doxorubicin on day 1 of the cycle, prednisone for 21 days) with or without ZINECARD. Asparaginase will also be given during the consolidation phase once a week during weeks 7-26. Patients who received high dose methotrexate on day 22 of induction will also receive it on weeks 7, 10 and 13 of consolidation. At weeks 22-24, all patients will receive radiation therapy to the brain. During continuation (weeks 34-108), patients will receive vincristine, prednisone (every day for five days) and 6-MP (every day x 14 days) every three weeks. Methotrexate, will be given every week except during those weeks when patients receive intrathecal medications.

Progress: No patients were enrolled in this study in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/059 **Status**: Ongoing

Title: POG 9405: ALinC 16: Protocol for Patients With Newly Diagnosed Standard Risk Acute Lymphoblastic Leukemia (ALL)

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	Est. Completion Date:	Periodic Review:
12/16/1994	Dec 99	09/30/1998

Study Objective: (1) To determine in a randomized trial, the efficacy of a higher (2.5 gms/m^2) vs standard (1 gm/m^2) dose methotrexate (MTX) infusion during consolidation. The major endpoint will be event free survival among those achieving a complete remission. Secondary comparisons will include site specific events and adverse drug reactions; (2) To determine in a randomized comparison, the efficacy of delivering oral 6-MP on a once vs twice daily schedule during continuation; (3) To study laboratory correlates from POG 9400 and clinical correlates with outcome in pooling studies 9201, 9405 and 9406; and (4) To assess the prognostic significance of the percent of marrow blasts after two weeks of induction therapy.

Technical Approach (revised 3 Jan 96): **INDUCTION:** Low risk subjects will receive intensive combination chemotherapy for 4 weeks consisting of Prednisone, given orally for 28 days; vincristine, given by IV push on days 1, 8, 15, and 22; L- asparaginase, injected (IM) on days 2, 5, 8, 12, 15, and 19. The drugs methotrexate, Ara- C and hydrocortisone will be administered IT at various intervals throughout both the induction and intensive periods for central nervous system prophylaxis. **CONSOLIDATION (WEEKS 5-49)** will be divided in four week courses with subjects receiving high dose methotrexate (200 mg/m^2 IV push, then 800 mg/m^2 over 24 hours in 2400 ml/m^2 [100 ml/m^2/hr]) plus high dose C-MP (200 mg/m^2 IVP, then 800 mg/m^2 IV over 6 hours in 700 cc/m^2 [116.6/m^2/hr]) during the first week of each course and methotrexate (20 mg/m^2 IM x 3) plus 6-MP (75 mg/m^2 p.o. qhs) on weeks 2, 3, and 4 of each course. This will continue for 12 courses. Leucovorin will be given during this period to help protect patients from toxicity of methotrexate. **CONTINUATION (WEEKS 50-130):** Low risk patents will receive methotrexate at a dose of 20 mg/m^2/wk IM plus 6-MP at a dose of 75 mg/m^2 p.o. qhs. High risk patients will receive methotrexate at a dose of 20 mg/m^2/wk IM plus 6-MP 37.5 mg/m^2 p.o. BID. The subject will be taken off study in case of relapse in the bone marrow, or any other site, or if the subject fails to achieve a complete remission during the induction phase of the study..

Progress: This protocol closed to patient accrual 26 Dec 95 due to excessive neurotoxicity. Two patients were enrolled at MAMC. One patient enrolled in this study at MAMC in FY95 and was taken off study but continues to be followed. The other patient enrolled in FY 96 was transferred to Beaumont Naval Med Center.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/060 **Status**: Ongoing

Title: POG 9406: ALinC #16 - Protocol for Patients With Newly Diagnosed High Risk Acute Lymphoblastic Leukemia (ALL)

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	Est. Completion Date:	Periodic Review:
12/16/1994	Dec 99	11/21/1997

Study Objective: (1) To determine the efficacy of a 2.5 gm/m^2 dose versus 1 gm/m^2 dose IV methotrexate infusions during intensified continuation therapy; (2) To determine whether intensified continuation therapy delivering pulses of Ara-C with asparaginase rescue is superior to standard intensified continuation with pulses of VM-26/Ara-C; (3) To study laboratory correlates and clinical correlates with other similar studies, and (4) To assess the prognostic significance of the percent of marrow blasts after 2 weeks of induction therapy. . The major endpoint will be event-free survival among those achieving a complete remission. Secondary comparison will include site-specific events (including secondary AML) and adverse drug reactions.

Technical Approach: Subjects will receive intensive induction chemotherapy with prednisone, orally for 28 days; vincristine, by IV infusion on days 1,8,15, and 22; and L-asparaginase, IM on days 2, 5, 8, 12, 15, and 19. Methotrexate, cytosine, Ara-c, and hydrocortisone will be administered IV at various intervals throughout induction. Daunomycin will be given IV on days 8, 15, and 22. Subjects will then be randomized to a regimen to include either standard or high does Methotrexate or low or high dose Ara-C. During the period known as consolidation, the subject will receive methotrexate and 6-mercaptopurine (6-MP) during weeks 5-6, 10-11, 15-16, 25-26, and 30-31. In the first week of each of these periods, methotrexate (either the standard or the intensified higher dose) will be given IV followed by a 24-hr infusion. Leucovorin will be given to help protect the patient from the toxicity of methotrexate. Immediately after the methotrexate, 6-MP will be given by IV infusion over 20 min followed by an infusion over 6 hrs. On the second week of therapy, the subject will receive IM methotrexate on day 1 and 6-MP daily by mouth for 7 days. At weeks 7, 17, and 27 the subject will receive high-dose Ara-C as a continuous infusion for 72 hrs or low-dose SQ. VM-26 will be given as a 45-min IV infusion before the start of Ara-C and on day 2 with standard dose Ara-C. If the subject receives intensified Ara-C, the subject will also receive PEG and G-CSF. At weeks 12, 22, and 32, Ara-C will be infused over 72 hrs as described above. Daunomycin will be given as a 30-min infusion before the start and at the end of the Ara-C. In addition, vincristine is given IV on days 1 and 8, prednisone orally on days 1 and 7, and PEG/L-asparaginase IM on day 1. During weeks 35-130, standard dose 6-MP will be given orally each day, and methotrexate IM once a week. The subject will be taken off study in case of relapse or if the subject fails to achieve a complete remission during the induction phase.

Progress: One patient was enrolled in this study in FY 96, but, due to an adverse event during induction was taken off study. Another patient accepted in transfer from SUNY relapsed while on therapy and went on to a bone marrow transplant. Both patients continue to be followed. No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/089 **Status**: Ongoing

Title: POG 9421: Phase III Evaluation of Standard vs. High Dose ARA-C Induction Followed by the Randomized Use of Cyclosporine A As An MDR Reversal Agent, Compared to Allogeneic BMT, in Childhood AML

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/17/1995	Jan 01	02/20/1998

Study Objective: 1) To determine the effect of high dose vs. standard dose Ara-C induction on CR (clinical remission) and EFS (event free survival) in Childhood AML. 2) To compare EFS in Childhood AML after 3 cycles of consolidation with or without the MDR (multidrug resistance) modulator CSA (cyclosporine A). 3) To compare the EFS between patients genetically randomized between allogenic BMT and chemotherapy. 4) To evaluate the impact of EFS of various clinical and laboratory factors such as cytogenetics and MDR expression. 5) To confirm the superior response of Down syndrome patients utilizing standard induction and non-CSA containing consolidation, and identify specific biologic and pharmacokinetic characteristics in these patients.

Technical Approach: Phase III evaluation of standard vs. high dose Ara-C induction followed by the randomized use of Cyclosporine A as an MDR (multidrug resistant) reversal agent, compared to allogeneic BMT, in childhood AML. Patients will be randomized (assigned by chance, such as flipping a coin) at the time of diagnosis to receive either standard doses or high doses of ARA-C during the initial course of therapy. The chances of receiving any of the therapies is approximately equal. Later in the course of therapy, patients (according to how they were previously randomized) will or will NOT receive the drug Cyclosporine A in combination with the chemotherapy agents, Mitoxantrone and Etoposide. Patients with Down syndrome will not be randomized, but will receive the standard therapy. Earlier studies have shown the three year event-free survival rate for Down syndrome children significantly superior to children without Down syndrome using standard therapy. Also, for this reason Down syndrome patients will not receive Cyclosporine A. If a sibling who is matched for bone marrow transplantation, will receive bone marrow transplantation, which has been shown to be a more effective treatment in controlling AML compared to chemotherapy, providing that consent from the sibling donor can be obtained. If not a sibling donor, studies have shown chemotherapy is superior to matched unrelated donor BMT. However, should the patient choose to pursue an unrelated matched BMT instead of continuing with consolidation chemotherapy, the subject may discontinue the study. At the time of bone marrow aspiration, blood sampling, or spinal tap, cells obtained may also be used for research studies.

Progress: One patient accepted in transfer from WRAMC is off protocol therapy and continues to be followed. No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/071 **Status**: Ongoing

Title: POG 9425: Advanced Stage Hodgkin's Disease, A POG Phase III Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/21/1997	Jul 03	03/20/1998

Study Objective: 1) To test the efficacy of DBVE-PC, an intensive treatment regimen for advanced stage Hodgkin's disease that administers doxorubicin, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide with G-CSF at 3 week intervals in a dose intensive manner (using cumulative drug doses that may minimize long term toxicity), followed by consolidative radiotherapy; 2) To tailor therapy based on rapidity of response in order to minimize cumulative drug dosages. Those in CR after 3 cycles of DBVE-PC will receive only low dose RT. Those who are not in CR will receive 2 additional cycles of DBVE-PC (+ low dose RT); 3) To determine, in a randomized trial, whether the addition of Dexrazoxane reduces pulmonary and cardiac toxicity of DBVE-based therapy without compromising response. This randomization will include all patients with Hodgkin's disease on POG 9425 (advanced stage) and 9426 (early stage) or not to receive the investigational drug Zinecard just prior to the administration of the chemotherapy drugs bleomycin and doxorubicin. Following disease staging with radiologic imaging and laboratory evaluations, patients will receive 3 cycles of the drug combination etoposide, vincristine, bleomycin, doxorubicin cyclophosphamide, prednisone combination with G-CSF in 3 week intervals. Patients will be restaged after receiving these three chemotherapy courses. Those showing large tumor response will go on to radiation therapy, while those showing partial response will receive 2 additional cycles of chemotherapy and then go on to radiation therapy. Follow-up will continue for a minimum of 10 years at least on a yearly basis after completion of therapy.

Technical Approach: Registered study patients will be randomized to receive or not to receive the investigational drug Zinecard just prior to the administration of the chemotherapy drugs bleomycin and doxorubicin. Following disease staging with radiologic imaging and laboratory evaluations, patients will receive 3 cycles of the drug combination etoposide, vincristine, bleomycin, doxorubicin cyclophosphamide, prednisone combination with G-CSF in 3 week intervals. Patients will be restaged after receiving these three chemotherapy courses. Those showing large tumor response will go on to radiation therapy, while those showing partial response will receive 2 additional cycles of chemotherapy and then go on to radiation therapy. Follow-up will continue for a minimum of 10 years at least on a yearly basis after completion of therapy.

Progress: No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/054 **Status**: Ongoing

Title: POG 9426: Response Dependent Treatment of Stages IA, IIA, and IIIA(1-micro) Hodgkin's Disease with DBVE and Low Dose Involved Field Irradiation with or without Zinecard

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC

Start Date:	Est. Completion Date:	Periodic Review:
02/21/1997	Jul 03	02/20/1998

Study Objective: 1) To tailor chemotherapy courses based on the patients' initial response to therapy; 2) To examine the activity of variable courses of doxorubicin, bleomycin, vincristine, and etoposide (DBVE) and low-dose involved field irradiation; 3) To monitor safety and feasibility of the response-dependent approach, and morbidity, immediate and long term toxicities of the above regimen; 4) To evaluate if limited therapy is adequate for patients with early response; 5) To examine if addition of Zinecard can reduce pulmonary toxicity while not significantly reducing response rate or event-free survival; 6) To determine if the frequency and magnitude of myocardial injury during therapy, as measured by an elevation of cardiac Troponin-T in the serum, is reduced by the addition of Zinecard.

Technical Approach: Registered study patients will be randomized to receive the investigational drug Zinecard just prior to the administration of the chemotherapy drugs bleomycin and doxorubicin. Following disease staging with radiologic imaging and laboratory evaluations, patients will receive 2 courses of the four drug combination etoposide, vincristine, bleomycin and doxorubicin at 28 day intervals. Patients will be restaged after receiving these two chemotherapy courses. Those showing remission will go on to radiation therapy, while those showing residual disease will receive 2 more courses of the four drug combination and then go on to radiation therapy. Follow-up will continue for a minimum of 10 years at least on a yearly basis.

Progress: One patient was enrolled in this study at MAMC in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/097 **Status**: Ongoing

Title: POG 9440: National Wilms Tumor Study - 5: Therapeutic Trial and Biology Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC

Start Date:	Est. Completion Date:	Periodic Review:
04/19/1996	Jul 02	04/17/1998

Study Objective: 1) To increase the survival rate of children with favorable histology Wilms tumor and other renal tumors of childhood; 2) to determine if loss of heterozygosity for chromosome 16q markers in tumor tissue is associated with a poorer prognosis for children with favorable histology Wilms tumor; 3) to determine if loss of heterozygosity for chromosome 1p markers in tumor tissue is associated with a poorer prognosis for children with favorable histology Wilms tumor; 4) to determine if increased DNA content in tumor cells is associated with a poorer prognosis; 5) to decrease the acute and long term morbidity of treatment of children with Wilms tumor; 6) to improve the survival of patients with unfavorable histology tumors including Wilms tumor with diffuse anaplasia and clear cell sarcoma of the kidney by using a new treatment regimen that includes etoposide and cyclophosphamide; 7) to improve survival of patients with malignant rhabdoid tumor of the kidney; 8) to study biology and pathology of patients who present with bilateral Wilms tumor; 9) to conduct hypothesis-driven trials led by diagnostic radiologists in order to develop guidelines; and 10) to establish a biological samples bank containing touch preparations, paraffin blocks, frozen tumor, normal kidney tissue, and serum and urine.

Technical Approach: Wilms tumor is the most frequent malignant renal tumor in children. This proposed therapeutic trial involves a number of experimental regimens that are designed either to reduce treatment for the subgroup of patients with the most favorable prognosis, or to intensify treatment for several subgroups with the least favorable prognosis. Patients will be stratified into the appropriate treatment regimens by age, size of tumor at diagnosis and staging of the tumor (Stages 1-V) with favorable/unfavorable histology, including rhabdoid, clear cell sarcomas and Wilms tumor with diffuse or focal anaplasia. Treatment will include nephrectomy or surgical debulking of tumor, radiation therapy to abdomen and/or lungs, and appropriate chemotherapy regimens.

Progress: One patient was enrolled in this study at MAMC in FY 96 and was transferred to Portsmouth Naval Hospital. One patient was accepted in transfer from Tripler AMC, Honolulu, Hawaii and continues to receive treatment. No new patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/090	**Status**: Ongoing

Title: POG 9442: National Wilms Tumor Late Effects Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG		**Facility**: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
07/17/1998	Jul 03	N/A

Study Objective: To determine (1) the frequency of Wilms tumor and other cancers in family members of Wilms tumor patients in order to estimate the recurrence risk in siblings and offspring; test the plausibility of specific genetic modes of inheritance in homogeneous subgroups; and identify familial cancer syndromes (if any) that may involve Wilms tumor, (2) To determine fertility rates of Wilms tumor patients and rates of perinatal mortality, low birth-weight and adverse pregnancy outcomes in relation to the type and amount of cancer treatment received in childhood, (3) To estimate the rates of selected congenital defects and of specified single gene disorders (sentinel phenotypes) in the offspring of Wilms tumor patients, (4) to estimate the rates of second malignancy neoplasms in relation to the dosage of radiation therapy and the use of specific chemotherapeutic agents (actinomycin D, doxorubicin, cytoxan and etoposide) received in childhood, (5) to compare the incidence rate of congestive heart failure among Wilms tumor survivors in relation to the dose of radiation therapy received to abdomen and/or lungs and to the use of specific chemotherapeutic agents.

Technical Approach: The large number of Wilms tumor survivors ascertained by the NWTS during its first twenty years of operation constitutes an ideal cohort for the study of familial risk and late effects of treatment. Four protocol studies have been conducted; treatment protocols and results for the first three studies have been published. A large fraction of the total national U.S. incidence of Wilms tumor has been registered on these studies, probably as much as 70% of an estimated 450-500 cases occurring nationally since 1980. Over 2,500 children who were followed on NWTS treatment protocols have now survived 5 or more years since their original diagnosis. Many of those treated more than a decade ago have reached sexual maturity, so that their reproductive history and the status of their offspring may be evaluated by entry into this study.

Progress: No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/039 **Status**: Ongoing

Title: POG 9457: Intensive Therapy with Growth Factor Support for Patients with Ewing's Tumor Metastatic at Diagnosis

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; LTC Luke M. Stapleton, MC; LTC Kenneth A. Bertram, MC; LTC Robert B. Ellis, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	Est. Completion Date:	Periodic Review:
12/15/1995	Sep 99	11/21/1997

Study Objective: 1) To evaluate the response rate, and duration of response in patients with Ewing's tumor, metastatic at diagnosis, treated with maximally intensified therapy. (2) To evaluate the response to new agents utilized in an upfront window. Initially, topotecan will be used as a single agent. When the maximally tolerated dosages of the combination of topotecan and cyclophosphamide are available, the combination will be employed. (3) To assess the role of surgical treatments with regard to local control of primary and metastatic sites and disease course. (4) To determine whether individual variability in ifosfamide and cyclophosphamide metabolism correlated with toxicity and/or response. (5) To evaluate the rise in the absolute neutrophil count following one dose of G-CSF just prior to a chemotherapy cycle as a measure of bone marrow reserve and subsequent myelosuppression.

Technical Approach: In the absence of effective new agents in Ewing's Tumor, attempts to increase the rate of cure have recently centered around increasing dose intensity. Ifosfamide will be used at a dosage level 25% higher than that currently being used, for the first 3 cycles. The dosage will be reduced for the 2 continuation cycles. Cyclophosphamide will also be used in increased dosage with vincristine and adriamycin. This study will encourage the use of surgery for local control, with irradiation of the primary tumor bed, unresectable primary tumors and selected metastatic sties. Topotecan is a camptothecin, a topoisomerase I inhibitor. Initially, this study will use 2 cycles of single agent topotecan 3 weeks apart. At least 14 patients will be registered. When the maximum tolerated dosages of the combination of topotecan and cyclophosphamide are available, subsequent patients will be treated with the combination.

Progress: No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 98/048	**Status**: Ongoing

Title: POG 9464: Cyclophosphamide Plus Topotecan in Children with Recurrent or Refractory Solid Tumors

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG	**Facility**: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/20/1998	Jul 03	N/A

Study Objective: To determine the response rate of recurrent or refractory solid tumors and brain tumors to cyclophosphamide plus topotecan and to further define the toxicity of cyclophosphamide plus topotecan in children.

Technical Approach: Following evaluation, patients will be hospitalized to receive IV fluid hydration for 30 minutes prior to receiving cyclophosphamide and topotecan, both administered IV over a period of 30 minutes. This entire sequence will be repeated for 5 consecutive days. On day 6, G-CSF will be administered until the absolute neutrophil count is recovered from the effects of the chemotherapy. Patients entering the study are expected to complete 2 courses of therapy unless significant toxicity occurs. Evaluations will be repeated prior to the second and third courses of therapy. Patients will be removed from the study if clear evidence of progressive disease is documented after the first course of topotecan and cyclophosphamide or after any subsequent courses. Patients should continue treatment with the study drugs after the second course as long as CR, PR, or NR/SD is present unless alternative therapy is planned. Patients may be electively removed from the study to pursue such therapy after the second course.

Progress: One patient was entered in this study at MAMC in FY 98; however he was taken off study and died due to progressive disease.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/143 **Status**: Completed

Title: POG 9485: Intergroup Protocol, Assessment of the Role of Minimal Access Surgery in the Treatment of Childhood Cancer: Intergroup Laparoscopy Protocol

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; MAJ Randall M. Holland, MC

Start Date:	Est. Completion Date:	Periodic Review:
07/19/1996	Jul 98	12/18/1997

Study Objective: 1) To investigate the role of minimal access abdominal surgery (MAS) in terms of the perioperative complication rate and the mortality rate; 2) to compare the impact of MAS and open laparotomy on quality of life (QOL). Several domains of QOL will be examined including surgery-related pain, physical, social and emotional functioning, and global ratings of health and overall QOL; 3) to compare the impact of MAS and open laparotomy on economic costs; 4) to compare the complete tumor resection rate for MAS with open surgery within specific diagnostic groups; 5) to assess the impact of minimal access surgery on compliance with specimen eligibility requirements for therapeutic protocols.

Technical Approach: Pediatric patients less than or equal to 21 years old who require surgery to obtain biopsy material, lymph node sampling for staging, liver biopsies, tumor excisions, organ excision, second-look procedures, etc., will be considered for entry and will be randomized to either open or a minimal access procedure. Protocol eligibility is linked with the requirement to obtain adequate surgical specimens. MAS offers the potential to minimize a potential barrier to enrollment onto protocol therapy. Biologic specimens will be assessed for their adequacy in terms of both the specimen quantity and quality. Demographic data, procedural and overall economic costs, operative time, anesthesia and post-operative analgesia, length of post-operative stay, interval between procedure and subsequent actions, and perioperative morbidity will all be evaluated. Methods of evaluations will include Quality-of-Life assessment, Pain Ratings, Play-Performance/Karnofski assessment, operative and overall mortality, surgery characteristics, radiology review and imaging guidelines.

Progress: Protocol was closed to patient entry 25 November 1997 due to poor patient accrual. No patients were enrolled in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/035 **Status**: Ongoing

Title: POG 9490: Topotecan Followed by Multimodal, Multiagent Therapy for Children and Adolescents with Newly Diagnosed Stage IV/Clinical Group IV Rhabdomyosarcoma, an IRS-V Pilot Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC

Start Date:	Est. Completion Date:	Periodic Review:
11/17/1995	Jun 97	09/30/1998

Study Objective: 1) To evaluate the toxicity of the topoisomerase I inhibitor, topotecan, when given alone at a maximum tolerated dose by bolus injection daily X 5 days/course for 2 courses to untreated children and adolescents with Stage IV and/or Clinical Group IV rhabdomyosarcoma, all patients with metastatic disease. (2) To estimate the response rate (complete or partial) of such patients to topotecan. (3) To evaluate the toxicity of a new chemotherapy combination comprising topotecan, cyclophosphamide, and vincristine (VTC) given in alternating cycles with vincristine, actinomycin D, and cyclophosphamide (VAC) to patients who have achieved an objective response partial response (PR) or complete response (CR) to topotecan.

Technical Approach: Patients with rhabdomyosarcoma, clinical stage IV disease will receive Topotecan upfront at 2.0 mg/m²/day X 5 IV. Following evaluation, patients with partial response or complete response will go on to VAC treatment, alternating with VTC treatment. Those with stable or progressive disease will proceed to VAC alone. Radiation therapy will begin following evaluation at week 15 in conjunction with vincristine and cyclophosphamide. Continuation therapy begin following evaluation at week 25 with VAC/VTC for patients showing PR and CR.

Progress: Closed to patient accrual 1 Nov 96. One patient was enrolled in this study at MAMC in FY 96 and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/089 **Status**: Ongoing

Title: POG 9553: A Phase II of Neoadjuvant Vincristine, Ifosfamide, Doxorubicin, and G-CSF in Children with Advanced Stage Non-rhabdomyosarcoma Soft Tissue Sarcomas

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC

Start Date:	Est. Completion Date:	Periodic Review:
04/18/1997	Jul 03	04/17/1998

Study Objective: 1) To estimate the response rate to the combination of vincristine, ifosfamide, and doxorubicin (VID), with G-CSF support, in children with newly diagnosed inoperable or metastatic non-rhabdomyosarcoma soft tissue sarcomas; 2) To estimate the 2-year survival and event-free survival of children treated with VID in combination with radiotherapy and/or surgery; 3) To establish a bank of frozen tissue (tumor and peripheral blood) for use in further molecular studies.

Technical Approach: Registered study patients will receive the three drug combination Vincristine, Ifosfamide, and Doxorubicin; two courses within a 6 week period. Cyclophosphamide will be substituted for those patients who cannot tolerate Ifosfamide. Patients will then be evaluated for response. If the tumor shrinks, patients will go on to XRT/chemotherapy, with or without prior surgical resection at this time. If the tumor has grown or stayed the same, patients will be taken off study treatment and offered other therapy. After XRT and chemotherapy, patients will be reimaged and another six weeks of chemotherapy will be given at this time unless the tumor has grown or come back.

Progress: No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 96/120	**Status**: Ongoing

Title: POG 9605: ALinC 16: Protocol for Patients With Newly Diagnosed Standard Risk Acute Lymphoblastic Leukemia (ALL)

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG	**Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/17/1996	Jul 03	05/22/1998

Study Objective: 1) To determine in a randomized trial whether the addition of 6 months of delayed intensification with divided dose oral methotrexate (ddMTX) improves event-free survival (EFS) of children with standard risk acute lymphoblastic leukemia; 2) to determine in a randomized trial the effect on EFS of delivering oral 6-mercaptopurine (6-MP) on a divided (twice daily) vs once a day schedule, during delayed intensification and continuation; 3) to study how laboratory data from POG 9400 correlates with outcome by pooling studies 9201, 9405, 9605, and 9406; 4) to assess the prognostic significance of the percent of marrow blasts after two weeks of induction therapy; 5) to describe the occurrence of elevated transaminases and correlation of these with outcome.

Technical Approach: This treatment protocol involves 130 weeks of chemotherapy beginning with standard induction therapy of generally 4 (but up to 6) weeks of chemotherapy consisting of vincristine, prednisone, and L-asparaginase plus triple intrathecal therapy of combined methotrexate, hydrocortisone and Ara-C. Post induction, the treatment is divided into consolidation, intensification, and maintenance phases of therapy. Registration on study occurs post induction therapy at which time patients are randomized to receive 1 of 4 regimens which vary beginning in the intensification phase of therapy.

Progress: One patient enrolled in this study at MAMC in FY 96 transferred to WRAMC. One patient accepted in transfer from SUNY in FY 96 continues to be followed. Two patients were accepted in transfer in FY 98, one from WRAMC and the other from Tripler AMC. Three patients continue to receive treatment.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/065 **Status**: Ongoing

Title: POG 9641: Primary Surgical Therapy for Biologically Defined Low-Risk Neuroblastoma; A Pediatric Oncology Group Children's Cancer Group, Phase III, Intergroup Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/20/1998	Jul 03	N/A

Study Objective: 1) To determine if low risk INSS stage 2A/2B asymptomatic neuroblastoma patients treated with surgery alone will have a three year survival rate of 95%, (2) To determine if low risk INSS stage 1 asymptomatic neuroblastoma patients treated with surgery alone will have a three year survival rate of 95%, (3) To determine if low risk INSS stage 4S asymptomatic neuroblastoma patients treated with surgery alone will have a three year survival rate of 95%, (4) To estimate the response and 3 year event-free survival (EFS) rates of symptomatic patients with chemotherapy, (5) To estimate the EFS and survival rates in patients who relapse or progress after initial treatment with surgery alone, (6) To determine the acute and long-term morbidity/toxicities associated with treating low-risk neuroblastoma with surgery alone or with surgery and chemotherapy, (7) To further define and evaluate the prognostic importance of other biologic factors as determined on studies POG #9047 (or its successor), CCG #B973, and by International Neuroblastoma Risk Group criteria, (8) To collect resource utilization data regarding number of hospital days, the extent of transfusion support, and the use of diagnostic imaging, and to compare these with historical CCG study 3881 data.

Technical Approach: Patients in this study will be stratified by stage and extent of disease to either surgery alone or surgery with chemotherapy. Further studies done on patient's tumor specimens may change their classification to "intermediate" or "high" risk neuroblastoma, in which case they will be taken off study and more intensive chemotherapy will be administered.

Progress: No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/064 **Status**: Ongoing

Title: POG 9701 (A09701): A Phase II Study of Temodal (SCH 52365; Temozolomide, IND #52797) in Children and Adolescents with Recurrent Central Nervous System (CNS) Tumors

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/20/1998	Jun 03	N/A

Study Objective: To determine the response rate to Temodal in several strata of recurrent CNS tumors of childhood and to further assess the toxicity of Temodal in a larger group of patients treated at the recently defined maximally tolerated dose (MTD).

Technical Approach: The study is divided into two treatment strata; prior history of craniospinal (CSI) or total spinal radiotherapy. Patients without prior CSI will receive Temodal 200 mg/m^2/day orally for five consecutive days, following overnight fast. Patients may not eat for two hours after administration of capsules. Subsequent courses may begin on day 28, if all toxicities have resolved.

Patients with prior CSI will receive Temodal 180 mg/m^2/day orally for five consecutive days, following overnight fast. Patients may not eat for two hours after administration of capsules. Subsequent courses may begin on day 28, if all toxicities have resolved.

Patients benefiting from Temodal after 2 courses (patients with stable disease or a response) may continue up to 10 additional courses. Treatment must be stopped when disease progresses or when a total of 12 total courses of Temodal have been administered.

Progress: One patient entered in this study at MAMC in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/066 **Status**: Ongoing

Title: POG 9720: Idarubicin and Cladribine in Recurrent and Refractory Acute Myeloid Leukemia: A Pediatric Oncology Group Phase II Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/20/1998	Jul 03	N/A

Study Objective: 1) To determine the complete remission (CR) rate of the combination of Idarubicin (IDA) and Cladribine (CDA) in patients with recurrent AML; 2) To determine the CR rate of the combination of IDA and CDA in patients with primary refractory AML; 3) To determine the CR rate of the combination of IDA and CDA in patients with recurrent or primary refractory secondary AML and myelodysplastic syndromes (not related to Down's Syndrome); 4) To determine the toxicities of the combination of IDA and CDA; and 5) To define the pharmacokinetics of CDA administered as a 2 hour infusion.

Technical Approach: Eligible patients will be stratified and receive a five day treatment consisting of IV Idarubicin daily for 3 days and IV Cladribine, 2 hours daily for 5 days. Twenty-four hours after completion of chemotherapy, patients will begin daily subcutaneous injections of G-CSF until blood counts stabilize. A bone marrow aspirate will be done at 3 weeks to assess response. A second course may be given. If patients have progressive disease they will be taken off study.

Progress: No patients enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/088 **Status**: Ongoing

Title: POG A9961: A Phase III Prospective Randomized Study of Craniospinal Radiotherapy Followed by One of Two Adjuvant Chemotherapy Regimens (CCNU, CDDP, VCR, or CPM, CDDP, VCR) in Children with Newly-Diagnosed Average Risk Medulloblastoma

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC

Start Date:	Est. Completion Date:	Periodic Review:
04/18/1997	Apr 03	04/17/1998

Study Objective: 1) To determine if a cyclophosphamide arm will increase the rate of progression-free survival compared to a CCNU containing arm for children with average-risk medulloblastoma; 2) To determine the progression-free survival and overall survival of children treated with craniospinal (2340 cGy) and local boost radiotherapy (3240 cGy) for a total dose of S580 cGy, and adjuvant vincristine, CCNU and cisplatin chemotherapy; 3) To determine the progression-free survival and overall survival of children treated with craniospinal (2340 cGy) and local boost radiotherapy (3240 cGy) for a total dose of 5580 cGy, and adjuvant vincristine, cyclophosphamide and cisplatin chemotherapy; 4) To determine the long-term neurocognitive, endocrinologic and cardiopulmonary sequelae of radiotherapy plus adjuvant chemotherapy in children with average-risk medulloblastoma treated with 2340 cGy of craniospinal radiation therapy, local boost radiotherapy, and either one of two drug regimens and to determine if the replacement of CCNU with cyclophosphamide will alter the incidence and degree of sequelae experienced; 5) To determine if cellular/biologic parameters, including tumor molecular genetic analysis, DNA ploidy, mitotic activity markers and immunohistochemical analysis are correlated with progression-free survival, survival and the pattern of disease relapse in children with average-risk medulloblastoma; 6) To determine the utility of routine MR surveillance studies of the head and spine to detect subclinical recurrent disease.

Technical Approach: A9961 is an intergroup research study which plans to evaluate the overall progression-free survival of children with average-risk medulloblastoma treated with craniospinal radiation and local boost radiotherapy plus one of two adjuvant chemotherapy regimens differing in the replacement of CCNU by cyclophosphamide. The long-term neurocognitive, endocrinologic and cardiopulmonary sequelae of radiotherapy with adjuvant chemotherapy will be determined, as well as the feasibility of routine surveillance scans to detect subclinical recurrent disease. Another objective of this study will be to evaluate the sensitivity of molecular and biochemical techniques (i.e., molecular genetic analysis, DNA ploidy, mitotic activity markers and immunohistochemical analysis, to predict progression-free survival and disease relapse.

Following surgery, patients will be randomized to receive Regimen A or B of treatment. Both regimens will include 2340 cGy of craniospinal radiation and 3240 cGy of boost radiation directly to the primary tumor with weekly vincristine doses. Six weeks following the completion of radiotherapy, patients will begin 8 cycles of maintenance chemotherapy for Regimen A (CCNU, cisplatin and vincristine) or Regimen B (cyclophosphamide, cisplatin and vincristine).
The study is expected to accrue between 240 and 300 patients over a minimum of 4 year accrual period.

Progress: No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/090 **Status**: Ongoing

Title: POG D9501: Topotecan and Cyclophosphamide, Followed by Multimodel, Multiagent Therapy for Children & Adolescents with Newly Diagnosed Stage IV/Clinical Group IV Rhabdomyosarcoma, an IRS-V Pilot Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC

Start Date:	Est. Completion Date:	Periodic Review:
04/18/1997	Jul 03	04/17/1998

Study Objective: 1) To evaluate the toxicity of cyclophosphamide and the topoisomerase I inhibitor, topotecan, when given together by 30 minute infusion daily x 5 days/course for 2 courses to untreated children and adolescents with Stage IV and/or Clinical Group IV rhabdomyosarcoma, all patients with metastatic disease; 2) To estimate the response rate (complete or partial) of such patients to cyclophosphamide and topotecan; 3) To evaluate the toxicity of a new chemotherapy combination comprising vincristine (VCR), cyclophosphamide, and topotecan given in alternating cycles with vincristine, dactinomycin, and cyclophosphamide (VAC) to patients who have achieved an objective response, partial response (PR) or complete response (CR) to topotecan.

Technical Approach: Patients with advanced stage rhabdomyosarcoma will receive two courses of Topotecan & Cyclophosphamide upfront. Following evaluation patients with partial response (PR) or complete response (CR) will go on to VAC treatment, alternating with VTC treatment. Those with stable or progressive disease will proceed to VAC alone. Radiation therapy will begin following evaluation at week 15 and in conjunction with vincristine and cyclophosphamide. Continuation therapy begins following evaluation at week 25 with VAC/VTC for patients showing PR and CR; and VAC alone for patients with stable or progressive disease. Patients will be evaluated again at week 44.

Progress: No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/145 **Status**: Ongoing

Title: POG D9602: Actinomycin D and Vincristine with or without Radiation Therapy for Newly Diagnosed Patients with Low-Risk Rhabdomyosarcoma or Undifferentiated Sarcoma: An IRS-V Protocol

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility**: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:	Est. Completion Date:	Periodic Review:
09/19/1997	Jul 03	09/15/1998

Study Objective: 1) Treatment of IRS-V low-risk patients with actinomycin D (AMD) and vincristine (VCR), plus local radiotherapy (XRT) for microscopic or gross residual tumor, will result in a failure-free survival rate of 88% at 2 years and an overall survival rate of about 95% at S years from initial diagnosis; 2) Treatment of IR8-V low-risk patients with alveolar rhabdomyosarcoma or undifferentiated sarcoma with vincristine and actinomycin D plus cyclophosphamide (collectively called VAC) will result in a failure-free survival rata of greater than or equal to 70% at two years and an overall survival rate of about 80-90% at 5 years; 3) Reduction in radiation therapy dose for patients with Clinical Group II disease to 36 Gy (from 41.3 Gy) and for Group III patients with orbital disease to 45 Gy (from 50-S' Gy) will result in local control rates of about 90%.

Technical Approach: Patients in Group I have no residual tumor following surgery and will receive no radiation therapy. Patients in Group II have microscopic residual tumor and will receive radiation therapy at a dose lower than the current standard. Patients in Group III, orbit tumor only, have visible residual tumor after biopsy and will receive radiation therapy. The results will be compared to current intergroup rhabdomyosarcoma study results.

All patients will begin chemotherapy with the two-drug combination of vincristine and actinomycin D, given over a 3-week period while their tumor specimen is being classified at the IRS Group Pathology Center in Columbus, Ohio.

Patients whose tumor is classified as embryonal or botryoid rhabdomyosarcoma will continue to receive vincristine and actinomycin D, given at weeks 12 through 21, 24 through 33, and 36 through 45.

Patients whose tumor is classified as alveolar rhabdomyosarcoma or undifferentiated sarcoma will have the chemotherapy drug cyclophosphamide added to the combination of vincristine and actinomycin D, given at weeks 3, 6, 9, 12, 15, 18, 24, 27, 30, 36, and 42. Cyclophosphamide will be added on Week 0 for these patients who show molecular genetic or cytogenetic evidence of the t(2;13) or t(1;13) translocation, or the PAX 3-FRHR or PAX 7-FRER gene fusion product.

Progress: No patients were enrolled in FY 98.

Detail Summary Sheets

Radiological Diagnostic Oncology Group

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/136 **Status**: Ongoing

Title: RDOG(5) 6881: Stereotactic Fine Needle Aspiration Biopsy and Core Needle Biopsy in the Work-up of Lesions Detected by Mammography

Principal Investigator: MAJ Donald V. Smith, MC

Department: RDOG **Facility**: MAMC

Associate Investigator(s): Charlene P. Holt, M.D.; MAJ Vincent B. Ho, MC; LTC William C. Williard, III, MC; Preston L. Carter, M.D.; MAJ Barbara A. Crothers, MC; MAJ Janice C. Stracener, MC; COL Sankaran S. Babu, MC; MAJ Mark A. Myers, MC

Start Date:	Est. Completion Date:	Periodic Review:
06/16/1995	Jun 98	09/30/1998

Study Objective: The overall objective of this research protocol is to conduct a randomized clinical trial to study whether stereotactically-guided and/or ultrasound-guided fine needle aspiration (FNA) and/or core needle biopsy (CNB) can replace open surgical biopsy in the diagnostic evaluation of nonpalpable mammographically-detected breast lesions.

Technical Approach: This is a randomized clinical trial to be carried out in mammographic centers nationwide within two consortia. This offers the opportunity to cover the spectrum of experience, equipment and patient populations, all using an agreed protocol to evaluate the use of fine needle and core biopsy used in the work-up of non-palpable breast lesions. The two consortia will enroll a total of 3,600 patients with an expected average MAMC enrollment of two subjects per day for the length of the study. Women having had the appropriate mammographic evaluation and meeting the inclusion criteria will be entered either to stereotactic or ultrasound arms of the study. Those in the stereotactic arm will be randomized to FNA followed by CNB, or CNB alone, both followed by open surgical biopsy or when indicated, 6, 12, and 24 month follow-ups. Those in the ultrasound arm will be randomized to FNA/CNB or CNB. All mammograms will have second readings by experts, and all pathology and cytology will have second readings by reference experts. Data analysis will consist of accuracy determination, agreement analysis, and logistic regression modeling for evaluation of important co-variants on the estimates. In addition, analysis of observer variability, insufficient sample rates, and predictive ability of specific mammographic characteristics will be conducted.

Progress: Study is closed to patient entry. Thirty-eight (38) subjects were entered at MAMC. The final patient will finish protocol in October 1998.

Detail Summary Sheets

Southwest Oncology Group

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 77/054	**Status**: Ongoing

Title: SWOG 7406: Advanced Hodgkin's Disease: Remission Induction (MOPP #5). Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG	**Facility**: MAMC

Associate Investigator(s): LTC H. Irving Pierce, MC; COL Friedrich H. Stutz, MC; LTC Howard Davidson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/18/1977	Feb 82	02/20/1998

Study Objective: (1) To compare the effectiveness of two MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) + bleomycin + adriamycin combinations against MOPP + bleomycin for remission induction in patients with advanced Hodgkin's disease without prior chemotherapy; (2) To evaluate systematic restaging of patients in apparent complete remission; (3) To assess the length of unmaintained remission after intensive induction with ten courses of treatment and after documentation of complete remission (CR) status by careful restaging; (4) To evaluate by crossover design the remission induction potential of the other study combinations for patients who relapse during unmaintained remission.

Technical Approach: All previously untreated patients with Ann Arbor Stages IIIB or IV A+B Hodgkin's disease who meet the other criteria as outlined in the protocol will be randomized to one of the induction programs as specified in the protocol. Ten courses of treatment at 4-week intervals will constitute remission induction. If induction results in a CR and this is confirmed by restaging, then no further treatment will be given. If at least a partial remission (PR) is indicated another 4 courses will be administered in a second attempt to achieve a CR. Persistence of disease after 14 courses will constitute an induction failure and the patient will be taken off study. Relapsing patients will be crossed over to one of the other induction combinations.

Progress: Closed to patient entry 31 Aug 78. Two patients where entered in previous years, one patient is still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 77/053 **Status**: Ongoing

Title: SWOG 7433: Non-Hodgkin's Lymphomas (Stages I, IE, II, and IIE). A Phase III Study.

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC H. Irving Pierce, MC; COL Friedrich H. Stutz, MC; LTC Howard Davidson, MC

Start Date:	Est. Completion Date:	Periodic Review:
02/18/1977	Feb 82	02/20/1998

Study Objective: To compare the remission rate, remission duration and survival in patients with non-Hodgkin's lymphoma, pathologic stages I, IE, II and IIE treated with extended field radiotherapy (supradiaphragmatic mantle or abdominal field) alone or with extended Hydroxyl-daunorubicin (adriamycin), Oncovin (vincristine), and Prednisone.

Technical Approach: Patients newly diagnosed (no type of prior therapy) with non-Hodgkin's lymphoma except mycosis fungoides and diffuse lymphocytic well differentiated lymphoma will be thoroughly evaluated for extent of disease and then randomized to either radiation therapy or radiation therapy plus chemotherapy. If the patient does not achieve a complete remission after completion of his treatment course, he will be removed from the study. Those achieving complete remission will be followed for two years or until relapse.

Progress: This protocol was closed to patient entry 1 Oct 82 and was previously reported as closed. In fact, 2 patients were entered at MAMC, 1 has died and the other is still being followed. The protocol was reactivated in December 1993 in order to allow SWOG to continue to collect data on these patients.

Detail Summary Sheet

Date: 30 Sep 98	**Number**: 77/024	**Status**: Ongoing

Title: SWOG 7436: Combined Modality Therapy of Breast Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG	**Facility**: MAMC

Associate Investigator(s): COL Friedrich H. Stutz, MC; LTC H. Irving Pierce, MC; LTC Howard Davidson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/21/1977	Jan 82	02/20/1998

Study Objective: To compare the effect of two adjuvant chemotherapy programs upon the time to recurrence and upon the percentage of recurrences in post-operative breast carcinoma patients who have a high risk of developing metastases. To compare the effect of these adjuvant chemotherapy programs upon the survival pattern of such patients.

Technical Approach: Melphalan and combination (5-Fluorouracil, Methotrexate, Vincristine, Cyclophosphamide, Prednisone) will be used as chemotherapy as outlined in the protocol. The adjuvant chemotherapy will be instituted (regardless of radiation therapy) two weeks after radical mastectomy, unless local or systemic post-operative complications of surgery contraindicate onset of therapy. In such cases, therapy will be instituted when the primary physician involved feels it is not contraindicated by the clinical condition of the patient. The interval between surgery and the institution of adjuvant chemotherapy cannot be greater that six weeks for entry into the study. All therapy will be discontinued after one year.

Progress: This protocol was closed to patient entry in 1 Nov 1979 and was previously reported as closed. The protocol was reactivated in December 1993 so that SWOG could continue to collect data on 10 patients that had been entered. One patient expired in FY 97, 18 years after treatment. Five other patients expired previously and four patients are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 77/018 **Status**: Ongoing

Title: SWOG 7510: Intensive Adjuvant Chemotherapy with or without Oral BCG Immunotherapy for Patients with Locally Advanced Adenocarcinoma of the Large Bowel

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC H. Irving Pierce, MC; COL Friedrich H. Stutz, MC; LTC Howard Davidson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
10/15/1976	Oct 81	02/20/1998

Study Objective: To determine the efficacy of adjuvant chemotherapy with the highly effective combination of Methyl CCNU (MeCCNU) and 5-Fluorouracil (5-FU) and to determine whether this is added to by immunotherapy with oral Bacillus Calmette-Suerin (BCG) on the disease-free interval and survival of patients with Duke C large bowel adenocarcinoma.

Technical Approach: Patients will be randomly assigned to either of the two following regimens; (1) chemotherapy alone - Methyl CCNU, given orally on day 1, plus intravenous 5-Fluorouracil, given intravenously weekly for three doses would constitute one course. Courses would being every eight weeks; (2) chemotherapy plus immunotherapy - Chemotherapy as described above plus immunotherapy in the form of oral BCG given every two weeks.

Progress: This protocol was closed to patient entry 20 Aug 1980 and was previously reported as closed. Eleven patients were entered at MAMC, 8 have died, 3 are still being followed. The protocol was reactivated in December 1993 so that SWOG could continue to collect data on these patients.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 78/002 **Status**: Ongoing

Title: SWOG 7713/14: Chemoimmunotherapy in Non-Hodgkin's Lymphoma CHOP vs CHOP + Levamisole vs CHOP + Levamisole + BCG for Remission Induction Therapy: Levamisole vs No Maintenance After Remission Induction

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC H. Irving Pierce, MC; COL Friedrich H. Stutz, MC; LTC Howard Davidson, MC

Start Date:	Est. Completion Date:	Periodic Review:
10/21/1977	Jun 79	10/17/1997

Study Objective: 1) To compare the effectiveness, in terms of rate of response of two chemoimmunotherapy regimens (CHOP + levamisole vs CHOP + levamisole + BCG) against CHOP for remission induction in previously untreated patients with non-Hodgkin's lymphoma; (2) For patients proven to be in complete remission after induction, to compare the duration of documented complete response obtained by continued maintenance immunotherapy with levamisole vs no maintenance therapy; (3) For patients with impaired cardiac function (not eligible for treatment with adriamycin), with mycosis fungoides, or with only a partial response to 11 courses of treatment with levamisole + BCG, to estimate the complete response rate obtained by continued chemoimmunotherapy with COP + levamisole; (4) To estimate the CNS relapse rate in patients with diffuse lymphomas when CNS prophylaxis with intrathecal cytosine arabinoside is used; (5) To continue to evaluate the impact of systematic restaging of patients judged to be in complete remission and the value of expert hematopathology review of diagnostic material from all cases; (6) To establish baseline and serial data on immunologic status in bother chemoimmunotherapy groups.

Technical Approach: Patients with a diagnosis of non-Hodgkin's lymphoma established by biopsy with no prior chemotherapy are eligible. Patients with chronic lymphocytic leukemia are ineligible. Patients with preexisting cardiac disease or mycosis fungoides are ineligible for the CHOP programs, but will be treated with COP + levamisole. Patients will be stratified according to nodular or diffuse histologies, adequate or impaired bone marrow reserves, presence or absence of bone marrow involvement, and performance status. Initial drug doses are based on bone marrow reserve. Treatment plans as outlined in the protocol.

Progress: This protocol was closed to patient entry 1 Oct 1982 and was previously reported as completed. Four patients were entered at MAMC, 3 have died, one patient is still being followed. The protocol was reactivated in December 1993 so that SWOG could continue to collect data on these patients.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 78/047 **Status**: Ongoing

Title: SWOG 7808: Combination Modality Treatment for Stage III and Stage IV Hodgkin's Disease, MOPP #6

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL Friedrich H. Stutz, MC; LTC H. Irving Pierce, MC; Suresh B. Katakkar, M.D., DAC; LTC Howard Davidson, MC

Start Date:	Est. Completion Date:	Periodic Review:
07/31/1978	Jan 88	10/17/1997

Study Objective: To attempt to increase the complete remission rate induced with MOP-BAP (nitrogen mustard, vincristine, procarbazine, prednisone, adriamycin, and bleomycin) alone utilizing involved field radiotherapy in patients with Stages III and IV Hodgkin's disease achieving partial remission at the end of 6 cycles; and to determine if immunotherapy maintenance with levamisole or consolidation with low dose involved field radiotherapy will produce significantly longer remission durations over a no further treatment group when complete remission has been induced with 6 cycles of MOP-BAP in Stages III & IV Hodgkin's.

Technical Approach: Patients (>15 yrs) must have histologic diagnosis of Hodgkin's disease; no prior chemotherapy. Patients with a history of congestive heart failure, valvular heart disease, or serious obstructive or restrictive pulmonary disease will be excluded. Normal marrow patients will receive six cycles of MOP-BAP. Impaired bone marrow patients will receive six cycles of MOP-BAP with dose modifications. Complete Remission (CR) patients with prior radiotherapy will be randomized to Treatment 3 (no treatment) or Treatment 4 (levamisole). CR patients without prior radiotherapy will receive Treatment 5 (radiotherapy). Partial remission (PR) patients without prior radiotherapy or residual bone marrow involvement will receive Treatment 6 (radiotherapy). PR patients with prior radiotherapy or those with residual bone marrow involvement will receive Treatment 7 (4 additional cycles of MOP-BAP); after 10 total cycles of MOP-BAP, patient will continue study on MOP-BAP therapy at the discretion of the investigator.

Progress: This study was closed to patient entry 1 Dec 87. Thirteen patients were enrolled in previous years and 5 are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 79/096 **Status**: Ongoing

Title: SWOG 7827: Combined Modality Therapy for Breast Carcinoma, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL Friedrich H. Stutz, MC; Suresh B. Katakkar, M.D., DAC; COL Irwin B. Dabe, MC; LTC Howard Davidson, MC

Start Date:	Est. Completion Date:	Periodic Review:
09/21/1979	Sep 81	10/17/1997

Study Objective: To compare the disease-free interval and recurrence rates in: (1) estrogen receptor positive (ER+) premenopausal patients with Stage II disease using combination chemotherapy alone vs combination chemotherapy and oophorectomy; (2) ER+ postmenopausal patients with Stage II disease using combination chemotherapy plus tamoxifen vs tamoxifen alone vs combination chemotherapy alone; (3) estrogen receptor negative (ER-) patients with Stage II disease using one vs two years of combination chemotherapy; to compare the effect of adjuvant therapy in Stage II breast cancer using partial mastectomy and radiation vs modified radical or radical mastectomy; to compare the effect of the various adjunctive therapy programs upon survival patterns; and to correlate the estrogen receptor status with disease-free interval and survival.

Technical Approach: Patients with a histologically proven diagnosis of breast cancer (Stage II or Stage III) with one or more pathologically involved axillary nodes will receive one of the following treatments: (CMFVP = cyclophosphamide, methotrexate, 5-FU, vincristine, and prednisone): (1) CMFVP for 1 yr. pre- or postmenopausal ER patients. (2) CMFVP for 2 yr pre- or postmenopausal ER patients. (3) CMFVP for 1 yr premenopausal ER+ patients. (4) Oophorectomy + CMFVP premenopausal ER+ patients. (5) Tamoxifen alone for l yr postmenopausal ER+ patients. (6) CMFVP for 1 yr postmenopausal ER+ patients. (7) Tamoxifen + CMFVP for l yr postmenopausal ER+ patients. Patients undergoing segmental mastectomy (lumpectomy) will receive 6 wks of radiation therapy in addition to the treatment they are randomized to receive.

Progress: This study was closed to patient entry 15 Aug 89. Thirty-five patients were enrolled at MAMC. Twenty patients are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 84/018 **Status**: Ongoing

Title: SWOG 8216/38: Comparison of BCG Immunotherapy and Adriamycin for Superficial Bladder Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL William D. Belville, MC; COL Friedrich H. Stutz, MC; COL Irwin B. Dabe, MC; MAJ Thomas M. Baker, MC; MAJ Alfred H. Chan, MC; MAJ Timothy J. O'Rourke, MC; MAJ Michael D. Stone, MC; LTC Howard Davidson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/18/1983	Sep 85	10/17/1997

Study Objective: To compare the effectiveness of intravesical BCG immunotherapy with intravesical Adriamycin in chemotherapy with respect to disease-free interval and two-year recurrence rate; to compare the toxicity of topical immunotherapy and chemotherapy; and to obtain experience regarding disease-free interval and the recurrence rate in patients who develop tumor recurrence and are then crossed over to the alternative treatment arm.

Technical Approach: Following a standard transurethral resection, patients will be stratified by the presence or absence of documented carcinoma in situ and as to prior chemotherapy and then randomized to receive BCG immunotherapy or Adriamycin chemotherapy. Patients who develop tumor recurrence following treatment will be eligible for crossover to the other treatment arm.

Progress: This study was closed to patient entry 20 Dec 85. Three patients were enrolled at MAMC and are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 85/076 **Status**: Ongoing

Title: SWOG 8269: Concurrent Chemo-Radiotherapy for Limited Small Cell Carcinoma of the Lung, Phase II

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL Irwin B. Dabe, MC; MAJ Michael D. Stone, MC; CPT David R. Bryson, MC; MAJ Thomas M. Baker, MC; LTC Howard Davidson, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/23/1985	Jun 87	10/17/1997

Study Objective: To explore the response rate with the concurrent use of radiation therapy plus chemotherapy utilizing cis-platinum, VP-16, and vincristine in limited small cell carcinoma of the lung and to observe the toxicities of this combined modality program.

Technical Approach: Patients will be started on chemotherapy consisting of cis-platinum, VP-16, and vincristine and concurrent radiation therapy to the primary site. After completion of radiation therapy to the chest, prophylactic cranial radiation therapy will be given. After a brief rest period, the patients will be treated with 12 more weeks of conventional chemotherapy consisting of adriamycin, cytoxan, VP-16, vincristine, and methotrexate. Patients who show a complete response will be followed. Patients with less than a complete response will be taken off study and offered alternative therapy.

Progress: This study was closed to patient entry 19 March 86. It was previously reported as completed. In fact, two patients were entered and one is still being followed. The protocol was reactivated in December 1993 so that SWOG could continue to collect data on these patients.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 83/056 **Status**: Ongoing

Title: SWOG 8294: Evaluation of Adjuvant Therapy and Biological Parameters in Node Negative Operable Female Breast Cancer (ECOG, EST-1180), Intergroup Study

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC James E. Congdon, MC; COL Friedrich H. Stutz, MC; COL Irwin B. Dabe, MC; MAJ Timothy J. O'Rourke, MC; MAJ Alfred H. Chan, MC; MAJ Thomas M. Baker, MC; LTC Howard Davidson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/18/1983	Feb 85	10/17/1997

Study Objective: To assess the impact of short-term intensive chemotherapy with CMFP to prevent disease recurrence and prolong survival in node negative patients with any size estrogen receptor negative tumors and node negative patients with estrogen receptor positive tumors whose pathological size is >3 cm; to assess the impact of surgical procedure, estrogen receptor status, menopausal status and tumor size; to develop guidelines referable to histopathological features of node negative tumors which are reproducible and to assess their prognostic impact for disease-free survival and survival; to assess the value to CEA in predicting recurrence and survival rates; to assess the natural history of a subgroup with node negative, estrogen receptor positive small tumors (3 cm).

Technical Approach: Patients will have laboratory evaluations to ensure that there is no evidence of disseminated disease. They will be stratified into a number of treatment groups based on the site of tumor, estrogen receptor status, age, and menopausal status. Patients with primary tumors less than 3 cm in diameter who are estrogen receptor positive will be followed by close observation only to determine the natural history of their tumor. All other patients who have a somewhat greater likelihood of relapse will be randomized to receive either close observation only or 6 cycles of systemic chemotherapy. The chemotherapy will consist of 4 agents: cyclophosphamide, methotrexate, 5-fluorouracil, and prednisone given for six 28 day cycles. The dosage of the individual agents will be determined by body height and weight.

Progress: This study was closed to patient entry 15 May 88. Twelve patients were enrolled in previous years and nine continue to be followed. Three have expired.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 84/059 **Status**: Ongoing

Title: SWOG 8313: Multiple Drug Adjuvant Chemotherapy for Patients with ER Negative Stage II Carcinoma of Breast, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL Friedrich H. Stutz, MC; COL Irwin B. Dabe, MC; MAJ Thomas M. Baker, MC; MAJ Timothy J. O'Rourke, MC; MAJ Michael D. Stone, MC; LTC Howard Davidson, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/18/1984	May 86	10/17/1997

Study Objective: To compare through a randomized prospective study the recurrence rates and disease-free intervals for postoperative axillary node positive estrogen receptor negative breast cancer patients given adjuvant therapy with either short term intense chemotherapy (FAC-M) or one year standard chemotherapy (CMFVP); to compare the effect of these two adjuvant therapies on survival; to compare the relative toxicity of the two therapies; to compare the quality of life of patients with operable breast cancer randomized to receive one year of CMFVP or a short intensive regimen of FAC-M x 4 courses; and to compare a multiple item questionnaire for assessing quality of life.

Technical Approach: Women who have histologically proven breast cancer with axillary lymph node metastasis and negative estrogen receptors will be entered 14-21 days post-lumpectomy or within 14-42 days post-mastectomy and randomly assigned to receive: Arm I a tapering course of oral prednisone for 6 weeks, weekly IV vincristine for 10 weeks, weekly IV methotrexate, and weekly IV 5-FU plus daily oral cyclophosphamide for a total of one year; or Arm II four cycles of adriamycin (IV day 1), cyclophosphamide (IV day 1), 5-FU (IV days 1 and 8), and methotrexate (IV day 22). Each cycle will be five weeks and total duration of therapy in this arm is approximately 20 weeks. Questionnaires to compare quality of life will be completed at 72 hours prior to chemotherapy. Added to this protocol will be a sub-study to determine the prognostic significance of circulating human mammary epithelial antigens. This will involve blood tests prior to chemotherapy and then once every three months.

Progress: This study was closed to patient entry 15 Jun 90. Three patients were enrolled, 2 have died and 1 continues to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 85/009 **Status**: Ongoing

Title: SWOG 8410: Combination Chemotherapy of Intermediate and High-Grade Non-Hodgkin's Lymphoma with m-BACOD, Phase II

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL Friedrich H. Stutz, MC; COL Irwin B. Dabe, MC; MAJ Timothy J. O'Rourke, MC; MAJ Michael D. Stone, MC; CPT David R. Bryson, MC; MAJ Thomas M. Baker, MC; LTC Howard Davidson, MC

Start Date:	Est. Completion Date:	Periodic Review:
11/16/1984	Oct 86	10/17/1997

Study Objective: To determine an approximate complete remission rate and remission duration for the treatment program of cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin with intervening moderate dose of methotrexate and leucovorin rescue (m-BACOD) in patients with intermediate and high grade non-Hodgkin's lymphoma and to assess the feasibility of using this regimen in the SWOG with the intent of using m-BACOD in a future Phase III trial.

Technical Approach: Patients will be stratified according to marrow reserve status and creatinine clearance. Treatment will consist of ten 3-week courses. Cytoxan, adriamycin, vincristine, and bleomycin will be given IV on day 1. Dexamethasone will be given by mouth daily for 5 days, and methotrexate will be given on days 8 and 15 at 200 mg/m^2. Leucovorin will be given 10 mg/m^2 by mouth after each methotrexate injection every 6 hours for eight doses. An adequate trial will be defined as the completion of two complete cycles of m-BACOD. Patients with documented progressive disease or less than complete response after an adequate trial will be taken off study. Those with complete response will continue on study with no further chemotherapy.

Progress: This study was closed to patient entry 26 April 1985 and reported as completed. However, two patients had been enrolled in the study and are still being followed. The study was reactivated in December 1993 so that SWOG could continue to collect data on these patients.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 86/007 **Status**: Ongoing

Title: SWOG 8417/19: Evaluation of Two Consolidation Regimens in the Treatment of Adult Acute Lymphoblastic Leukemia, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL Irwin B. Dabe, MC; LTC Lauren K. Colman, MC; LTC Howard Davidson, MC; MAJ Thomas M. Baker, MC; MAJ Michael D. Stone, MC; CPT David R. Bryson, MC; MAJ Paul C. Sowray, MC

Start Date:	Est. Completion Date:	Periodic Review:
10/18/1985	Sep 87	10/17/1997

Study Objective: To compare the effects on remission duration and survival of two consolidation regimens: the L-10-M consolidation used in SWOG 8001 versus a regimen employing daunomycin, cytosine, arabinoside, 6-thioguanine and escalating methotrexate/L-asparaginase in patients with adult lymphoblastic leukemia and to compare the toxicities of the two consolidation regimens.

Technical Approach: Patients will begin remission induction with vincristine, prednisone, adriamycin, methotrexate, cyclophosphamide, and adriamycin (36 days), followed by a 14 day rest period. On day 30, patients will have an Ommaya reservoir placed in the frontotemporal area of the skull. Patients failing to achieve an A1 marrow status on induction therapy will go off study. Patients with complete remission will be randomized to one of the following consolidation regimens: ARM I (L-10-M) methotrexate and Ara-c, daily x 5 on days 1, 36, and 71; Ara-c and 6-thioguanine every 12 hr for 12 doses on days 15, 50, and 85; methotrexate days 15, 17, 57, and 59; vincristine and prednisone days 50 and 57; L-asparaginase beginning day 99, three times weekly for a total of 6 doses, and cyclophosphamide day 110 following last dose of L-asparaginase. Arm II: daunomycin days 1-3, Ara-C continuous infusion days 1-5, 6-thioguanine every 12 hr days 15, followed by a 21-28 day rest period. Methotrexate every 10 days from 28-98, L-asparaginase every 10 days 29-99. After a 2-week rest period, maintenance therapy will begin with vincristine, prednisone, adriamycin, 6-mercaptopurine, methotrexate (IT), methotrexate PO, dactinomycin, vincristine, prednisone, BCNU, cyclophosphamide, 6-mercaptopurine, and methotrexate (repeated every 21 weeks for 36 months or until relapse. An adequate trial will be the completion of remission induction.

Progress: This study closed to patient entry 15 Nov 91. Seven patients were enrolled MAMC. All original patients enrolled at MAMC have died but one patient has transferred in (previous FY) and is being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 87/107 **Status**: Ongoing

Title: SWOG 8507: Maintenance versus No Maintenance BCG Immunotherapy of Superficial Bladder Cancer, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL Irwin B. Dabe, MC; COL William D. Belville, MC; COL Victor J. Kiesling, MC; LTC Lauren K. Colman, MC; MAJ Thomas M. Baker, MC; MAJ David M. Dunning, MC; MAJ Ruben D. Sierra, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/21/1987	Aug 90	10/17/1997

Study Objective: To compare the effectiveness of intravesical and percutaneous BCG immunotherapy given on a maintenance versus no maintenance schedule with respect to disease-free interval and rate of tumor recurrence in patients with transitional cell carcinoma of the bladder; to assess the toxicity of maintenance and no maintenance BCG immunotherapy; and to assess the association of intermediate strength PPD skin test reactivity with disease free status in patients treated with BCG immunotherapy.

Technical Approach: Patients will be stratified according to prior chemotherapy, disease type, and PPD skin test conversion. One week following a standard transurethral resection, BCG, 120 mg lyophilized BCG organisms will be diluted in 50.5 cc of sterile, preservation-free saline. Fifty cc will be administered intravesically and 0.5 cc will be administered percutaneously. The BCG administration will be repeated weekly for a total of six weeks. Patients will then be randomized to the BCG maintenance or no maintenance arms. The BCG maintenance arm will consist of weekly intravesical and percutaneous BCG immunotherapy administrations repeated for three consecutive weeks at three months, six months, and every six months thereafter for a total treatment period of 36 months. Patient removal from the study will be determined by the type of tumor. Any patient with progression of disease, defined by an increase in tumor grade or stage beyond the highest previous grade or stage or an increase in the number or frequency or recurrences will be removed from the study.

Progress: This study closed to patient entry 15 Dec 88. Eleven patients were entered in the study and 10 are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 86/080 **Status**: Ongoing

Title: SWOG 8516: A Phase III Comparison of CHOP versus m-BACOD versus ProMACE-CytaBOM versus MACOP-B in Patients with Intermediate or High-Grade Non-Hodgkin's Lymphoma

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): MAJ Thomas M. Baker, MC; COL Irwin B. Dabe, MC; LTC Lauren K. Colman, MC; MAJ David M. Dunning, MC; CPT David R. Bryson, MC; LTC Howard Davidson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
08/15/1986	Jul 89	10/17/1997

Study Objective: To compare in a randomized group-wide setting the complete response rate, response duration, and survival of patients with intermediate and high grade non-Hodgkin's lymphoma treated with one of four combination chemotherapy regimens: CHOP, m-BACOD, ProMACE-CytaBOM, or MACOP-B; and to compare the toxicities of each regimen in this patient population.

Technical Approach: Patients with prior chemotherapy or radiotherapy are ineligible. Arm I (CHOP every 3 weeks for 8 consecutive cycles): cyclophosphamide (IV), doxorubicin (IV), vincristine (IV) and prednisone (PO). Arm II (m-BACOD every 3 weeks x 10): cyclophosphamide (IV), doxorubicin (IV), vincristine (IV), bleomycin (IV), dexamethasone (PO), methotrexate (IV), and calcium Leucovorin rescue after each MTX dose. Arm III (Pro-MACE-CytaBOM every 21 days, treated until complete remission plus 2 additional cycles): cyclophosphamide (IV), doxorubicin (IV), VP-16 (IV), Prednisone(PO), Ara-C (IV), bleomycin (IV), vincristine (IV), methotrexate (IV), calcium leucovorin rescue after each MTX dose, and trimetheprim-sulfamethoxazole (PO). Arm IV (MACOP-B will be given over 12 weeks): methotrexate (IV), calcium leucovorin rescue after each MTX bolus, doxorubicin (IV), cyclophosphamide (IV), vincristine (IV), bleomycin (IV), prednisone (PO), and trimethoprimsulfa (PO). Patients with documented progressive disease may be taken off study at any time; however patients will preferably be restaged upon completion of the treatment program to assess response. Patients with less than a complete response at restaging will be taken off study. Patients whose clinical disease has disappeared and who appear to be in complete remission will undergo a complete and thorough laboratory and radiographic search for evidence of persistent lymphoma approximately one month after completion of therapy. If complete remission is confirmed, the patient will be observed with no further therapy.

Progress: This study was closed to patient entry 15 June 1991, and was previously reported as completed. However, two patients were transferred in to MAMC from another Army medical center so it was reactived in Dec 93. MAMC now follows these patients.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 85/073 **Status**: Ongoing

Title: SWOG 8590: Phase III Study to Determine the Effect of Combining Chemotherapy with Surgery and Radiotherapy for Resectable Squamous Cell Carcinoma of the Head and Neck, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): MAJ Thomas M. Baker, MC; COL Friedrich H. Stutz, MC; COL Irwin B. Dabe, MC; COL William J. Gernon, MC; MAJ Timothy J. O'Rourke, MC; MAJ Michael D. Stone, MC; CPT David R. Bryson, MC; LTC Donald B. Blakeslee, MC; LTC Howard Davidson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/28/1985	May 87	10/17/1997

Study Objective: To test whether the addition of chemotherapy to surgery and radiotherapy prolongs disease-free survival and survival between the two study groups; to test whether the addition of chemotherapy to surgery and radiotherapy increases local control rates at the primary site and/or the cervical neck nodes; and to determine if the patterns of failure have been changed with the addition of chemotherapy.

Technical Approach: After surgery, patients will be randomized to either chemotherapy plus radiation therapy or radiation therapy alone. In the chemotherapy plus radiation therapy group, the chemotherapy will start 2-4 weeks after surgery and the radiotherapy will start approximately two weeks after completing chemotherapy. In the radiation therapy alone group, the radiation therapy will begin 2-4 weeks after surgery. Chemotherapy will be cisplatinum give day 1 and 5 FU given days 1-5 and repeated every 21 days for three courses. Patients who develop local or distant recurrence following therapy will be treated at the physician's discretion.

Progress: This study was closed to patient entry 1 Feb 90. Three patients were entered in previous years and are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 87/045 **Status**: Ongoing

Title: SWOG 8600: A Randomized Investigation of High-Dose Versus Standard Dose Cytosine Arabinoside with Daunorubicin in Patients with Acute Non-lymphocytic Leukemia

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL Irwin B. Dabe, MC; LTC Lauren K. Colman, MC; LTC Howard Davidson, MC; MAJ Thomas M. Baker, MC; MAJ David M. Dunning, MC; MAJ Ruben D. Sierra, MC; CPT David R. Bryson, MC; MAJ Paul C. Sowray, MC

Start Date:	**Est. Completion Date:**	**Periodic Review:**
02/27/1987	Feb 90	02/20/1998

Study Objective: To compare, among patients with acute nonlymphocytic leukemia, the rate of complete remission produced by induction regimens of either standard dose cytosine arabinoside and daunorubicin or high-dose cytosine arabinoside and daunorubicin; to compare the duration of complete remission and of disease-free survival among patients who receive one of the three combinations of induction and consolidation regimens listed below; to determine the comparative toxicities of these three programs, and to determine the feasibility of implementing a predetermined approach to supportive care for these patients in a multi-institutional cooperative group setting.

Technical Approach: Patients will be stratified according to age and institution. Induction therapy will consist of standard dose Ara-C plus daunorubicin (Arm I) or high dose Ara-C + daunorubicin (Arm II). Patients requiring a second cycle of induction will receive the same doses as cycle 1, following the recovery of hematologic toxicities. Consolidation chemotherapy will begin when bone marrow and blood counts have recovered or on day 28 after the last induction cycle. Patients initially randomized to Arm I will be randomized to Arm III (high dose, one cycle only) or Arm IV (standard dose, two cycles). Patients initially randomized to Arm II (high dose) will be assigned to Arm III. Following the completion of consolidation, no further therapy will be given and patients will be followed only. Supportive care will include a predetermined antibiotic regimen determined by the physician.

Progress: This study was closed to patient entry 1 Dec 91. Of the seven patients enrolled at MAMC, 5 have died and 2 are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 90/039 **Status**: Completed

Title: SWOG 8710: Trial of Cytectomy Alone Versus Neoadjuvant M-VAC + Cytectomy in Patients with Locally Advanced Bladder Cancer (INT-0080/EST-1877, CALGB-8891)

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Paul C. Sowray, MC; MAJ Mark H. Kozakowski, MC; MAJ Everardo E. Cobos Jr., MC; MAJ Patrick L. Gomez, MC; CPT Denis Bouvier, MC; MAJ Rodney C. Davis, MC; LTC Robert L. Sheffler, MC; LTC John A. Vaccaro, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/16/1990	Mar 92	02/20/1998

Study Objective: To study insulin induced hypoglycemia as a model of acute stress and to determine if the change in testosterone seen with acute stress is related to cortisol alone or whether it can also be seen with the stimulation of other adrenal precursor products.

Technical Approach: Ten healthy male volunteers (18-35 years) who are without evidence of current acute or chronic illness will have an insulin tolerance test done with blood samples drawn for cortisol, testosterone, immunoactive LH, bioactive LH, estradiol, and glucose, every 15 minutes for one hour prior to the human insulin bolus to establish baseline values. Blood samples will continue to be drawn every 15 minutes for 180 minutes after injection of the insulin. SHBG will be measured on the first and last sample and endorphin levels will be measured at baseline and at times corresponding to maximal hypoglycemia. A standard multiple dose metyrapone test will be performed one month from the insulin tolerance test. Just before the first dose and four hours after the last dose, serum samples will be obtained for cortisol, estradiol, immunoactive LH, bioactive LH, testosterone, ACTH, SHBG, endorphins, and 11-deoxycortisol. The relationship of bioactive LH to immunoactive LH will be compared using the biologic to immunologic ratio both before and during the acute stress. The data from the metyrapone test will be used to determine if metyrapone can cause a decrease in serum testosterone acutely. Again, the B/I ratio will be compared pre and post-test. Changes in serum concentrations of the measured hormones will be analyzed by repeated measures analysis of variance.

Progress: No patients have been entered in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 88/065 **Status**: Ongoing

Title: SWOG 8736: Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL Irwin B. Dabe, MC; CPT Denis Bouvier, MC; LTC Steven S. Wilson, MC; MAJ Rahul N. Dewan, MC; LTC Howard Davidson, MC

Start Date:	Est. Completion Date:	Periodic Review:
07/15/1988	Jun 91	10/17/1997

Study Objective: To evaluate, in a cooperative group setting, the difference in survival, time to treatment failure, and toxicity of two curative approaches to the treatment of patients with localized, intermediate or high grade non-Hodgkin's lymphoma.

Technical Approach: All patients must have biopsy proven non Hodgkin's lymphoma of intermediate or high grade histology except lymphoblastic lymphoma. Patients must have had all visible tumor removed (excisional biopsy) and must have clinically adequate liver and myocardial function to begin treatment at full doses. Patients with known central nervous system disease, previous cancer with a possibility for recurrence which might affect survival or prior chemo or radiotherapy will be ineligible. All patients will be stratified at the time of initial registration by the following: (1) age (<65 years vs >65 years); (2) Stage (I or Ie vs nonbulky II or IIe); (3) histology (diffuse large cell vs other); (4) location of disease (GI involved vs non-GI, abdominal vs non-GI, other); (5) all disease resected vs residual measurable disease. Patients will be randomized to CHOP (Arm I) or to CHOP plus radiation therapy (Arm II). A complete course of chemotherapy on Arm I will consist of the administration of CHOP every 21 days for eight consecutive cycles unless progressive disease develops. A complete course of chemotherapy for Arm II will consist of the administration of CHOP every 21 days for three consecutive cycles unless progressive disease develops. Radiation therapy will begin immediately after the third cycle of CHOP. Radiation therapy dose, duration, and treatment volume will be determined jointly by the radiation oncologist and the medical oncologist. All patients will be followed at three month intervals until death. CHOP: Cyclophosphamide, 750 mg/m^2 IV, day 1; Doxorubicin, 50 mg/m^2 IV, day 1; Vincristine, 1.4 mg/m^2 IV, day 1; Prednisone, 100 mg/day po, days 1-5.

Progress: This study closed to patient entry 15 June 95. Nine patients have been enrolled at MAMC. Two have expired; seven continue to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 88/076 **Status**: Completed

Title: SWOG 8738: Treatment of Extensive Non-small Cell Lung Cancer: Standard Dose Cisplatin versus High-Dose Cisplatin in Hypertonic Saline Alone versus High-Dose Cisplatin/Mitomycin-C, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL Irwin B. Dabe, MC; MAJ Mark H. Kozakowski, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC

Start Date:	Est. Completion Date:	Periodic Review:
09/16/1988	Sep 91	10/17/1997

Study Objective: To compare standard dose cisplatin chemotherapy to high dose cisplatin in hypertonic saline alone to high dose cisplatin/mitomycin-C in a randomized study with stratification for known important prognostic factors with regard to response rate, response duration, and survival duration; and to compare the relative toxicities of these three chemotherapy regimens in patients with extensive non-small cell lung cancer.

Technical Approach: Patients will be randomized to one of the following arms: Arm I: standard dose cisplatin (50 mg/m^2, IV) every four weeks for a maximum of eight cycles; ARM II: high dose cisplatin alone (100 mg/m^2, IV) every four weeks for a maximum of four cycles; ARM III: high dose cisplatin (100 mg/m^2 IV) plus mitomycin-C (8 mg/m^2 IV) given every four weeks for a maximum of four cycles. All patients will have an initial assessment of response after two cycles and then reassessment after four cycles of therapy. Patients on Arm I who respond to treatment may receive continued therapy to a maximum of eight cycles. Upon progression of disease, unacceptable toxicity, or patient request, patients will be taken off treatment. All patients will be followed until death.

Progress: This study was closed to patient entry 1 Jun 90. Six patients were enrolled at MAMC in previous years and one continues to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/119 **Status**: Ongoing

Title: SWOG 8794: Treatment of Pathologic Stage C Carcinoma of the Prostate With Adjuvant Radiotherapy

Principal Investigator: MAJ Raymond S. Lance, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL John N. Wettlaufer, MC; COL John C. Norbeck, MC; LTC Kurt L. Hansberry, MC; CPT Timothy O. Taylor, MC; CPT Michael D. Bagg, MC; CPT Bradley F. Schwartz, MC; MAJ J. Brantley Thrasher, MC; LTC Luke M. Stapleton, MC; LTC Kenneth A. Bertram, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/03/1994	Jun 98	10/17/1997

Study Objective: 1) 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. 2) To assess the qualitative and quantitative toxicities of patients with pathologic Stage C (T3N0M0) carcinoma of the prostate when treated with external beam radiotherapy.

Technical Approach: Patients who have undergone radical prostatectomy and pelvic lymphadenectomy for clinical Stage A or B disease with a histologically proven diagnosis of pathologic Stage C (T3N0M0) carcinoma of the prostate will be randomized to receive either postoperative adjuvant radiation therapy (ARM I) or no adjuvant therapy (ARM II). The studies primary objective is to determine whether adjuvant radiation therapy has an effect on local control of the cancer and cancer-specific survival.

Progress: This study was closed to patient entry, 1 Jan 97. One patient was enrolled at MAMC and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 88/066 **Status**: Ongoing

Title: SWOG 8796: Combination Chemotherapy for Advanced Hodgkin's Disease, Phase III Intergroup (INT 0074)

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL Irwin B. Dabe, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC

Start Date:	Est. Completion Date:	Periodic Review:
07/15/1988	Jun 91	10/17/1997

Study Objective: To compare the effectiveness of the MOPP/ABV hybrid with sequential MOPP-->ABVD in patients with advanced or recurrent Hodgkin's disease and to determine which regimen is superior with respect to the following parameters: complete response rate, duration of complete response, freedom from progression, and survival.

Technical Approach: Patients must have histologic confirmation of Hodgkin's disease with no prior chemotherapy. Patients will be stratified according to age, prior radiotherapy, bulky disease, and performance status. They will then be randomized to MOPP repeated every 28 days for 6 cycles (Arm I) or to MOPP/ABV Hybrid repeated every 28 days for six cycles (Arm II). Patients on Arm I with a complete response will go on to ABVD repeated every 35 days for three cycles. Those with partial response will receive two MOPP cycles and then go on to ABVD for three cycles. Those with no change will go off study. Those patients on Arm II with complete response will receive two more cycles of MOPP/ABV. Those with partial response will continue MOPP/ABV to complete response or until a maximum of 12 cycles. Those with no change will be taken off study. MOPP: Nitrogen mustard, 6 mg/m^2 IV, days 1 and 8, Vincristine, 1.4 mg/m^2 IV, days 1 and 8, Procarbazine, 100 mg/m^2 PO per day x 14 days, Prednisone 40 mg/m^2 PO per day x 14 days. ABVD: Adriamycin, 25 mg/m^2 IV, days 1 and 15, Bleomycin, 10 units/m^2 IV, days 1 and 15, Vinblastine, 6 mg/m^2 IV days 1 and 15, DTIC, 375 mg/m^2 IV, days 1 and 15. The MOPP/ABV hybrid consist of the MOPP regimen plus adriamycin, 35 mg/m^2 IV, day 8; bleomycin, 10 units/m^2 IV day 8; and vinblastine, 6 mg/m^2 IV, day 8.

Progress: This study was closed to patient entry 1 Aug 89. One patient was enrolled at MAMC (FY88) and is still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 90/064 **Status**: Ongoing

Title: SWOG 8809: A Phase III Study of Alpha-Interferon Consolidation Following Intensive Chemotherapy with ProMACE-MOPP (Day 1-8) in Patients with Low Grade Malignant Lymphomas

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Mark H. Kozakowski, MC; MAJ Everardo E. Cobos Jr., MC; MAJ Patrick L. Gomez, MC; CPT Denis Bouvier, MC; MAJ Paul C. Sowray, MC; LTC Robert L. Sheffler, MC

Start Date:	Est. Completion Date:	Periodic Review:
04/20/1990	Apr 94	10/17/1997

Study Objective: To compare the disease-free survival of patients with low grade malignant lymphoma who receive alpha-interferon consolidation therapy after intensive induction with chemotherapy, with or without radiation therapy, to those who receive induction therapy alone; to determine the complete response rate, response duration, and survival of low grade lymphoma patients treated with ProMACE-MOPP; and to compare the toxicities of induction and induction plus consolidation therapy in this patient population.

Technical Approach: Patients must have biopsy proven, measurable, Stage III or IV non-Hodgkin's lymphoma of low grade histology. Patients will receive 6 cycles of induction chemotherapy (ProMACEMOPP, days 1-8) unless progressive disease develops during this treatment. At the completion of induction therapy, patients will be restaged to assess response. Patients whose clinical disease has disappeared and who appear to be in complete remission will undergo a complete radiographic and laboratory evaluation for evidence of persistent lymphoma approximately one month after completion of chemotherapy. If no evidence of disease is found these patients will be randomized to Alpha IFN or observation. Patients in partial response and whose bone marrow remains positive after 6 cycles of induction chemotherapy will receive 2 additional cycles of chemotherapy and then be reevaluated. If the bone marrow remains involved or the patient has less than a partial response after a total of 8 cycles, the patient will be removed from further protocol therapy. If after 8 cycles, the bone marrow is negative and the patient is in partial response, the patient will receive radiotherapy. Complete responders after induction chemotherapy; complete responders after induction chemotherapy plus radiation therapy; and partial responders after chemotherapy plus radiation therapy will be randomized to consolidation alpha interferon or observation, approximately one month after completion of therapy.

Progress: This study was closed to patient entry 15 Nov 94. Four patients have been entered at MAMC. All patients are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 89/080 **Status**: Ongoing

Title: SWOG 8814 (ECOG 4188, NCCTG 883051): Phase III Comparison of Adjuvant Chemoendocrine Therapy with CAF and Concurrent or Delayed Tamoxifen to Tamoxifen Alone in Postmenopausal Patients with Breast Cancer Having Involved Axillary Nodes and Positive Hormone Receptors

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): MAJ Paul C. Sowray, MC; MAJ Mark H. Kozakowski, MC; MAJ Everardo E. Cobos Jr., MC; MAJ Patrick L. Gomez, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC; LTC Robert L. Sheffler, MC

Start Date:	Est. Completion Date:	Periodic Review:
09/15/1989	Sep 99	10/17/1997

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 chemoendocrine therapy with CAF, followed by long-term Tamoxifen or with concurrent chemoendocrine therapy with Tamoxifen and CAF and to compare the relative toxicity of the three therapies.

Technical Approach: Tumors must be pathologic stage T1, T2, or T3; N; MO (Stage II or selected Stage IIIA). Patients must have histologically proven adenocarcinoma of the breast with at least one positive lymph node (tumor and/or nodes must not be fixed). Patients must have undergone a radical, modified radical, or breast sparing procedure plus axillary dissection (level I or level II). Patients with bilateral breast cancer are ineligible. Estrogen and progesterone receptors must be assayed and one and/ or the other must be positive by the institutional laboratory standards of >10 fmol/mg protein. Prestudy studies must reveal no evidence of metastatic disease. Prior hormonal or chemotherapy is not allowed and prior postmenopausal estrogen therapy is allowed but must be discontinued before registration. Stratification factors will include: involved nodes (1-3, >4); PgR+ (ER positive or negative) vs PgR(ER positive); time from surgery to randomization (<6 vs >6 weeks). Patients will be randomized to one of three treatment arms: Arm I: Tamoxifen x 5 years, Arm II: Intermittent CAF x 6 courses followed by Tamoxifen x 5 years, Arm III: Intermittent CAF x 6 courses with concurrent Tamoxifen x 5 years.

Progress: This study closed to patient entry 1 Aug 95. Seven patients have been entered in this study at MAMC. One patient expired in FY 96, 6 others are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 91/087 **Status**: Ongoing

Title: SWOG 8819: Central Lymphoma Repository Tissue Procurement Protocol; Companion Protocol to SWOG Studies: 8516, 8736, 8809, 8907, and 8954

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; LTC Luke M. Stapleton, MC; MAJ Patrick L. Gomez, MC; MAJ Everardo E. Cobos Jr., MC; LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; CPT Jennifer L. Cadiz, MC; MAJ James S. D. Hu, MC; MAJ Paul C. Sowray, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/02/1991	Aug 95	09/15/1998

Study Objective: To acquire fresh snap-frozen lymphoma tissue to establish a central lymphoma tissue repository; to establish a standard set of procedures for routine acquisition, banking, and study of lymphoma tissues within the cooperative group; to use repository tissue to establish clinical correlations via presently activated phenotyping studies and future projected molecular studies assessing specimen DNA and RNA status; and to determine if pretreatment phenotype or genotype predict patient outcome with respect to complete response rate, time to progression, and survival using prospective trial designs.

Technical Approach: Patients will be treated according to guidelines outlined in the specific SWOG studies. Treatment decisions will not be based on findings of the Central Lymphoma Laboratory, although clinical variables will be correlated with laboratory findings. The tissue samples will be taken from the pretreatment diagnostic biopsy or rebiopsy based on clinical decisions. Fresh biopsies (from any organ site) will be snap-frozen and submitted with one stained (hematoxylin and eosin) histologic section with accompanying pathology report. The H&E stained slide and report will accommodate morphologic correlation with immunologic findings. Tissue section analysis will be performed at the University of Arizona using three stage immunohistochemistry. Future molecular studies entailing hybridization studies of RNA and DNA fragments using DNA probes will be performed as outlined in future protocols.

Progress: This is a companion study using tissue from other SWOG protocols. Tissue has been collected on three patients.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 90/027 **Status**: Ongoing

Title: SWOG 8851 (EST 5811, INT-0101): Phase III Comparison of Combination Chemotherapy (CAF) and Chemohormonal Therapy (CAF + Zoladex or CAF + Zoladex + Tamoxifen) in Premenopausal Women with Axillary Node-Positive, Receptor-Positive Breast Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): MAJ Paul C. Sowray, MC; MAJ Mark H. Kozakowski, MC; MAJ Everardo E. Cobos Jr., MC; MAJ Patrick L. Gomez, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC; LTC Robert L. Sheffler, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/19/1990	Dec 99	02/20/1998

Study Objective: To compare the recurrence rates, disease-free intervals, relative toxicities, and hormone-receptor-positive survival for premenopausal women with axillary lymph node-positive breast cancer given adjuvant therapy with combination chemotherapy using cyclophosphamide, doxorubicin, and 5-FU (CAF) alone or CAF followed by Zoladex, or CAF followed by Zoladex plus Tamoxifen; and to assess the effect of CAF, CAF plus Zoladex, and CAF plus Zoladex and Tamoxifen on hormone levels (LH, FSH, and estradiol) in these patients.

Technical Approach: Patients will be nonpregnant females who have undergone excision of the primary breast tumor mass, proven histologically to be invasive breast adenocarcinoma and must have one or more pathologically involved axillary nodes. Patients who undergo total mastectomy may receive post-operative radiotherapy at the discretion of the investigator. Patients who have had prior hormonal therapy or chemotherapy for breast cancer are ineligible. Patients will be randomized to CAF alone for six cycles or to CAF for 6 cycles followed by monthly Zoladex for 5 years, or to CAF for 6 cycles followed by daily Tamoxifen and monthly Zoladex for 5 years. Adjuvant therapy will be instituted as soon as possible after mastectomy or lumpectomy. The interval between definitive surgery and initiation of adjuvant chemotherapy will not be >12 weeks. When planned, radiation therapy may be administered prior to or after (within 4 weeks of) completion of 6 cycles of adjuvant chemotherapy.

Progress: This study closed to patient entry 1 Feb 94. Six patients have been enrolled at MAMC in previous years. One patient has been lost to follow-up, five are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 90/047 **Status**: Ongoing

Title: SWOG 8854: prognostic Value of Cytometry Measurements of Breast Cancer DNA from Postmenopausal Patients with Involved Nodes and Receptor Positive Tumors: A Companion Protocol to SWOG 8814

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/16/1990	Mar 98	10/17/1997

Study Objective: To determine if ploidy analysis of breast cancer by routine clinical flow cytometry (CFM) technique can predict response to therapy and survival of patients registered to SWOG 8814 and to determine if ploidy analysis by image processing technique more accurately predicts patient response to therapy and survival than ploidy analysis by flow cytometry.

Technical Approach: Two paraffin blocks, one representing the highest grade region of the primary tumor, the second representing the highest grade regional metastasis in a positive lymph node, will be used. From each of these blocks, two to five sections will be cut and a nuclear suspension prepared. From each suspension, a cytospin preparation will be prepared and stained with Dif-Quik to ensure that the cells present in the H & E slide are represented adequately in the nuclear preparation. A second cytospin preparation will be prepared for staining by the Feulgen technique for image processing DNA analysis. The remainder of the nuclear preparation will be stained with propidium iodide following RNase digestion for FCM DNA analysis. Cox regression modeling will be used to explore the prognostic value of ploidy status as determined by FCM and by image processing, in conjunction with the covariates tumor size, age, ER and PgR levels, and number of nodes.

Progress: This study closed to patient entry 15 Feb 95. This is a companion study using tissue from SWOG 8814. Six samples have been studied, one of the patients has expired.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 91/067 **Status**: Ongoing

Title: SWOG 8855: Prognostic Value of Cytometry Measurements of Cellular DNA Parameters in Locally Advanced, Previously Untreated Head and Neck Cancer Patients

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Paul C. Sowray, MC; MAJ Everardo E. Cobos Jr., MC; LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Patrick L. Gomez, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/14/1991	Jun 94	09/15/1998

Study Objective: To evaluate the prognostic value of cellular DNA parameters of degree of DNA aneuploidy (DNA index) and proliferative activity (SPF) in predicting treatment response, time to treatment failure, and survival in patients with squamous cell carcinoma of the head and neck treated initially with cytotoxic therapy and to assess the correlation of DNA index and SPF with other patient clinical characteristics.

Technical Approach: Squamous cell cancers of the head and neck display a high degree of responsiveness to chemotherapy and/or radiotherapy, but a significant minority are exquisitely resistant to these treatment modalities. This will be a companion study to all SWOG head and neck cancer protocols utilizing chemotherapy as initial treatment and will use the patients registered on those studies. This study will use flow cytometrically determined cellular parameters, particularly cellular DNA content, to help identify prognostic outcome in this group of tumors. Specimens will be obtained at the time of biopsy for diagnosis, at completion of therapy if the tumor persists, or if a biopsy is performed to confirm a clinical complete response or document recurrence. All resected specimens will be sent for flow cytometry analysis. The degree of DNA aneuploidy (DNA index) and proliferative activity (SPF) will be determined by flow cytometry. These measurements will be correlated with the clinical characteristics of the patient at the time of biopsy to help predict treatment response, time to treatment failure, and survival in patients with squamous cell carcinoma of the head and neck.

Progress: Four patients have been entered in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 90/055 **Status**: Ongoing

Title: SWOG 8892 (EST-2388, RTOG-8817, INT-0099): A Study of Radiotherapy with or without Concurrent Cisplatin in Patients with Nasopharyngeal Cancer, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Paul C. Sowray, MC; MAJ Mark H. Kozakowski, MC; MAJ Everardo E. Cobos Jr., MC; CPT Denis Bouvier, MC; MAJ Patrick L. Gomez, MC; LTC Robert L. Sheffler, MC; MAJ Michael R. Morris, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/16/1990	Mar 93	10/17/1997

Study Objective: To compare radiotherapy with radiotherapy and concurrent cisplatin, followed by three courses of 5-FU + cisplatin for complete response rate, time to treatment failure, overall survival, pattern of recurrence, and qualitative and quantitative toxicities.

Technical Approach: To be eligible, patients must have histologically proven nasopharyngeal carcinoma (excluding adenocarcinoma), Stage III or IV with no evidence of distant metastatic disease, and must not be eligible for higher priority SWOG studies. Patients will be randomized as follows: Arm I: radiation therapy alone for approximately 7 weeks; Arm II: 3 courses of cisplatin (days 1, 22, and 43) concurrent with radiotherapy followed by three courses of 5-FU + cisplatin. Measurable disease must be assessed at least every eight weeks the first year of follow-up. Patients will be seen in follow-up every two months the second year, every three months the third year, and every four months thereafter. A tumor biopsy for flow cytometry will be obtained if tumor recurs.

Progress: This study was closed to patient entry 1 Feb 93. Nine patients were enrolled in previous years, one expired in FY 96 and the other eight are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 90/029 **Status**: Ongoing

Title: SWOG 8897 (EST-2188, CALGB-8897, INT-0101): Phase III Comparison of Adjuvant Chemotherapy With or Without Endocrine Therapy in High-Risk, Node Negative Breast Cancer Patients, and a Natural History Follow-up Study in Low-Risk, Node Negative Patients

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): MAJ Paul C. Sowray, MC; MAJ Mark H. Kozakowski, MC; MAJ Everardo E. Cobos Jr., MC; MAJ Patrick L. Gomez, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC; LTC Robert L. Sheffler, MC

Start Date:	Est. Completion Date:	Periodic Review:
01/19/1990	Jan 93	02/20/1998

Study Objective: To compare disease-free survival and overall survival of high risk primary breast cancer patients with negative axillary lymph nodes treated with standard adjuvant chemotherapy for 6 cycles; either CMF (cyclophosphamide, methotrexate, 5-FU) or CAF (cyclophosphamide, adriamycin, 5-FU); to assess the value of the addition of tamoxifen for five years compared to no tamoxifen in these patients; to compare the toxicity of the therapies; to assess the prognostic significance of DNA flow cytometry in patients with small, occult invasive breast cancer treated by local therapy only; and to evaluate the disease-free survival and survival of low risk invasive breast cancer patients determined by receptor status, tumor size, and % S phase treated by local therapy only.

Technical Approach: Patients must have undergone a radical, modified radical, or breast sparing procedure plus level 1 and 2 axillary lymph node dissection. Patients with bilateral breast cancer, prior hormonal or chemotherapy, or previous or concurrent malignancy are ineligible. Low risk patients will be followed but will not receive adjuvant therapy. High risk patients will be randomized to: (1) CMF x 6 cycles; (2) CAF x 6 cycles; (3) CMF x 6 cycles followed by tamoxifen; or (4) CAF x 6 cycles followed by tamoxifen. Patients will start adjuvant chemotherapy within 12 weeks of definitive surgery. Patients who have had a breast sparing procedure and axillary dissection will receive radiation therapy, either before or after CMF or CAF (at the discretion of the treating physician). Radiotherapy and tamoxifen may be given together. Patients will be removed from the study for unacceptable toxicity, development of local/regional or metastatic disease; or noncancer related illnesses that prevent continuation of therapy or regular follow-up. Patients will be followed until death.

Progress: This study was closed to patient entry 1 Feb 93. Nine patients were enrolled in previous years, one expired in FY 97 and the other seven are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 89/021 **Status**: Ongoing

Title: SWOG 8899: A Prospectively Randomized Trial of Low-Dose Leucovorin = 5-FU, High-Dose Leucovorin + 5-FU, Levamisole + 5-FU, or Low-Dose Leucovorin + 5-FU + Levamisole Following Curative Resection in Selected Patients with Duke's B or C Colon Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL Irwin B. Dabe, MC; MAJ Mark H. Kozakowski, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC; MAJ Everardo E. Cobos Jr., MC

Start Date:	Est. Completion Date:	Periodic Review:
02/17/1989	Feb 92	02/20/1998

Study Objective: To assess the effectiveness of 5-FU + high-dose Leucovorin as surgical adjuvant therapy for resectable colon cancer, when compared to surgery alone.

Technical Approach: Patients must have received a potentially curative surgery for colon cancer with neither gross nor microscopic evidence of residual disease following the complete resection. The resected specimen must pathologically verify a diagnosis of modified Duke's B-2, B-3, or C. The primary tumor must be above the peritoneal reflection. Patients may not have had any prior chemotherapy nor exposure to 5-FU. Patients must be maintaining oral nutrition and be ambulatory 50% of the day and have adequate bone marrow function. Patients may not have a concurrent second malignant disease nor any previous malignant tumor within three years. Patients will be stratified by extent of invasion (limited to bowel wall vs into or through serosa vs perforation vs adherence to adjacent organs vs invasion of adjacent organs); extent of regional nodal metastases (none vs 0-4 vs >4); regional/ mesenteric implants resected enbloc (yes/no); and obstruction (yes/no). RANDOMIZE TO: (1) Observation; (2) Leucovorin 20 mg/m^2 + 5-FU 425 mg/m^2; days 1-5; repeat at 4 and 8 wks, then every 5 wks for a total of 6 courses; (3) Leucovorin 500 mg/m^2 + 5-FU 600 mg/m^2; Leucovorin by IV 2 hour infusion, 5-FU IV push beginning 1 hr after start of Leucovorin infusion, repeated weekly for 6 wks, followed by a 2-wk rest period, each 8-wk cycle (1 course) will be repeated for 4 courses. Revision (Jan 90): Observation arm closed (due to positive results seen in SWOG 8591); two new arms added (5-FU + levamisole & 5-FU + low dose leucovorin + levamisole).

Progress: Eighteen patients were enrolled at MAMC prior to closure to patient entry on 30 Jul 92. One patient was lost to follow-up, five patients have died from their disease and 12 continue to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 91/089 **Status**: Ongoing

Title: SWOG 8947: Central Lymphoma Serum Repository Protocol; Companion Protocol to SWOG Studies 8516, 8736, 8809, and 8816

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Paul C. Sowray, MC; MAJ Patrick L. Gomez, MC; MAJ Everardo E. Cobos Jr., MC; LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; CPT Jennifer L. Cadiz, MC; MAJ James S. D. Hu, MC; LTC Luke M. Stapleton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
08/02/1991	Aug 95	09/15/1998

Study Objective: To establish a central lymphoma serum repository that will serve as a resource to provide specimens for current and future scientific studies and to utilize the Southwest Oncology Group clinical data base to perform clinicopathologic correlations with the results of those studies.

Technical Approach: No therapy will be utilized in this study and patient treatment will not be based on this study. Patients must meet the eligibility criteria and be registered to one of the following SWOG protocols: 8516, 8809, 8736, or 8816. Ten cc's of blood will be drawn prior to protocol treatment and shipped to the SWOG Lymphoma Serum Repository at Loyola University Medical School.

Progress: This is a companion protocol to other SWOG studies. Two specimens have been collected in previous years .

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 91/007 **Status**: Ongoing

Title: SWOG 8957: Feasibility Trial of Post-Operative Radiotherapy Plus Cisplatin Followed by Three Courses of 5-FU Plus Cisplatin in Patients with Resected Head and Neck Cancer, Phase II Pilot

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Paul C. Sowray, MC; MAJ William A. Phillips; LTC Luke M. Stapleton, MC; MAJ Everardo E. Cobos Jr., MC; LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Patrick L. Gomez, MC

Start Date:	Est. Completion Date:	Periodic Review:
10/19/1990	Oct 93	10/17/1997

Study Objective: To evaluate the feasibility of administering three courses of chemotherapy to resected patients who have received cisplatin and radiation therapy post-operatively and to evaluate the qualitative and quantitative toxicities.

Technical Approach: Patients who have had resected squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx are eligible for the study. Chemotherapy used prior to surgery or radiotherapy in untreated head and neck cancer patients has produced particularly high rates of response. However, previous studies have shown that 20-25% of these patients will refuse further surgery or radiotherapy because of an initial good overall response with chemotherapy alone. To avoid this problem, the chemotherapy in this study will be given after surgery, along with radiation and as maintenance afterwards. Cisplatin, 100 mg/m^2, on days 1, 22, and 43 will be given concomitant with radiation therapy. Three to four weeks post-radiation therapy, maintenance chemotherapy will be started. Maintenance chemotherapy will consist of cisplatin, 100 mg/m^2, day 1 every 21 days for three courses and 5-FU, 1000 mg/m^2, days 1-4, every 21 days for three courses.

Progress: This study closed to patient entry 1 May 92. One patient was enrolled in FY92 and is still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 90/056 **Status**: Ongoing

Title: SWOG 8997 (ECOG 3887): Phase III Chemotherapy of Disseminated Advanced Stage Testicular Cancer with Cisplatin Plus Etoposide with Either Bleomycin or Ifosfamide

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): MAJ Paul C. Sowray, MC; MAJ Mark H. Kozakowski, MC; MAJ Everardo E. Cobos Jr., MC; MAJ Patrick L. Gomez, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC; LTC Robert L. Sheffler, MC; LTC John A. Vaccaro, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/16/1990	Mar 93	10/17/1997

Study Objective: To determine the objective response rate and duration of remission of BEP compared to VIP combination chemotherapy; to determine the toxicity of VIP compared to BEP combination chemotherapy; to confirm the efficacy and toxicity of intravenous Mesna as a urothelial protective agent.

Technical Approach: Patients must have a histologic diagnosis of advanced disseminated germ cell tumor and no prior chemotherapy or radiation therapy. Patients will be randomized to VIP (cisplatin, ifosfamide, mesna, and etoposide) to BEP (cisplatin, etoposide, and bleomycin). The regimen will be repeated every three weeks for four cycles. Bleomycin will be omitted for postsurgery chemotherapy in BEP patients. Patients in complete remission at the end of four courses of therapy will receive no further treatment. If there is radiographic or serologic evidence of persistent disease and residual tumor is surgically resectable, surgery will be performed. Patients who have complete or near complete resection of residual radiographic abnormalities with the pathologic finding of fibrosis/necrosis and those who have complete resection of mature or immature teratoma will receive no further treatment. Patients who have complete resection of residual disease which histologically shows viable carcinoma will receive two more courses of the original induction therapy. If residual tumor is deemed unresectable, patients will be followed monthly until disease progression with no further therapy. If relapse occurs in complete or partial responders less than 4 weeks after day 1 of the last course of induction therapy, the patient will be taken off study.

Progress: Prior to closure to patient entry (9 Apr 92) two patients had been enrolled at MAMC. One patient is still being followed (one died Jan 93).

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/056 **Status**: Ongoing

Title: SWOG 9003: Fludarabine for Waldenstrom's Macroglobulinemia (WM): A Phase II Study for Untreated and Previously Treated Patients

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/05/1993	Mar 98	10/17/1997

Study Objective: 1) To estimate response rates and survival in patients with Waldenstrom's Macroglobulinemia (WM) receiving fludarabine, with stratification according to whether they have prior therapy. 2) To define prognostic factors that may relate to response, time to progression and overall survival, separately for newly diagnosed and previously treated patients. 3) To estimate the associated hematologic and non-hematologic toxicities.

Technical Approach: Persons with a diagnosis of WM and meeting enrollment criteria can be registered for this study. After the initial workup, to include bone marrow aspiration, those patients without symptoms and with no progression of the disease will be entered in the Observation phase. If they are symptomatic or have progression of the disease or if onset of symptoms and/or progression occurs during the Observation phase immediate Re-registration to the Treatment phase will occur. Fludarabine 30 mg/m^2 IV will be administered on days 1 - 5. This schedule will be repeated every 28 days for 4 cycles until the patient's condition is stable without remission, progression occurs, or the disease is stable. If the disease becomes stable without remission or progresses, treatment will be stopped. If there is complete remission, partial remission or improvement the patient will receive an additional 4 cycles of therapy or 2 cycles beyond maximum response, whichever occurs earlier.

Progress: Two patients were enrolled in FY 93 and are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 91/094 **Status**: Ongoing

Title: SWOG 9007: Cytogenetic Studies in Leukemia Patients, Ancillary

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Paul C. Sowray, MC; LTC Luke M. Stapleton, MC; MAJ Patrick L. Gomez, MC; LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; CPT Jennifer L. Cadiz, MC; MAJ James S. D. Hu, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/06/1991	Aug 94	09/15/1998

Study Objective: To compare these primary aspects of quality of life, according to treatment assignment: 1) Treatment specific symptoms 2) Physical Functioning 3) Emotional functioning To compare three secondary quality of life variables, according to treatment assignment: 1) General symptoms 2) Global perception of quality of life 3) Social functioning.

Technical Approach: This is a companion to SWOG 8794. Patients will be assigned to the same treatment groups as in the companion protocol (prostatectomy followed by adjuvant radiotherapy versus prostatectomy alone) and must be able to complete a quality of life questionnaire prior to registration and randomization on SWOG-8794. Standardized instructions will be read to the patients by the nurse/data manager at each site. Additional questionnaires will be completed at week 6, 6 months, 12 months, and then yearly for the next 4 years. Quality of life profiles will be compared for the two treatment groups at different points in time: baseline, where no differences are expected at six weeks, where the two treatment groups are expected to show maximum differences on some measures; six months, one year and annually for a total for five years, where the treatment means for quality of life measures are expected to come together and level off. For key continuous variables, repeated measures analyses of variance should help to make comparisons at fixed points in time and across time. For the discrete variables such as occurrence or non-occurrence of specified complications, standard methods of categorical data analysis will be employed.

Progress: Five patients have been enrolled in previous years. One patient continues to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 92/051 **Status**: Ongoing

Title: SWOG 9008: Trial of Adjuvant Chemoradiation After Gastric Resection for Adenocarcinoma, Phase II

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Rahul N. Dewan, MC; LTC Luke M. Stapleton, MC; MAJ Patrick L. Gomez, MC; LTC Robert B. Ellis, MC; LTC Robert L. Sheffler, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/03/1992	Mar 95	10/17/1997

Study Objective: To evaluate the possible benefit of adjuvant chemoradiation therapy in patients with resected gastric cancer to include: comparison of overall and disease free survival between patients being treated with surgical resection only and those being treated with surgery plus adjuvant therapy; comparison of incidence and patterns of disease failure between surgery and surgery plus adjuvant therapy treated patients; and assessment of patient tolerance of upper abdominal chemoradiation after gastric resection.

Technical Approach: Patients will be randomized to either observation or adjuvant therapy. Adjuvant therapy will consist of one course of 5-FU and Leucovorin given IV. Four weeks later the patient will receive a second course of 5-FU with Leucovorin with concomitant radiation therapy. While receiving radiation therapy, the patient will receive a third course of 5-FU and Leucovorin, which will occur during the fifth week of radiation therapy. After completing radiation therapy, the patient will receive two additional courses of chemotherapy to begin approximately 35 days after completion of radiotherapy.

Progress: One patient was enrolled (FY 94) and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 91/033 **Status**: Ongoing

Title: SWOG 9013 (RTOG 89-11, INT-0113): A Prospective Randomized Comparison of Combined Modality Therapy for Squamous Carcinoma of the Esophagus: Chemotherapy Plus Surgery Versus Surgery Alone for Patients with Local Regional Disease

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ William A. Phillips; LTC Luke M. Stapleton, MC; MAJ Patrick L. Gomez, MC; LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; COL Joseph F. Homann, MC; COL Daniel G. Cavanaugh, MC; MAJ Everardo E. Cobos Jr., MC; MAJ Paul C. Sowray, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/01/1991	Jan 94	02/20/1998

Study Objective: To compare, using a prospective controlled randomized study design, the outcomes of therapy of surgery alone versus pre and postoperative chemotherapy and surgery for patients with local regional esophageal cancer (outcome is defined as survival and relapse pattern); to assess the toxicities of a multimodality approach to esophageal carcinoma involving systemic chemotherapy and surgery (the toxicities of surgical resection as initial therapy or following chemotherapy will be assessed as operative morbidity and mortality); to compare the local and distant control rates with the two approaches and to define the pattern of failure; and to compare the impact on overall and disease free survival of multimodality therapy with surgery alone.

Technical Approach: Esophageal cancer is seen in over 10,000 patients a year in the United States and only about 7% of these patients are cured as demonstrated by a five year survival. This study is designed to see whether or not giving chemotherapy will improve that survival. To be eligible patients must have histologic proof of squamous cell carcinoma of the esophagus, disease limited to the total regional area (clinical stage T1-T3, NX,MO), no prior surgery, radiation therapy, or chemotherapy, and adequate bone marrow, liver function, renal function, and pulmonary reserve. Patients must be physiologically fit for proposed chemotherapy and surgery and be greater than 18 years of age. Patients will be randomized to surgery alone, or to receive three cycles of preoperative cisplatinum and 5-FU and then to undergo definitive surgery followed by two more cycles of cisplatinum and 5-FU, starting two to six weeks after surgery.

Progress: This study was closed to patient entry 31 Dec 95. Three patients have entered this study in previous years. Two are being followed and one died of the disease.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/143 **Status**: Ongoing

Title: SWOG 9019: A Phase III, Randomized, Prospective Comparison Between Chemotherapy Plus Radiotherapy, and the Same Chemotherapy Plus Radiotherapy Together With Surgery for Selected Stage IIIA (Positive Mediastinal Nodes) and Selected Stage IIIB (No Malignant Effusion) Non-Small Cell Lung Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; LTC Luke M. Stapleton, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC

Start Date:	Est. Completion Date:	Periodic Review:
06/09/1993	May 98	10/17/1997

Study Objective: 1) To assess whether concurrent chemotherapy and radiotherapy, followed by surgical resection, results in a significant improvement in progression-free, overall, and long-term survival compared to the same chemotherapy plus standard radiotherapy alone for patients with stage IIIa (N2 Positive) and selected IIIB non-small cell lung cancer. 2) To evaluate the patterns of local and distant failure for patients enrolled in each arm of the study, in order to assess the impact of the therapy on local control and distant metastasis.

Technical Approach: Patients with regionally advanced non-small cell lung carcinoma will be randomized to one of two arms. Arm I: patients will receive induction radiation therapy to a "tight" field to 4500 cGy. They will receive concurrent cisplatin on days 1 and 8 and on days 29 & 36 with VP-16 days 1-5, repeated on days 29-33 (2 cycles). After completion of induction, patients will be re-evaluated for extent of disease. If there is no progression of the disease, patients will go to exploratory thoracotomy for complete removal of the primary lesion and sampling of nodes.

If the tumor is unresectable or the margins are positive or the mediastinal nodes are positive, an additional 2 cycles of chemotherapy with a radiation boost will be given. Patients who complete the induction phase but have persistent supraclavicular node metastases will also receive 2 more cycles of concurrent chemo-radiotherapy will not go to surgery.

Arm II patients receive "standard" lung field radiation therapy to 4500 cGy and concurrent cisplatin and VP-16 for 2 cycles.

One week prior to completing radiation therapy, patients will be re-evaluated for response. Those patients with no evidence of distant metastases or local progression will continue radiation therapy with no break for an additional 1600 cGy with a boost. They will also receive 2 more cycles of chemotherapy concurrent with radiation.

Any patient who shows local or distant progression after induction chemo-radiation will be taken off protocol.

Progress: This study was closed to patient entry 1 Dec 95. Two patients have been enrolled in this study in previous years (1 in FY95). One patient continues to be followed and the other died of the disease.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 92/052 **Status**: Ongoing

Title: SWOG 9031: A Double Blind Placebo Controlled Trial of Daunomycin and Cytosine Arabinoside With or Without rhG-CSF in Elderly Patients With Acute Myeloid Leukemia, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Paul C. Sowray, MC; LTC Luke M. Stapleton, MC; MAJ Patrick L. Gomez, MC; LTC Robert B. Ellis, MC; LTC Robert L. Sheffler, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/03/1992	Jun 94	10/17/1997

Study Objective: To compare the complete response rates and duration of survival in patients 56 or older with acute myeloid leukemia (AML) when treated with standard doses of cytosine arabinoside (Ara-C) and daunorubicin (DNR), with or without recombinant human granulocyte-colony stimulating factor (rhG-CSF); to assess the frequency and severity of toxicities of the two treatment regimens; to compare the duration of neutropenia and thrombocytopenia, the total number of febrile days, the number of days of antibiotic therapy, the number and type of infection episodes, and the number of hospital days in patients treated with or without rhG-CSF; and to correlate biological parameters including cell surface immunophenotype, ploidy, and cytogenetics with clinical response.

Technical Approach: Patients aged 56 and older with AML will be randomized to receive treatment with either Ara-C/DNR plus rhG-CSF or Ara-C/DNR plus placebo (Ara-C days 1-7, C/DNR days 1-3, and blinded drug begins on day 10) Patients who had regrowth of leukemia during this course of treatment will receive a second identical course of treatment except the blinded drug will not be started until the marrow shows <5% blasts. The blinded drug will not be given in the second induction course if the patient has regrowth of leukemia following the first induction course. Following completion of induction therapy, patients who achieve complete remission will be registered to receive two cycles of post-remission therapy, utilizing the same regimen to which they were originally randomized.

Progress: No patients were enrolled in FY 98.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 92/095 **Status**: Completed

Title: SWOG 9032: A Controlled Trial of Cyclosporine as a Chemotherapy-Resistance Modifier in Blast Phase Chronic Myelogenous Leukemia

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; LTC Luke M. Stapleton, MC; MAJ Patrick L. Gomez, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/07/1992	Sep 94	10/17/1997

Study Objective: To compare the duration of survival in patients with chronic myelogenous leukemia (CML) in blast phase, when treated with either chemotherapy (Ara-C/Daunomycin) alone or chemotherapy plus the resistance modifier, cyclosporine-A (CyA); to estimate the frequency of P-glycoprotein expression and its association with blast lineage and prognosis; and to compare the frequency and severity of toxicity of the two treatment regimens.

Technical Approach: Patients will be randomized to receive treatment with either Ara-C/Daunomycin alone or Ara-C/Daunomycin + CyA. If the day 14 bone marrow shows less than or equal to a 50% reduction in the absolute blast count per 500 cell differential compared with the pretreatment bone marrow, the patient will be considered a treatment failure and removed from the study. If there is more than a 50% reduction in the blast count as stated above, but the patient has not achieved a complete remission or restored chronic phase status, a second course of the original induction regimen will begin on or after day 21. Patients who do not achieve complete remission or restoration of chronic phase after two inductions will be removed from the protocol. Patients who achieve complete remission or restored chronic phase will receive one course of consolidation therapy (same regimen as for induction therapy).

Progress: No patients have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/062 **Status**: Ongoing

Title: SWOG 9035: Randomized Trial of Adjuvant Immunotherapy with an Allogeneic Melanoma Vaccine for Patients with Intermediate Thickness, Node Negative Malignant Melanoma, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Richard F. Williams, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ John R. Caton, MC

Start Date:	Est. Completion Date:	Periodic Review:
01/20/1995	Jan 99	02/20/1998

Study Objective: 1) To compare disease-free survival and overall survival between patients with T3NOM0 malignant melanoma who receive adjuvant immunotherapy with an allogeneic melanoma vaccine versus no adjuvant treatment. 2) To evaluate the toxicity of adjuvant immunotherapy with an allogeneic melanoma vaccine in patients with T3NOI10 malignant melanoma. 3) To explore the interaction between the patients' defined HLA types (i.e., whether they are compatible with the HLA phenotypes of the vaccine) and the vaccine treatment effectiveness in terms of disease-free survival and overall survival.

Technical Approach: The study is a randomized study of Interferon Alfa-2b as adjuvant immunotherapy in patients with T3NOM0 malignant melanoma following complete resection. After complete staging, including assessment of any abnormal lymph nodes by biopsy, patients will be randomized either to treatment with four cycles of intramuscular vaccine therapy or observation only and will be followed until death for recurrence.

Progress: One patient was enrolled in FY95 and is still being followed. The protocol was closed to patient entry, 15 Nov 96.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 91/069 **Status**: Ongoing

Title: SWOG 9040 (CALGB-9081, INT-0014): Intergroup Rectal Adjuvant Protocol, A Phase III Study

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): MAJ Everardo E. Cobos Jr., MC; MAJ Paul C. Sowray, MC; MAJ Patrick L. Gomez, MC; MAJ Rahul N. Dewan, MC; LTC Steven S. Wilson, MC; LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; LTC Howard Davidson, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/14/1991	May 93	10/17/1997

Study Objective: To determine the relative efficacy of: 5-FU; 5-FU plus leucovorin; 5-FU plus levamisole; and 5-FU plus leucovorin and levamisole when combined with pelvic radiation therapy in the treatment of Stages B-2 and C (TNM Stage II and III) rectal cancer. End points used will include local recurrence rates, probability of distant metastases, disease free survival rates, and overall survival.

Technical Approach: This will be a 4-armed study with the same radiation therapy program in all arms, but with varying drug regimens as listed in the objective. 5-FU with radiation therapy will comprise the control arm of the study. Patients will be randomized to treatment arms and they will be stratified by type of operation (abdominal perineal or anterior resection); nodal involvement (none, 1-3, or >3); and invasion through bowel wall or into adjacent organs (none, through muscularis propria, or adherence to or invasion of adjacent organs or structures). Each drug regimen will be given alone on days 1-5 and 29-33, followed by radiation therapy (five weeks) with concomitant chemotherapy on days 57-60 and 85-88. The chemotherapy regimen will then be repeated beginning 28 days after the completion of radiation therapy on days 1-5 and 29-33. If evidence of recurrence is obtained, protocol treatment will be discontinued and the patient followed until death. In the absence of recurrent disease, follow-up observations will be continued for a minimum of 5 years after surgery.

Progress: This study was closed to patient entry on 22 Nov 92. Three patients were enrolled in previous years and continue to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/104 **Status**: Ongoing

Title: SWOG 9041: Chemoprevention of Recurrent Adenomas and Second Primary Colorectal Carcinoma. A Phase III Pilot Study.

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Timothy P. Rearden, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/06/1994	May 98	09/15/1998

Study Objective: This is a preliminary effort towards the long-term research goal of determining whether calcium, as a nutritional supplement, can prevent colorectal adenomas and new primary carcinomas in surgically treated colorectal carcinoma (CRC) patients.

Technical Approach: Patients with previously resected colon cancer, Stages 0, I, or II or rectal carcinomas, Stages 0, I are eligible to participate in this study. During the 3 month Run In period, patients will be placed on placebo 3 tablet a day. After successful completion of the Run In (patients must have taken > 80% of tablets) patients will be randomized to regimen A (3 - 600 mg tablets of calcium carbonate daily for 5 years) or regimen b (3 placebo tablets daily for 5 years). The pills will be provided to the patients every three months for the first two years and every six months for the next three years. Patients will be monitored for compliance, hypercalcemia, renal toxicity and gastrointestinal or hepatic toxicity. Endpoint is the efficacy of supplemental oral calcium in reducing recurrence of adenomas or second primary carcinomas.

Progress: Seven patients were enrolled in this study in FY 97 for a total of 16 patients who are being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/096 **Status**: Ongoing

Title: SWOG 9059 (E1392, INT-0126): Phase III Comparison of Standard Radiotherapy versus Radiotherapy plus Simultaneous Cisplatin, versus Split-Course Radiotherapy plus Simultaneous Cisplatin and 5-Fluorouracil, in Patients with Unresectable Squamous Cell Carcinoma of the Head and Neck

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:	Est. Completion Date:	Periodic Review:
05/16/1997	Apr 00	04/17/1998

Study Objective: 1) To compare the effectiveness of standard radiation therapy alone to radiation therapy and simultaneous chemotherapy with cisplatin to split-course radiation therapy with cisplatin and 5-fluorouracil infusion in patients with unresectable Stage III and IV squamous cell carcinoma of the head and neck. Endpoints will include complete response rate, time to treatment failure, and overall survival. 2) To compare the relative toxicities of these treatment arms, in this patient population. 3) To compare patterns of relapse or treatment failure among these regimens. 4) To further assess the role, timing, and success of surgery in patients achieving a response to non-operative therapy.

Technical Approach: Unresectable Squamous Cell Carcinoma has a dismal prognosis with 3 year survivals in the 25' range. Several studies have shown that adding chemotherapy to radiation therapy may improve response rates and may allow some patients to get surgery after therapy. There are two approaches to adding chemotherapy to radiation therapy. One way is to give concurrent therapy with Cisplatinum alone with combined continuous radiation therapy (Al Sarraf regimen) or to give combination Cisplatinum and 5-FU with split course (Adelstein Regimen). These two regimens have met with some success in single ARM Phase II studies and have resulted in some patients having subsequent surgeries translating into longer survivals. It is thus the aim of this study to evaluate efficacy of three different regimens with continuous radiation therapy alone serving as the third ARM. Toxicities from these regimens are reasonable.

Progress: No patients have been entered in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/032 **Status**: Ongoing

Title: SWOG 9061 (EST-2190, INT 0121): A Phase III Study of Conventional Adjuvant Chemotherapy vs High Dose Chemotherapy and Autologous Bone Marrow Transplantation or Stem Cell Transplantation as Adjuvant Intensification Therapy Following Conventional Adjuvant Chemotherapy in Patients with Stage II and III Breast Cancer at High Risk of Recurrence

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Timothy P. Rearden, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/04/1992	Nov 95	10/17/1997

Study Objective: To compare the sites and rates of recurrence, disease-free survival and overall survival, and toxicity of adjuvant chemotherapy (CAF) with adjuvant chemotherapy plus high-dose therapy with cyclophosphamide and the TEPA with autologous marrow infusion in patients with breast cancer with 10 or more positive lymph nodes.

Technical Approach: Patients will be stratified according to estrogen receptor status, age, and menopausal status. Patients will be randomized to either CAF (cyclophhosphamide, doxorubicin, 5-FU) for six cycles (28 days) followed by radiotherapy (once/day for 5 days for 5 weeks) plus tamoxifen for five years **OR** randomized to high-dose chemotherapy(cyclophosphamide 6000 mg plus ThioTEPA, 800 mgs as a continuous infusion over 96 hours) and transplant. Autologous bone marrow infusion only, peripyheral blood stem cell infusion only, or autologous bone marrow infusion plus peripheral blood stem cell infusion are all acceptable types of transplant. After infusion, either GM-CSF or G-CSF will be given at the physician's discretion (GM-CSF is highly recommended. Treatment will continue until the patient has achieved an absolute neutrophil count of 1000 cells/ul or greater on 3 consecutive days or a planned duration of 28 days of treatment. These patients will then receive radiation therapy once/day 5 days/week for 5 weeks. After the completion of all therapy, Tamoxifen will be given for 5 years. At measured times during the study a Breast Chemotherapy Questionnaire (BCQ) will be completed to separately document the changes in psychosocial function that occur on the two regimens.

Progress: One patient has been entered in this studdy.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 92/053 **Status**: Completed

Title: SWOG 9119: Primary Chemotherapy of Poor Prognosis Soft Tissue Sarcomas, Phase II

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; LTC Luke M. Stapleton, MC; MAJ Paul C. Sowray, MC; MAJ Patrick L. Gomez, MC; LTC Robert B. Ellis, MC; LTC Robert L. Sheffler, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/03/1992	Mar 95	10/17/1997

Study Objective: To evaluate, in patients with high grade soft tissue sarcoma of the extremity, the trunk, or the head and neck, the efficacy of primary chemotherapy, wide surgical resection, adjuvant chemotherapy, and radiotherapy on local control, metastasis free survival, and overall survival; To evaluate the utility of tumor response to primary chemotherapy as an indicator of local and systemic disease control in high grade soft tissue sarcoma; and to evaluate the toxicity of primary chemotherapy, surgery, adjuvant chemotherapy, and radiation therapy in this patient population. Secondary objectives include those listed for SWOG 9136, a companion protocol studying biologic parameters.

Technical Approach: Patients with a high grade soft tissue sarcoma of the extremity, trunk, or head and neck area are eligible. Patients will receive chemotherapy using the drugs adriamycin, DTIC, and ifosfamide, given concurrently for three cycles at 21 day intervals. Patients will then undergo wide surgical excision of the primary tumor. Following recovery from surgery, patients with partial or complete response or stable disease will receive another three courses of therapy, followed four weeks after completion of chemotherapy by radiation therapy to the whole area (days 1-5 for 6-8 weeks).

Progress: No patients have entered this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 92/017 **Status**: Ongoing

Title: SWOG 9125: A Phase II Trial of CVAD/Verapamil/Quinine for Treatment of Non-Hodgkin's Lymphoma

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Paul C. Sowray, MC; LTC Luke M. Stapleton, MC; MAJ Patrick L. Gomez, MC; LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; CPT Jennifer L. Cadiz, MC; MAJ James S. D. Hu, MC

Start Date:	Est. Completion Date:	Periodic Review:
12/06/1991	Oct 92	10/17/1997

Study Objective: 1) To evaluate the effectiveness of the CVAD chemotherapy regimen (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) when administered in combination with chemosensitizers (verapamil and quinine) which are intended to block the emergence of multidrug resistance in previously untreated patients with intermediate and high grade non-Hodgkin's lymphoma. The effectiveness of CVAD plus verapamil and quinine will be based on the estimate of the complete response rate and the time to treatment failure. 2) To assess the toxicities and side effects associated with the CVAD regimen when combined with verapamil and quinine. Secondary objectives are to further investigate the utility of the proliferative rate (determined by Ki-67 monoclonal antibody), the importance of cell-cell recognition molecules, the role of host response, and the value of detectable levels of p_glycoprotein as prognostic indicators of outcome in conjunction with companion study SWOG 8819; and to further utilize the central serum repository enabling clinicopathologic correlations with the results of studies on the material collected (see companion study SWOG 8947).

Technical Approach: Currently, regardless of the regimen used, 30 to 60% of advanced stage non-Hodgkin's lymphoma patients will relapse and the emergence of clinical drug resistance is a significant problem in these patients. In this study, patients will receive oral verapamil and quinine on days 1-6 as chemosensitizers. They have been shown to reverse the multidrug resistance associated with P-glycoprotein. Starting on day 2, patients will receive a continuous infusion of Adriamycin and vincristine for four days, Cytoxan will be given IV on Day 2 and oral decadron will be given days 2-5. Patients with documented progressive disease at any time will be taken off protocol treatment. Patients with stable disease will receive 2 courses (6 weeks) of chemotherapy. Patients responding to treatment will receive a maximum of 8 courses of chemotherapy. Patients will be restaged upon completion of the treatment program to assess response, with a complete laboratory and radiographic evaluation one month after the completion of therapy. All patients will be followed until death.

Progress: This study was closed to patient entry 15 Feb 93. Two patients were enrolled in previous years and are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/154 **Status**: Completed

Title: SWOG 9126: A Controlled Trial of Cyclosporine as a Chemotherapy-Resistance Modifier in High Risk Acute Myelogenous Leukemia, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; MAJ Timothy P. Rearden, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; CPT Diana S. Willadsen, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	Est. Completion Date:	Periodic Review:
08/06/1993	Sep 94	10/17/1997

Study Objective: 1) To compare the complete remission rate and duration of survival in patients with high-risk AML when treated with either chemotherapy (Ara-C/Daunomycin) alone or chemotherapy plus the resistance modifier cyclosporine-A (CyA). 2) To estimate the frequency of p-glycoprotein expression and the correlation with prognosis in patients with relapsed AML, primarily refractory AML, and secondary AML.

Technical Approach: Patients will be randomized to receive either high-dose Ara-C3 g/m^2/d on days 1-5 and daunorubicin 45 mg/m^2/d on days 6-8, a standard induction regimen for poor-prognosis AML or the same therapy plus cyclosporine A. The cyclosporine A will be given as a loading dose of 6.0 mg/kg IV over 2 hours on day 6 starting 8 hours before the daunorubicin, then 4.0 mg/kg over the next 6 hrs, then 16 mg/kg continuous 24 hr infusion beginning concurrently with the daunorubicin on days 6-8. Bone marrow aspirate and biopsy should be performed on day 14 of induction. Subsequent marrow evaluations should be performed every 7 - 14 days to assess response and recovery period to the next course of chemotherapy.

Patients achieving remission will go on to consolidation. Therapy will consist of the same drugs and dosages except ARA-C will be given on days 1-3 and daunomycin on days 4-6. Cyclosporine A will be given on days 4 - 6 as outlined above. No additional protocol directed treatment will be conducted after consolidation.

Progress: One patient was enrolled in this study at MAMC in FY93 and one patient in FY 94. Both are now deceased.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/097 **Status**: Ongoing

Title: SWOG 9133: Randomized Trial of Subtotal Nodal Irradiation versus Doxorubicin Plus Vinblastine and Subtotal Nodal Irradiation for Stage I-IIA Hodgkin's Disease, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Mark E. Robson, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/06/1994	Sep 01	09/15/1998

Study Objective: The main objective of this study is to compare progression-free and overall survivals of clinically stage (non-laparotomized) patients with early stage (IA,IIA), good-prognosis Hodgkin's Disease treated with either standard subtotal nodal irradiation or with short-course chemotherapy plus standard irradiation. In addition, the study will attempt to identify subgroups of patients who may do better with one approach or the other, and to follow patients for long-term toxicities associated with either regimen.

Technical Approach: Patients will be clinically staged by standard methods and then, if they appear to have localized, good-prognosis disease, they will be randomized to receive either standard radiotherapy to mantle and para-aortic fields (subtotal nodal irradiation) or three cycles (6 doses) of chemotherapy followed by the same radiotherapy. Management of both patient groups will be identical apart from the chemotherapy.

Progress: Two patients were enrolled in this study, both in FY 94, and continue to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 92/056 **Status**: Completed

Title: SWOG 9136: Biologic Parameters in Soft Tissue Sarcomas: A Companion Study to Select Southwest Oncology Group Clinical Trials with Soft Tissue Sarcoma Patients

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; LTC Luke M. Stapleton, MC; MAJ Paul C. Sowray, MC; MAJ Patrick L. Gomez, MC; LTC Robert B. Ellis, MC; LTC Robert L. Sheffler, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; MAJ George F. Hodeges, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/03/1992	Mar 95	10/17/1997

Study Objective: 1) To develop a cooperative group mechanism to study biologic parameters of soft-tissue sarcomas in patients entered onto companion SWOG protocols (see SWOG 9119). 2) To determine cellular DNA content parameters (DNA CCP) (DNA Ploidy, S-Phase Fraction) of soft tissue sarcomas and to evaluate the effect of these parameters on disease free survival and overall survival. To study the changes in DNA CCP as a result of chemotherapy, and the relationship of these changes to prognosis in patients with soft tissue sarcoma. 3) To characterize cytogenetic aberrations of soft-tissue sarcomas in the study population. To evaluate the relationship of defined cytogenetic abnormalities to prognosis. 4) To estimate the level of expression of the multi-drug resistant (MDR) phenotype in untreated soft-tissue sarcoma, and the effect of chemotherapy treatment on the expression of MDR. To evaluate the impact of MDR expression on response to chemotherapy, disease free survival, and overall survival. 5) To provide a repository of frozen tissue for future molecular studies in this group of patients.

Technical Approach: As a companion protocol to SWOG 9119 (adjuvant soft-tissue sarcoma trial), DNA CCP, tumor karyotypes, and estimation of the expression of the MDR phenotype of sarcomas entered onto trial will be done.

Progress: No patients have entered this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/042 **Status**: Ongoing

Title: SWOG 9201 (RTOG 91-11): Phase III Trial to Preserve the Larynx: Induction Chemotherapy and Radiation Therapy versus Concomitant Chemotherapy and Radiation Therapy Versus Radiation

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.; LTC Steven S. Wilson, MC; MAJ Nyun C. Han, MC; MAJ Mark E. Shaves, MC; CPT Brent L. Kane, MC

Start Date:	Est. Completion Date:	Periodic Review:
12/19/1996	Nov 00	09/15/1998

Study Objective: The normal treatment of cancer of the throat is surgery with removal of the voice box. The purpose of this study is to try to preserve the larynx by using a non-surgical treatment. Three treatments will be compared: 1) chemotherapy followed by radiation, or 2) chemotherapy given at the same time as radiation, or 3) radiation alone.

Technical Approach: Treatment 1: Cisplatin and 5-FU will be given twice 3 weeks apart. Treatment 2: Cisplatin will be given once every 21 days (for three doses on Days 1, 22, and 43) during radiation which is given once a day, 5 days a week for 7 weeks. Radiation can be given on an outpatient basis. Cisplatin is given into the vein over 20-30 minutes. 5-FU is given into the vein by continuous infusion over 120 hours following cisplatin administration in Treatment 1.

Progress: No patients have entered this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/097 **Status**: Ongoing

Title: SWOG 9205: Central Prostate Cancer Serum Repository Protocol

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Robert L. Sheffler, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Timothy P. Rearden, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/07/1993	Mar 95	09/15/1998

Study Objective: 1) To store serum of patients with confirmed adenocarcinoma of the prostate entered onto clinical trials conducted by the SWOG Genitourinary Committee. 2) To provide the serum of the above patients entered onto SWOG studies for specific clinical-laboratory investigations outlined on separate SWOG protocols approved by the Genitourinary Committee Tumor Biology Subcommittee.

Technical Approach: This serum bank is to provide the opportunity for study of new or existing markers or other tests in a prospective or retrospective fashion, in order to test their usefulness as diagnostic or management tools in prostate cancer at all stages. Specific information regarding the nature of individual tests to be conducted on the serum samples of these patients will be described in individual protocols.

All serum samples (approx. 3 - 5 cc) will be collected from patients in the frequency and timing indicated on specific protocols. Samples will be spun 15 minutes after collection and stored at a minimum of -20°C. Samples will be frozen and shipped to the Serum Bank Coordinator.

Progress: No new patients were enrolled in FY 98. Four patients were enrolled in previous years. Two patients have expired and two are being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/115 **Status**: Ongoing

Title: SWOG 9208: Health Status and Quality of Life in Patients With Early Stage Hodgkin's Disease: A Companion Study to SWOG 9133

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ James S. D. Hu, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/03/1994	Jun 98	09/15/1998

Study Objective: 1) 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. 2) To describe the short-term, acute effects of two treatments for early stage Hodgkin's Disease patients on patient report of symptoms and on patient QOL. 3) To evaluate the intermediate and long-term effects of two treatments for early stage Hodgkin's Disease patients on patient QOL over five years.

Technical Approach: Patients enrolled in the companion protocol, SWOG-9133, will be asked to complete questionnaires before registration into this study, at 6 months; and annually for seven years. These questionnaires seek to identify and quantitate those differences pertaining to quality of life issues that the added chemotherapy may have in early stage Hodgkin's disease patients.

Progress: No patients have been enrolled in this study.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/107 **Status**: Completed

Title: SWOG 9210: A Phase III Randomized Trial of Combination Therapy for Multiple Myeloma Comparison of (1) VAD-P to VAD-P/Quinine for Induction; (2) Randomization of Prednisone Dose Intensity for Remission Maintenance

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; MAJ James S. D. Hu, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/07/1993	May 98	10/17/1997

Study Objective: 1) To compare the effectiveness of the VAD-P chemotherapy regimen when administered alone or in combination with the chemosensitizer quinine intended to block the emergence of multidrug resistance during remission induction in previously untreated patients with multiple myeloma. 2) To evaluate the chemosensitizing potential of quinine to reverse drug resistance in myeloma patients randomized to VAD-P induction who fail to achieve at least 25% regression with chemotherapy alone. 3) To compare the value of alternate day prednisone 10 mg versus 50 mg for remission maintenance for patients proven to achieve at least 25% regression.

Technical Approach: Patients with proven multiple myeloma (all stages) who have not received prior chemotherapy are eligible for participation in this trial. A dynamic allocation scheme will be used to randomize patients to one of the two induction treatment arms. INDUCTION: ARM I patients will receive Vincristine 0.4 mg IV q.d. on days 1-4, Doxorubicin 9 mg/m^2 q.d. IV on days 1-4, Dexamethasone 40 mg q.d. PO on days 1-4, and Prednisone 50 mg Q.O.D. on days 9, 11, 13, 15, 17, and 19. This cycle will be repeated Q 21 days for a minimum of 6 to 8 cycles (6 months) or a maximum of 17 cycles (12 months). Patients who fail to achieve = 25% tumor regression after 12 months of treatment on Arm I (VAD-P) or relapse or progress on Arm I, will be eligible for crossover to VAD-P/Q. ARM II and Crossover schedule patients will receive VAD-P as outlined above on days 2-5 and will also receive Quinine 400 mg t.i.d. on days 1-6 (VAD-P/Q). Patients with = 25% tumor regression after 9 to 12 months of induction therapy or patients who achieve = 50% tumor regression after 6 months of induction therapy will be randomized to either of two maintenance regimens. If, in the judgement of the physician the patient will continue to benefit from induction therapy, they may continue up to 12 months. MAINTENANCE: ARM III patients will receive Prednisone, 10 mg Q.O.D., until relapse and ARM IV patients will receive Prednisone 50 mg Q.O.D. until relapse.

Progress: One patient was enrolled in FY 94 and died of his disease 9/30/97.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/010 **Status**: Ongoing

Title: SWOG 9217: Chemoprevention of Prostate Cancer with Finasteride (Proscar), Phase III, Intergroup

Principal Investigator: MAJ Raymond S. Lance, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC

Start Date:	Est. Completion Date:	Periodic Review:
10/01/1993	Nov 03	09/15/1998

Study Objective: The primary objective of this trial will be to determine if finasteride can reduce the development of prostatic cancer in males 55 years and older.

Technical Approach: Men who have attained 55 years of age have never been diagnosed as having prostatic cancer will be randomized to receive Finasteride 5 mg or Matched Placebo PO daily for 7 years. Patients will be followed with clinic visits at 6 months, 1 year and then annually. Annual laboratory screening will include PSA. Triggers are in place to initiate prostatic biopsies. The final endpoint is biopsy proven presence/absence of carcinoma of the prostate after seven years.

Progress: Approximately 50 patients have been enrolled in this study and continue to receive treatment. The protocol has been closed to patient entry.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/023 **Status**: Ongoing

Title: SWOG 9219: A Phase II Evaluation of Interleukin-4 (IL-4) in Patients With Non-Hodgkin's Lymphoma or Hodgkin's Disease

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ James S. D. Hu, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/18/1994	Nov 98	09/15/1998

Study Objective: 1) To assess the response rate of refractory low grade non-Hodgkin's lymphoma, refractory intermediate or high grade non-Hodgkin's lymphoma and refractory Hodgkin's disease treated with interleukin-4, and 2) to assess the qualitative and quantitative toxicities of interleukin-4 administered in a Phase II study.

Technical Approach: Following pretreatment with acetaminophen (650 mg PO) to prevent chills and fever, patients will receive a subcutaneous injection of interleukin-4 (at an initial dose of 3 ug/kg daily for 28 days). Patients must be observed in a medical facility for at least 2 hours after the first 2 daily injections. If no significant side effects occur the patient or family member will be instructed on how to administer subsequent injections at home. Patients will be reevaluated after 28 days with a possible rest period of one or two weeks between 28 day cycles of this treatment.

Progress: No patients have been enrolled at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/136 **Status**: Ongoing

Title: SWOG 9221, MDACC ID 91-025, INT-191-001: Phase III Double-Blind Randomized Trial of 13-Cis Retinoic Acid (13-cRA) to Prevent Second Primary Tumors (SPTs) in Stage I Non-Small Cell Lung Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; LTC Robert D. Vallion, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; MAJ Timothy P. Rearden, MC; CPT Diana S. Willadsen, MC

Start Date:	Est. Completion Date:	Periodic Review:
07/02/1993	Jul 98	09/15/1998

Study Objective: To evaluate: (1) the efficacy of 13-cis-retinoic acid (13-cRA) in reducing the incidence of SPTs in patients who have been treated for Stage I non-small cell lung cancer with complete surgical resection; (2) the qualitative and quantitative toxicity of 13-cRA in a daily administration schedule; and (3) compare the overall survival of patients treated with 13-cRA vs. patients treated with placebo.

Technical Approach: Patients enrolling into this study will be stratified according to histology, T stage and smoking status then registered into a Single-Blind, 8 week run-in period to test compliance. All patients will receive placebo during this period. After Run-in the patients will be randomized into a double-blind trial to receive 13-cRA (30 mg p.o./d x 3 yrs vs. Placebo (30 mg p.o./d x 3 yrs). Each group will have a 4 year follow-up period.

The final analysis will be undertaken shortly after seven years. The primary hypothesis for the study is whether 13-cRA lowered the rate of second primary tumors (SPT). All patients randomized will be grouped according to the assigned treatment. Patients who are either purely lost to follow up or died without a SPT occurring will be included in the actuarial analysis with a censored status on the last day of contact. The primary hypothesis of treatment benefit will be tested using the proportional hazards model.

Progress: Ten patients have been enrolled in this study (none in FY 98). Two expired in FY 96, and one has been permanently transferred to Keesler AFB. Seven are still being followed at MAMC

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/108 **Status**: Ongoing

Title: SWOG 9237: Evaluation of Topotecan in Refractory and Relapsing Multiple Myeloma

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ James S. D. Hu, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/07/1993	May 98	10/17/1997

Study Objective: 1) To evaluate the response rate for refractory myeloma treated with topotecan; 2) To evaluate the qualitative and quantitative toxicities of topotecan administered in a Phase II study; 3) To measure topoisomerase levels in multiple myeloma cells.

Technical Approach: Patients with proven multiple myeloma, with protein criteria present, who have received exactly one prior regimen, and have shown, in the opinion of the investigator, to have disease progression are eligible for this study. All patients will receive topotecan 1.25 mg/m^2 q.d. IV over 30 minutes on days 1-5 repeated q 21 days. This schedule will continue as long as patients show complete remission, partial remission or stable disease and toxicity is acceptable. Topotecan dosage can be adjusted on nadir counts of the preceding cycle.

It is assumed that topotecan will be of interest if a true response rate of 20% or more is achieved in the treatment of patients with relapsed or refractory multiple myeloma.

Progress: This study closed to patient accrual 1 Feb 95. One patient was entered in this study in FY93 and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/092 **Status**: Ongoing

Title: SWOG 9245: Central Lymphoma Repository Tissue Procurement Protocol for Relapse or Recurrent Disease

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Mark E. Robson, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; CPT Diana S. Willadsen, MC; LTC Robert D. Vallion, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
04/02/1993	May 95	09/15/1998

Study Objective: 1. To acquire fresh snap-frozen lymphoma tissue from patients who relapse or have recurrent disease after being treated on Southwest Oncology Group treatment protocols. 2. To establish a standard set of procedures for routine acquisition, banking, and study of lymphoma tissues within the cooperative group. 3. To use the repository tissue to establish clinical correlations via presently activated phenotyping studies and future projected molecular studies assessing specimen DNA and RNA status. 4. To examine the biology of therapy failure in relationship to changes in pretreatment and post-therapy iummunophenotypic data.

Technical Approach: Fresh frozen tissues will be acquired from relapsed patients for basic science protocols, both current and future, designed to better define the biology of relapsed non-Hodgkin's lymphoma. This is not a treatment protocol, nor will results be used to guide treatment decisions.

Fresh biopsies (from any organ site) will be snap-frozen and submitted with one stained (Hematoxylin and Eosin) histologic section with accompanying pathology report to The Department of Pathology at the University of Arizona in Tucson.

Progress: No patients have entered this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/161 **Status**: Ongoing

Title: SWOG 9250 (INT-0136): Phase III Intergroup Prospectively Randomized Trial of Perioperative 5-FU After Curative Resection, Followed by 5-FU/Levamisole for Patients With Colon Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; LTC Robert B. Ellis, MC; MAJ Timothy P. Rearden, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/21/1994	Sep 98	09/15/1998

Study Objective: To determine if (1) adjuvant therapy with one week of continuous 5-FU given within 24 hours of a curative colon resection followed by 12 months of 5-FU/Levamisole is effective in prolonging the disease free interval and increasing survival in patients who are treated with 5-FU/Levamisole only. Endpoints include: treatment failure - as described by recurrence of local/regional or distant metastases - and survival. (2) To establish within ECOG a Central Tissue Repository for paraffin blocks and a frozen tissue bank.

Technical Approach: Patients with primary colon cancer will be randomized to either receive 7 days of continuous intravenous 5-fluorouracil (5-FU) within 24 hours completion of colon surgery or not to receive any perioperative chemotherapy.

The only investigational part of this protocol is the administration of chemo-therapy during the period right after subjects colon operation. The operation and the use of 5-FU/levamisole are all standard treatment.

Progress: No patients have been enrolled at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/073 **Status**: Ongoing

Title: SWOG 9300: A Randomized Phase II Evaluation of All Trans-Retinoic Acid (ATRA) with Interferon-Alfa 2a (IFN-alfa 2a) or All Trans-Retinoic Acid with Hydroxyurea (HU) in Patients with Newly Diagnosed Chronic Myelogenous Leukemia in Chronic Phase

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Mark E. Robson, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	Est. Completion Date:	Periodic Review:
03/04/1994	Mar 94	10/17/1997

Study Objective: 1). To estimate whether treatment of Chronic Myelogeneous Leukemia (CML), with all-transretinoic acid in combination with either hydroxyurea or interferon alfa-2a is sufficiently effective based on either hematologic or cytogenetic response, to justify its investigation in phase III trials. 2). To assess the toxicities associated with all-transretinoic acid plus hydroxyurea or interferon alfa-2a in chronic phase CML.

Technical Approach: Patients qualifying for this study will be stratified by age (< 45 vs >=45), splenomegaly (present vs absent), prior hydroxyurea (yes or no), and ANC at diagnosis (<50,000 ul). Patients will then be randomized to one of two treatment arms as follows: Arm I: ATRA and HU or Arm II: ATRA and IFN. This randomization will be dynamically balanced to assure roughly equal numbers of patients within levels of the stratifying factors.

All patients in both arms will begin treatment with HU to control or keep the WBC <= 20,000/ul and platelets <=800,000/ul. All therapy will include allopurinol. Patients will receive this HUS treatment for a minimum of 21 days and a maximum of 42 days. Patients with WVA <= 20,000/ul, platelets <=800,00/ul, and no evidence of progressive splenomegaly after 21 - 42 days of HU will then begin treatment on their assigned regimens. Patients who do not achieve a WBC <= 20,000/ul, platelets <=800,000/ul, and absence of progressive splenomegaly after 42 days will be removed from protocol treatment.

Arm I patients will receive ATRA 150/mg/m^2/d x 7 days followed by 7 days rest and HU 500 mg qd adjusted to maintain WBC and platelets to predefined levels.

Arm II patients will receive acetaminophen 650 mg 1/2 hr before administration of IFN initiated a 3 MIU/m^2/d 5 days/week escalated by 1 MIU/m^2 each week to a maximum of 5 MIU/m^{2}day/ and ATRA 150 mg/m^2/d x 7 days followed by 7 days rest.

Treatment regimens will continue until the onset of accelerated or blast phase or relapse from CR or PR. Bone marrow aspiration and biopsy to monitor disease status are required at 3 and 6 months and every 6 months thereafter. Serial blood and urine specimens will be obtained for laboratory analysis.

Progress: No patients have been enrolled in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 93/166 **Status**: Ongoing

Title: SWOG 9303: Phase III Study of Radiation Therapy, Levamisole, and 5-Fluorouracil versus 5-Fluorouracil and Levamisole in Selected Patients With Completely Resected Colon Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; MAJ Timothy P. Rearden, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/03/1993	Oct 98	10/17/1997

Study Objective: To determine whether 5-FU, levamisole and radiation therapy results in superior overall survival when compared to 5-FU and levamisole without radiation therapy in the management of patients with completely resected pathologic stage T4BN0-2 colon cancer and selected patients with T3N1-2 colon cancer.

Technical Approach: This randomization clinical trial will compare radiation therapy, 5FU and levamisole with 5FU and levamisole in patients with completely resected colon cancer at high risk for local-regional recurrence and limited risk for system disease.

We will compare 5FU and levamisole, as delivered in the prior intergroup study, with one month of 5FU and levamisole followed by 5-5 1/2 weeks of 5FU, levamisole, and local-regional RT (45-50.4 Gy in 25-28 fractions), followed by 43 weeks of 5FU and levamisole.

Progress: This study was closed to patient entry, 17 Dec 96. One patient has been enrolled in this study at MAMC in FY95 and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/111 **Status**: Ongoing

Title: SWOG 9304: Postoperative Evaluation of 5-FU by Bolus Injection vs 5-FU by Prolonged Venous Infusion Prior to and Following Combined Prolonged Venous + Pelvic XRT vs Bolus 5-FU +Leucovorin + Levamisole Prior to and Following Combined Pelvic XRT + Bolus 5-FU + Leucovorin in Patients with Rectal Cancer, Phase III Intergroup

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Timothy P. Rearden, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	Est. Completion Date:	Periodic Review:
05/06/1994	May 98	09/15/1998

Study Objective: 1) To compare the effectiveness of 5-FU by bolus injection vs. 5-FU by prolonged venous infusion given prior to and following combined pelvic x-ray (XRT) therapy + protracted venous infusion (PVI) vs. 5-FU by bolus injection plus LV plus LEV given prior to and following combined pelvic XRT plus bolus 5-FU plus LV in the treatment of modified Aster-Coller Stages B2, B3 and C rectal cancer. This will be evaluated in terms of survival and relapse-free survival.
2) To obtain descriptive information regarding relapse patterns and tolerance.

Technical Approach: Patients entering this study will be randomized to one of three treatment arms. Patients in all arms will receive pelvic radiotherapy. Those randomized to Arms A and B will receive concomitant 5-FU by PVI (225 mg/m²/d) during radiotherapy. Each patient will be randomly allocated to receive 5-FU +- LV and levamisole for 2 months prior to and for 2 months following combined chemo-radiotherapy. Patients will be randomized to chemotherapy prior to and following chemo-radiotherapy as follows:
a. Arm A: bolus IV injection of 5-FU alone
b. Arm B: protracted venous infusion of 5-FU alone
c. Arm C: bolus 5-FU + LV + levamisole before and after pelvic radio therapy; bolus 5-FU + LV during pelvic radiotherapy.

After completion of all therapy patients will be followed every 4 months X 2 years, then every 6 months X 4 years.

Progress: Three patients have been enrolled in this study at MAMC. One patient expired in FY 96, two continue to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/170 **Status**: Ongoing

Title: SWOG 9313: Phase III Comparison of Adjuvant Chemotherapy With High-Dose Cyclophosphamide + Doxorubicin vs Sequential Doxorubicin Followed by Cyclophosphamide in High-Risk Breast. with 0-3 Positive Nodes

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; LTC Robert B. Ellis, MC; MAJ Timothy P. Rearden, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/21/1994	Sep 98	09/15/1998

Study Objective: 1) To compare disease-free survival, overall survival, and toxicity of high-risk primary breast cancer patients with negative axillary lymph nodes or with one to three positive nodes treated with adjuvant high-dose chemotherapy with doxorubicin plus cyclophosphamide, versus high-dose sequential chemotherapy with doxorubicin followed by cyclophosphamide. 2) To obtain tumor tissue for biologic studies.

Technical Approach: Women with primary breast invasive adenocarcinoma, will be randomized to one of two treatments: 1) High dose doxorubicin + cyclophosphamide x 6 cycles, or 2) High dose sequential doxorubicin x 4 cycles, followed by high dose cyclophosphamide x 3. Women who are postmenopausal and have receptor + will receive Tamoxifen for 5 years.

Progress: The protocol was closed to patient entry, 15 Apr 97. One patient has been enrolled in this study at MAMC and is being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/107 **Status**: Ongoing

Title: SWOG 9321: Standard Dose Versus Myeloablative Therapy for Previously Untreated Symptomatic Multiple Myeloma, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ James S. D. Hu, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/06/1994	May 98	09/15/1998

Study Objective: 1. To perform a randomized trial, in newly diagnosed patients with symptomatic multiple myeloma (MM), of standard therapy versus myeloablative therapy, in order to examine whether the greater tumor cytoreduction effected by intensive therapy and manifested by higher incidence of complete remission translates into extended overall survival and progression-free survival.
2. To randomize responding patients with >= 75% tumor cytoreduction to interferon-alpha 2b (IFN) versus no maintenance in order to evaluate the role of IFN in MM.

Technical Approach: Symptomatic patients of all stages of multiple myeloma with reasonable performance status will be randomized to high dose chemotherapy with autologous bone marrow transplant or standard VBMCP combination chemotherapy after induction VAD therapy. A required peripheral stem cell harvest will be done for those randomized to the ABMT arm for future high dose therapy if failure occurs. This will be an option for those randomized to the standard arm. Those patients that have an HLA compatible sibling donor will be eligible for allogeneic BMT. A second randomization will be done for those with continued greater than 75 percent regression of disease in the ABMT or standard chemotherapy arm while those receiving allo-BMT will be continued on GVHD prophylaxis.

Progress: No patients have been enrolled in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/116 **Status**: Completed

Title: SWOG 9327: Randomized Phase II Pilot Study of Pentoxifylline (Trental) and Placebo in Patients with Metastatic Malignancy and Anorexia/Cachexia Syndrome

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:	Est. Completion Date:	Periodic Review:
05/17/1996	May 99	10/17/1997

Study Objective: 1) To evaluate the effect of pentoxifylline on the quality of life in patients with anorexia/cachexia syndrome related to malignancy; 2) to evaluate the effect of pentoxifylline on the nutritional status of patients with cancer cachexia and on various laboratory measurements of nutritional status; and 3) to assess the feasibility of accruing patients with cancer cachexia in a cooperative group setting.

Technical Approach: The Anorexia/Cachexia Syndrome is a well known entity in patients with metastatic cancer. The mechanism of this entity is felt to be mediated by several factors including cytokine release. Tumor necrosis factor is directly involved in suppressing anabolic enzymes as well as inducing inflammatory and pyrogenic effects by the body. These are all felt to be related to the above syndrome. Pentoxifylline, a TNF inhibitor, has been used in the past for vascular diseases and is well tolerated and will be used in this study to see if any improvement in the anorexia/cachexia syndrome occurs. The end points will be measured by a quality of life questionnaire for both anorexia and fatigue.

Progress: No patients have been entered in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/058 **Status**: Ongoing

Title: SWOG 9331 (E2192): Outcome Prediction by Histologic Grading in EST 1180 (SWOG 8294), Ancillary

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Timothy P. Rearden, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
02/04/1994	Nov 03	02/20/1998

Study Objective: 1) To evaluate the reproducibility of a combined histopathologic grading system of breast cancer. 2) To evaluate the ability of the grading system to predict time to treatment relapse (TTR) and survival. 3) To use multivariate analyses to evaluate the prognostic importance of the grading data relative to the other clinical and biological factors determined as part of SWOG 8294.

Technical Approach: This is a pathology study utilizing the patient set from SWOG 8294. Patients reviewed as part of that study (where cases with adequate specimens for flow cytometry were evaluated and provisionally graded) will be registered to this study. Slides will be reviewed by three investigators and cases will be grouped into 3 prognostic categories. The power calculation for testing the association of this grading system with survival will be based on the "2 degree of freedom" log rank test. The Cox proportional hazards model will also be used in the analysis to adjust the comparisons for effects of other factors.

Progress: This study closed to patient accrual 5 Oct 95. Seven patients were enrolled in this study in FY 94 and all are still being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/147 **Status**: Ongoing

Title: SWOG 9333: A Randomized Controlled Trial of Mitoxantrone & Etoposide vs Daunomycin & Cytosine Arabinoside as Induction Therapy in Patients Over Age 55 with Previously Untreated Acute Myeloid Leukemia

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/16/1995	Jun 99	06/19/1998

Study Objective: To compare the complete remission (CR) rate, duration of survival and duration of relapse-free survival (time for CR until relapse or death) for patients aged 56 or older with acute myeloid leukemia (AML) treated with daunomycin (daunorubicin, DNR) and cytosine arabinoside (Ara-C) or with mitoxantrone (Mito) and etoposide. To assess the frequency and severity of toxicities and the durations of neutropenia, thrombocytopenia, and first hospitalization associated with the two induction chemotherapy regimens.

Technical Approach: Acute myelogenous leukemia in the elderly population is usually a fatal disease. Although complete remission rates are about 40-60% with standard chemotherapy induction, relapse rates are high and morbid and sometimes fatal toxicities will occur. This multi-center study aims to improve the remission rate and toxicity profile of induction chemotherapy for AML in the elderly using mitoxantrone and VP-16 and comparing it to standard daunorubicin and Ara-C followed by standard consolidation. Colony stimulating factors with GM-CSF will be given prophylactically as well as prophylactic antibiotics with Fluconazole, Ciprofloxacin, and Acyclovir. We expect 3-4 subjects per year and the entire multi-center recruitment is projected to be 100 per year.

Progress: No patients have been enrolled in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/121 **Status**: Ongoing

Title: SWOG 9336: A Phase III Comparison Between Concurrent Chemotherapy Plus Radiotherapy, and Concurrent Chemotherapy Plus Radiotherapy Followed by Surgical Resection for Stage IIIA (N2) Non-Small Cell Lung Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): COL Daniel G. Cavanaugh, MC; COL Walter G. Graves, MC; LTC Maceo Braxton Jr, MC; LTC Blaine R. Heric, MC; MAJ Rahul N. Dewan, MC; LTC Steven S. Wilson, MC; MAJ Nyun C. Han, MC; LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; LTC Robert D. Vallion, MC; MAJ Patrick L. Gomez, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/03/1994	Jun 98	09/15/1998

Study Objective: 1) Access whether concurrent chemotherapy and radiotherapy followed by surgical resection results in a significant improvement in progression-free, median, and long-term (2 year, 5 year)s survival compared to the same chemotherapy plus standard radiotherapy alone for patients with stage IIIa (N2-positive) non-small cell lung cancer.
2) Evaluate the patterns of local and distant failure for patients enrolled in each arm of the study, in order to assess the impact of the therapy on local control and distant metastases.
3) To obtain exploratory descriptive information on the relationship of tobacco use, alcohol use and dietary patterns on toxicity and outcomes in males and females.

Technical Approach: Patients with biopsy-proven Stage IIIa Non-Small Cell carcinoma will be randomized to one of two arms. Arm I and II patients will receive Induction Radiotherapy (45 Gy + concurrent induction chemotherapy (CT) of Cisplatin 50 mg/m^2 IVPB days 1, 8, 29, 36 and VP-16 50 mg/m^2 IVPB, days 1-5, 29-33. Arm I patients will be re-evaluated 2-4 weeks after completion of induction and Arm II will be re-evaluated 7 days before completion of induction. All patients, after re-evaluation, will proceed to Registration 2. If there is no evidence of local progression or distant metastases patients will be assigned options 3 or 4 (Arm I) or option 5 (Arm II. Option 3 consists of surgery plus 2 additional cycles CT starting 4-6 weeks postoperatively, Option 4 of 2 additional cycles CT at least 3 weeks after cycle 2 and Option 5 of continuing RT with no break and beginning 2 additional cycles of CT 3 weeks after cycle 2, day 8. RT boost field will be planned by CT scan. The major endpoints will be median, 2-year and 5- year progression-free and overall survival. Evaluation of patterns of relapse is a secondary endpoint.

Progress: Two patients were enrolled in this study (FY 95). Both patients are now deceased.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/012 **Status**: Completed

Title: SWOG 9347: Phase III Comparison of Tamoxifen versus Tamoxifen with Ovarian Ablation in Premenopausal Women with Axillary Node-Negative Receptor-Positive Breast Cancer < 3cm, Intergroup

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	Est. Completion Date:	Periodic Review:
10/20/1995	Jul 99	11/21/1997

Study Objective: (1) To compare the disease-free survival, overall survival, and toxicity of treatment in hormone receptor-positive, premenopausal women with axillary lymph node-negative breast cancer measuring 3 cm or less given adjuvant therapy with tamoxifen alone, or tamoxifen with ovarian ablation. (2) To obtain tumor tissue form these patients for future biologic studies of relevance to this patient population. (3) To compare menopausal symptoms, sexual function and quality of life in patients receiving tamoxifen alone with patients receiving tamoxifen plus ovarian ablation.

Technical Approach: Studies form Scottish trials have shown significant benefit to ovarian ablation for ER receptor positive and lymph node positive breast cancer that are at least as good in terms of overall survival compared to chemotherapy. This study tries to answer this question for patients with less than 3 cm tumors, node negative, ER positive breast cancer patients who are premenopausal. The study has two arms: Tamoxifen vs. Tamoxifen and ovarian ablation. Ovarian ablation will be carried out with either surgical, hormonal or radiation treatment. End points are disease free and overall survival. In addition, tissue will be sent for biologic studies.

Progress: No patients have been enrolled in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/024 **Status**: Ongoing

Title: SWOG 9349: A Randomized Phase II Trial of CHOP with G-CSF Support or ProMACE-CytaBOM With G-CSF Support for Treatment of Non-Hodgkin's Lymphoma

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ James S. D. Hu, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
11/18/1994	Nov 98	10/17/1997

Study Objective: To evaluate the effectiveness of the dose intense CHOP chemotherapy regimen with G-CSF support and the dose intense ProMACE-CytaBOM chemotherapy regimen with G-CSF support in previously untreated patients with intermediate and high grade non-Hodgkin's lymphomas. The effectiveness of the regimens will be based on the estimate of the complete response rate, the time to treatment failure, and ultimately overall survival. To assess the toxicities and side effects associated with the regimens. Also to further utilize the central serum and tissue repositories enabling clinicopathologic correlations with the results of studies on the material collected.

Technical Approach: This study attempts to assess whether dose intense CHOP or Promace-CytaBOM with growth factor support will have any effect on improvement of standard first line therapy in non-Hodgkin's lymphoma. Ninety-eight patients will be accrued for each of the two arms. This number of patients will allow for both the complete response rate and probability of treatment failure two years after treatment to be estimated to within at most +/-0.10 for each measure. A successful outcome for either regimen is one that has a true probability of 60% or higher of patients being alive without disease at two years. No formal statistical comparisons between arms will be made.

Progress: This protocol was closed to patient entry, 1 Jan 97. Three patients were enrolled in this study in FY 96, and are being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/003 **Status**: Ongoing

Title: SWOG 9401: A Controlled Phase III Evaluation of 5-FU Combined with Levamisole and Leucovorin as Surgical Adjuvant Treatment Following Total Gross Resection of Metastatic Colorectal Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	Est. Completion Date:	Periodic Review:
10/21/1994	Oct 98	10/17/1997

Study Objective: To determine in patients who have undergone complete gross surgical resection of metastatic colorectal cancer whether postoperative adjuvant chemotherapy with a new regimen of 5-fluorouracil (5-FU) plus leucovorin plus levamisole will result in improved survival compared to postoperative adjuvant chemotherapy with a standard 5-FU plus levamisole regimen.

Technical Approach: Patients will be randomly selected to treatment Arm I or treatment Arm II. Arm I consists of the standard regimen of 5-FU given by rapid intravenous infusion for 5 consecutive days, plus levamisole given by mouth three times daily for three consecutive days every other week for one year. Arm II is a new chemotherapy regimen which adds leucovorin in addition to the 5-FU and levamisole. 5-FU and leucovorin are given by rapid intravenous injection for five consecutive days every four to five weeks for one year. Levamisole is given by mouth three times per day for three days in a row every two weeks during the first two months, then every 2-3 weeks for a total of one year.

Progress: This study was closed to patient entry 10 Sep 96. One patient was enrolled in FY 96 and is being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/093 **Status**: Ongoing

Title: SWOG 9402: Phase III Intergroup Randomized Comparison of Radiation Alone vs Pre-Radiation Chemotherapy for Pure and Mixed Anaplastic Oligodendrogliomas

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; CPT Diana S. Willadsen, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/17/1995	Feb 99	09/15/1998

Study Objective: 1) overall survival 2) compare time to tumor progression between the two arms 3) the frequency of severe (= grade 3) toxicities will be examined. 4) compare quality of life and neurologic function between the two arms. 5) identify the key histopathologic criteria necessary to make the diagnosis of anaplastic oligodendroglioma and mix oligo-astrocytoma; evaluate the diagnostic and prognostic relevance of chromosomal alterations; evaluate the diagnostic and prognostic relevance of DNA ploidy and indices of proliferation including percent S and percent G2M; study the diagnostic and prognostic relevance of immunohistochemical markers of cellular function and/or glial development; and evaluate the transnational relevance of tumor suppressor genes and oncogenes.

Technical Approach: This is a non-blinded randomized intergroup study and is different from other randomized trials for malignant glioma in three respects. First, it will evaluate the role of adjuvant chemotherapy in a recognizable subset of patients with malignant glioma, those with oligodendroglial differentiation. Second, the RT treatment volume will be based on a postoperative pre-randomization MR image, rather than the customary preoperative diagnostic CT or MR. Third, in the experimental arm of this study, chemotherapy will be given prior to RT. Patients whose tumors progress on chemotherapy will proceed to RT immediately. There will be a central pathology review prior to randomization, central radiology review to assess response to PCV and to substantiate tumor progression, and a quality of life assessment (QLA) to document the acute and chronic toxicities of chemotherapy and radiation including effects on cognitive function. Surgery and radiotherapy ± PCV may adversely affect a patient's physical and emotional functioning. The Karnofsky performance status (KPS) will measure physical well-being. To complement KPS, the Mini-Mental Status exam (MMSE) will be administered to patients to assess cognitive ability. Assessment of differences in quantitative survival will be performed between the two therapeutic regimens supplemented with qualitative survival by the assessment of KPS, MMSE, and QLA.

Progress: No patients have been enrolled in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/163 **Status**: Ongoing

Title: SWOG 9410 (INT 0148): Doxorubicin Dose Escalation, With or Without Taxol, As Part of the CA Adjuvant Chemotherapy Regimen for Node Positive Breast Cancer: A Phase III Intergroup Study

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; LTC Robert B. Ellis, MC; MAJ Timothy P. Rearden, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/21/1994	Sep 98	09/15/1998

Study Objective: To determine (1) whether dose escalation of doxorubicin used as an adjuvant with cyclophosphamide in patients with early breast cancer will increase disease free and overall survival; (2) whether the use of Taxol as a single agent after the completion of 4 cycles of cyclophosphamide and doxorubicin in combination will further improve disease-free and overall survival compared to cyclophosphamide and doxorubicin alone; (3) if Taxol following standard dose cyclophosphamide and doxorubicin will be as effective or more effective than high dose cyclophosphamide and doxorubicin without Taxol; (4) to access the toxicity of the different doses of cyclophosphamide and doxorubicin with and without Taxol using the end point of life threatening or lethal toxicity; (5) whether the longer duration of chemotherapy treatment for patients randomized to receive Taxol is associated with a reduction in local recurrence in patients with lumpectomy and radiotherapy.

Technical Approach: Women with breast cancer, who have been treated with either mastectomy or segmentectomy will receive adjuvant chemotherapy. All patients will receive 4 courses of cyclophosphamide and doxorubicin (21 day cycle), but the doxorubicin dose will vary depending upon the randomization. Patients randomized to high dose doxorubicin will also receive G-CSF & ciprofloxacin. Some women will be randomized to receive Taxol after 4 cycles of AC chemotherapy is completed. They will receive taxol day 1 of a 21 day cycle for 4 cycles. Women with ER positive tumors will be given tamoxifen for 5 years.

Progress: Eight patients have been enrolled in this study at MAMC; none in FY 98. Two have expired and six continue to be followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/094 **Status**: Ongoing

Title: SWOG 9415: Phase III Randomized Trial of 5-FU/Leucovorin/Levamisole versus 5-FU Continuous Infusion Levamisole as Adjuvant Therapy for High -Risk Resectable Colon Cancer, Intergroup

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/17/1995	Feb 99	09/15/1998

Study Objective: To compare the effectiveness of bolus 5-FU, leucovorin, levamisole versus 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 a secondary endpoint.

Technical Approach: This trial is an intergroup trial involving the Southwest Oncology Group, Eastern Cooperative Oncology Group and the Cancer and Leukemia Group B. Based on previous experience with accrual to INT-0089, and assuming that roughly 1/3 of patients eligible for that study will be entered we anticipate an annual accrual of approximately 600 patients having curative resection of B2, C1, or C2 colon cancer. The primary objective of this study is to compare the survival in patients with high risk resectable colon surgery treated in an adjuvant setting with either 5-FU, leucovorin, levamisole or continuous infusion 5-FU, levamisole. The continuous infusion arm would be judged superior if the true increase in survival is 35%. A secondary endpoint will be disease-free survival. The dose of continuous infusion 5-FU selected for this study of 250 mglm2/d is currently being piloted at an individual institution, and is lower than the common dose of 300 mg/m^2/d, which required dose reductions in a previous pilot. In order to verify the appropriateness of this dose in the intergroup setting, we will evaluate toxicity and compliance in the first 40 patients randomized to the continuous infusion arm. Should the frequency of dose reductions or toxicities warrant concern, the study may be amended or temporarily closed while the continuous infusion therapy is reassessed.

Progress: One patient has been enrolled (FY 97) in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 95/151 **Status**: Ongoing

Title: SWOG 9416: A Phase II Intergroup Trial of Induction Chemoradiotherapy Followed by Surgical Resection for Non-Small Cell Lung Cancer Involving the Superior Sulcus (Pancoast Tumors)

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
06/16/1995	Jun 99	06/19/1998

Study Objective: To assess the feasibility and toxicity of treating patients who have pancoast tumors without mediastinal or supraclavicular nodal involvement (T3-4, N0-1) with Cisplatin and VP-16 for two cycle, concurrent with a program of continuous, fractionated chest radiation followed by surgical resection and boost chemotherapy. To assess the objective response rate, resectability rate, and proportion of patients free of microscopic residual disease after such an approach.

Technical Approach: This oncology group protocol is a Phase II chemoradiation induction of superior sulcus (pancoast) tumors, non-small cell lung cancer followed by surgical resection. There are no extraordinary requirements of this study. This study should recruit 4-5 MAMC patients a year, 18 or older, and of either sex with selected Stage IIIa (T3, N0-1) or Stage IIIb (T4, N0-1) tumors involving the superior sulcus. The main goals of this study are to estimate the response, toxicity, and resectability rates following the combined chemoradiotherapy. We plan to accrue a total of 99 patients which will allow for estimation of rates and provide a sufficient number which will undergo resection. The precision of estimation of rates within stage IIIA or IIIb will depend on the breakdown by stage.

Progress: No patients have been enrolled in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/134 **Status**: Ongoing

Title: SWOG 9419: Tumor Tissue Biopsy for Thymidylate Synthase Expression in Patients with Colorectal Cancer, Ancillary

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
08/15/1997	Apr 01	08/20/1998

Study Objective: 1) To measure thymidylate synthase (TS) expression by polymerase chain reaction in tumor biopsies prior to initiation of fluorinated pyrimidine based therapy in patients with disseminated colorectal cancer and correlate tumor response with level of TS expression; 2) To correlate TS expression in tumor tissue obtained during a potentially curative resection and disease-free survival in patients with Stage II and III large bowel cancer prior to receiving adjuvant therapy with 5-FU based regimen on targeted Southwest Oncology Group trials.

Technical Approach: Tissue samples from patients already on other SWOG protocols will be used. These protocols are: SWOG 9250, SWOG 9303, SWOG 9304, SWOG 9415, and SWOG 9420. Patient treatment will not be affected by registration on this protocol. TS expression will be measured using polymerase chain reaction. The following comparisons will be made: The relationship of TS expression (which may be the most important determinant of whether 5-FU will be effective) with tumor response in the disseminated setting and the relationship of TS expression with recurrence free survival in the post-operative adjuvant patients.

Progress: No patients have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/006 **Status**: Ongoing

Title: SWOG 9420: A Phase III Trial of Continuous Low-Dose Infusion Versus Intermittent High-Dose Infusion of 5-Fluorouracil in Patients with Disseminated Colorectal Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
10/18/1996	Oct 00	09/15/1998

Study Objective: 1) To determine whether dose intensity of 5-FU administered for treatment of disseminated colorectal cancer has an impact upon survival; 2) Compare response to 5-FU therapy by continuous low-dose versus high-dose intermittent infusion in thymidylate synthase gene expression within metastatic colorectal cancer tumor biopsies.

Technical Approach: Metastatic colorectal cancer is incurable. Intervention with chemotherapeutic drugs has shown response rates in the 35 to 50 percent range. Most of these regimens used a biological modulator such as leucovorin in conjunction with 5-FU. Few studies have shown an overall improved survival benefit with chemotherapy compared to observation alone, and in the studies that did show a benefit this prolongation of survival was small. Recently different routes of infusion have been utilized with 5-FU and it is felt that response rates are comparable if not better with continuous infusion as continuous infusion allows perhaps greater total dosage than if given by bolus or it may be related to the greater exposure of drug to tumor in the infusional treatments. This study proposes to compare a treatment incorporating 5-FU by protracted venous infusion compared to high dose weekly infusional 5-FU. The main endpoint is survival. In addition, this study will use data from tumor specimens to correlate Ts gene expression to response rates in the two arms.

Progress: Three patients were entered in the study (FY 97) at MAMC and are being followed. One patient was transferred in from TAMC and expired three months later.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/039 **Status**: Ongoing

Title: SWOG 9431: Cytogenetic, Molecular, and Cellular Biology Studies in Metastatic Melanoma Patients, Ancillary

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ Richard F. Williams, MC; MAJ Matthew P. Jones, MC; Rakesh Gaur, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
01/16/1998	Jul 01	N/A

Study Objective: (1) To characterize the frequency of non-random cytogenetic abnormalities in regional and distant melanoma metastases (AJCC Stage III or IV) and explore their association with clinical outcome of melanoma patients enrolled in Southwest Oncology Group trials; (2) to characterize the frequency of specific genetic alterations at either the DNA, mRNA, or protein level and explore the association of these abnormalities with clinical outcome in patients with regional and distant metastases (AJCC Stage III or IV) who are enrolled in Southwest Oncology Group melanoma trials. The specific genes to be studied in this protocol will initially include p16 (MTS1) and nm23; (3) to characterize the host immunologic response to metastatic melanoma by determining whether the *in vitro* pattern of cytokine expression is consistent with specific subsets of T helper cells (TH1 or TH2) within melanoma deposits and to explore whether host immunologic response varies based on the site of metastatic disease and/or correlates with clinical outcome in patients enrolled in Southwest Oncology Group trials; (4) to obtain peripheral blood, sera and paraffin embedded tumor blocks from patients with metastatic melanoma to create a tissue, cell and sera bank for future studies.

Technical Approach: The patients must have previously been enrolled to and eligible for a SWOG coordinated melanoma treatment trial and about to undergo biopsy/surgery for regional lymph node or disseminated metastatic disease or the patient must have metastatic melanoma (AJCC III or IV) and must be planning to enroll to a SWOG coordinated melanoma treatment trial within 56 days of registration to SWOG 9431. Paraffin-embedded tissue samples obtained during surgical resection or biopsy, peripheral blood obtained at time of surgery, and fresh sterile tumor specimen obtained during surgical resection or biopsy will be submitted to the University of Cincinnati Tumor Tissue Bank for study. If possible, fresh snap frozen specimens obtained during surgical resection or biopsy will also be submitted.

Progress: No patients have been entered in this study.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/113 **Status**: Ongoing

Title: SWOG 9444: Gastrointestinal Tumor Repository Protocol, Ancillary

Principal Investigator: MAJ David E. McCune, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Kenneth A. Bertram, MC; MAJ Matthew P. Jones, MC

Start Date:	Est. Completion Date:	Periodic Review:
09/15/1998	Apr 02	N/A

Study Objective: 1) To establish a central gastrointestinal tumor repository to serve as a tissue resource for current and future scientific studies, 2) to utilize the Southwest Oncology Group clinical database to perform clinicopathologic correlation with the results of those studies, and 3) to test new hypotheses as they emerge.

Technical Approach: Patients must be enrolled in a SWOG coordinated gastrointestinal treatment protocol and must have adequate diagnostic tissue available defined as at least one formalin-fixed, paraffin-embedded block from a representative area of the primary tumor, one formalin fixed, paraffin-embedded block from normal gastrointestinal mucosa or from a normal lymph node, and one formalin fixed, paraffin-embedded whole lymph note if metastases are present. If available a portion of the primary tumor that is viable and non-necrotic, a portion of normal mucosa, and a representative H&E stained slide will also be submitted to the repository.

Progress: One patient has been entered in this study.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/102 **Status**: Ongoing

Title: SWOG 9445: Prognostic Factor Panel to Predict Preferred Therapy for Node Positive Postmenopausal Breast Cancer Patients (CAF vs Tamoxifen) (A Companion Protocol to SWOG 8814

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/17/1996	Apr 96	05/22/1998

Study Objective: Overall objective is to correlate a panel of markers with clinical outcome and responsiveness to adjuvant therapy of node positive post menopausal breast cancer patients who participated in SWOG 8814. Specifically: 1) To evaluate if c-erbB-2 can allow the discrimination of node positive breast cancer patients who markedly benefited from adjuvant therapy with CAF (those with over-expressed c-erbB-2) from patients who did not obtain additional benefit from dose intensive CAF (those with low c-erbB-2 expression); 2) to measure a panel of prognostic factors (histologic and nuclear grade, estrogen and progesterone receptors, c-erbB-2, p53, Ki67, flow cytometrically determined DNA index and S-phase), angiogenesis, hsp27 (heat shock protein 27), nuclear and histologic grading, and immunohistochemically measured estrogen and progesterone receptors on node positive postmenopausal breast cancer patients; 3) to test the association of the factors listed above with biological and clinical features, including recurrence, survival and apparent efficacy of CAF chemotherapy in patients entered on SWOG 8814; and 4) to cut and store additional sections to allow the evaluation of markers that are mechanistically interesting but in the early development stage in breast cancer prognostic work which may be identified within the next 2-3 years, to be analyzed for prognostic significance and impact on the apparent benefit obtained by adjuvant CAF.

Technical Approach: This is a prognostic factor study attempting to find a correlation of several molecular, biochemical, and immunohistochemical, markers with outcomes in node positive breast cancer. It also seeks a correlation of C-erB-2 expression with benefits of adjuvant chemotherapy compared to tamoxifen therapy alone. The paraffin blocks will be submitted for all patients that are registered on SWOG 8814 who have adequate tissue to submit. It will be submitted to University of Texas Health Science Center in San Antonio, Texas.

Progress: Two patients have been entered in this study in previous years. One patient expired in FY 96 and the other is still in follow-up

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/094 **Status**: Ongoing

Title: SWOG 9446: Chemoprevention Trial to Prevent Second Primary Tumors with Low-Dose 13-Cis Retinoic Acid in Head and Neck Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Robert L. Sheffler, MC; MAJ John R. Caton, MC; LTC Robert B. Ellis, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; Rakesh Gaur, M.D.

Start Date:	Est. Completion Date:	Periodic Review:
05/17/1996	Mar 99	02/20/1998

Study Objective: 1) To test the efficacy of prolonged low-dose 13-cRA in reducing the risk of second primary tumors (SPTs) in patients who have had head and neck cancer controlled by surgery and/or radiotherapy; and 2) to evaluate the qualitative and quantitative toxicity of low-dose 13-cRA administered daily for three years.

Technical Approach: Head and neck cancer accounts for 5% of all cancers in the US with 45,000 new cases and 15,000 deaths annually. The standard treatment for early Stage I and II disease is either surgical excision or radiotherapy. However, the major cause of failure in early stage patients is the development of second primary tumors (SPT). The prognosis for patients with SPTs, especially of the lung, is very poor, with a median survival of 5 to 10 months, and less than 10% of patients survive more than 2 years. Toxicity data and the necessity for long-term therapy suggest the need for new chemoprevention approaches to controlling head and neck cancer. Based on recent data showing the greater effectiveness of low dose 13-cRA over B-carotene and mild, tolerable toxicity, we will investigate the efficacy and safety of long-term, low dose 13-cRA for preventing second primary tumors in early stage head and neck cancer.

Progress: No patients have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 94/164 **Status**: Terminated

Title: SWOG 9450: Prostate Cancer Intervention vs Observation Trial (PIVOT): A Randomized Trial Comparing Radical Prostatectomy vs Palliative Expectant Management for the Treatment of Clinically Localized Prostate Cancer

Principal Investigator: MAJ Raymond S. Lance, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Kurt L. Hansberry, MC; MAJ J. Brantley Thrasher, MC

Start Date:	Est. Completion Date:	Periodic Review:
09/21/1994	Sep 04	11/21/1997

Study Objective: To determine which of 2 treatment strategies is superior in reducing all-cause mortality in patients with clinically localized prostate cancer (1) radical prostatectomy and early intervention of subsequent disease persistence or recurrence or (2) expectant management with reservation of therapy for palliative treatment of symptomatic or metastatic disease progression.

Technical Approach: Patients will be randomized to one of the two groups listed (1) will have a radical prostatectomy; (2) will be assigned to Watchful Waiting Management.

Patients in group 1 will have 2 surgical procedures; removal of the lymph nodes from near the prostate gland (pelvic lymph node surgery); and then proceed with the prostatectomy.

Patients in group 2 will not have their cancer removed. Patients will be closely observed; if the cancer causes symptoms, treatment will be aimed at providing relief of these symptoms.

Progress: No subjects have been entered in this study. Subjects have been unwilling to be randomized.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/009 **Status**: Ongoing

Title: SWOG 9457: Paclitaxel (Taxol) and Carboplatin for Advanced Transitional Cell Carcinoma of the Urothelium

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
10/18/1996	Nov 00	09/15/1998

Study Objective: 1) To assess the efficacy and feasibility of utilizing a 3 hour infusion of paclitaxel in combination with carboplatin in cases of previously untreated advanced urothelial tract transitional cell carcinoma. 2) To assess efficacy of this regimen with advanced urothelial tract transitional cell carcinoma refractory to platinum-based therapy. 3) To evaluate the toxicity of this regimen in these groups of patients.

Technical Approach: Advanced stage urothelial cancer that is not totally resected has a very high relapse rate. In fact in node positive disease it can be argued that these patients are incurable despite local resection. Of course M1 disease is incurable. Standard therapy for these tumors is cisplatinum based (MVAC or CMV) with very good response rates in the 50 to 70 percent range. Phase II studies has seen response rates with single agent carboplatin in this range and Taxol single agent response rates in 25 to 30% range. This study is a Phase II study evaluating the efficacy of combined Carboplatin plus Taxol in patients with measurable advanced transitional cell carcinoma of the bladder.

Progress: One patient was entered in FY 97 and is being followed.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/059 **Status**: Ongoing

Title: SWOG 9503 (NCCTG 93-72-52): Phase III Trial of BCNU and Cisplatin Versus BCNU Alone and Standard Radiation Therapy Versus Accelerated Radiation Therapy in Patients with Grade 4 Glioma

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:	Est. Completion Date:	Periodic Review:
02/21/1997	Feb 00	02/20/1998

Study Objective: To conduct a 2 x 2 factorial study to compare treatment outcomes in patients with glioblastoma multiforme treated with AHRT (accelerated hyperfractionated radiation therapy) + BCNU + CDDP and those treated with SRT (standard ration therapy) + BCNU + CDDP. Primary goals: 1) To compare the survival distributions of patients treated with AHRT vs patients treated with SRT. 2) To compare the survival distributions of patients treated with BCNU + CDDP before, during, and after radiation therapy vs patients treated with BCNU during and after radiation therapy.

Technical Approach: The median survival for patients with high grade gliomas is about 9 to 11 months. The 5 year survival is less than 20% with standard therapy using surgery and radiation therapy. The use of chemotherapy combined with radiation therapy after surgery has shown some small benefit and is considered the standard therapy in most trials. As for radiation therapy, the standard fractionation scheme of 180 cGy has been tested with equivalent results shown in fashion over 15 days (4800 reds total dose). this study will compare 4 treatment Arms using BCNU + standard radiation therapy vs BCNU + accelerated hyperfractionation vs BCNU + Cisplatinum and standard radiation therapy vs BCNU + Cisplatinum and accelerated hyperfractionation for high grade gliomas. The toxicity of the two radiation therapy schedules are equivalent and the addition of Cisplatinum to BCNU may radiosensitive with radiation.

Progress: No patients have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/147 **Status**: Completed

Title: SWOG 9509: A Randomized Phase III Trial of Paclitaxel Plus Carboplatin Versus Vinorelbine and Cisplatin in Untreated Advanced Non-Small Cell Lung Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:	**Est. Completion Date:**	**Periodic Review:**
06/21/1996	Jun 00	06/19/1998

Study Objective: To compare the effect of paclitaxel plus carboplatin to vinorelbine plus cisplatin on overall survival, progression-free survival and tumor response rate in patients with Stage IV and selected Stage IIIB non-small cell lung cancer. To compare the toxicity of the two treatment regimens in patients with Stage IV and selected Stage IIIB non-small cell lung cancer.

Technical Approach: The primary objective of this study is to compare the survival in patients with advanced non-small cell lung cancer treated with cisplatin/vinorelbine with that in comparable patients treated with the combination of carboplatin/paclitaxel. Carboplatin/paclitaxel would be judged superior to the standard regimen of cisplatin/vinorelbine if the true increase in median survival is 50%. Based on the previous Group-wide Phase II study in this disease (SWOG), it is anticipated that 300 total eligible patients per year will be accrued to this study. An accrual period of 16 months should thus result in a study of 200 eligible patients per arm. A median survival of 8 months is anticipated on the cisplatin/vinorelbine. Assuming exponential survival, 16 months of patient accrual, and an additional 12 months of follow-up, a sample size of 200 patients per arm in a study with power 0.94 to detect a 50% increase in median survival in he combination arm, using a one-sided log rank test at level 0.025.

Progress: Three patients have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/041 **Status**: Ongoing

Title: SWOG 9510: Evaluation of Topotecan in Hormone Refractory Prostate Cancer, Phase II

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
12/19/1996	Dec 00	09/15/1998

Study Objective: 1) To evaluate the response (CR and PR only) rate to topotecan in patients with metastatic, hormone-refractory prostate cancer. 2) To assess the qualitative and quantitative toxicities of topotecan administered in a phase II study to patients with metastatic, hormone-refractory prostate cancer.

Technical Approach: Prostate cancer that is refractory to standard first line hormonal manipulations including surgical and chemical orchiectomy has a median survival of about 6 months. The standard of care for hormone refractory prostate cancer is not defined. Response to chemotherapy is poor at about 10 to 15%. This study will assess the response rate and toxicities of Topotecan in hormone refractory prostate cancer patients. The schedule with a 21 day infusion had been tested at New York University and showed only some grade 3 and one grade 4 myelotoxicity. Other side effects are fatigue, nausea, vomiting and diarrhea.

Progress: Three patients were enrolled in this study in FY 97 at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/095 **Status**: Ongoing

Title: SWOG 9514: Phase III Double-Blind, Placebo-Controlled, Prospective Randomized Comparison of Adjuvant Therapy with Tamoxifen vs. Tamoxifen & Fenretinide in Postmenopausal Women with Involved Axillary Lymph Nodes and Positive Receptors, Intergroup

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:	Est. Completion Date:	Periodic Review:
04/19/1996	May 99	04/17/1998

Study Objective: 1) To compare disease-free survival and overall survival of postmenopausal primary breast cancer patients with involved axillary nodes and positive estrogen or progesterone receptors who are treated with standard adjuvant tamoxifen vs. tamoxifen and fenretinide; 2) to gain wider experience and toxicity information on the combination of tamoxifen and fenretinide; and 3) to obtain tumor tissue from these patients for future biologic studies of relevance to this patient population.

Technical Approach: The present standard of therapy for node positive and ER positive post menopausal women is Tamoxifen alone. There are some studies that suggest that the addition of adjuvant chemotherapy combined with hormonal therapy will prolong relapse free and overall survival. However, not all patients, especially in the over 65 year old age group, can tolerate or want the significant side effects of chemotherapy. Thus, a less toxic regimen is needed. This study attempts to use a chemoprophylactic approach along with the standard Tamoxifen treatment for this group of patients. This new retinoid has shown some effectiveness in Phase I and II studies when given in combination with Tamoxifen to untreated metastatic breast cancer patients. This study will test its use in a Phase III randomized, prospective, placebo-controlled trial. The side effects seem to be fairly minimal except for night blindness which will be closely monitored during this trial.

Progress: One patient was entered in this study in FY 97 at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/118 **Status**: Ongoing

Title: SWOG 9515: Phase III Intergroup Trial of Surgery Followed by (1) Radiotherapy vs. (2) Radiochemotherapy for Resectable High Risk Squamous Cell Carcinoma of the Head and Neck

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.; Steven Wilson; MAJ Nyun C. Han, MC; CPT Brent L. Kane, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/17/1996	Jun 00	05/22/1998

Study Objective: 1) To determine the efficacy of concurrent cisplatinum and radiotherapy following surgical resection in patients who have advanced squamous cell carcinoma of the head and neck region; 2) to test whether the use of concurrent chemoradiotherapy following surgery increases locoregional control rates; 3) to determine if the patterns of first failure are changed by the use of concurrent chemotherapy; 4) to determine whether the use of concurrent chemoradiotherapy prolongs disease-free survival and/or overall survival; and 5) to compare the toxicity of concurrent chemoradiotherapy versus radiation alone in the postoperative setting.

Technical Approach: In head and neck squamous cell carcinomas with high risk features, there is a 20 to 50 percent recurrence rate after surgical resection. These high risk features include greater than 2 lymph nodes positive, extracapsular extension of cancer in lymph nodes, and positive resection margins. In the past, patients with these high risk features had received radiation therapy for local control. There is evidence, however, that the addition of cisplatinum with concurrent radiation therapy may help in local control. This data comes from in vitro as well as in vivo data showing cisplatinum may be a radiation sensitizer that may have synergistic local effects on malignancies. The study is a Phase III randomized study that will compare standard radiation therapy against concurrent cisplatinum and radiation therapy for resected squamous cell carcinoma of the head and neck. The added toxicities of neuropathy, nausea and emesis, renal failure, and bone marrow suppression are tolerable and can be prevented with medical measures. It is hoped that local recurrence will be reduced with this approach with minimal added toxicity.

Progress: One patient has been entered (FY 96) at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/005 **Status**: Completed

Title: SWOG 9518: Phase II Trial of Continuous Topotecan Infusion in Patients with Advanced Soft Tissue Sarcomas

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
10/18/1996	Sep 00	10/17/1997

Study Objective: To evaluate the response rate of advanced soft tissue sarcoma treated with a prolonged infusion of topotecan, and to define the qualitative and quantitative toxicities of topotecan when administered as a continuous infusion to patients in a cooperative setting.

Technical Approach: The most active agents for advanced soft tissue sarcomas are DTIC, Adriamycin, Ifosfamide however, improvements in response are needed in the form of newer agents. Topotecan is a Topoisomerase I inhibitor that has been used in non small cell lung cancer studies and its main toxicity is diarrhea, thrombocytopenia, and neutropenia. In this phase II study, Topotecan will be given on a continuous infusion schedule to assess what the response rate may be with this agent in the hopes of increasing the response rate in soft tissue sarcoma.

Progress: No patients have been enrolled in this study as MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/160 **Status**: Completed

Title: SWOG 9519: Evaluation of Tomudex in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/20/1996	Aug 00	11/21/1997

Study Objective: 1) To evaluate the response rate of histologically confirmed recurrent or metastatic squamous cell carcinoma of the head and neck following Tomudex treatment, in order to assess whether Tomudex should be advanced to further studies; and 2) to assess the qualitative and quantitative toxicities of Tomudex.

Technical Approach: Recurrent and metastatic head and neck cancer is incurable. Response rates with chemotherapy have varied, but range from 30 to 75 percent. These response rates are usually not durable and will usually progress within less than 6 months. Chemotherapeutic agents used are cisplatinum and 5 FU alone or in combination, methotrexate, and bleomycin. Tomudex is a new agent that is a specific thymidilate synthetase inhibitor. 5 FU is a TS inhibitor but is non-specific. Tomudex has been used in North America and European trials in colorectal cancer and has shown about a 30 percent response rate. Tomudex will therefore be used to assess its response rate and duration of response in a Phase II trial. The main side effects are diarrhea and cytopenia (especially leukopenia), and reversible liver function test abnormalities.

Progress: One patient was entered in Sep 96 and died of disease in Oct 96

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 96/119 **Status**: Completed

Title: SWOG 9520: Controlled Phase II Study of Doxorubicin and Paclitaxel as Frontline Chemotherapy for Women With Metastatic Breast Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
05/17/1996	Apr 99	10/17/1997

Study Objective: 1) To evaluate the complete remission rate of the doxorubicin plus paclitaxel combination in advanced breast cancer patients with no prior chemotherapy for metastatic disease and either no prior adjuvant chemotherapy or one prior adjuvant chemotherapeutic regimen (non-anthracycline or taxane containing). This evaluation will be made over six cycles of the combination regimen. 2) To test the combination of doxorubicin and paclitaxel for toxicity with particular emphasis on the degree of myelosuppression and the possible cardiac toxicity.

Technical Approach: Metastatic breast cancer is an incurable disease with median survivals of approximately 18 months being reported in many trials. The biologic behavior is very heterogeneous and differences in survival can be seen from study to study. Presently adriamycin-based chemotherapy regimens have shown the most efficacy in terms of response rates, however, long term survivals are the exception. Taxol has shown to have significant activity in metastatic breast cancer and has been combined with adriamycin to treat metastatic breast cancer in single arm trials. Evaluations in this study will be done in conjunction with a concurrently randomized control arm (of doxorubicin and cyclophosphamide) which will be used mainly to assess whether the new regimen has been rested in a patient population with historically expected rates of complete remission and congestive heart failure. This evaluation will be made over six cycles of the combination regimen. Because of the incidence of cardiac toxicity with the Milan regimen, close follow-up of cardiac function will be done in all patients in this trial with maximum doses of Adriamycin to be held well below the threshold of 450 mg/m^2.

Progress: No patients have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 98/112 **Status**: Ongoing

Title: SWOG C9581: Phase III Randomized Study of Adjuvant Immunotherapy with Monoclonal Antibody 17-1A Versus No Adjuvant Therapy Following Resection for Stage II (Modified Astler-Coller B2) Adenocarcinoma of the Colon

Principal Investigator: MAJ David E. McCune, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Kenneth A. Bertram, MC; MAJ Matthew P. Jones, MC

Start Date:	**Est. Completion Date**:	**Periodic Review**:
09/15/1998	Sep 02	N/A

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 (pT3NO or pT4bNO) colon cancer, (2) to evaluate a panel of prognostic markers, in order to correlate these measures with survival and recurrence after adjuvant therapy in patients who have undergone resection of a Stage II (pT3NO or pT4bNO) colon cancer. The specific aims of the substudies will be: (a) to determine whether alterations in the expression of cell cycle related genes (thymidylate synthase, p53, and the cyclin-dependent kinase inhibitors p21 and p27) predict the risk of survival and recurrence in this patient population, (b) to determine whether alterations in markers of metastatic potential-expression of DCC and measures of tumor angiogenesis (microvascular density and vascular endothelial growth factor expression)-predict the risk of survival and recurrence in this patient population, (c) to determine whether a marker of cellular differentiation-sucrase isomaltase-predicts the risk of survival and recurrence in this patient population, and (d) to determine whether interactions among these tumor markers identify subsets of patients with significantly altered outcome.

Technical Approach: Subjects will be randomized and assigned to one of two treatment groups following standard surgical removal of their tumor. Group 1 will receive standard care which is surgery with no additional therapy after the tumor has been removed. Subjects will continue with routine check-ups, doctor visits and tests. Group 2 will receive five antibody treatments using MoAb 17-1A. Subjects will receive the drug as an intravenous infusion over a 2-hour time period once each 28 days. This 2-hour infusion will be repeated every 4 weeks for a total of 5 treatments. During treatment, various blood tests and x-rays will be used to determine whether the disease has returned.

With subject's approval, tissue, body fluids, and other specimens obtained during the normal course of treatment will be forwarded to a special research laboratory for storage and scientific testing. Subjects will also be asked to complete a background information form to help define groups of patients being treated.

Progress: No patients have been entered in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 97/070 **Status**: Ongoing

Title: SWOG JBR.10 (NCIC CTG BR.10): A Phase III Prospective Randomized Study of Adjuvant Chemotherapy with Vinorelbine and Cisplatin in Completely Resected Non-Small Cell Lung Cancer with Companion Tumour Marker Evaluation

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility**: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:	**Est. Completion Date**:	**Periodic Review**:
03/21/1997	Mar 00	03/20/1998

Study Objective: 1) To compare the duration of overall survival (OS) between completely rejected patients with T2 NO, T1-2N1 non-small cell lung cancer (NSCLC) who have received either adjuvant chemotherapy with vinorelbine and cisplatin or observation alone. 2) To determine disease-free survival. 3) To confirm the prognostic significance of ras mutations when present in the primary tumor. 4) To provide a comprehensive tumor bank linked to a clinical data base for the further study of molecular markers in rejected NSCLC. 5) To measure and compare health related quality of life in both treatment arms throughout the study period. 6) To evaluate toxicity related to chemotherapy.

Technical Approach: The role of adjuvant chemotherapy in Non-small cell lung cancer is controversial. Most clinical trials have shown no benefit to adjuvant chemotherapy. In the early 80's the lung cancer study group showed some benefit with combination chemotherapy in terms of survival, however, the control arm was not a strict observational arm and contained a "biological response modifier" in it. Thus with recent improved survival in Stage IV lung cancer shown compared to observation, it is assumed that using platinum based therapies may enhance survival in patients that have completely rejected non-small cell lung cancer. In patients with rejected Stage I, II, and III Non-small cell lung cancer it is known that the long term survival rates are 50 to 60%, 30 to 50%, and 19 to 49% respectively. It is thus the aim of this study to assess whether adjuvant therapy with Cisplatin and Vinorelbine will improve survival and relapse free survival compared to observation. In addition to the above study, tissue samples will be sent to the University of Washington for evaluation of Ras mutations to assess its prognostic importance.

Progress: No patients have been entered at MAMC.

Detail Summary Sheets

University of Washington Neuro-Oncology Group

Detail Summary Sheet

Date: 30 Sep 98 **Number**: 89/013 **Status**: Completed

Title: UWNG 88-01: Phase II Study of High Dose Methotrexate and Craniospinal Irradiation for the Treatment of Primary Lymphoma of the Central Nervous System

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: UWNG **Facility**: MAMC

Associate Investigator(s): Robert Goodkin, M.D.; Edythe A. Albano, M.D.; MAJ Joseph H. Piatt, MC; MAJ Frank A. Zimba, MC; COL Irwin B. Dabe, MC; CPT Denis Bouvier, MC; MAJ Mark H. Kozakowski, MC; MAJ Everardo E. Cobos Jr., MC; LTC Howard Davidson, MC

Start Date:	Est. Completion Date:	Periodic Review:
01/20/1989	Nov 92	09/30/1998

Study Objective: To evaluate this regimen, the end-points of analysis will be: time to progression of disease from beginning of therapy, response rates and disease stabilization rates, survival time measured from the beginning of therapy, quality of life, and activity level measured by Karnofsky performance status.

Technical Approach: Patients must have a non-Hodgkin's lymphoma of the central nervous system with adequate renal, bone marrow, and liver function, and a performance status of >70%. HIV antibody titer must be negative. No prior chemotherapy or radiotherapy is permitted.

Methotrexate, 4 g/m^2, will be administered over a four hour period. Calcium leucovorin, 25 mg, will be administered beginning 20 hours after completion of the methotrexate infusion and repeated for 8 doses, parenterally, on an every 6 hour basis, following which an additional four doses will be administered every six hours by mouth. The methotrexate regimen will be administered every two weeks for three courses. Radiotherapy will begin two weeks after completion of methotrexate and will consist of 5040 cGy to whole brain at 180 cGy/fraction (28 fractions) and 3060 cGy at 170 cGy/fraction (19 fractions) to spinal axis. Time to progression will be measured from the initiation of therapy until progression is documented. At that time, the patient will be removed from the protocol and can be treated with other therapy as indicated. Patients will be followed until death.

Progress: The protocol has been closed to patient entry. One patient, enrolled in FY 89, now resides in a full service nursing home due to a debilitating stroke and is no longer followed by the Oncology Service at MAMC.

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