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14. ABSTRACT This Behavioral Center of Excellence in Breast Cancer contains three separate, but related research projects focused on breast cancer patients' quality of life and functional status. There is also a Biostatistic's Core Facility supporting all three studies. The three projects are: <u>Project 1</u>) Menstrual Cycle Maintenance and Quality of Life Following Treatment for Breast Cancer: A Prospective Study. This is a study of women aged 45 years and younger diagnosed with a first breast cancer. <u>Project 2</u>) Investigating Mechanisms to Explain Age Associated Differences in Quality of Life Among Breast Cancer Patients. This study examines psychosocial and clinical factors associated with patient's (aged 18-80+ years) coping and quality of life during the first 18 months post-diagnosis. <u>Project 3</u>) Research on Optimal Recovery Practices in Breast Cancer (RESTORE). This is a randomized exercise intervention trial with a lymphedema prevention program. Project 1 is a continuation of a study that was initiated in January of 1998. Projects 2 and 3 are new protocols, which will begin patient recruitment in the fall of 2002. All three studies have the potential to greatly improve the functional status and life quality of breast cancer patients during treatment and beyond.					
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OVERVIEW OF CENTER ACTIVITIES

I. Progress of the Center-Specific Projects and Biostatistic's Core Facility

Summaries of the activities and progress of the 3 research projects and the Biostatistic's Core Facility are included in the annual reports for each specific project and Core. (See Table of Contents.)

II. Post-Doctoral Fellows

Our second post-doctoral fellow, Dr. Deborah Farmer, completed her training on August 1, 2006. Her accomplishments while on the fellowship were outlined in detail in last year's report.

Dr. Farmer left Wake Forest University to become an Assistant Professor in the Department of Social Sciences at Winston-Salem State University in Winston-Salem, North Carolina. She continues to collaborate with us on papers from this center grant, and has the following manuscript out for review from data collected for Project 1.

Farmer D, Ip E, Case LD, Naughton MJ. Spirituality in Young Breast Cancer Survivors One to Three Years Post-Diagnosis. (Submitted to the journal of *Psycho-Oncology*.)

We have been advertising for our third and final post-doctoral fellow since October of 2006 and have been unsuccessful in receiving any suitable applicants. We will continue to solicit candidates through June 20, 2007 in order to attempt to fill this position.

III. Advisory Board Activities

No formal advisory board meetings were held during this past grant year. An Executive Committee meeting of all of the Principal Investigators and Co-Investigators across the three research projects and the biostatistic's core facility is planned for July of 2007 in order to facilitate data sharing and project planning across the three research projects.

Project 1: Menstrual Cycle Maintenance and Quality of Life After Breast Cancer
Treatment: A Prospective Study

Michelle J. Naughton, Ph.D.
Kimberly VanZee, M.D.

About 15% of new breast cancer cases occur in women of childbearing age and the majority will be long-term survivors. For those patients who receive adjuvant chemotherapy, almost half will experience amenorrhea, resulting in infertility, menopausal symptoms, and changes in their life quality. The purposes of this study are: 1) to continue to follow prospectively a cohort of 628 young women, ages 18-45, diagnosed with breast cancer, stages 1-3, recruited through a previous award (DAMD17-96-1-6292); and 2) to recruit an additional 200 women from two participating clinical centers (Memorial Sloan-Kettering Cancer Center in New York, and the University of Texas Southwestern in Dallas, Texas). The major objectives of this study are to track the menstrual bleeding patterns of these young women, identify determinants of treatment-related amenorrhea, track subsequent pregnancies and outcomes, examine the women's quality of life longitudinally, and evaluate the patients' disease-free and overall survival. All participants will be followed for a minimum of 2.5 years to a maximum of 8 years. To our knowledge, this is the largest prospective study of young breast cancer patients being conducted in the United States or elsewhere. At 18 months post-diagnosis, 60% of the patients report some menstrual bleeding. Patients also report arm swelling (30%), hot flashes (56%), and vaginal dryness (43%). Patients' life quality is lower during treatment but improves significantly 12-18 months post-diagnosis.

breast cancer, quality of life, premature menopause, young women

PART I - INTRODUCTION

About 15% of new breast cancer cases occur in women of childbearing age and the majority will be long-term survivors. For those patients who receive adjuvant chemotherapy, almost half will experience amenorrhea, resulting in infertility, menopausal symptoms, and changes in their life quality. Very little is known about the incidence, onset, time course, and symptomatology of premature menopause induced by breast cancer therapy, or the impact on the young survivor's quality of life. The purposes of this study are: 1) to continue to follow prospectively a cohort of 628 young women, ages 18-45, diagnosed with breast cancer, stages 1-3, recruited through a previous award (DAMD17-96-1-6292); and 2) to recruit an additional 200 women from two participating clinical centers (Memorial Sloan-Kettering Cancer Center in New York, and the University of Texas Southwestern in Dallas, Texas). The major objectives of this study are to track the menstrual bleeding patterns of these young women, identify determinants of treatment-related amenorrhea, track subsequent pregnancies and outcomes, examine the women's quality of life longitudinally, and evaluate the patients' disease-free and overall survival. All participants will be followed for a minimum of 2.5 years to a maximum of 10 years. To our knowledge, this is the largest prospective study of young breast cancer patients being conducted in the United States or elsewhere.

PART II - BODY: STATEMENT OF WORK

Task 1: Continued Follow-up of Study Participants (Months 1-78):

- a. Clinical Center staff will mail follow-up surveys at 6 month intervals, and menstrual bleeding calendars at 3 month intervals to participants already enrolled in the protocol from the previous DOD award (DAMD17-96-1-6292).**

The coordinating center personnel at Wake Forest University have continued to mail follow-up forms to previously recruited study participants at the prescribed intervals (i.e., bleeding calendars every 3 months; and study questionnaires every 6 months). The total number of participants who were recruited to this study under the previous award is 628 participants. Patients were recruited from the following clinical centers beginning in January of 1998: Memorial Sloan-Cancer Center in New York City (n=450 participants); M.D. Anderson Cancer Center in Houston, Texas (n=92); Wake Forest University (n=49 participants); and Presbyterian Hospital in Dallas, Texas (n=37 participants). Recruitment ended at Wake Forest University, M.D. Anderson Cancer Center, and Presbyterian Hospital in Dallas on December 31, 1999. The current award permits the additional accrual of 200 patients from only two clinical sites: Memorial Sloan-Kettering Cancer Center in New York City, and a new site, the University of Texas-Southwestern Medical Center and its affiliates.

In general, the participants recruited under the former award are well-educated, with 63% having at least a 4 year college degree. Approximately 55% are employed full-time, and 14% are employed part-time, mostly in professional (51%) or managerial positions (17%). Seventy-five

percent of the participants are married or are living in a married-like relationship. Roughly 71% of the participants have children. The average age at recruitment to the study was 39 years of age. Approximately 88% of the participants are white (non-Hispanic), 5% are African-American, 4% are Hispanic, and 3% are Asian.

The following table provides information on the current follow-up status of the 628 participants accrued previously:

<u>Participation Status</u>	<u>n</u>	<u>%</u>
Active:	380	60.5%
Completing questionnaires and bleeding calendars	255	67.0%
Completing questionnaires only*	125	31.8%
Dropped/Lost-to-Follow-up:	177	28.2%
Deaths	<u>71</u>	<u>11.3%</u>
	628	100.0%

* Participants who have had a hysterectomy or who have not had a menstrual period for 2 continuous years post-treatment complete study questionnaires only

Rates of participant dropout/lost to follow-up have been spread fairly equally across the clinical centers, except for Presbyterian Hospital in Dallas. These patients had to be re-consented in the spring of 2003, and as a result, 9 participants from that site, declined to continue in the study any longer.

	<u>Active</u>	<u>Dropped/Lost to Follow-up</u>	<u>Deaths</u>
Memorial Sloan-Kettering	280 (62.4%)	124 (27.6%)	45 (10.0%)
M.D. Anderson	53 (57.6%)	23 (25.0%)	16 (17.4%)
Wake Forest	29 (58.0%)	16 (32.0%)	5 (10.0%)
Presbyterian Hospital	18 (48.6%)	14 (37.8%)	5 (13.5%)
	380 (60.5%)	177 (28.2%)	71 (11.3%)

Of the 177 persons (28.2%) who have been dropped or lost to follow-up as of May 30, 2007, the following listing provides reasons for study dropouts:

- 75 could not be reached by mail, phone, or personal contacts (i.e., lost to follow-up)
- 66 lost interest in participating in the study any longer
- 7 cited a lack of time
- 3 cancer recurrence or metastatic disease
- 2 illness/treatment side effects/other medical problems
- 4 too overwhelmed to continue participating
- 2 questions too personal/confidentiality issues
- 2 personal/family obligations
- 1 questions were depressing to a participant
- 1 husband asked her to stop participating
- 1 poor English
- 1 upset about her clinical care at her clinical center
- 1 participant began a 2 year sailing trip and asked to be dropped
- 9 patients from Presbyterian Hospital who opted not to be re-consented
- 1 believes study is a waste of time
- 1 agreed to only 5 years

In January of 2007, we began our 9th year of follow-up on our earlier enrolled participants. We have currently retained approximately 60.5% of our original participants and have lost 11.3% of our patients to death. Efforts are continuing to try to retain the existing study cohort for additional years of follow-up.

Task 2: Study Set-Up/IRB Approvals (Months 1-12):

a. Review procedures already established for study conduct, patient recruitment, and patient follow-up.

The Manual of Procedures for this study was completed in year 1.

b. Obtain final IRB site-specific approval for this protocol from the University of Texas Southwestern Medical Center and its affiliates in Dallas, Texas.

Site-specific IRB approval for the University of Texas Southwestern Medical Center in Dallas, Texas was approved for the Aston Ambulatory Care Center and the Zale Lipshy University Hospital in July of 2001. Approval to accrue patients from the Parkland Health and Hospital System was obtained on September 17, 2001.

Obtain final IRB approval from the DOD for the continued follow-up of previously enrolled participants, as well as for the new recruitment of study participants from Memorial Sloan-Kettering Cancer Center in New York City, and the University of Texas Southwestern Medical Center in Dallas, Texas.

IRB approval from the DOD was obtained for the continued follow-up of patients originally recruited at Wake Forest University, Memorial Sloan-Kettering Cancer Center, and the M.D. Anderson Cancer Center.

Permission to accrue 200 new patients from the Memorial Sloan-Kettering Cancer Center and the University of Texas-Southwestern Medical Center affiliates was approved in September of 2002.

Approval to re-consent 27 active patients, originally recruited from Presbyterian Hospital in Dallas, to the clinical center at Wake Forest University (Dr. Naughton, Principal Investigator), was obtained in April of 2003. This change was made at the request of Dr. James Strauss (PI) of the Presbyterian Hospital Clinical Center. Participants were sent IRB approved informed re-consent forms and personal health authorization forms. Of these 27 patients, 18 participants agreed to be re-consented, and 9 participants declined to be re-consented for the extended follow-up period. These 9 participants were dropped from our participant tracking system, and no further study materials have been sent to these women.

In August of 2004, Dr. Elizabeth Naftalis, the PI of the University of Texas – Southwestern site left that institution. On September 1, 2004, Dr. Naftalis was replaced as PI by Dr. David Euhus, Associate Professor in the Division of Surgical Oncology at the University of Texas Southwestern.

Task 3: Patient Recruitment (Months 13-20):

a. Identify eligible patients from patient registries at the Memorial Sloan-Kettering Cancer Center and the University of Texas Southwestern Medical Center.

Staff at the University of Texas-Southwestern Medical Center was trained on September 9, 2002 in procedures of patient identification, patient recruitment, and patient registration by Dr. Michelle Naughton. Staff persons at this site are continually locating eligible patients from patient rosters.

Staff at Memorial Sloan-Kettering in New York continues to identify eligible participants from their hospital billing records and cancer registries. These staff persons worked on the previous award, and thus did not need to undergo additional training.

- b. Begin the recruitment of eligible patients to the protocol. Patients recruited to the protocol from the clinical centers will be registered online using a web-based system developed by the Biostatistic's Core Facility.**

New patient recruitment ended on December 31, 2005. An additional 209 patients were recruited to the study. Study coordinators at Memorial Sloan-Kettering recruited 188 participants, and staff at the University of Texas-Southwestern Medical Center recruited 21 patients. These patients were registered on-line, using the new registration system developed by the Biostatistic's Core. Thus we have achieved 105% (209/200) of our recruitment goal.

- c. Clinical Center staff will mail baseline, eligibility, and screening forms to the Coordinating Center at Wake Forest University.**

Study coordinators at Memorial Sloan-Kettering and UT-Southwestern have mailed the baseline, eligibility, and screening forms to the project managers at the coordinating center at Wake Forest University. Copies of these forms also remain in the patients' files at Sloan-Kettering and UT Southwestern, along with the original copy of the signed informed consent forms. Wake Forest University does not keep copies of the patients' consent forms.

Task 4: New Patient Follow-up (Months 13-75):

- a. Coordinating Center will mail out bleeding calendars every 3 months, and follow-up questionnaires every 6 months to the newly enrolled participants.**

The recruited patients have been entered into the study tracking system, and receive bleeding calendars and questionnaires from staff at the coordinating center at the above specified intervals.

Three of the 209 participants have died since enrollment. Seventeen of the 209 participants or 8.1% have dropped. The reasons for participant dropout are as follows:

- 6 - no longer interested
- 6 - cannot be reached
- 2 - overwhelmed
- 1 - too much paperwork
- 1 - didn't want to be reminded of her cancer
- 1 - metastatic disease
- 3 - deaths

- b. Clinical Center staff will complete the Chart Review Form at 12 months post-recruitment on the newly enrolled patients.**

All new participants recruited to the study have Chart Review Forms completed at 12 months post-recruitment. Staff at the participating clinical centers are notified as to when chart

review forms are due. Completed forms are mailed to the Project Manager at Wake Forest University for data entry. To date, all but 36 chart reviews have been completed on the enrolled participants, and those should be completed by June 30, 2007.

Task 5: Data Cleaning and Management (Months 1-78):

- a. Biostatistic's Core will perform all data-related tasks, including devising the patient registration, data entry and data management systems. SAS data sets will be developed for interim and final analyses of study data.**

The Biostatistic's Core Facility has completed the following tasks for this protocol in the past year:

- 1) provided a series of error reports to assist in data cleaning and maintaining data quality.
- 2) prepared interim analyses of study data.
- 3) maintained SAS data sets of collected study data.
- 4) completed data analyses of participant menstrual bleeding and amenorrhea, arm and hand swelling, quality of life, and sexual satisfaction and arousal.

Further details about the activities of the Biostatistic's Core can be found in the annual report document from that core facility.

- b. Data cleaning will be performed by the Project Manager's in conjunction with the Biostatistic's Core programmers.**

Data cleaning continues on a regular basis in conjunction with the study programmers. Project managers review all baseline and follow-up study forms as they are received from the clinical centers and the study participants, respectively, in order to check for errors or missing data. Participants are contacted if questions about the study forms arise.

Task 6: Adherence and Retention (Months 1-78):

- a. Receipt of participants' bleeding calendars and forms will be tracked by staff at the Coordinating Center.**

All enrolled patients are entered into our study tracking system, which cues our study staff when follow-up forms and bleeding calendars are to be mailed to participants. Patient forms are mailed approximately 3 weeks prior to their target completion date in order to allow time for participants to receive the forms in the mail and complete them in their homes. Participants who have not returned their study forms within 14 days of their target completion date, are sent a reminder post-card regarding the study forms. If the forms have still not been received within 22 days of their target completion date, these participants are called by our Assistant Project Manager to inquire regarding the status of the forms. The Assistant Project

Manager works with individual participants who are having difficulty completing study forms, for whatever reason, to try to make the completion of the study requirements as easy as possible.

Study project managers also check all follow-up questionnaires completed by participants to check whether scores on the Beck Depression Inventory are within normal ranges. During the past 12 months, 8 patients achieved Beck Depression scores above the cutoff score of 15 points. The PIs of the participants' respective institutions were contacted, and the participants were referred to health professionals and/or support groups, if they were not already seeking assistance in controlling depressive symptoms. No adverse outcomes have occurred with any of these 8 patients.

b. Incentives for maintaining high levels of patient participation in follow-up activities will continue to be devised.

Retention of study participants is paramount in the current protocol. All participants will be followed for a minimum of 3.5 years to a maximum of 10 years. Participants receive no monetary compensation for their participation, but donate their time in completing the study requirements. In addition, the study participants are located in 20+ states in the United States, and three other countries, with no face-to-face contact with study coordinators after their initial study recruitment. Thus, there is no means to reinforce, in-person, the importance of study participation outside of mailed contacts with study staff.

Current Retention Activities Used:

Birthday Cards – all participants are sent cards on their birthdays each year.

Special Event Cards - participants are sent cards to celebrate special events in their lives, (that they share with us), including weddings, births, receiving a promotion, etc. Similarly, sympathy cards are sent to participants who have experienced a loss, and to the spouses/partners/relative of a study participant who has died.

Quarterly Drawings for Gift Certificates - Quarterly drawings of gift certificates were initiated in January 2000, to provide an additional “boost” to study participation. Study drawings are conducted using the following procedure:

All participants receive some type of mailing (i.e., bleeding diaries or bleeding diaries plus a study questionnaire) from the study coordinating center each quarter. Participants are informed that by returning their diaries and/or questionnaires by the due date listed on the label attached to their forms, that they will be automatically included in a quarterly drawing for gift certificates. Once the participants' packets are mailed back to the coordinating center, the extra ID labels attached to their study forms are cut off by Ms. Carol Corum, the study Project Manager, and are stored in large envelopes designated for the participants' initial recruitment site (i.e., Memorial Sloan-Kettering; Wake Forest; Presbyterian Hospital; M.D. Anderson Cancer Center). At the end of each quarter, seven winners are selected in the following proportions to match the number of participants at each clinical center: 4 winners from Memorial Sloan-

Kettering, 1 from Wake Forest, 1 from the patients originally registered through Presbyterian Hospital in Dallas, and 1 from M.D. Anderson Cancer Center. No participants are allowed to receive a prize more than once, and if a repeat winner is drawn, another label is drawn from that site. If no label is available from that site, a label is randomly selected from any of the four sites.

After a winner has been drawn, Ms. Corum calls the participants to inform them that they have won the quarterly drawing and to see if they would like to accept a gift certificate. (Only 3 women have declined a gift certificate since the initiation of this incentive.) Participants may choose a gift certificate from: Home Depot, Lowe's Home Improvement, Wal-Mart, or a Long-distance calling card. Because our participant population is geographically diverse, we have chosen large retail chains, so that most participants have 2 or more of these stores in their area from which to choose.

As of March 31, 2007, 198 gift certificates have been provided to study participants.

To date, the participant drawings have gone smoothly, and we have received no complaints from any participants regarding the conduct of these drawings. We are continuing to seek out new ways to provide incentives to the participants in this study, but the drawings have motivated many participants to return their study forms in a timely manner.

c. A study newsletter will continue to be written and sent to all patients at least twice a year.

A study newsletter is being prepared currently, and will be mailed to the participants in June of 2007.

d. Birthday cards will be mailed to all participants.

Birthday cards were mailed to all active study participants on their birthdays during this past year.

e. Holiday cards will be mailed to participants every year.

A holiday greeting was sent in December 2006.

Task 7: Data Analyses/Manuscript Preparation/ Presentations (Months 6-78):

a. Abstracts, manuscripts and posters will be prepared from interim data (i.e., data sets comprised of participants 1, 2, 3, and 4 years post-recruitment).

Task is on-going. See below: "PART IV – Reportable Outcomes"

b. Annual reports will be written to the DOD.

Task completed on May 31, 2007.

Task 8: Final Analyses and Report Writing, (Months 54-78):

- a. **Final analyses of data assessing primary study endpoints will be performed, and manuscripts will be written and submitted for publication in peer-reviewed journals.**

Task is underway. See below: “PART IV – Reportable Outcomes”

PART III - KEY RESEARCH ACCOMPLISHMENTS (Since the last annual review)

Recruitment:

- 837 women have been recruited to this protocol since 1998, (209 have been recruited under the new award. Retention of the entire study cohort is approximately 62% after up to 113 months of study follow-up. Retention of the newly recruited participants is 90.8% (189/209 participants).

Patterns of Amenorrhea:

- In examining the resumption of menstrual cycles following chemotherapy, 41% of the participants experienced an initial six months of amenorrhea, and 29% were amenorrheic for at least 1 year following therapy.
- 48% of the women with 6 month amenorrhea and 29% with 1 year amenorrhea resumed bleeding in the subsequent three years, usually in the year following their amenorrheic episode.
- Of the 22% of women who experienced an initial two-year period of amenorrhea, only 10% resumed menstrual bleeding within 3 years.
- Resumption of menstrual bleeding differed significantly by regimen following a 6 month period of amenorrhea (68% for those receiving adriamycin and cyclophosphamide (AC); 57% who received adriamycin and cyclophosphamide and paclitaxel (ACT); and 23% for those women who received cyclophosphamide, methotrexate, and 5-FU (CMF).

Pregnancy Outcomes:

- Pregnancy outcomes: 96 pregnancies have been reported among 66 participants during the follow-up period resulting in 67 live births (including 4 sets of twins).

Arm and Hand Swelling:

- 54% reported arm or hand swelling by 36 months after surgery, and 32% reported persistent swelling.

- Swelling was reported to occur in the upper arm (43%), the hand only (34%), and both the arm and hand (22%).
- Factors associated with an increased risk of developing swelling included: having a greater number of lymph nodes removed, being obese as compared to normal weight, and being married. Persistent swelling was also related to having more lymph nodes removed and being obese. Weight management may be a potential intervention for those at greater risk of lymphedema.
- Women with swelling reported a significantly lower quality of life, as measured by the FACT-B and the SF-12.

Depressive Symptoms:

- Approximately 17% of the participants reported depressive symptoms associated with clinical depression at some point during the first 3 years after diagnosis.
- Higher rates of depressive symptoms were associated with being African-American as compared to Caucasian, and being divorced, widowed or separated.
- Lower rates of depressive symptoms were associated with having better physical and mental health, being more satisfied with physical appearance, and having greater social support.

Spirituality:

- Spirituality was moderately high at baseline and did not change significantly during the first 36-42 months after diagnosis.
- Higher spirituality was associated with being Hispanic or African-American as compared to Caucasian; having a religious affiliation; less cigarette smoking; greater satisfaction with appearance; greater levels of social support; and better physical and mental health.
- Regarding clinical and treatment characteristics: Higher spirituality was also associated with stage I versus stage II disease, and having a mastectomy with immediate reconstructive surgery versus a lumpectomy.

PART IV - REPORTABLE OUTCOMES

1) Abstracts and poster presentations completed during this past grant year:

None this past year. Several are planned for the fall of 2007.

2) Published Journal Articles in the past year:

Paskett ED, Naughton MJ, McCoy TP, Case LD, Abbott JM. The Epidemiology of Arm and Hand Swelling in Premenopausal Breast Cancer Survivors. Cancer Epidemiology, Biomarkers & Prevention. 16 (4):775-782, 2007.

Naughton MJ, Sukumvanich P. In Reply. Journal of Clinical Oncology 25 (12): 1632. (Reply to a Letter to the Editor)

PART V - CONCLUSIONS

Further data analyses are planned during 2007-2008 to examine changes in patients' health status, bleeding patterns, menopausal status, pregnancies, symptom profiles/clusters, and health-related quality of life post-treatment.

The data from this research study are answering critical questions regarding the risks (or non-risks) of childbearing after breast cancer, is assisting in predicting which women may be more likely to lose their menstrual cycles following breast cancer treatment, and is providing much needed, longitudinal data on the quality of life of young cancer patients following treatment from breast cancer. Few studies have examined the impact of breast cancer diagnosis and treatment on young women long-term. Younger women are at a different life stage than patients in their 60's and 70's, and face different kinds of challenges than older women. The development of interventions to assist younger women in maintaining optimal quality of life following treatment is critical.

PART VI - REFERENCES

N/A

Project 2: Investigating mechanisms to explain age associated differences in quality of life among breast cancer patients.

Nancy E. Avis, Ph.D.
Kimberly VanZee, M.D.
David Euhus, M.D.
Michelle Naughton, Ph.D .

The primary purpose of this study is to examine mechanisms that may explain age differences in the health-related quality of life of women who have been diagnosed with a first-time breast cancer. The study will examine psychosocial factors such as social support, coping strategies, resiliency, and the impact of cancer on life responsibilities as explanations of age-associated factors affecting HRQL. This project is an observational, longitudinal study of women aged 18 and over who are newly diagnosed with breast cancer. In order to examine both the short- and longer-term impact of breast cancer on HRQL, the study will survey women post diagnosis and follow them at 3, 6, 12, and 18 months. A secondary purpose of the proposed study is to have this large cohort of breast cancer patients serve as a comparison group for the other studies in the Behavioral Center of Excellence. Patients for the proposed study will be recruited from two clin

breast cancer, quality of life, aging

PART I - INTRODUCTION

The primary purpose of this research is to examine mechanisms that may explain age differences in the health-related quality of life of women who have been diagnosed with a first-time breast cancer. The study examines psychosocial factors such as social support, coping strategies, resiliency, and the impact of cancer on life responsibilities as explanations of age-associated factors affecting HRQL. This project is an observational, longitudinal study of women aged 18 and over who are newly diagnosed with breast cancer. In order to examine both the short- and longer-term impact of breast cancer on HRQL, the study surveys women post-diagnosis and follows them at 3, 6, 12, and 18 months. A secondary purpose of the study is to have this large cohort of breast cancer patients serve as a comparison group for the other two studies in the Behavioral Center of Excellence. Patients for the study were recruited from two clinical centers: Memorial Sloan-Kettering Cancer Center (MSK) and University of Texas - Southwestern University (UT-SW).

PART II – BODY: STATEMENT OF WORK

The primary activities during the past two years have been to complete study recruitment at the Memorial Sloan Kettering Cancer Center and at the University of Texas- Southwestern, and to complete participant follow-up. The tasks described in the original statement of work have not changed. However, delays in the Human Subjects approval from the Department of Defense moved the original timeline back over a year. Because of these delays, we received additional funding for a 5th project year and a no cost extension.

Task 1: Develop research protocol (months 1-15)

a. Finalize research questionnaires

The questionnaires were finalized and submitted with the 2002 report.

b. Review protocol with sites

The protocol was reviewed and approved by the Human Subjects Internal Review Boards (IRB) at all sites. The DOD Office of Human Subjects Protection approved the protocol for Memorial Sloan Kettering Cancer Center in April 2003, and the protocol for the University of Texas – Southwestern in February 2004.

Task 2: Develop data management system (months 3-12)

- a. Develop data management requirements
- b. Develop reporting requirements
- c. Develop contact record
- d. Train data manager

These tasks have all been completed. Please see the Biostatistics Core Report for a review of these ongoing activities.

Task 3: Identify, recruit, and conduct baseline interviews of eligible patients (months 16-33)

- a. Study sites identify and recruit eligible patients
- b. Patients recruited and interviewed

Recruitment has been completed at both sites. Because of the delays in obtaining Human Subjects Approval from DOD we extended recruitment until February 28, 2006, at which time 658 women were recruited to the study. Please see the below table for a distribution by age of study participants. The age category of 18-45 years with no menstrual bleeding was unable to be filled due to much lower than expected rates of hysterectomy and premature menopause in this age group. Recruitment proportions in the other age groups were 72.5%, 98.5%, 84%, and 71.5%, respectively, of our target goals. Even though we did not meet our recruitment goals in each age category, we will have sufficient power to examine quality of life and psychosocial differences by age among our study participants.

Table of Study Recruitment by Age Category as of February 28, 2006

Ages 18-45 (No menstrual bleeding)	Ages 18-45* (Menstrual Bleeding)	Ages 46 – 54 years	Ages 55 – 64 years	Ages 65+ Years	Total
4 .1%	145 22.1%	196 30.0%	169 25.9%	144 21.9%	658 100%

* Participants in the age 18-45 (menstrual bleeding) category are shared with Project 1: Menstrual Cycle Maintenance and Quality of Life Following Breast Cancer Treatment.

- c. Quality control (ongoing)

Quality control is an ongoing activity. See the Biostatistics Core Report for a review of these ongoing activities.

- d. Medical record review

Medical record review is completed at both sites 12 months from the date of the participants' recruitment. This task is ongoing, and will be completed for all participants in June of 2007.

- e. Data entry system developed

This task has been completed for both sites.

- f. Data entry of questionnaires (ongoing)

This task is being completed for the recruited participants.

Task 4: Ongoing follow-up of patients (months 19-73)

- a. Tracking of women in study
- b. Mailing of follow-up questionnaires

All women who have been recruited have been entered into a tracking data base. Follow-up forms are mailed at 2 ½, 5 ½, 11, and 17 months following baseline – for the 3- and 6-, 12 and 18- month follow-ups. To date, only 15 women have dropped out of the study. Reasons for study drop-out were:

- Not interested (6)
- Illness/treatment side effects (1)
- Could not be reached (3)
- Death (5)

The following table shows the number of follow-up questionnaires completed to date:

	3 mo. FU		6 mo. FU		12 mo. FU		18 mo. FU	
	N	%	N	%	N	%	N	%
Due	0	0.0%	0	0.0%	0	0.0%	4	0.6%
Due and out of window	35	5.3%	37	5.6%	57	8.7%	78	11.9%
Due and booklet returned	623	94.7%	621	94.4%	601	91.3%	521	79.2%
Not due	0	0.0%	0	0.0%	0	0.0%	55	8.4%
Not due-booklet returned	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total	658		658		658		658	

- c. Contacting non-responders

Women who do not return their survey by the due date are sent a postcard reminder. Follow-up phone calls are made if forms are not received 10 days after the postcard reminder is sent.

- d. Mailing of incentives

A drawing for gift certificates is held each quarter to reward participants for returning follow-up questionnaires. All participants who return their questionnaire booklets in a given quarter are entered into a drawing for a \$50 gift certificate from one of the following vendors: Lowe's Home Improvement, Home Depot, Wal-Mart, and a Long Distance Phone card. As of March 31, 2007, we have mailed out 58 gift certificate incentives. Only two people have refused a gift certificate.

- e. Follow-up medical record reviews

Medical record review is completed at both sites 12 months from the date of the participants' recruitment. Follow-up medical record reviews are completed only on the small proportion of patients (1-2%) for whom more information is needed due to incomplete data.

Task 5: Data Analysis and Report Writing (months 33-73)

- a. Data entry of questionnaires received from the participants:

Task on-going through October 31, 2007

- b. Data management and merging of baseline, follow-up and medical chart review forms:

Data files will be merged to create baseline and follow-up data files for statistical analyses at periodic intervals between May 1, 2006 and October 31, 2007.

- c. Data cleaning:

The project managers will work with the programmer in the Biostatistic's Core to conduct data cleaning during the creation of the study data sets.

- d. Data analysis:

Baseline data cleaning and analysis will begin in the summer of 2006. Follow-up data analysis is expected to begin during late 2006 and early 2007. Data analysis will continue after the end of the DOD grant funds.

- e. Presentation of results at professional meetings:

Task to be initiated in 2007.

- f. Initial manuscripts prepared:

Manuscripts will be prepared in the next 12 months using baseline quality of life data. Some examination of the short-term follow-up endpoints (e.g., 6 week, 3 and 6 months) regarding the quality of life and psychosocial outcomes, may also be initiated within the next 12 month period.

PART III - KEY RESEARCH ACCOMPLISHMENTS

- Completion of study recruitment
- Good retention of study participants from the 3 – 18 months follow-up assessment time points.

PART IV - REPORTABLE OUTCOMES

Avis, NE. "Survivorship and Aging." Invited presentation at Cancer SIG Preconference Course: Cancer and Aging: Challenges and Opportunities Across the Cancer Control Continuum, Society of Behavioral Medicine, Washington, D.C. March 21, 2007.

Part V - CONCLUSIONS

This section is not applicable at this point.

PART VI - REFERENCES

Not applicable

Project 3: Research on Optimal Recovery Practices in Breast Cancer (RESTORE)

Roger T. Anderson, Ph.D.

Paul Ribisl, Ph.D.

Breast cancer is one of the most prevalent diseases among women, and one of the most feared. Although society has benefited from advances in medical and surgical treatments leading to increased survivorship, there has been a general lag in the development of post treatment health care programs to improve the quality of life for women following breast cancer. RESTORE focuses on two issues post-surgery that affect the lives of women with breast cancer: quality of life and lymphedema. There is now ample data in the literature on fatigue, emotional distress, and the recovery phase from the diagnosis of cancer and its treatment to conclude that for at least some women psychosocial issues may be significant and lasting posing additional barriers to recovery from cancer. Further, as the majority of women now receive axillary node dissection, risk for lymphedema (swelling of the arm), leading to pain, psychological distress, and impairment of physical, vocational, social and sexual functioning is increasingly important. The goal of this project is to test whether a combined intervention program can improve health-related quality of life and physical functioning for women newly diagnosed with breast cancer. This program is a tailored exercise program, which includes a lymphedema prevention program, and patient education. Results from this study will be used to recommend post-operative cancer care strategies to enhance well-being and quality-of-life for women

breast cancer, quality of life, lymphedema prevention, exercise

Part I – INTRODUCTION

Breast cancer is one of the most prevalent diseases among women. Although advances in medical and surgical treatments have led to increased survivorship, there has been a general lag in the development of post-operative health care programs. This research project tests an intervention (with a control group) designed to enhance the quality of life and physical well-being of adult women recently treated for breast cancer in the Piedmont Triad region of North Carolina. We randomized 100 women with stage I, II or III breast cancer to one of the following: (1) usual care consisting of patient education, and 2) a comprehensive program of tailored exercise. Identification of eligible women occurred through medical and surgical oncologists' offices, and area Piedmont Triad cancer treatment centers. Age and stage eligible women were enrolled 6 to 12 weeks post surgery and followed for 18 months. The exercise programs were center-based and tapered to home sessions to promote high adherence levels by integration into daily life. The Comprehensive Tailored Exercise Program focused on improving muscle strength and flexibility, and also included a swelling prevention program focused specifically on arm exercises, massage techniques, and wearing of an elastic sleeve. Outcomes included change from baseline in the 6-minute walk test, and the FACT-B (Functional Assessment of Cancer Therapy – Breast) health-related quality of life scale during the 18-month period following randomization.

Part II – Body: ORIGINAL STATEMENT OF WORK

Task 1. Identify, contact, and recruit eligible women

- a. Recruit and consent eligible patients into the study (a 28-month period inclusive of months 09-36).

Status: Task Completed. 105 participants were recruited to this study. Originally, 200 participants were to be recruited to this trial. However, changes in surgical practice patterns from the more standard use of axillary node dissection to the use of sentinel node dissection, necessitated that the lymphedema primary outcome be removed from the study. This reduced the sample size needed to assess the quality of life and fitness outcomes to 100 participants. This sample size reduction was approved by the Wake Forest University Institutional Review Board, and by the DOD Human Subjects review board in March and April of 2004, respectively. The revision was formally enacted after the additional approval by the RESTORE Data Safety Monitoring Board (DSMB) in May 2004. Project data will still be sufficient to statistically determine if the exercise intervention is associated with changes in arm swelling.

Task 2. Conduct Baseline 1 visit.

- a. Schedule participant visits to Reynolda Campus for baseline visit 1 to assess fitness and Health-Related Quality of Life (HRQL).

Status: COMPLETED

Task 3. Conduct 3-month visit: Baseline 2.

- a. Assess QOL, fitness, swelling, anthropometrics and health status:

Status: COMPLETED.

- b. Assess resting metabolism and diet at GCRC:

Status: Completed

- c. Conduct baseline DEXA scan:

Status: COMPLETED

Task 4. Conduct Tailored Exercise Program (CTEP) to CTEP group.

- a. Develop and begin tailored physical activity.

Status: COMPLETED.

Task 5. Conduct 6-month follow-up visit.

- a. Assess QOL, fitness, swelling, anthropometrics and health status.

Status: COMPLETED

Task 6. Conduct 9-month follow-up visit. End center-based exercise phase.

- a. Assess QOL, fitness, swelling, anthropometrics and health status.

Status: COMPLETED

- b. Begin home-based exercise phase.

Status: COMPLETED

Task 7. Conduct 12-month Telephone Call.

- a. Assess Fatigue and HRQL.

Status: COMPLETED

Task 8. Conduct 15-month follow-up visit. (months 18-44).

- a. Assess QOL, fitness, swelling, and health status.

Status: COMPLETED

Task 9. Conduct final visit. (Months 21-47).

- a. Assess QOL, fitness, swelling, and health status.

Status: COMPLETED

- b. Assess resting metabolism and diet at GCRC.

Status: COMPLETED

- c. Conduct DEXA scan.

Status: COMPLETED

Task 10. Create analytic database.

- a. Develop study forms for web-based data entry.

Status: COMPLETED

Part III. KEY RESEARCH ACCOMPLISHMENTS

- 105 patients have been recruited to the study.
- All participants have completed study the 18 month follow-up period.

Part IV. REPORTABLE OUTCOMES

Adverse Events

Since the last report, we have recorded no adverse events.

Paper Presentations:

Preventing Lymphedema with Tailored Exercise: Exploratory Results from the RESTORE Trial. Kimmick G, Anderson RT, Mihalko S, McCoy T, Ribisl P. Poster presentation. Cancer Survivorship: Embracing the Future conference Washington DC, September 8 2006.

Part V. CONCLUSIONS

Not applicable at this time. Study follow-up was completed last fall, and the data sets have now been cleaned and prepared for analyses. The final year of this study will be spent in completing the baseline and follow-up main outcomes papers for this study.

Part VI. REFERENCES

N/A

Biostatistics Core Facility

L. Douglas Case, Ph.D.

The overall objective of the Biostatistics Core Facility for this Behavioral Center of Excellence is to collaborate with investigators in each project throughout all phases of the research. Major responsibilities are assumed for statistical, methodological, logistical, and computer related issues including study design, data collection, quality control, database development and management, data analysis, and manuscript preparation, each of which is vitally important to the success of the BCE. The Core Facility has been involved in all phases of these projects. Staff members have collaborated with individual investigators in defining objectives for each research project, defining end points to quantify treatment effect, selecting appropriate information for data collection, determining sample sizes that ensure adequate power, and developing randomization schemes that ensure valid treatment comparisons. The Core Facility will continue to be involved in these studies during close-out, data analysis, and manuscript preparation.

breast cancer, quality of life, data management, data analyses

PART I - INTRODUCTION

The main objective of the Biostatistics Core Facility is to collaborate with the investigators of each project in the analysis, interpretation, and reporting of study data collected during the grant period. Staff members initially collaborated with individual investigators in defining objectives for each research project, defining end points to quantify treatment effect, selecting appropriate information for data collection, refining data collection forms, determining sample sizes that ensured adequate power, and developing randomization schemes that ensured valid treatment comparisons. Subsequently, staff members collaborated with the investigators in designing and programming a web-based data entry and tracking system, implementing quality control features, and performing preliminary analyses. At this point in the center grant, the Biostatistic's Core Facility is primarily analyzing data from all projects, and working with study investigators to produce manuscripts, posters and presentations from the study data.

PART II – BODY: STATEMENT OF WORK

Task 1: Study Design (Month 1)

- a. Help formulate primary and secondary study hypotheses and define important outcome variables;**
- b. Determine sample sizes that ensure adequate power;**
- c. Develop randomization schemes that ensure valid treatment comparisons.**

Completed in Year 1

Task 2: Protocol and Form Development (Months 2 – 3)

- a. Assist with the development of Manual of Operations. Manuals of Procedure will be developed which will clearly define all procedures and contingency plans. All procedures will be tested before accrual of any patients.**
- b. Help develop concise, easily understood data collection forms. Assess their inter- and intra-tester reliability.**

Completed in Year 1

Task 3: Database Setup (Months 4 - 10)

- a. Design and implement a computer database management system. A computer database will be established that allows web-based data entry.**
- b. Design and implement quality control procedures for data checking, storing and updating data while maintaining security and confidentiality.**

- Completed the design in Year 1; this database continues to be maintained and enhanced with new forms and additional functionalities.
- Maintain security measures on data collected in all three projects. All data entered into the web site is saved onto a secure database server located in the Department of Public Health Sciences. The server is located behind the Wake Forest University Health Sciences' firewall and the data is backed up to tape nightly. These tapes are stored onsite in a fireproof cabinet for 2 weeks, after which they are moved offsite. Offsite, the tapes are stored in a lock box, in a vault, maintained by WFUSM Information Services. The web site utilizes Secure Socket Layer Encryption software to encrypt data moving to and from each user's PC. Website security authorization complies with HIPAA regulations. Access to each area of the web site is determined by access privileges based on role and is stored in a SQL Server database.

Task 4: Data Management (Months 11 – 40)

- Perform interim analyses and provide feedback to the investigators regarding patient accrual and quality control.**
- Tabulate and summarize measures of protocol adherence and numbers of dropouts for coded treatment group assignment and, when available, record reasons for lack of adherence or dropping out.**
- Develop graphical reports that dynamically show actual vs expected accrual. Develop programs to monitor for unexpected side effects and adverse events.**
- Check and clean data as they are collected.**

For Project 3, interim analyses were performed while accrual was ongoing, and summaries were provided for DSMB deliberations. Analysis of data from the all projects continued during the last year, leading to presentations, abstract, drafts of papers, manuscript submissions, and publications. (See the individual reports from each project for a summary of these activities.)

Tracking reports listing participant adherence and the receipt of participants' forms continue to be run weekly, so that participants can be contacted by coordinating center personnel if forms have not been received by their deadline dates.

Dropped participants reports are run for each project.

Quality Control Checks:

Menstrual Cycle Maintenance (Project 1):

We continue to perform quality control checks on the Menstrual Cycle Maintenance data. SAS programs were previously developed to check the validity of data within each form and to provide extensive error checking for chart reviews, demographic, medical history, medical history follow-up, symptoms, quality of life, and diary forms.

Age Differences (Project 2):

Quality control features were built into the screens (e.g., range checks, field checks, skip patterns, etc.) to allow data validation at the point of data entry. Also, validation error reports were implemented, displaying outstanding errors for all forms, by Participant ID.

Restore (Project 3):

Quality control features were programmed (e.g., range checks, field checks, skip patterns, etc.) to allow data validation at the point of data entry. Follow-up has been completed on this study. An analysis file was created; additional cross-form edit checks were done at that time and queries addressed by the project manager from Project 3.

Task 5: Analysis and Report (Months 41 – 72)

- a. Convert the database to SAS and ASCII data sets for final analyses.**
- b. Help develop a publications and presentations policy.**
- c. Perform final data analyses and help prepare manuscripts and reports.**

Once all the data have been collected, edited, and corrected, a final SAS database will be created, including documentation for variable names and transformations. SAS transport and ASCII datasets will also be created to ensure maximum portability. These datasets will be stored on tape and on CDs (or the medium appropriate at that time). These tasks will be completed during the carryover period as follow-up is completed.

Preliminary analysis files have been created for each project. Follow-up continues on Projects 1 (Menstrual Cycle Maintenance) and 2 (Age Differences), so the analysis files for these projects will be updated every six months. Follow-up is complete for Project 3 (Restore), and an analysis file has been created. Some changes will be made to this file in the coming months to make it easier for study personnel to use. Documentation will be completed in the coming grant period.

New Task 6: Continuation of Analysis and Reporting (Months 61 – 72)

Data management (quality control and creation of analysis files), data analysis and manuscript preparation will take the majority of our efforts in the remaining grant months. Planned papers are listed below. Most of these analyses have begun and drafts have been written for many of these papers.

- baseline paper for the Restore study (Project 3);
- effect of the exercise intervention on quality of life and physical function (Project 3);
- effect of the exercise intervention on arm swelling (Project 3);
- fertility and pregnancy outcomes following cancer treatment (Project 1);
- baseline paper from the age differences study (Project 2);
- effect of age on quality of life and coping following diagnosis and treatment (Project 2).

PART III – KEY RESEARCH ACCOMPLISHMENTS

- Analysis files created/updated for each study.
- Analyses were completed on published papers, abstracts and poster presentations in 2006-2007 for the Menstrual Cycle Maintenance Study. (See the report from Project 1 for a description of these materials.)
- Analyses were completed for a 2007 presentation on the effect of age on quality of life. (See the report from Project 2 for the citation for this presentation.)
- Analyses were completed for abstracts and poster presentations in 2006-2007 for the Restore Study. (See the report for Project 3 for the citations for these presentations.)
- Continued analysis and manuscript writing for:
 - the clinical and quality of life main outcome data (Project 1);
 - the effect of chemotherapy on the incidence of amenorrhea (Project 1);
 - spirituality in young women with breast cancer (Project 1);
 - depression during the first 3 years following diagnosis (Project 1); and
 - baseline Restore paper (Project 3).

PART IV – REPORTABLE OUTCOMES

Papers, abstracts, and presentations prepared with the assistance of the Biostatistics Core are reported in the summaries of each separate project.

PART V - CONCLUSIONS

During the last year, more focus was placed on creating analysis files and performing data analysis. Papers have been published on bleeding, sexual function and swelling, and additional papers have been written on amenorrhea, spirituality, depression and quality of life. Follow-up was completed for Project 3. Patient follow-up is continuing for Projects 1 and 2. During the next period, follow-up will be completed and analyses will be done to address the primary and secondary aims of each study.

PART VI – REFERENCES

N/A