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About 15% of the 186,000 estimated annual cases of breast cancer this year will occur in women of childbearing age. Most will undergo adjuvant chemotherapy and almost half will suffer therapy-induced menopause. Even without desire for childbearing, the quality of life of these young patients may be compromised by premature menopause with symptoms such as hot flashes, sleep disturbances, decreased libido, and vagina dryness. Very little is known about the incidence, onset, time course, and symptomatology of premature menopause induced by breast cancer therapy and virtually nothing is known about its impact on the young survivor's quality of life. No prospective study heretofore exists. A comprehensive analysis on a large prospective study cohort as proposed herein will elucidate determinants of premature menopause. Now unavailable, such an individual risk profile of premature menopause could be critical to the clinician and to the young patient in considering options and decision-making about chemotherapy.

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Menstrual Cycle Maintenance and Quality of Life Ater Breast Cancer Treatment: A Prospective Study

Jeanne Petrek, MD

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INTRODUCTION

MENSTRUAL CYCLE MAINTENANCE AND QUALITY OF LIFE: A PROSPECTIVE STUDY

PROTOCOL SUMMARY - MODIFICATION APPROVED OCTOBER 28, 1997

INTRODUCTION The frequent morbidity associated with most cancers and their treatments make the measurement of health-related quality of life a critical mechanism for determining the toll of the entire disease. Young breast cancer patients additionally may face treatment-induced menopause and with it may experience hot flashes, mood changes, sleep disturbances, vaginal dryness, and the cascading effect of anxiety and depression. In the United States, Bowman Gray University has particular expertise in quality of life with naturally occurring menopause. Bowman Gray is the Co-ordinating Center in this issue for the Women's Health Initiative, funded by the National Institute of Health, which will accrue more than 100,000 study subjects.

Very little is known about the incidence, onset, time course, and symptomatology of premature menopause induced by breast cancer therapy. No prospective study exists. The purpose of the present study is to identify determinants of treatment-related amenorrhea and its effect on quality of life in a cohort of young breast cancer patients.

SUMMARY OF EXPERIMENTAL DESIGN This multi-center study, under the direction of Jeanne Petrek, will include patients from Memorial Sloan Kettering Cancer Center, M.D. Andersen Cancer Center, and Bowman Gray University.

Extensive baseline data will be collected by an in-depth chart review and interview for additional data. Information will be gathered on demographic, clinical, menstrual/reproductive and treatment variables.

The study intervention consists of collecting data on bleeding through the bleeding diary and on health-related quality of life through specific questionnaires. The data collection instruments will be obtained at baseline and every six months. Follow-up will range between 24 - 42 months for participants. The 6-month follow-up contact provides an opportunity to collect data on study parameters and monitor the status of reproductive events, disease recurrence, complications of treatment such as lymphedema, or other illnesses. Data collection instruments will be mailed to each participant at regularly scheduled 6-month intervals accompanied by a stamped, addressed envelope. If study forms are not returned within three weeks by the participant, the participant will be called. The study measurements are : 1. Bleeding Diary, 2. Rand Health Status Profile, 3. Beck Depression Inventory, 4. Sleep Disturbance Scale, 5. Watts Sexual Functioning Questionnaire, 6. Physical symptom check list, 7. Rand Social Support Questionnaire, 8. Spirituality Sub Scale, 9. Fact B, 10. Self Concept Scale, and 11. Interval Medical History.

OBJECTIVES

The proposed study design. The study strategy is to evaluate menstrual cycle maintenance and its effect on the quality of life. Data on menstrual cycle maintenance, quality of life and some short term data on reproductive events will be obtained during the study period but an essential follow up period for disease-free survival will be beyond the study limits. Additional funding will be obtained in order to continue the close contact established on this singular database established under the Department of Defense funding.

Study Objectives. The overall goal of the proposed research is to recruit and follow young breast cancer patients aged 45 and younger, in order to examine menstrual cycle maintenance, a surrogate of ovarian function.

Primary Study Objectives.

1. To describe the bleeding patterns of young breast cancer patients (including those without systemic therapy): frequency, duration, amount.

2. To describe the incidence, symptomatology, and time course of treatment related amenorrhea i.e., no menstrual bleeding for more than six months after the start of the treatment

3. To compare health-related quality of life (HRQL) of women who are experiencing amenorrhea to that of women who are not experiencing amenorrhea.

Secondary Objectives.

1. To examine possible predictors of treatment-related amenorrhea including age, smoking history, race, and treatment variables.

BACKGROUND AND RATIONALE

It has long been established that systemic cancer therapy can cause premature ovarian failure. While some of the rare severe consequences of cancer chemotherapy, such as leukemogenesis and cardiac damage are being confronted and evaluated [1], ovarian failure seems relatively neglected. Therapy-induced menopause has been poorly characterized as to the incidence, time course and permanence, as reviewed below; it has been wholly uncharacterized as to its symptomatology and its impact on the quality of life.

Background of research in systemic therapy-induced menopause There are probably two reasons for the meager analysis of therapy-related menopause: in the past, menopause induction itself in adjuvant chemotherapy programs was thought to increase survival from breast cancer; and secondly the occurrence of menopause, a natural phenomenon in every woman's later life, was deemed not so important.

However, a 1994 review of previous adjuvant trials concludes that the benefit of chemotherapy in the premenopausal patient is not dependent upon menopause induction[2] as does the even more recently published 20-year results of the Milan study.[3] Also at this time natural menopause is undergoing scrutiny as to quality of life and the predisposition to chronic diseases.[4] The extent of the scanty scientific data systemic therapy-induced menopause is noted in that review "Amenorrhea following chemotherapy for breast cancer: Effect of disease-free survival".[2] Forty key trials which included premenopausal patients on adjuvant chemotherapy (i.e., no evidence of metastatic disease) were examined. Only 15 papers reported incidence of amenorrhea.

Acknowledged factors in menopause induction The two factors consistently found are age and drug/dose. The category of drugs most likely to induce ovarian failure is that of the alkylating agents, such as cyclophosphamide -- the most common drug in breast cancer treatment, while antimetabolites have lesser effect.[5] One study found that amenorrhea in similar age women occurred in 63% treated with CMF (cyclophosphamide, methotrexate and 5-fluorouracil) versus 70% with cyclophosphamide alone. This indirectly shows little effect on ovarian function for the two antimetabolite agents.[6] In a study of 18 premenopausal patients, amenorrhea occurred after a mean cyclophosphamide total dose of 9.3 gr in women younger than 40, and after a mean dose of 5.2 gr in women older than 40.[7]

Of the non-alkylating agents, doxorubicin is the most common in breast cancer therapy. In a study of 128 patients less than 35 years old treated with the drug in combination with cyclophosphamide and 5-fluorouracil, 58% had regular menstrual cycles after chemotherapy, 32% experienced temporary amenorrhea and 9% permanent amenorrhea. [8] The potential for amenorrhea with other categories of antineoplastic agents has not been extensively studied. For new drugs, such as taxol[9] or vinorelbine[10], no data are available: amenorrhea is not even mentioned in two recent reviews. Specific aspects of chemotherapy have not been considered such as the modern use of cytokines and role of serious intercurrent illnesses, e.g., hospitalization for neutropenia.

There are little data regarding ovarian failure as a result of tamoxifen alone since the practice is rare. Tamoxifen may be prescribed to premenopausal patients with permanent menopause if estrogen receptors are found on their tumors. The mechanism for tamoxifen-induced amenorrhea, which has been reported [11] is not known. In premenopausal women on Tamoxifen estrogen levels are frequently elevated and the normal feedback could be lost[12] causing amenorrhea.

Limitations of retrospective studies on menstrual cycle maintenance In these reports, weaknesses include variable definitions of temporary/permanent amenorrhea, variable lengths of followup on menses or no followup after chemotherapy administration, and retrospective data collection. It appears that one study[13] collected prospective data by twelve monthly questionnaires on 95 patients but with no menses data beyond the year. Most importantly, the study design in these reports is focussed on the analysis of disease-free survival and overall survival in a typical double or triple arm therapy protocol. Therefore, data on amenorrhea, a non-life threatening complication, is understandably relegated to a secondary analysis. Such data are weaker than that obtained in a study designed and conducted for primary endpoint of amenorrhea.

Two broad categories of age are typically reported -- less than 40 years and greater than 40 years. In one study[14] of 221 patients the category of patients over 40 years is subdivided into greater of less than 45 years. It is clear that menopause varies greatly by age regardless of the particular regimen.[2] Nevertheless, beyond stating that 38% of women aged 39 years or less have permanent amenorrhea after 12 months of CMF,[15] there is no characterization of who did or did not undergo permanent menopause.

Unstudied factors associated with age of natural menopause In spite of these limitations, the most important factors causing the wide range of premature menopause incidence within a particular age group and chemotherapy regimen may be factors influencing age at natural menopause. These have never been assessed in a breast cancer population or any cancer population.

In multivariate analyses of longitudinal study population, factors influencing the age of natural menopause include, smoking history,[16-17] parity, [17,18] body mass index[16,19] history of irregular periods before age 25 or first birth,[18] and socioeconomic class / education / income.[17-19] These factors could be responsible for one 35 year old breast cancer patient becoming permanently menopausal while another 35 year old woman maintains normal menses. It is intuitive that ovarian failure is not a random phenomenon and that a comprehensive analysis as proposed will shed light on the determinants of therapy-induced menopause.

Health related quality of life in the breast cancer survivor Recent years have witnessed a growing recognition among cancer researchers of the importance of systematically measuring health-related quality of life (HRQL) and psychosocial factors, both to characterize the health status and well-being of this patient population, as well as to assess treatment efficacy.[20-23] The frequent morbidity associated with most cancer and their treatments make the measurement of HRQL and psychosocial variables a critical mechanism for determining the toll of the entire disease. Common responses of patients with breast cancer include anxiety, depression, anger,

guilt and fear.[24-27]

Additionally young breast cancer survivors face the possible impact of specific chemotherapy agents on ovarian function. Those women may experience such symptoms as changes in mood, sleep disturbances, vaginal dryness, and hot flushes and the cascading effect of anxiety and depression. For those women who were desirous of becoming pregnant following breast cancer, a premature menopause may be most distressing particularly for those women who had delayed childbearing and were childless.

In the past 10 years, significant progress has been made in the reliable and valid assessment of health related quality of life (HRQL) and other psychosocial variables. [27-30] Although there has been some debate regarding the definition of HRQL, a recent international conference co-chaired by one of the proposal's co- investigators - Dr. Sally Shumaker, reached agreement on the fundamental dimensions essential to any HRQL assessment.[31] These include: physical functioning, psychological functioning, social functioning and role activities, and the individual's overall life satisfaction and perception of their health. For specific populations, other commonly assessed dimensions of HRQL may be important, such as sleep disturbance, pain, symptoms, and intimacy and sexual functioning.

Data suggests that aspects of HRQL and psychosocial factors (e.g., emotions, family relations) are rated by patients as more important to their well-being than clinical factors directly related to the effects of the disease and its treatment[32] further underscoring the importance of measuring HRQL in clinical research in breast cancer. Thus far the potential multiple outcomes of breast cancer treatment in young women have not been investigated: morbidity and mortality, menopausal symptoms, and the psychological impact of premature menopause and the loss of childbearing potential.

Results on the health-related quality of life from the proposed study may assist the perspective on hormone replacement for breast cancer survivors.[33] For example, if the proposed study shows no decrease in health-related quality of life due to menopause itself, then recommendations of hormone replacement to breast cancer survivors will be considered more for prevention of the long-term sequelae of osteoporosis and heart disease and less for "making the patient feel better."

Menstrual cycle maintenance: fertility and pregnancy outcome after systemic therapy The assisted reproductive methods for the inception and maintenance of pregnancy have been described in the literature for older women with natural menopause.[34] However, it is very unlikely that the breast cancer patient will undergo the oral and systemic high-dose hyperstimulation required for this procedure. In those breast cancer patients who maintain menstrual cycles after systemic therapy, even general figures on fertility are unknown.[35-36] In a retrospective cohort study of 2,283 adolescent survivors of all cancers from 1945 to 1975, relative fertility (healthy siblings were controls) was decreased and varied with cancer and whether chemotherapy and/or radiotherapy was administered.[37]

Even though apparently normal menstrual cycling may be maintained after systemic

therapy and the patient chooses to become pregnant, the incidence of pregnancy and successful childbearing is unknown. The above general studies on adolescent cancer populations may be indicating subtle and unmeasured defects in fertility in spite of maintained menstrual cycles.

The potential of breast cancer chemotherapy on adverse outcome of subsequent pregnancy has not been specifically evaluated. However, a study reported on 58 pregnancies occurring after treatment for various malignancies and found no excess congenital anomalies. The study noted a total of 40% abnormal pregnancies, with most of these occurring in the first year after chemotherapy. The abnormal pregnancies consisted mainly of premature termination and low birth weights both of which was attributed to dysfunction of the uterine hormonal gestational milieu.[38]

POTENTIAL BENEFIT FOR SOCIETY

About 15% of the 186,000 estimated new cases of invasive cancer this year will occur in women of childbearing age and the majority will be long-term survivors. Most young women with invasive breast cancer will undergo adjuvant chemotherapy and almost half will suffer therapy-induced menopause. Foregoing motherhood either for iatrogenic infertility or for concern about its safety can be overwhelmingly distressing. However, even without desire for childbearing, the quality of life of these young patients may be compromised by premature menopause with symptoms such as hot flashes, sleep disturbances, decreased libido, and vagina dryness.

Very little is known about the incidence, onset, time course, and symptomatology of premature menopause induced by breast cancer therapy and virtually nothing is known about its impact on the young survivor's quality of life. No prospective study exists. Since the improved survival following chemotherapy appears independent of menopause induction in recent data, the possibility of premature menopause should be factored into the risk/benefit assessment.

A comprehensive analysis on a large prospective study cohort as proposed herein will elucidate determinants of premature menopause. Now unavailable, such an individual risk profile of premature menopause could be critical to the clinician and to the young patient in considering options and decision-making about specific therapy. Not only must the quality of life with premature menopause be considered in the young, but also the long term predisposition to osteoporosis, heart disease, and genital atrophy, particularly in those with a good prognosis in whom a long survivorship is expected.

BODY

EXPERIMENTAL METHODS

See Appendix A which is the proposal of re-organization of the research activities and Appendix B which is the approval for the re-organization. As explained in detail in the appendices, the re-organization of the research was necessary due to the departure from Memorail Sloan Kettering of two key personnel form the data management section: Dr Ruby Senie and May Nah Ho. The following is the restructured activities for the research, with approval of an extension of an 12 months without additonal funds.

Clinic Prinicpal Investigators:

Memorial Sloan Kettering Cancer -- Center Jeanne Petrek, MD
MD Anderson Cancer Center -- Eva Singletary, MD
Bowman Gray -- Electra Pasket, PhD

Principal Investigators at each of the three clinic sites will direct their local study coordinator in meeting the scientific and operational objectives of the study. They will provide leadership in developing the study protocol and forms, develop recruitment plans specific for their sites and accrue patients in a timely manner. An important component of their role will be to review and correct all clinical data on the extensive baseline medical and treatment forms and the followup forms. Clinic Investigators will attend all Steering Committee meetings and contribute towards the analysis and publishing of study data.

Clinic Study Coordinators and Co-ordinating Center

Study Coordinators will work with individuals at the Coordinating Center in the development and testing of forms and the Manual of Operating Procedures. Study Coordinators will be responsible for identifying and recruiting participants for the study by working closely with clinicians in Surgery, Radiation Oncology, Medical Oncology and through the local Tumor Registry at their particular clinic site. The clinic study coordinator will be responsible for explaining the study and obtaining informed consent from the participant and securing release for medical records from other physicians. This individual will complete the comprehensive chart review dealing with diagnosis, surgery, radiation, medical oncology, pathology and bleeding history as well as obtaining all baseline data collection items through interview as necessary. All data will be reviewed by the local principal investigator prior to mailing the information to the Coordinating Center. This individual will participate in the Steering Committee meetings and in the Study Coordinators/Quality Control Meetings.

Since 1990, faculty in the Department of Public Health Sciences at the Bowman Gray

School of Medicine have served as the coordinating center for several menopause-related, women's health, or cancer studies, which have contained HRQL and psychosocial endpoints. The following table provides a listing of the major studies, in which the PI and Co-Investigators of the coordinating center for the current project have been involved:

Study	Funding	Size	Investigators
Postmenopausal Estrogen/Progestin Intervention Study (PEPI)	5 NIH Institutes	7 CC; n=875	Legault
PEPI Safety Follow-up Study: PEPISF	NHLBI	7 CC; n=875	Legault
Women's Health Initiative: Clinical Center	NIH/NHLBI	1 CC; n=2,500+	Paskett
Women's Health Initiative Coordinating Center Subcontract	NIH/NHLBI	40 CC; n=100,000+	Naughton, Shumaker
Transdermal Estradiol/NETA Patch - US	Phone-Poulenc Rorer	20 CC; n=3,000	Naughton, Shumaker
Transdermal Estradiol/NETA Patch - Europe	Phone-Poulenc Rorer	24 CC; n=2,000+	Naughton, Shumaker
Hepatic Metastases in Colorectal Cancer	CALGB Foundation	12 CC; n=380	Naughton
Soy Estrogen Alternative	NHLBI	1 CC; n=340	Naughton
HRQL and Treatment for Small Cell Lung Cancer	Bristol Myers-Squibb	14 CC; n=350	Naughton, Shumaker

On average, greater than 90% completion has been obtained on all study forms, excluding people who were dropped from the protocols due to death. Based on our previous experience in coordinating clinical trials and prospective studies, we are not anticipating that missing data will be a major issue in the current study. In fact, a comment we have heard frequently from female participants has been that they appreciate the fact that clinicians/researchers are actually interested enough in their life quality to be asking questions which could potentially assist other persons in the future.

Recruitment

A total of 800 women will be recruited from three clinical centers:

Bowman Gray School of Medicine	188
M.D. Anderson Cancer Center	252
Sloan-Kettering Cancer Center	360

Local sources of patients have been identified by the participating investigators. One or more of the following strategies will be utilized in recruiting participants into the study at each clinical center:

1. Patient Identification Through Tumor and Surgical Registries. The majority of patients will be identified through tumor and/or surgical registries at the participating institutions. Once women with stage 1-3 breast cancer have been identified, the patients' oncologists/surgeons will be contacted by clinic staff to obtain approval to approach the patient. If the physician approves, the patient will be approached at the clinic site, (if she is scheduled for a follow-up or treatment visit), or the patient will be sent a letter describing the purpose of the study, which will be followed by a telephone call. The clinic staff person will screen the person to ensure she meets the eligibility criteria, and then will ask the patient to participate in the study is she is eligible. The patient will be scheduled for the baseline study clinic visit at which time she will sign the informed consent form, a medical record release, and will complete all baseline study questionnaires. The patients' physicians will be notified as to whether the patient has enrolled in the study.

2. Referral Through Physicians. Participants will also be identified by the clinical center's participating investigators, oncologists, surgeons, and radiologists. In most instances, these physicians will have already explained the study to the participant, and the clinic staff will contact the patient to invite her to participate in the study. The patient will be screened to ensure that she meets all eligibility criteria. If the patient is eligible and willing to participate, she will be scheduled for a baseline clinic visit. At this visit, the patient will sign the informed consent and medical record release forms, and will complete all baseline questionnaires. Her physician will be notified as to her decision to participate.

3. Self-Referral. Women receiving treatment from any of the three centers may hear of the study and want to participate. These women may self-refer with physician approval. They will be screened for study eligibility, and will be asked to join the study if the eligibility criteria are met. The patients will be scheduled for the baseline study clinic visit at which time they will sign the informed consent form, a medical record release, and will complete all baseline study questionnaires. The patients' physicians will be notified as to their decision to enroll in the study.

The Clinical Coordinating Center at the Bowman Gray School of Medicine will monitor recruitment and issue monthly recruitment reports to each participating institution. Strategies will be developed to assist the clinical centers in meeting their recruitment goals, if necessary.

3.d. Informed Consent

In accordance with local institutional review board guidelines, informed consent procedures and consent forms will vary somewhat by clinical center. All consent forms will stress the voluntary and confidential nature of participation in this research investigation. Patients will be told that a decision not to participate in this study will in no way influence their treatment or medical care. Study staff will inform the participants about the purpose of the study and their requirements for participation in this research protocol. Patients will be told that they may drop out of the study at any time without penalty.

If the patient agrees to participate in the study, she will sign the informed consent form at the baseline clinic visit, prior to the completion of any study questionnaires.

3.e. Primary Physician Contact

Upon entering the study, each participant will be asked to name her primary care physician, as well as her oncologist, radiologist and/or surgeon. The participants will be asked to indicate which of these physicians has primary responsibility for their treatment (i.e., the physician they see most often for follow-up care). Once this physician has been named, a letter will be sent from the Principal Investigator of each of the clinical centers requesting the patients' medical records. Once the records are received, a clinic staff person at each clinical center will abstract the medical chart using the Medical Chart Review Form.

It should be noted that all three of the Principal Investigators of the clinical centers have close working relationships with the oncologists, radiologists, and breast surgeons at their respective institutions. Many have collaborated on research projects in the past, and already have procedures in place to ensure the process of identifying participants and accessing clinical data and charts for research investigations.

3.f. Measures

3.f.1. Baseline Clinic Visit. The following study forms will be completed at the enrollment/baseline clinic visit, which will be approximately 1 hour and 15 minutes in length. The baseline administration time for all study questionnaires is approximately 35-45 minutes. These estimates are based on the pre-testing of these forms at the Bowman Gray School of Medicine with young breast cancer patients currently undergoing treatment. Participants will be provided with opportunities to rest during the completion of the study forms at baseline, if necessary. The study coordinators will also be able to assist the patients as needed.

The following information will be obtained at baseline:

1) Demographics. Basic demographic information will be obtained on all participants including: age, marital status, educational background, employment status, occupation, and income. (This questionnaire takes approximately 3 minutes to complete.)

2) Medical and Reproductive History. Information will be collected regarding the patients' comorbid conditions; family history of breast and ovarian cancer; and reproductive history, including parity, pelvic surgery, menstrual cycling, contraceptive use, and plans for future childbearing. (This instrument is completed in approximately 5-7 minutes.)

3) Arm and Hand Swelling. Treatment-related swelling of the arm and hand will be assessed to document the occurrence, duration, and circumstances surrounding arm and hand swelling. (This instrument takes approximately 1-3 minutes to complete.)

4) Personal Habits Questionnaire. Information will be obtained regarding the patients' smoking and alcohol use, height and weight, weight cycling, and exercise habits. (This

instrument takes approximately 3-5 minutes to complete.)

5) Health-Related Quality of Life. The following instruments and subscales will compose the quality of life questionnaire. All of these measures are standardized instruments, with excellent psychometric properties. All instruments were developed using a combination of focus groups, patient interviewing, and adaption from other established scales in the area of interest. Thus, both qualitative and quantitative methodologies were used to develop each scale.

a) Functional Assessment of Cancer Therapy - Breast (FACT-B). This 44 item questionnaire is a multidimensional HRQL scale. This instrument was developed after extensive interviewing and testing with cancer patients, and has excellent psychometric properties. This scale assesses the patients' physical well-being, social/family well-being, relationship with doctor, emotional well-being, fulfillment/contentment, and concerns specific to breast cancer patients. Scores can be calculated for each of the 6 subscales, and a total HRQL score composed of all 6 subscales can be calculated as well. (This scale takes approximately 5-10 minutes to complete.)

b) Beck Depression Inventory. This is a 21-item scale that will be used to assess the depressive symptomatology/general distress of the participants in the study. This instrument has been used with a variety of clinical and non-clinical populations, and has been validated as a reliable screening tool for depression. A total score is calculated from this instrument. In general, scores above 15 are considered to indicate persons who need further evaluation to determine if clinical depression exists. (This inventory takes approximately 5-7 minutes to complete.)

c) Physical Symptoms Checklist. Physical symptoms associated with breast cancer treatment and menopause will be assessed. A total score is calculated from this scale to indicate both the occurrence and bothersomeness of physical symptoms. (This checklist takes approximately 3-5 minutes to complete.)

d) Sleep Disturbance Scale. Sleep patterns and sleep quality may be disrupted by treatment regimens and physical and emotional symptoms. Lack of restful sleep has been related to greater emotional distress and depressive symptomatology, as well as to general fatigue, in both clinical and non-clinical populations. To measure these effects, a 6 item sleep disturbance scale will be used to assess the overall quality of the participants' sleep. This scale was developed for an international study evaluating the effect of hormone replacement on peri-menopausal women. This scale was recently validated on 70,000 women from the baseline data of the Women's Health Initiative, which is examining the impact of hormone replacement therapy, diet, and calcium/vitamin D on the long-term morbidity and mortality of post-menopausal women. A total score is calculated from this scale. (Completion time for this scale is approximately 1 minute.)

e) Watts Sexual Functioning Questionnaire. The arousability and satisfaction subscales of the Watts Sexual Functioning Questionnaire will be used to assess the impact of treatment and/or amenorrhea on sexual functioning. Two subscale scores are calculated from these items, one for arousability and one for satisfaction with sexual

activity. (These subscales take approximately 2-3 minutes to complete.)

f) MOS Social Support Questionnaire. The social support questionnaire developed in conjunction with the Medical Outcomes Study, completed by the RAND Corporation, will be used to assess the amount of instrumental and emotional support available to the participants. Social support has been found to be an important predictor of adherence to treatment regimens, one's emotional health, and overall health-related quality of life. This 20-item measure produces a total score, as well as 4 subscale scores: tangible support, affectionate support, positive social interactions, emotional-informational support. (This scale takes approximately 5 minutes to complete.)

g) Self-Concept Scale. This 10-item scale assesses the participants' satisfaction with different areas of their body and their overall weight. Persons undergoing surgery for breast cancer may experience an alteration in their perception of their body image, which may affect their psychosocial status and intimate relationships. This scale is being assessed as a secondary HRQL endpoint, and was developed by Dr. David Cella, (Director, Center on Outcomes Research and Education at Northwestern University), through his work with breast cancer patients. (Administration time for this instrument is approximately 1-2 minutes.)

h) Spirituality Subscale. Spiritual beliefs have been identified recently as an important predictor of patients' coping and hopefulness for the future when dealing with a serious illness. To measure this construct, we will be using a 7-item scale developed by Dr. David Cella. (Administration time is approximately 1 minute.)

6) Monthly Menstrual Bleeding Diary. At the baseline visit, patients will be instructed as to how to complete the menstrual bleeding diary. The participants will be asked to indicate on the diary each day whether they experienced either "no bleeding," "spotting," or "bleeding" (i.e., mild, moderate, or heavy). From this form, the frequency, duration, and amount of menstrual flow can be calculated for every participant each month.

7) Medical Chart Review. Medical chart reviews will be performed by clinical staff on all patients following the baseline clinic visit. The information to be obtained includes the: date of breast cancer diagnosis, stage and grade, size and number of positive lymph nodes, estrogen and progesterone receptors (positive and negative), treatment prescribed (e.g., surgery, radiation, and/or chemotherapy; adjuvant therapy), dose and duration of treatment, whether reconstructive surgery was performed, current medications, comorbid conditions, and patients' height and weight.

All data forms completed at the baseline visit will be checked for completeness by the study coordinators before the patient has left the clinic. Any missing items will be double-checked with the participants to inquire as to whether they intended to leave items blank or chose not to answer the questions. Staff will also be asked to check the participants' response to question #9 on the Beck Depression Inventory to see if the patient is strongly considering suicide. Patients who make a response of "3" on question 9 will be referred to the Principal Investigator of the

respective clinical center for immediate physician follow-up. (See Section 3.g. Alert Values below.)

3.f.2. Follow-Up of Study Participants. Participants will be followed at six month intervals from the date they enroll in the study. Follow-up will range between 24 and 36 months for all participants. Data collection during the follow-up period will be centralized in that all follow-up forms will be mailed to participants, along with a self-addressed stamped envelope, at 6 month intervals by the Clinical Coordinating Center staff at the Bowman Gray School of Medicine. If the study forms are not returned to the coordinating center in a timely manner (i.e., within 15 days of the date the forms were mailed), a member of the coordinating center staff will complete a reminder call to the participants and complete a phone interview, if necessary. Because only updates of several of the forms will be required at the 6 month assessment points, the questionnaire completion time will be shorter at follow-up (i.e., approximately 25-35 minutes).

Once the follow-up questionnaires have been received by the clinical center, the project managers will examine each returned follow-up questionnaire for completeness. Participants with greater than 10% missing data on any of the study forms will be telephoned in order to reduce the occurrence of missing data.

The project managers will also score the Beck Depression Inventory, and check whether response "3" was marked on question #9 of this instrument. If the total score is 16 or greater and/or if the participant marked response "3" to question 9, the principal investigator of the participants' institution will be notified immediately. (See section 3.g. below.)

3.f.2.a. Follow-up Measures

The measures described below will be mailed to the participants during the follow-up period:

1. Demographic and Contact Information: Updates

2. Medical and Reproductive History: Updates will be completed on the patients' co-morbid status, menstrual cycling, contraceptive use, pregnancies and outcomes, and plans for future childbearing.

3. Arm and Hand Swelling Form

4. Personal Habits: Updates on patients' smoking and alcohol use status, height and weight, and exercise habits.

5. Health-Related Quality of Life Form

6. Menstrual Bleeding Diaries. The monthly menstrual bleeding diaries will be completed each month from the patients' time of enrollment to the end of the study data collection

period (i.e., April, 2001). Patients will be instructed to return the diaries to the clinical coordinating center every three months. The coordinating center will, in turn, mail the participants the next consecutive, three months of diaries each quarter. Unusual bleeding patterns will be determined, and the principal investigators of the participating institutions will be notified, if necessary. (See section 3.g. below.)

7. Medical Chart Review. Medical chart reviews will be performed on patients who have serious complications resulting from treatment, undergo additional treatment(s) and/or have a cancer recurrence during the study period. Information to be obtained on these individuals includes the stage and grade of cancer, size and number of positive lymph nodes, estrogen and progesterone receptors, prescribed treatment, medications, and comorbidities.

3.g. Follow-up Alert Values Safety Monitoring.

During the course of the study certain safety monitoring procedures will be maintained to detect unusual bleeding patterns and higher than average rates of depressive symptomatology. The operational definitions of these two alert values are described below:

3.g.1. Unusual Bleeding Patterns. Participants' bleeding patterns will be recorded on the monthly bleeding diaries. Alert values for bleeding and spotting have been defined as follows:

1. Any episode of bleeding lasting longer than eight days. (A bleeding episode is defined as two or more consecutive days of bleeding or spotting bounded by at least two bleeding-free days.)

2. An interval between bleeding episodes of less than twenty-four days.

3. "On and off" bleeding within a 15 day period (e.g., 3 days bleeding, 2 days no bleeding, 4 days of bleeding).

A notice has also been placed on the bottom of the bleeding diary form asking the women to call their physician if they experience any unusual bleeding in terms of frequency, duration, or amount.

3.g.2. Depressive Symptomatology. The Beck Depression Inventory will be used, in part, as a screen for clinical depression. A cutoff score of 16 or greater is indicative of individuals who are experiencing higher than average depressive symptomatology, which could indicate the presence of clinical depression.

Item 9, response choices #3 on the Beck Depression Inventory also concerns whether the person is considering suicide. Persons who mark either response #3 ("I would kill myself if I had the chance.") will be referred for immediate consultation.

3.g.3. Process of Referral for Alert Values. For both unusual bleeding patterns, and the detection

of higher than average depressive symptomatology and/or the consideration of suicide, the Principal Investigators of the Clinical Centers will be notified using the following procedures:

At baseline, the clinic staff persons will be asked to examine question #9 of the Beck Depression Inventory to see if the participant marked response category "3." If the person marked this category, the PI of the clinical center will be notified. The PI, in turn, will notify the participants' designated physician for further evaluation for clinical depression.

At the follow-up assessments, the Principal Investigators of the clinical centers will be contacted should any of their participants have an unusual bleeding pattern (as described above), a Beck Depression Inventory score of 16 or greater and/or if the participant marked response "3" on question 9 of this form. The Principal Investigators will then be responsible for contacting the patients' designated physician for further follow-up.

4. Data Analyses and Management

4.a. Sample Size Determinations. A total of 800 women will be followed in this study. This sample size will provide a statistical power ≥ 80% to detect a difference of 14%-22% in the proportions of women with treatment related amenorrhea (TRA) between two groups. The following group comparisons are of interest: 1) cyclophosphamide but no tamoxifen versus tamoxifen but no cyclophosphamide (C vs T); 2) cyclophosphamide but no tamoxifen versus cyclophosphamide and tamoxifen (C vs CT); and 3) tamoxifen but no cyclophosphamide versus cyclophosphamide and tamoxifen (T vs CT).

Assuming that losses to follow-up will be about 20%, 640 (800*0.80) women will complete at least 24 months of follow-up. We expect that 10% (n=64) will have received a treatment that did not include cyclophosphamide nor tamoxifen, 10% (n=64) will have had a treatment that includes tamoxifen but no cyclophosphamide, 35% (n=224) cyclophosphamide but no tamoxifen, and 45% (n=288) will have received both cyclophosphamide and tamoxifen as part of their treatment.

The following table shows the detectable differences that were obtained using a two-sided chi-square test with the above sample sizes, 80% power and a significance level of .0167 to control for the 3 group comparisons.

Comparisons	n_o	n_1	p_o[1]	m[2]	p_1[3]	Δ[4]
C vs T	224	64	.7	3.5	<.48 or >.89	.22
C vs CT	224	288	.7	.78	<.56 or >.82	.14
T vs CT	64	288	.8	4.5	<.60 or >.95	.15

[1] Proportion of women with TRA in group 0, based on published studies
[2] n_o/n_1
[3] Detectable proportion of women with TRA in Group 2

[4] Detectable difference in proportions of women with TRA

4.b. Data Analyses: Chemotherapy-Related Amenorrhea. Descriptive statistics will be presented regarding the frequency, duration and amount of bleeding experienced by all participants. The duration and amount of bleeding will be analyzed with longitudinal mixed models. Transformation of the dependent variables will be explored to satisfy assumptions of linearity, homogeneity and normality. Variables believed to be related to bleeding will be included in the models. Maximum likelihood techniques will be used to estimate parameters.

Treatment related amenorrhea will be defined as six months of amenorrhea occurring within three months of stopping treatment. Multivariate logistic regression analysis will be employed to identify the major predictive factors for developing amenorrhea. The binary outcome will be the presence or absence of amenorrhea. Multivariate models including characteristics possibly related to amenorrhea, such as age and treatment modality, will be fitted. Logistic regression diagnostics will be used to summarize the agreement of observed and fitted values.

In secondary analyses, survival modeling will be used to investigate the time to amenorrhea from the start of chemotherapy treatment. In most instances, amenorrhea will occur during the first year after diagnosis, but survival analyses will allow us to take into account the different follow-up times for each participant and the possibility that amenorrhea may occur later for some participants. With these models, we will explore the factors that might influence amenorrhea, using all the data available.

4.c. Health Related Quality of Life

4.c.1. Primary and Secondary Endpoints. Various statistical analyses, as described below, will be used to compare patient's HRQL and psychosocial outcomes with respect to their treatments and the maintenance of ovarian function (i.e., those amenorrheic and those not rendered amenorrheic), and to estimate the association between these variables. The following primary and secondary HRQL endpoints have been defined.

Primary Endpoints:

1) FACT-B (Total Score: Continuous Variable)

Secondary Endpoints:

1) Beck Depression Inventory (Total Score: Continuous Variable)

2) Physical Symptoms Checklist (Total Score: Continuous Variable)

3) Sleep Disturbance Scale (Total Score: Continuous Variable)

4) Watts Sexual Functioning: (Arousal Subscore: Continuous Variable)

(Satisfaction Subscore: Continuous Variable)

5)	MOS Social Support Questionnaire	(Total Score: Continuous Variable)
6)	Self-Concept Scale	(Total Score: Continuous Variables)
7)	Spirituality Scale	(Total Score: Continuous Variable)

4.c.2. Power Calculation for the Primary HRQL Quality of Life Endpoint. A higher number of women will be recruited at the beginning of the study recruitment period through reviews of cancer registers and other sources available at each institution. Assuming a uniform drop-out rate of 20%, after recruiting 75 women each month during the first 6 months, and 35 women monthly for months 7- 16, 640 women will be followed for 24 months, and 240 will be followed for 36 months. Based on previous studies on breast cancer patients, estimates of the mean and standard deviations for the primary quality of life endpoint is as follows:

Endpoint	**Mean**	**Standard Deviation**
FACT-B	117.2	24.7

Assuming that at least 50% of the participants will experience treatment related amenorrhea (TRA), the following differences can be detected with 80% power at the .05 two-sided significance level.

Endpoint	**Mean**	**Std. Dev.**	**% with TRA**	**Follow-up**	**N**	**Δ***	**(Δ/Mean) * 100**
FACT-B	117.2	24.7	.5	36 months	240	8.9	7.6 %
				24 months	640	5.5	4.7%

* Δ: Detectable difference

A total sample size of 800 patients will ensure 80% power for detecting 36-month relative effects of 7.6% or more for the FACT-B at the .05 two-sided significance level in a t-test analysis, assuming that 20% of the patients will be lost to follow-up. Both detectable relative effects are less than 20%, which represents a clinically meaningful cutpoint.

4.c.3. Data Analyses: Health-Related Quality of Life. Descriptive statistics consisting of frequency tables and percents will be tabulated for categorical variables, and means, medians, standard deviations, ranges, etc., will be calculated for all continuous variables at the baseline and follow-up assessment points. Logistic regression will be used to assess differences in the categorical outcomes, and analysis of covariance will be used to assess treatment differences in

the continuous variables. These analyses adjust for pre-study values of the outcome measures and other factors, such as age and stage of disease, to correct for chance imbalances in the covariates between groups and to reduce the variance of the estimate of the group effect, thus increasing the statistical power. All test hypotheses and reported p-values will be two-sided. Regression diagnostics and residual plots will be used to find appropriate transformations, if needed, to satisfy the assumptions of the various analyses, including linearity for both, and homogeneity of variances and normality for the covariance analyses.

Spearman rank correlations will also be used to estimate the association between the various factors at each measurement time. In addition, these associations will be examined by studying bivariate scatterplots. Regression analyses will be completed to assess multivariate relationships and to see if the relationships differ over the course of the study.

All significance tests will be two-sided. Clinical center will be included in all models. Secondary analyses will explore the presence of amenorrhea in subgroups of patients according to the specific drug they were prescribed. We will also perform subgroup analyses for the different treatment modalities that did not involve chemotherapy. Interim analyses will be performed by the Coordinating Center to provide information for reviewing the conduct and progress of the study. A description of the characteristics of the dropouts will be provided and comparisons with the participants will be presented.

4.d. Pregnancy Data Base. As the number of pregnancies is expected to be small, the analyses will be exploratory. The pregnancies reported during the study will be described and important factors like treatment modality, and age of the mother will also be reported in association with pregnancy data. Short term survival of the patients will be analyzed if the number of pregnancies allows it. The main focus will be maintaining a high quality database for further follow-up and analysis.

4.e. Data Management in the DOD Breast Cancer Study. The goal of data management is to ensure the accuracy and completeness of study data, and to make the data available for analysis and reporting. To that end, data entry, editing and reporting systems will be utilized at the clinical coordinating center (CCC) at BGSM. Because the protocol requires only minimum contact between the participant and the clinical center after the baseline visit, all data management operations will take place centrally, at the CCC.

4.f. Data Flow. Completed paper forms will be mailed to the CCC by staff at the clinical centers (baseline) or by the participants themselves (follow-up). After an initial review by the project manager, data forms will be entered electronically. Logical consistency checks will be run on the full data set. Errors will be identified and corrected, and the correct data will be re-entered and re-edited. Finally, the entire study database will be "frozen" periodically to provide a stable data set for interim analyses. The freeze process involves resolving outstanding discrepancies and copying all data into permanent SAS data sets. Only data that have passed all quality assurance checks will be frozen for analysis.

4.g. Quality Assurance. Quality assurance will be a major activity of the CCC throughout

the study. Initial screening of the data will be done by the project manager when the forms are received. She will verify that the forms are legible, and that they are filled out correctly and completely. Any problems identified will be resolved before the data entry step. If necessary, the clinic or participant will be contacted to provide missing information or to correct items where there are obvious inconsistencies. Participant ID and visit verification will be incorporated into the data entry system, as will gross range checking. More refined range checking, logical consistency, and longitudinal edits will be done in a separate step after data entry. Initially, a random 10% sample of study forms will be selected for duplicate data entry. Data from the first and second entry will be compared, and error rates calculated. The results will be used to determine the need for future double keying of all data or of key study variables.

In addition to the main study data, an inventory will be maintained, containing participant contact information, follow-up status information, and form status and completion date information. This inventory will form the core of the data and participant tracking system. Most study management reports, including recruitment reports, missed visit reports, and missing form reports will be generated from this inventory.

4.h. Hardware and Software. The data management system will be implemented on a Sun SparcServer 1000E in the Department of Public Health Sciences at the Bowman Gray School of Medicine. The data entry application will be developed using FoxPro software, which will have built in validation and range checking. Quality assurance checks and routine study reports will also be done in SAS. Statistical analysis will be done using SAS and Splus.

All study data will reside on the SparcServer's disk drives. Full file system backups to tape are made each weekday night. In general, in the event of a hard disk failure no more than a day's worth of work will need to be repeated.

5. Study Organization

The organizational structure for this study includes the following key components: the Clinical Centers (CC) and the Clinical Coordinating Center (CCC).

5.a. Clinical Centers. Three clinical centers are participating in the current protocol:

Memorial Sloan-Kettering Cancer Center, (Jeanne Petrek, M.D., Principal Investigator)
M.D. Anderson Cancer Center, (Eva Singletary, M.D., Principal Investigator)
Bowman Gray School of Medicine, (Electra Paskett, Ph.D., Principal Investigator)

Each clinical center is composed of an inter-disciplinary team of clinical investigators and staff who provide the areas of expertise necessary for the successful completion of the study. The responsibilities of the clinical center staff and investigators include:

1. Identifying and recruiting eligible participants for the study.

2. Completing medical record chart reviews regarding breast cancer diagnosis and treatment, and comorbidities.

3. Collecting high quality data in accordance with the study protocol.

4. Collaborating in the analysis and dissemination of study results.

5.b. Clinical Coordinating Center. The clinical coordinating center for the current study will be located at the Bowman Gray School of Medicine, Department of Public Health Sciences, (Michelle Naughton, Ph.D., Principal Investigator).

The clinical coordinating center has the primary responsibility for collecting the follow-up data, monitoring the quality of data collected, and analyzing data generated by the clinical centers. Additional responsibilities of the CCC include:

1. Preparing (with the aid of the clinical center investigators and staff) the protocol, forms, and Manual of Operations.

2. Developing the statistical design of the trial.

3. Working with the investigators in the development and pre-testing of forms and procedures, and assuming responsibility for the reproduction and distribution of forms.

4. Training study coordinators, data coordinators and other clinical center personnel.

5. Managing quality control aspects associated with the collection and management of the study data.

6. Monitoring clinical center performance through the use of summary data reports generated by the CCC (i.e., participant recruitment reports; quality control checks of collected data).

7. Monitoring follow-up activities, and monitoring quality control of follow-up data collected by the CCC staff.

8. Preparing, in collaboration with the clinical investigators, various manuscripts of the study results.

RESULTS - STATEMENT OF WORK

IRB approval of the re-organized research project was granted on December 9, 1997 at Memorial Sloan Kettering Cancer Center. See Appendix C. Based on this protocol summary and informed consent, Bowman Gray has also just received their local IRB approval. M.D. Andersen Cancer center will hopefully have the same shortly.

The following time line has been determined for the completion of this protocol.

Recruitment: January 1, 1998 - April 30, 1999
Follow-up: July 1, 1998 - April 30, 2001
Data Analyses: May 1, 2001 - October 20, 2001

A 16 month recruitment period is planned for all three clinical centers (January 1, 1998 - April 30, 1999). All participants will be reassessed at 6 month intervals from their time of entry into the study through April 30, 2001. (The study recruitment period will overlap with the follow-up period from July 1, 1998 - April 30, 1999.) At least 24 months of follow-up data will be obtained on all study participants. The final six months of the study will be devoted to the completion of data analyses and manuscript preparation.

CONCLUSIONS

NONE

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

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August 5, 1997

Juanita Bourne
U.S. Army
Medical Research Acquisition Activity
ATTN: MCMR-AAA
Fort Detrick
Frederick, MD 210702

RE: DAMD17-96-6292 Menstrual Cycle Maintenance and Quality of Life after Breast Cancer Treatment: A Prospective Study

Dear Ms. Bourne:

This is to request approval for restructuring activities of the above referenced grant effective 9/20/97 which is anticipated to be the start date for the accrual of study participants and analysis of data. Due to this prolonged startup period, we are requesting that the grant be extended for a period of twelve months to 10/19/01, without additional funds.

Reorganization of this research has become necessary due to the departure from Memorial Sloan-Kettering Cancer Center of two key personnel in the data management section. As you are aware, the original project was conceived and funded to include Dr. Ruby Senie, who has unique competence because of her large prospective data set of 1,000 Memorial Hospital breast cancer patients and May Nah Ho, who coordinated the information base of the National Polyp study, with a registry similar to the present project. (Dr. Senie has gone to another university where she can still participate.) Nevertheless, I no longer have the required expertise to directly manage the data from the menstrual cycle maintenance and quality of life at Memorial Sloan-Kettering Cancer Center. Fortunately Bowman Gray will be able to amplify its workscope with an expanded budget and assume the role of the data management/statistical coordinating center. Due to their prior experience in a similar role in the Women's Health Initiative with more than 100,000 normal women and menopause, Bowman Gray is eminently well suited to perform this task.

In order to effectively coordinate participant's accrual and analysis of data as well as to decrease the cost of research nurse, recruitment activities will be based in only three large clinical centers: Memorial Sloan-Kettering Cancer Center, Bowman Gray Medical Center and MD Anderson Medical Center. I will continue to be the principal investigator and organize and oversee all activities.

Memorial Sloan-Kettering Cancer Center
1275 York Avenue, New York, New York 10021
Telephone 212.639.8128/8130 • FAX 212.794.5812
E-mail: petrekj@mskcc.org

NCI-designated Comprehensive Cancer Center

A revised budget, justification and workscope are attached with a Table of Contents. Please note that the revised budget figures reflect the current unexpended funds to date for this project. In addition, although Memorial Sloan-Kettering Cancer Center's current negotiated indirect cost has risen to 63.3%, no additional funds are requested.

Please contact me at (212) 639-8128 if additional information is needed.

Sincerely,

Jeanne Petrek, MD
Prinicipal Investigator

James S. Quirk
Senior Vice President
Research Resources Management

DAMD17-96-6292

Menstrual Cycle Maintenance and Quality of Life after Breast Cancer Treatment: A Prospective Study

Jeanne A. Petrek, MD **Principal Investigator**

TABLE OF CONTENTS

Expenses Incurred To date 9/20/96-6/30/97

The expenses incurred through 6/30/97 are associated with the preliminary groundwork for this project. This includes a thorough review of current non-protocol patients conducted at MSKCC. During this pilot study, medical charts were reviewed to extract pertinent baseline medical information and to survey the treatment information consistently available from the record in order to develop the mechanism to obtain the remainder of the necessary treatment from other sources. Followup of Dr. Petrek's current premenopausal patients was undertaken in order to assess bleeding patterns and the best mechanism to consistently and accurately document them.. Drs. Petrek and Senie have also completed the design of the baseline questionnaire which will provide critical demographic and health related data on participants. In addition, as Principal Investigator, Dr. Petrek has prepared the finalized protocol to be submitted for approval to the multi-tiered Institutional Review Board at MSKCC.

Based upon the proposed centralization of coordinating center activities to Bowman Gray School of Medicine, the collaboration expenses incurred at this Center have been associated with: development of study protocols, forms, the Manual of Operating Procedures, completion of statistical design for the study, the development and management of quality control aspects and a central database that will track study participants.

The team at Bowman Gray has designed, formatted and validated the Health Related Quality of Life psychosocial data collection instruments intended to assess the effects of treatment-related premature menopause on the psychosocial status of young women with breast cancer. The psychosocial team has also convened focus groups comprised of young women with breast cancer of Hispanic, African-American and Caucasian backgrounds to assess the cultural sensitivity and relevance of the selected measures for the proposed research. Moreover, the team has concluded development of an analytic plan for all psychosocial and health related quality of life data.

An estimated breakdown of expenses-6/30/97 is as follows:

Salaries	$18,972
Fringe	$ 3,346
Supplies/Other	$ 859
Bowman Gray	$29,533
Total direct	$52,710
indirect	$13,635
Total	$66,345

Amount Awarded	$988,093
*expenses-6/30/97	$ 66,345
revised budget	$921,748

*approximate

OVERALL BUDGET JUSTIFICATION

Budget Justification

DAMD17-96-6292

While the goals, scope, and methods of this project remain unchanged from the initial proposal submitted to the DOD, reorganization of the budget and justification are based upon the shift of data and statistical activities to Bowman Gray School of Medicine for the reasons outlined in the cover letter. Consequently, the biostatistician, data coordinator-statistician and data entry personnel which were originally in the Memorial Sloan-Kettering budget now appear in Bowman Gray budget.

Jeanne Petrek, M.D.-Principal Investigator-Dr. Petrek will continue to direct the organization and administration of the Study's activities. She has published extensively on topics related to therapy-induced menopause, and pregnancy and breast cancer in both peer-reviewed publications and book chapters and has lectured on this issue at national meetings. This includes: developing tools necessary for recruitment, monitoring of overall recruitment at the three clinical centers and management and analysis of recruitment data. She will work closely with the collaborating center at Bowman Gray to ensure the effectiveness of data management, quality assurance and participant follow-up data. In her capacity as Surgical Director of the Lauder Breast Center and Attending Surgeon at Memorial Hospital (where over 1,000 new patients are surgically treated for intraductal or invasive breast cancers each year), Dr. Petrek will play a crucial role in ensuring patient accrual and compliance of other associated physicians. In addition, as the primary clinician directing the study, Dr. Petrek will contribute her expertise in the analysis and management of all significant medical data. Moreover, she will closely focus, maintain and analyze all baseline and prospective medical data collected that is significant to the effect of subsequent pregnancy on survival from breast cancer. Dr. Petrek will also continue to participate in the extensive outreach activities this study has engendered through continued lectures and dissemination of information to the public. Dr. Petrek's will devote 20% of her effort to this project.

Ruby T. Senie Ph.D.-Co Investigator-(Epidemiologist) Dr. Senie has recently transferred from Memorial Sloan-Kettering Cancer Center to Columbia University. However, she and Dr. Petrek remain close collaborators on many projects, including a retrospective study on subseauent pergnancy after breast cancer treatment. Dr. Senie will continue to share her expertise on the intricacies of the coordination of multi-site breast cancer projects. In addition, she works closely with Dr. Petrek in the development and administration of the baseline entry-questionnaire. This will provide vital demographic and epidemiological information about the study participants that will be contained in the project's database. Dr. Senie will devote 5% of her time to this project; 2.5% of her salary will be subcontracted to Columbia University.

TBN Study Coordinators-The Study Coordinator will devote 100% of time in years 2 and 3 to the recruitment of study participants. During the subsequent follow-up in years 4-5, she will devote 25% of time. The study coordinator will be responsible for: identifying and recruiting

participants to the study, explaining the study to potential participants, obtaining informed consent and administering all tools necessary for recruitment.

The study coordinator at Memorial Sloan Kettering Cancer Center will also maintain MSKCC records related to this study. Although 100% effort will be devoted to this project in years 2 and 3, during year 3 only 53% funding is requested. The remainder of the MSKCC Study Coordinator's salary will be supplemented by private philanthropic support available to the Dr. Petrek, the Principal Investigator. During years 4-5 funds to support 25% of the study coordinator's effort are requested. With the recent media attention to this research, several benefactors have donated with the expressed wish of funding this or closely related research.

Travel
As in the original proposal, funds are requested for Dr. Petrek to attend the North American Menopause Society meeting in Years 2-5.

Supplies
The team at Bowman Gray is requesting funds for general supplies for the administration of this grant. These funds will be utilized in order to facilitate data collection, analysis and biostatistical evaluation.

Forms/MOP
The team at Bowman Gray will be responsible for the preparation and distribution of the manual of Operations for each clinical center involved in the study and the preparation and dissemination of all forms necessary for participants. Since these forms will be scannable, fund are requested for the production and reproduction of these forms.

Telephone
Due to the intimate nature of the participant data which must be secured for this study, the team of researchers at Bowman Gray have found that study participants share this information more readily and extensively via telephone when necessary to complete or to correct the written questionnaire data. Since accurate and detailed information is vital to the success of this prospective study, funds for telephone interviews at Bowman Gray in years 2-5 are as follows: $2658, $2764, $3490 and 2,152.

Mailing
Baseline forms will be mailed to each clinic for their completion and will subsequently be returned to the Coordinating Center for monitoring. The quality of life questionnaires will be mailed to the study subjects every 6 months and will include self-addressed return. The Manual of Operations will also be mailed to each Clinic.

Supplement
The following additional expenses associated with this project will be incurred by the Memorial Collaborating Center:

47% Study Coordinator Year 3 -$22,104
(includes fringe benefits at 26%)

Supplies Years 2-5 -$3,240
Postage $2,240 ($560 per year)
Copying $1,000 ($250 per year)

Total direct costs $28,584

Since funds are not available to meet these expenses through the DAMD 17-96-1-6292, private philanthropic support will be utilized. Private benefactors have donated funds specifically designated for use only in this research or closely related projects.

GRANT AGREEMENT

GRANT NO: DAMD17-96-1-6292 Modification P80001	EFFECTIVE DATE See Grants Officer Signature Date Below	GRANT AMOUNT $988,093.00	Page 1 of 3 Juanita Bourne (301)619-7426

PROJECT TITLE: Menstrual Cycle Maintenance and Quality of Life After Breast Cancer Treatment: A Prospective Study

CFDA 12.420

PERFORMANCE PERIOD: 20 September 1996 - 19 October 2001 (Research ends 19 Sept 2001)	**PRINCIPAL INVESTIGATOR:** Jeanne A. Petrek, M.D.
AWARDED AND ADMINISTERED BY: U.S. Army Medical Research Acquisition Activity ATTN: MCMR-AAA- B 820 Chandler St. Fort Detrick Maryland 21702-5014	**PAYMENTS WILL BE MADE BY:** **EFT:T** Army Vendor Pay DFAS-SA-FPA 500 McCullough Avenue San Antonio TX 78215-2100
AWARDED TO: Sloan-Kettering Institute of Cancer Research Office of Sponsored Projects 1275 York Avenue New York NY 10021	**REMIT PAYMENT TO:** N/A

ACCOUNTING AND APPROPRIATION DATA:
N/A

SCOPE OF WORK:

See pages 2-3.

TOTAL AMOUNT PROVIDED TO DATE: $988,093

RECIPIENT		GRANTS OFFICER	
ACCEPTED BY: James S. Quirk **SIGNATURE**		**UNITED STATES OF AMERICA** Patricia M. McAllister **SIGNATURE**	
NAME AND TITLE James S. Quirk Senior Vice President Research Resources Management	**DATE** 10/21/97	**NAME AND TITLE** PATRICIA M. McALLISTER **GRANTS OFFICER**	**DATE** 28Oct97

USAMRAA FORM 25-R-E, MAR 97 (Previous editions are obsolete)

Pursuant to mutual agreement, the following changes are made to the terms and conditions of this grant. These changes are made in accordance with the Grantee's letter and revised budget dated August 5, 1997, which are hereby incorporated by reference:

1. The period of performance is changed as follows:

From: 20 September 1996 - 19 October 2000 (Research ends 19 September 2000)

To: 20 September 1996 - 19 October 2001 (Research ends 19 September 2001)

2. Based on the changes above, Paragraph 10 entitled, "Payment Schedule" subparagraph c, Year Two through Year Four is deleted in its entirety and replaced with the following:

Year One $327,888 REMAINS THE SAME

Year Two: $100,000

Amount	On or About
$25,000	1 October 1997
$25,000	1 January 1998
$25,000	1 April 1998
$25,000	1 July 1998

Year Three: $275,026

Amount	On or About
$68,757	1 October 1998
$68,757	1 January 1999
$68,756	1 April 1999
$68,756	1 July 1999

Year Four: $224,203

Amount	On or About
$56,051	1 October 1999
$56,051	1 January 2000
$56,051	1 April 2000
$56,050	1 July 2000

Year Five: $60,976

Amount	On or About
$15,244	1 October 2000
$15,244	1 January 2001
$15,244	1 April 2001
$15,244	1 July 2001

3. All other terms and conditions remain unchanged.

Institutional Review Board

TO: Dr. J. Petrek

FROM: Dr. Roger S. Wilson RSW
Chairman, Institutional Review Board

DATE: December 10, 1997

RE: Protocol and Consent Form # 97-127

Your protocol and consent form entitled "Menstrual Cycle Maintenance and Quality of Life: A Prospective Study" were re-reviewed at the December 9, 1997 Institutional Review Board meeting and were approved.

RSW:mmk
Enclosure

Memorial Sloan-Kettering Cancer Center
1275 York Avenue, New York, New York 10021
Telephone 212.639.7592

MENSTRUAL CYCLE MAINTENANCE AND QUALITY OF LIFE: A PROSPECTIVE STUDY

Principal Investigator:
Jeanne A. Petrek, MD

Co-Investigators:
Katherine N. Tran, BA
Melissa C. Heelan, BA

Breast Service, Department of Surgery
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10021

MENSTRUAL CYCLE MAINTENANCE AND QUALITY OF LIFE: A PROSPECTIVE STUDY

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MENSTRUAL CYCLE MAINTENANCE AND QUALITY OF LIFE: A PROSPECTIVE STUDY

PATIENT INFORMED CONSENT FOR CLINICAL RESEARCH

You have been asked to participate in a clinical research study. The doctors at Memorial Hospital of Memorial Sloan-Kettering Cancer Center study the nature of disease in the attempt to improve methods of handling the disease. This is called clinical research. In order to decide whether or not you should agree to become part of this research study titled "Menstrual Cycle Maintenance and Quality of Life: A Prospective Study", you should understand enough about its risks and benefits and what is required of you as a member of this research study in order to make informed consent.

This consent form gives information about the research study. Once you understand the study, its risks, benefits, and alternatives, you will be asked to sign this form if you wish to take part. You will be given a copy to keep.

PURPOSE OF THE RESEARCH

In this research project we wish to study two different aspects of a woman's life after breast cancer treatment: 1) the function of ovaries as known from the pattern of your menstrual cycles, also called monthly periods, and 2) the quality of your life as related to your health after breast cancer treatment.

We, the researchers, are interested in knowing what characteristics are found in women who stop their menstrual cycles. In women who stop their menstrual cycles, we are interested in knowing whether the menopause, also called change-of-life, is temporary or permanent. The second area of related research involves how you feel about the quality of life, as related to your health after breast cancer treatment.

DESCRIPTION OF RESEARCH PROCEDURES

In order to accomplish this research, we will need to record from your medical chart the details of the your health unrelated to the present treatment as well as details of the breast cancer treatment. We will ask your permission to contact your physicians outside of our hospital. This is necessary, for example, to obtain information on the treatments not given at Memorial Hospital.

Although most of the information is in the hospital chart, the research coordinator will need to ask you additional questions about childbearing before breast cancer treatment which may not appear on the chart, any problems you may have had with your female pelvic organs before breast cancer treatment, and about your monthly periods before treatment. These additional questions will take about 15 minutes of your time.

We wish to collect the following information from you every 6 months for five years.

1) The function of ovaries as known from your bleeding pattern We wish you to mark information concerning menstrual flow on a calendar given to you by the researchers every six months and then mail it back to the researchers. You will be asked to check off the days when any bleeding occurs and also to circle the initial "L, M or H" to note whether the amount of bleeding was Light, Moderate or Heavy. The time required for marking the research calendar is about five minutes per month.

2) Quality of life as related to your health The second kind of information is that concerning how you feel about the quality of your life as related to health after breast cancer treatment. The questionnaire uses multiple choice boxes to check off for the answers. This questionnaire will require 15 to 30 minutes each six months.

These forms will be mailed to you from Bowman Gray University in Winston-Salem, North Carolina. This center is famous for its excellent research into quality of life related to menopause in all populations of women. The forms will be mailed back to Bowman Gray in a pre-stamped, pre-addressed envelope approximately every six months. A new study calendar and questionnaire will also be sent to you every six months. A research coordinator will review your calendar and questionnaire. She may call if the information is unclear and she needs to confirm.

RISKS / SIDE EFFECTS

This research has no physical discomfort.

It is possible that answering multiple choice questions about the quality of life or logging menstrual bleeding on a calendar will cause psychological discomfort, although this is not likely. You should always feel free to skip any questions that you wish and not answer them.

If anxiety or emotional distress should occur, the interviewer or any of the doctors involved in this research can provide you with information and put you in touch with sources of support or professional services for psychological counseling in your community. You will not receive any money from Memorial Sloan Kettering Cancer Center or from the U.S. Army (the sponsor of the research) to pay for any psychologic counseling or psychiatric services.

COMPENSATION IN CASE OF RESEARCH - RELATED INJURY

If you are injured as a result of being in this research study, the hospital will provide the care you need or refer you to the appropriate source. The hospital will not give you any money to cover this care. You and / or your insurance carrier will be billed for it.

FINANCIAL COSTS

There are no research costs. The study calendar and questionnaires will be mailed to you. In order to return the information you will be given self-addressed and stamped envelope to mail back. If it is necessary to call the researchers about any questions there will be an 800 telephone number available in order to avoid telephone costs to you.

If you receive psychological counseling or psychiatric services as the result of being in this research study, Memorial Hospital will not give you any money to cover this care. The sponsor of this research, the U.S. Army Breast Cancer Research Program, will not give you any money to cover this care.

BENEFITS

Even though this research may benefit others in the future it will not benefit you.

ALTERNATIVES

There are no alternatives to this research study.

PRIVACY

Every effort will be made to keep your study records private. Neither your name nor anything else that could identify you will be used in any reports or publications that result from this study. Trained staff at Memorial Hospital and the Department of Defense may review your records if necessary.

RIGHT TO REFUSE OR WITHDRAW

The choice to take part in this study or not is yours. Make your choice based on what we have explained to you and what you have read about the study. If you decide not to take part, other options are available to you without prejudice. We will answer your questions about the study at any time. While you are part of the study, we will inform you of any results that might affect your willingness to continue in it. You have a right to withdraw at any time; if you do you will continue to be offered all care. You will lose no benefits to which you are entitled.

Any hospital that does research on people has an Institutional Review Board (IRB). This board reviews all new studies to make sure that patient's rights and welfare are protected. The IRB at Memorial Hospital has reviewed this study. The physician in charge of this research study is Dr. Jeanne A. Petrek (212) 639-8128. If you need to know more about this study before you decide to join, or at any other time, you may contact her. In the event that you do decide to take part in the study, she should be contacted if there are any side effects from the study.

A non-physician whom you may call for information about the consent process, research patients' rights, or research-related injuries is Janice Levy (212) 639-5804.

This research is funded by the U.S. Army Breast Cancer Research Program. The U.S. Army requires the following paragraph be included in the exact words for all the research it sponsors even if there is no medical portion or intervention.

You are authorized all necessary medical care for injury or disease which is the proximate result of your participation in this research. The U. S. Army requires that this institution provide such medical care when conducting research with private citizens. Other than medical care that may be provided, you will not receive any compensation for your participation in this research study; however, you should understand that this is not a waiver or release of your legal rights.

This research study has no medical portion and therefore there is no "medical care for injury or disease" as the result of this research.

As mentioned, psychological care or counseling may be necessary as the result of this research in the rare chance that the questionnaires cause anxiety or emotional distress. There is no payment for psychological care even if it is the result of this research study. You or your insurance carrier will be required to pay for any psychological care you receive.

PATIENT INFORMED CONSENT FOR CLINICAL RESEARCH

Title: **MENSTRUAL CYCLE MAINTENANCE AND QUALITY OF LIFE: A PROSPECTIVE STUDY**

STATEMENT OF INVESTIGATOR OBTAINING INFORMED CONSENT

I have fully explained this research study to the patient _____ _____. The nature and purpose, the potential benefits, and possible risks associated with participation in this research study have been explained and any questions have been answered.

Date _____ Investigator's Signature _____

Investigator's Name _____

PATIENT'S STATEMENT

I have read the description of the clinical research study or have had it translated into language I understand. I have also talked it over with the doctor to my satisfaction. I understand that my participation is voluntary. I know enough about the purpose, methods, risks and benefits of the research study to judge that I (the patient) want to take part in it.

Patient # _____ Patient's Signature _____

Date _____ Patient's Name _____

Patient's Address _____

_____

Witness Signature _____

Witness Name _____