

UNCLASSIFIED

AD NUMBER
ADB215798
NEW LIMITATION CHANGE
TO Approved for public release, distribution unlimited
FROM Distribution authorized to U.S. Gov't. agencies only; Proprietary Info.; 20 Jul 96. Other requests shall be referred to Commander, Army Medical Research and Materiel Command, Attn: MCMR-RMI-S, Fort Detrick, Frederick, MD 21702-5012.
AUTHORITY
USAMRMC, Fort Detrick, MD ltr dtd 2 Feb 1998

THIS PAGE IS UNCLASSIFIED

AD _____

GRANT NUMBER DAMD17-94-J-4220

TITLE: Implementation of the Southwestern Oncology Group
Committee on Women's Health Research Agenda: A Special
Sabbatical for the Chairperson

PRINCIPAL INVESTIGATOR: Kathy S. Albain, M.D.

CONTRACTING ORGANIZATION: Loyola University Medical Center
Maywood, Illinois 60153

REPORT DATE: July 1996

TYPE OF REPORT: Final

PREPARED FOR: Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Distribution authorized to U.S.
Government agencies only (proprietary information, 20 Jul 96).
Other requests for this document shall be referred to
Commander, U.S. Army Medical Research and Materiel Command,
ATTN: MCMR-RMI-S, Fort Detrick, Frederick, MD 21702-5012.

The views, opinions and/or findings contained in this report are
those of the author(s) and should not be construed as an official
Department of the Army position, policy or decision unless so
designated by other documentation.

19961114 106

DTIC QUALITY INSPECTED 2

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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

1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE July 1996	3. REPORT TYPE AND DATES COVERED Final (1 Jan 95 - 30 Jun 96)	
4. TITLE AND SUBTITLE Implementation of the Southwestern Oncology Group Committee on Women's Health Research Agenda: A Special Sabbatical for the Chairperson			5. FUNDING NUMBERS DAMD17-94-J-4220	
6. AUTHOR(S) Kathy S. Albain, M.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Loyola University Medical Center Maywood, Illinois 60153			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Commander U.S. Army Medical Research and Materiel Command Fort Detrick, Frederick, MD 21702-5012			10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Distribution authorized to U.S. Government agencies only (Proprietary Information, 20 Jul 96). Other requests for this document shall be referred to Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RMI-S, Fort Detrick, Frederick, MD 21702-5012.			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200) This Final Report documents the implementation of the breast cancer research agenda of the Committee on Women's Health of the Southwest Oncology Group by its chairperson, Kathy S. Albain, M.D. During the special sabbatical award period, Dr. Albain formed a multidisciplinary network of collaborators and designed, initiated, or completed all aspects of this broad research agenda. The four original Tasks were each addressed on multiple levels. This work is summarized in detail in this Report, with supporting appendices for each of the specific aims. Thus, under Task 1, multiple national database projects were either completed or are currently ongoing for the study of prognostic factor interactions among very young women with breast cancer. Various analyses of Task 2 are in progress to analyze the cooperative group database regarding the elderly with breast cancer. With the completion of full accrual of one large Intergroup trial in postmenopausal women, the more detailed analyses of older age interaction with demographic-, tumor- and treatment-related factors were initiated. Task 3 resulted in the first report of lumpectomy utilization rates with respect to multiple variables among women with non-metastatic breast cancer subsequently enrolled on national adjuvant therapy trials. A model Lay Advocates Pilot Project was organized and became operational under Task 4, and a menu of research projects to address recruitment and survivorship issues were designed and/or initiated. Dr. Albain and collaborators successfully competed for supplemental grants to support the conduct of these various research projects under all four Tasks, and received continuation funding from the National Cancer Institute to continue the efforts initiated under this sabbatical.				
14. SUBJECT TERMS Breast Cancer			15. NUMBER OF PAGES 372	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Limited	

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the US Army.

Where copyrighted material is quoted, permission has been obtained to use such material.

KSA Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

KSA Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Robert S. Allman MD 7/19/86
PI - Signature Date

TABLE OF CONTENTS

Front Cover	Page 1
Report Documentation SF 298	Page 2
Foreword	Page 3
Table of Contents	Page 4
Introduction	Page 5
Body	Page 7
Conclusions	Page 24
References	Page 25
Appendices	Pages
A. Curriculum Vitae/Bibliography	27
B. Young Women Project Data Summary	47
C. Communications with the EBCTCG	59
D. Southwest Oncology Group Study S8814	62
E. Southwest Oncology Group Study S9445	75
F. Breast Sparing Treatment Manuscript	91
G. Table of Recent Lumpectomy Analysis	124
H. Lay Advocates Pilot Project NAPBC Funded Grant	127
I. Pilot Project with Survivor Role Models	186
J. Enhancing Well Being During Breast Cancer Recurrence	212
K. Southwest Oncology Group Study S9626	238
L. Southwest Oncology Group Study S9342	276
M. Southwest Oncology Group Study S9630	295
N. Southwest Oncology Group Study S9631	337
O. Clonal Hematopoiesis After Chemotherapy	367

**FINAL REPORT OF THE IMPLEMENTATION OF THE SOUTHWEST ONCOLOGY GROUP
COMMITTEE ON WOMEN'S HEALTH BREAST CANCER RESEARCH AGENDA: A
SPECIAL SABBATICAL FOR THE CHAIRPERSON.**

INTRODUCTION

This sabbatical award provided salary support for Kathy S. Albain, M.D., to implement the Southwest Oncology Group (SWOG) Committee on Women's Health (CWH) breast cancer research agenda, in her position as its national Chairperson. The original proposal was submitted in November, 1993, when the CWH was in its infancy as a new clinical and translational research entity within the structure of the SWOG. The award was subsequently received and expended from January 1, 1995 - December 31, 1995, with a carry-over of funds to June 30, 1996 to allow closeout of certain studies and preparation of this Final Report.

The CWH breast cancer research focus of this sabbatical was unique in that it was designed to be distinct from, yet complementary to, the traditional cooperative group approach of treatment-related breast cancer studies. These research efforts were conducted to address four of the major emphases of the initial Broad Agency Announcement of the Breast Cancer Research Program of the USAMRMC: 1) one aspect of the problem of increased number of breast cancer cases in younger women; 2) underserved populations of women with breast cancer, including the elderly and the socio-economically disadvantaged; 3) the failure to effectively transfer lumpectomy technology to the majority of women with early breast cancer; and 4) the need for cooperative group research in barriers to recruitment and breast cancer survivorship needs and issues.

Thus, the sabbatical programs were organized into four Target Areas to address these specific research objectives:

1. Learn if the clinical outcome for very young women with breast cancer is worse, and if so, why. Explore interactions among young age, standard and newer putative prognostic factors, and adverse breast cancer outcome in four large early breast cancer data bases. Determine if the results of adjuvant therapy vary based on very young age alone, or on age in combination with other variables, or without regard to age.
2. Study breast cancer accrual patterns in the SWOG regarding older age groups, race, and socio-economic status. Analyze the interactions and/or influence of these factors on co-morbid diseases, dose intensity, toxicities, breast cancer outcome, competing cause of death, and late effects in a large phase III adjuvant trial. Propose prospective studies to better understand deficiencies that are found in proper representation of these groups on state-of-the-art trials.
3. Perform a retrospective multivariate analysis to explore interactions of multiple variables with low lumpectomy rates for women enrolled on intergroup adjuvant trials. Investigate the feasibility and implement a prospective study to investigate reasons for deficiencies.
4. Research appropriate trial designs for novel non-treatment studies which will incorporate the expertise of lay advocates. Implement breast cancer recruitment and survivorship studies.

Although this sabbatical provided funding for protected time for the principal investigator to devote to the development and implementation of this ambitious national breast cancer

research agenda, this was not directed funding for a specific research project. Thus, a number of factors interacted to focus, refine, and in some cases redirect the original aims of the overall proposal, as well as to reorder the priority over time of certain projects, as follows:

1. There was a 14-month lag between the initial submission of the sabbatical proposal and receipt of the award. Thus, as is outlined on the following pages, new breast cancer research areas of greater import than envisioned in 1993 were selected for priority development under this sabbatical in 1995. Nevertheless, these new projects remained true to the target areas and overarching objectives of the proposal.
2. The biostatistical collaborators within the Statistical Center of the SWOG as well as investigators from the other cooperative groups remained committed to all projects presented in the initial proposal. However, this award funded only the salary of the CWH Chair. Funding constraints were experienced by all cooperative groups in 1994-present, with resulting cutbacks in biostatistical support for the cooperative groups. These events were not anticipated at the time of the original proposal. Thus, several of the analytical data base projects and clinical trials were just recently initiated when external support could be obtained or additional expertise identified (eg: supplemental funding awards from the NIH, the addition of an epidemiologist to the sabbatical collaborators in late 1995-early 1996).
3. Similarly, the actual projects in the proposal were not supported by the sabbatical funding award. These studies were unfortunately not completely covered by the standing NIH awards to the cooperative groups for cancer treatment studies in 1995, because these awards were not increased as originally anticipated when the sabbatical proposal was submitted in 1993. Thus, Dr. Albain and her collaborators were required to seek external supplemental support for a number of the studies in this proposal. These efforts were overwhelmingly successful, but in many cases were time-consuming and therefore delayed initiation of the actual clinical studies.
4. Two large clinical trials on which several specific aims were based are not yet mature with a sufficient number of cancer events to permit the planned analyses. These will be done at the appropriate time based on the continued funding received from the National Cancer Institute of the CWH efforts (next paragraph). However, other analyses were initiated when new databases or research questions were identified to allow exploration of related questions. These circumstances are noted in detail in the Body of this report.

Nevertheless, despite the above constraints, all tasks and objectives within these four target research areas were either designed, initiated, completed, analyzed, published or some combination thereof during the sabbatical. As outlined in detail in the Body of this report to follow, all aims of this award have either been accomplished, or the work was recently initiated or is awaiting maturity of patient follow-up in order to allow completion of the specific project. Since the sabbatical funding has expired, support of these ongoing aspects of the sabbatical projects and of the broad breast cancer research agenda of the CWH was insured by recent notification of a Continuation Award to the SWOG for the CWH Chair (Dr. Albain) from the National Cancer Institute. The successful competition for this continuation grant was in large part due to the positive outcome of these sabbatical activities.

The results presented on the following pages confirm the impact (present and future potential) of this sabbatical effort on multiple dimensions of non-treatment related breast cancer clinical research in the cooperative group structure. In the conduct of these efforts, Dr. Albain

extended her clinical research skills beyond therapy-related clinical trials and enhanced her development as a national leader in women's health issues. As such, she was recently appointed as a charter member of the NIH Advisory Committee on Research on Women's Health. Despite the unanticipated obstacles (noted above), the goals of this sabbatical were accomplished through the following variety of parallel and complementary mechanisms, which optimized the travel opportunities funded by her CWH award from the National Cancer Institute, and which provided ancillary support or other means to compensate for the lack of funding for the specific projects or for her collaborators:

1. Generous donated support and active research involvement of multi-disciplinary national collaborators including biostatisticians; medical, surgical and radiation oncologists; behavioral and cancer control science and survivorship research experts; a medical anthropologist; cancer survivors and advocates; and the addition of epidemiologist in early 1996.
2. Intensive and productive meetings of Dr. Albain with these multidisciplinary collaborators on site at the SWOG meetings (every 6 months) of the CWH, its internal Advisory Board, the Breast Committee and its Executive Committee, the CWH Lay Advocates Steering Subcommittee and other ad hoc, project driven subcommittees.
3. Regular conference calls among the CWH leadership, Lay Advocates, the Statistical Center and the Operations Office.
4. Frequent communication via the Internet and conference calls between non-SWOG collaborators regarding research directions with the other databases.
5. Dr. Albain's appointment to and participation in the recent Oxford meeting and subsequent analyses of the Early Breast Cancer Trialists' Collaborative Group.
6. Active involvement of Dr. Albain in the Clinical Trials Working Group of the National Action Plan on Breast Cancer.
7. Regular participation of Dr. Albain in the activities of the Breast Intergroup Chairs Committee, sponsored by the National Cancer Institute.
8. Working discussions among Dr. Albain and her non-SWOG collaborators at the meetings of the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium.
9. Successful competition for external supplemental funding and support for sabbatical studies from the National Institutes of Health, the USAMRCM Breast Cancer Program, and the National Action Plan on Breast Cancer.

BODY

The body of this final report is organized into four sections based on the target areas identified in the original proposal (outlined above). The wording from the grant's Statement of Work is reproduced at the beginning of each of the four tasks. A major aspect of this sabbatical effort was Dr. Albain's successful organization of the network of investigators necessary for each project. These primary collaborators are named after the Statement of Work (see each Appendix for a complete listing of all those involved), followed by details regarding progress to date. For the activities outlined within each Section, Dr. Albain's role ranged from principal to co- to senior (or supervising) investigator, which was the intent of the original proposal.

SECTION ONE

Original Statement of Work for Task 1: Determine prognostic factor interactions accounting for adverse breast cancer outcome in the very young woman.

- Part a.** Perform an updated and expanded multivariate analysis of the San Antonio early breast cancer data base.
- Part b.** Validate these results in an independent node-negative data base from the first high risk, randomized Intergroup trial chaired by the Eastern Cooperative Oncology Group (ECOG), and assess interactions of biomarkers with very young age.
- Part c.** Utilize the Cancer and Leukemia Group B (CALGB) node-positive data set to validate the SWOG analyses, and perform additional combined data set models to derive prognostic equations.

Primary Collaborators: Part a: Gary Clark, Ph.D., D. Craig Allred, Ph.D.; Part b: Robert Gray, Ph.D., Nancy Davidson, M.D., Nicholas Robert, M.D., William Wood, M.D. and other investigators of the ECOG; Part c: Larry Norton, M.D., Donald Berry, Ph.D., I. Craig Henderson, M.D. and other investigators of the CALGB; Ongoing: Silvana Martino, D.O., Laura Hutchins, M.D., Stephanie Green Ph.D., Peter Ravdin, M.D., Ph.D., and other members of the National Cancer Institute Breast Intergroup.

Proprietary Aspects: Task 1a data summary from manuscript in preparation, all aspects of Task 1b, Task 1c, and Part d.

Task 1, Part a: Progress to Date

Young women with breast cancer have the worst survival if matched with similarly staged older cohorts in epidemiologic studies. We showed (in work in progress at the time of the original grant submission) with the large San Antonio database that very young women (< age 35) with breast cancer have more adverse prognostic factors and worse clinical outcomes than older patients. (1) We therefore initiated and completed a new study of the interactions between very young age and prognostic factors for disease-free survival (DFS) in the presence or absence of adjuvant breast cancer therapy. This research incorporated longer follow-up (median of 5 years), adjuvant therapy data, a new debris-stripping algorithm for S-phase, additional analyses of p53 abnormalities (2), and multivariate models of interactions among young age, adverse prognostic factors and treatment. These findings were recently published in abstract form (3) and selected for presentation at the May 1996 meeting of the American Society of Clinical Oncology (data and figures, updated from the published abstract and summarized in Appendix B). The following detailed review of the final analysis is taken from a manuscript in preparation as of this writing:

The objectives of this new and novel analysis were to 1) validate that very young women have poor clinical outcomes; 2) correlate very young age and other prognostic factors with clinical outcomes among three subsets of women who received A) no adjuvant therapy, B) chemotherapy with or without endocrine therapy in the node-positive subgroup, and C) endocrine therapy alone if node-positive; and 3) identify very young women with good clinical outcomes who do not need adjuvant therapy. Eligible patients were identified from the San Antonio

database who had early stage breast cancer (T1-3 N0-1 M0) and frozen tumor specimens large enough for standard biochemical estrogen receptor (ER) assays. Because this was a database derived from a tumor bank originally formed to do ER assays on referral, a variety of standard adjuvant chemotherapy and endocrine therapy regimens was given to the patients by their referring oncologists. Age groups were defined by 5-year intervals (<30, 30-35, 35-40, 40-45, 45-50, 50+). Prognostic factors studied included number of positive nodes (N), tumor size (T), ER and progesterone receptor (PgR) status, and percent with high S-phase fraction and with abnormal p53 expression, based on the importance of these factors in our initial analysis; other factors such as HER-2 neu were not correlated with young age (1) and thus not addressed in this new analysis. S-phase fraction and p53 data were available in a more highly characterized subset of the data base (to be referred to as "special group"). There were 6,477 patients in the entire data set, and 1,019 in the special group. Univariate survival analyses were performed by Kaplan-Meier curves and Cox multivariate models were applied to the three treatment subsets and to the entire subset < age 35.

There were 70 women < age 30 and 163 age 30-35 overall, and 11 and 29, respectively, in the special set. The breakdown by the three treatment subsets is shown under "Patient Characteristics" in Appendix B. Of note, 81 of the 3,122 patients who received no adjuvant therapy in the overall group were < age 35, whereas all women < age 35 in the special group had adjuvant therapy. The univariate survival figures by age category are shown in Appendix B for the node-positive and node-negative groups. Women < age 30 had significantly worse 5-year DFS than all other categories from age 40 up: node-positive, 26% v. 61-64% and node-negative, 68% v. 75-81%. Various adverse factors significantly correlated with very young age in univariate models: positive lymph nodes (> 0 vs. 0, 4+ vs. <4, and 10+ vs. <10), ER-negativity, PgR negativity, larger tumor size (T3 vs. T1 or 2), high S-phase fraction, and abnormal p53 expression. Overall, 37 of the 40 (92%) patients < age 35 had high S-phase and/or p53+ tumors (bar graph, Appendix B).

Cox models that included N, T, ER and PgR status and age groups were constructed for 3 treatment subsets: A) no adjuvant therapy (2.6% <35), B) N+ patients who received chemotherapy with or without endocrine therapy (6.8% <35), C) N+ patients who received endocrine therapy alone (1.4% <35); and D) for the entire subset of women under age 35. Independent predictors of DFS were: subset A) <35, N, T; subset B) <30, N, T; subset C) age 30-35, N, T, PgR.; and subset D) N only. Similar models were applied to each subset from the special group, adding S-phase and p53 to the other factors. Independent predictors of DFS in this smaller group were: subset A) N, T, S-phase, p53; subset B) N, T; subset C) age 35-40, N, T, p53; and subset D) N, S, p53.

Finally, we attempted to identify a cohort of very young women who do not need adjuvant therapy. As described above, among all 233 women < age 35, the only independent predictor of adverse outcome overall was N status. There were too few very young women in the special group to utilize Cox modeling for the purpose of derivation of a prognostic score. Thus, only nodes could be employed in this attempt. However, no subset could be identified with a 5-year disease-free survival of over 70%: for the N0 group, the survival was 66% +/- 5%, and for the N0 group which did not require adjuvant treatment in the opinion of the referring physician, the survival was 64% +/- 7%. For those < 35 with 4 or more positive nodes, this DFS was 24% +/- 6%.

Our conclusions were that 1) young age is an independent adverse factor for DFS regardless of adjuvant treatment category; 2) most very young patients have high S-phase and/or p53-positive tumors; 3) p53 positivity and/or high S-phase are independently predictive of poor

outcome; 4) in the node-positive cohort, p53 is not a strong predictor of outcome in the presence of chemotherapy (although it retained independent significance in the very young subset, all of whom received some form of adjuvant therapy); 5) no subsets among the very young cohort could be identified with very good prognosis utilizing standard factors, but prognostic equation modeling was prohibited by the very small number < age 35 in the special group with p53 and S-phase data; and 6) one cannot analyze these complex interactions among very young age, biomarkers, treatment without very large numbers of patients.

The implications of the research conducted under Task 1a are as follows. Given that the minority of patients with breast cancer have tumor stored and studied in national banks with simultaneous homogeneous treatment and long-term follow-up on clinical trials, and given that the incidence of breast cancer among very young women is relatively rare, no single national adjuvant trial (or even datasets as large as that studied in this task) with banked tumors for biomarker correlates will contain enough very young women to address the ultimate goal of defining which subsets of the very young merit more aggressive adjuvant approaches. Thus, additional possible strategies are under active discussion as of this writing (see below, 1d).

Task 1, Part b: Progress to Date

The collaboration with the ECOG was initiated to explore the feasibility of an independent assessment of prognostic factors and treatment effect with respect to very young women in their node-negative data set in order to validate and expand the analyses of the San Antonio database (Task 1a). A series of meetings among the collaborators on site and via email occurred to define the database and possible questions its analysis could answer. Preliminary analyses were conducted, and the future direction, if any, for this project is under active discussion as of this writing. A status report of this ongoing project follows.

The data set was defined by the primary clinical trial EST 1180 (4) and its two ancillary biomarkers studies, EST 2192 and EST 7186. Available variables were patient age, ER status, tumor size, grade, tumor necrosis, S-phase, ploidy, HER-2/neu, and p53 by paraffin block method. The following three patient cohorts were available as defined by the clinical trial: 1) ER positive tumors under 3 cm, registered to observation only; 2) ER positive tumors over 3 cm and all ER negative tumors, randomized to observation; and 3) ER positive tumors over 3 cm and all ER negative tumors, randomized to adjuvant chemotherapy with cyclophosphamide, methotrexate, 5-fluorouracil and prednisone (CMFP).

The initial meeting of the collaborators defined the goals of this analysis as follows: A) Validate the observation from our analysis in Task 1a that women under 35 have adverse outcome, and explore whether this was due to a greater percentage with a worse biomarker profile such as abnormal p53 and/or high S phase; B) Determine if the treatment effect for CMFP vs nothing is as strong in the very young cohort and if possible, assess treatment effect by age within various subsets such as normal/abnormal p53, HER2-neu and high/low S-phase fraction; C) Attempt to derive a prognostic equation for outcome in very young versus other ages if it is found that the very young have a different survival pattern. D) Consider whether a merger of this data set with the San Antonio database to increase the cohort under age 35 is feasible and if such work would yield additional information or better allow derivation of the equation.

Potential specific analyses to address the above were then outlined among the ECOG collaborators, Dr. Gary Clark and Dr. Albain: 1) Combine patient cohorts 1. and 2. to form a large untreated data set. Perform similar univariate analyses as in Task 1a with narrow age groups and with all the prognostic variables available, above. Apply Cox models with and without

biologic factors added to determine the independent contribution of young age. 2) The overall findings of the clinical trial (4) were that adjuvant CMFP improved DFS and survival over observation alone. Using patient cohorts 2. and 3., determine if the same benefit to treatment over observation exists in the very young versus all other ages. 3) If an age differential in degree of adjuvant treatment benefit is found, explore why if small numbers in subsets does not prohibit an analysis biomarker interactions with treatment and age. 4) Merge the San Antonio node-negative data base with the ECOG data set. Combine all untreated patients to form one cohort, and do the same for those treated with adjuvant chemotherapy, deleting the patients from the San Antonio database treated with endocrine therapy alone, and deleting those variables not common to both data sets such as tumor grade and necrosis. In the overall merged group, as well as in each the two treatment subgroups, explore various models such as Cox and recursive partitioning and amalgamation to determine if very young age is an independent descriptor of poor outcome and then define prognostic groups for predictive equations. In the overall model, add a treatment variable (chemotherapy yes or no). Also, separate models in the very young versus others, with the same treatment variable could be applied.

These analyses were initiated and are ongoing as of this writing. Very preliminary data is as follows. There were 924 eligible cases on this study, 473 in the low risk cohort 1 (ER+ and T <3 cm) and 451 high risk (ER- or T 3 cm or greater). Of the high risk cases, 220 were randomized to observation (cohort 2), 22 were directly assigned to CMFP (cohort 3) and 209 were randomized to CMFP (cohort 3). Seventy-five of the 924 cases (8%) were < age 35 at time of entry on study, 62/451 (14%) high risk and 13/473 (3%) low risk (the low risk stratum was much older on average).

Women < age 35 had a worse DFS, with an estimated relative risk of 1.41, 95% confidence interval (CI) .94 to 2.13, but this difference is not yet statistically significant ($p=.09$, logrank test stratified on risk group). The difference in survival is smaller ($p=.75$, estimated relative risk = 1.09, CI from .65 to 1.82). Effect of treatment on time to recurrence in the randomized subset (cohorts 2 and 3) also appears quite similar in the two age groups. The estimated relative risks (Observation/CMFP) and 95% confidence intervals are 2.0 (0.8, 4.6) for age < 35 and 2.1 (1.4, 3.2) for age \geq 35. For the effect of treatment on overall survival, the estimated relative risks do show some difference, but at this point the CI are very wide: 2.5 (.8, 7.7) for age < 35, 1.5 (1.0, 2.4) for age \geq 35.

Several issues were raised in the course of this collaboration regarding the S-phase and p53 data. First, the S-phase results were obtained prior to the newer debris stripping algorithms, and therefore a "high S-phase" as defined in this population may not be analogous to that defined in the San Antonio database (even though performed by the same investigators). Furthermore, p53 results were obtained on generally poor quality paraffin blocks, in contrast to the frozen material analyzed in Task 1a. There is recent documentation regarding the deterioration of p53 in paraffin material such that false negativity is common. (5) Of some concern is that the overall percentage of abnormal p53 in this ECOG data set is markedly lower than found overall in the San Antonio bank. Nevertheless, despite these concerns, very preliminary exploratory analyses were initiated regarding interactions of very young age with high S-phase and abnormal p53.

The S phase analysis showed a weak association with age < 35 within the low risk groups only. In the low risk group the proportion with high S was 5/9 (56%) for age < 35 and 100/241 (41%) for age \geq 35, while in the high risk group the proportion with high S was 25/33 (76%) for age < 35 and 147/198 (74%) for age \geq 35. However, overall, the median S phase was higher in the younger group (12.4% for age < 35, 6.2% for age \geq 35), though, so a more careful

analysis of this association will be needed. The median S phase percentages stratified by risk group are age <35, age \geq 35 high risk 13.7, 10.1; and low risk 9.9, 4.6. Note there were only 33 high risk and 9 low risk cases < age 35.

Abnormal p53 accumulation was evaluated from the (albeit poor quality) paraffin material using 3 different antibodies. The results presented here are for ab1801, but the others tended to be similar. When stratified by risk group, age <35 did not correlate with greater abnormal p53 accumulation ("p53 positive") in this study. However, the numbers of very young women in these smaller subsets are extremely low. In the low risk stratum, 2/8 cases (25%) age < 35 were p53 positive, whereas 46/278 (17%) age \geq 35 were p53 positive. In the high risk stratum, 14/39 (36%) age < 35 were p53 positive, while 89/240 (37%) of the older group was p53 positive.

The possibility of merging all patients followed with no treatment (cohorts 1 and 2) for multivariate models with age and biomarkers is under discussion. Since the risk group strata had different treatment options, and the factors defining these strata are associated with many other factors, it may not be appropriate to simply collapse the two strata into one data set for analysis of prognostic factors. The analyses presented above controlled for risk strata.

There is interest in proceeding to the multivariate models and the specific analyses discussed above, but there are concerns that this may not be very informative due to the very small numbers of very young women, especially in the low risk cohort. Even in the high risk group, comparisons may have poor power because of the need to assess multiple factors in the model in addition to an age variable. Thus, there are ongoing discussions as of this writing about the wisdom of a merger of the two data sets. The reality of the different S-phase and p53 methodology (above) may or may not preclude this aspect of the merged analysis, but other aspects of the planned combined analysis could proceed if the biostatisticians (Dr. Clark and Gray) concluded that the additional number of women < age 35 in the ECOG data set will allow greater multivariate potential. Dr. Albain has also initiated discussions of other possibilities at the Intergroup level (see Part 1d, below).

Task 1, Part c: Progress to Date

As noted in the grant application, our analysis of the SWOG node-positive adjuvant CMFV(vincristine)P database employed Cox and recursive partitioning methodology to study interactions of age, menopausal status and other standard prognostic factors. (6) Findings were indeterminate as to whether very young age was an independent adverse factor in this uniformly treated, node-positive population. Therefore, the objective of this aspect of Task 1 was to explore the CALGB node-positive database as both a validation set as well as its potential for other analyses given its additional biomarker information. This collaboration was initiated in the early months of the sabbatical, but was put on hold due to the need to complete biomarker studies on a critical clinical trial as well as an unanticipated change in the leadership of the CALGB Breast Committee. The biomarker work has been completed (addition of grade and p53 to the S-phase and HER-2/neu database), and under the new leadership (Dr. Larry Norton) and with his full support, the work will resume summer of 1996 with a conference call.

The available CALGB node-positive database was identified: Study 7581 (CMFVP vs CMF vs CMF-MER), Study 8082 (CMFVP +/- VATH - vinblastine, Adriamycin, thiotepa, halotestin) and study 8541 and its ancillary study 8869. The latter study of CAF dose intensity was a critical trial which showed that survival benefit to adjuvant CAF was dependent on achieving full doses of chemotherapy. (7) In the companion ancillary analysis with the biomarkers of S-phase and HER-2/neu, the investigators found that the significant dose-response

effect of adjuvant CAF was observed only in those patients with HER-2/neu overexpression, whereas survival was equivalent for all dose levels of CAF in the non-overexpressors. (8)

We determined that combined in all these CALGB studies there are approximately 267 women < age 35, which represents one of the largest sets in cooperative groups. Approximately 120 are in the 8541 (CAF dose intensity) study. Thus, we realized there is a unique opportunity to explore interactions of treatment, young age and biomarkers (HER-2/neu, Sphase, p53 and grade) in that study and that this should be the first priority of the series of planned collaborations. The upcoming conference call will solidify the analytic plans, but specific questions under consideration now are whether young women do poorly as a univariate for survival, whether the treatment effect of dose-intense CAF observed in the overall trial holds in the very young, and whether the observation that HER-2/neu overexpression is required to see treatment effect is true in the very young women. The proposed age grouping is < 35, 35-50 and > 50. Survival by age will first be explored with the two arms of 8541 combined to determine if the very young fared worse in the CALGB experience. If so, is this due to HER-2/neu and S phase status? In the San Antonio database analysis, the adverse outcome for the very young was not apparent when a data set with S phase and p53 was used (very high frequency of abnormal p53 and high S in very young), so we thought the CALGB trial would be an excellent validation set. It is also possible that if adverse outcome for the very young is found in this CALGB analysis, it may be due to lack of treatment benefit of higher dose CAF in this age group. Therefore, in this analysis, treatment effect within each age group by HER-2/neu and S phase status will be explored. Cox models will be applied as well.

We do not yet know if numbers in various subsets will be too small to address all these questions. We will explore a possible merger of the CALGB 8541 group with the chemotherapy-treated node-positive San Antonio database (HER-2/neu and S-phase also available). In this way the multivariate models might be stronger, and prognostic equations could be derived for the very young versus other to see if they differ. Therefore, following the upcoming conference call, we will proceed with the "first tier" analysis of CALGB study 8541, and let those results dictate the next directions.

Other future potential analyses of the CALGB database under discussion are as follows. One analysis to be considered is a combined CALGB CMFVP data set (or possibly the entire node-positive group). Cox and recursive partitioning models could be applied looking at narrow age categories to validate the SWOG CMFVP analysis, which, as noted above, was inconsistent regarding very young age as an adverse factor. Finally, we plan to consider the feasibility of a meta-analysis with the San Antonio, SWOG and CALGB node-positive databases combined, as well as some of the ideas in Part 1d, below.

Part d: Other Ongoing and Future Work

Other opportunities to address the critical objectives of this task not apparent when the proposal was submitted in 1993 were explored in 1995 and will be pursued throughout the next year by Dr. Albain and collaborators. These are briefly summarized as follows.

1. A 4,301-patient node-negative Intergroup adjuvant trial chaired by sabbatical collaborator Dr. Laura Hutchins for the SWOG (S8897) continues to mature in anticipation of its first analysis for publication. This trial had an observation group of 1,370 patients either initially at low risk for recurrence as defined by T and ER characteristics (n=741), or if initially of indeterminate risk, deemed low risk by favorable S-phase (n=629). The 2,931 patients at high recurrence risk (by

T and ER, or by unfavorable DNA profile) were randomly allocated among 4 treatment arms CMF +/- tamoxifen (T) and CAF +/- T. The number of women < age 35 (n < 35/total n) for the entire trial are: CMF, 51/736; CAF 49/737; CMF+T, 60/734; CAF+T 62/724; low risk observation, 18/741; low risk assigned by favorable DNA profile, 15/629. Thus, there were 255 women enrolled < age 35 (222 treated, 33 observed).

In an ancillary biomarkers trial, blocks were collected at the SWOG Breast Tumor bank for a large panel of standard and experimental prognostic factors. However, blocks were obtained only for the low and uncertain risk group, so that the 222 patients in the high risk category directly randomized to a treatment arm will not have blocks available for the molecular correlates. Thus, it must be decided whether these numbers will allow assessment of prognostic factor distribution and treatment effect by age. Supplemental support for the SWOG Breast Tumor Bank was requested by Drs. Ravdin, Martino and colleagues to, among other objectives, explore other molecular correlates including subcellular localization of BRCA1 protein and, if possible, to correlate these factors with age.

2. During the sabbatical, Dr. Albain was appointed a member of the Early Breast Cancer Trialists' Collaborative Group. In this capacity, she participated in the 1995 15-year overview meeting in Oxford, England, and is continuing to assist in the analysis and publication of the various trial subsets with other international colleagues (for example, see reference 9, Appendix A). Dr. Albain initiated and as of this writing continues communications with the EBCTCG Secretariat and Dr. William Wood (Chair of EBCTCG) regarding additional opportunities to utilize this very large database to analyze treatment effect in very young women. Two examples of this ongoing collaboration are provided in Appendix C.

3. A number of possibilities are under discussion at the Breast Intergroup level to address the concerns raised during the process of Task 1 projects regarding a) too few numbers of women < 35 in single trials or even in individual cooperative group databases to permit multivariate modeling in subsets (interactions of very young age with biomarkers and treatment effect) and b) the issue of non-standardized measurement of newer biomarkers (eg p53, S-phase) across the Groups. First, Dr. Albain participated in exploratory meetings last year of an Intergroup Correlative Sciences Subcommittee, which identified the possibility of a larger merged dataset than those under consideration above. We will continue to explore this option in the ensuing months with the Groups in question. In addition, the current generation of Intergroup Adjuvant trials established a bank of blocks (maintained by each Group) for correlative studies. The Group Chairs subsequently established a peer review process for proposals to this bank. It is possible the Intergroup will consider this resource for expanded study of the very young women on these trials. Finally, at the last meeting of the Breast Intergroup in May, 1996, Drs. Albain, Clark, Allred and Martino presented the need for additional prospective study of very young women utilizing the above resources of the Intergroup. It was recognized that no single Intergroup trial (past or current) will contain enough very young women with measured biologic factors to explore the questions identified during this Task. A desire was expressed to discuss means to overcome the major obstacle faced in this past years' efforts to merge the very young subset of the San Antonio, ECOG and CALGB databases (the same biologic factors were inconsistently available and when present in all studies, were measured with different methods).

Based upon the interest from each cooperative group to proceed with additional discussion, Dr. Albain will chair a conference call next month to pursue these issues and discuss specific research options.

In conclusion, following our completed work and based on the ongoing projects under Task 1 as well as the other plans in 1d, the goal of all these analyses will be to determine if practical recommendations can be made for less aggressive versus dose intensive adjuvant therapy based on age, or based on age plus other prognostic factors including the new biomarkers. Or, it is instead possible that the ultimate conclusion will be that age should not enter the decision tree when the new prognostic factors are considered. All of the collaborators on this Task still believe that it is critical to continue to study these databases to address the persisting concern that very young women do poorly on standard adjuvant therapy regardless of prognostic factors. Our challenge is to decide this next year which of the above options for additional analyses will provide the greatest yield.

SECTION TWO

Original Statement of Work for Task 2: Determine the influence of older age, race and socio-economic variables on accrual, toxicity and outcome in breast cancer clinical trials.

- Part a.** Study the yearly accrual patterns to all SWOG breast cancer clinical trials since 1986 using census-based and SEER-adjusted methodology.
- Part b.** Perform ancillary analyses regarding these factors in SWOG 8814, a three-arm randomized adjuvant trial for node- and receptor-positive postmenopausal patients with a tamoxifen-alone control.

Primary Collaborators: Stephanie R. Green, Ph.D., Polly Newcomb, Ph.D., Janet O'Sullivan, M.A., John J. Crowley, Ph.D., Peter Ravdin, M.D., Ph.D., D. Craig Allred, Ph.D., Deborah Powell, M.D., and Silvana Martino, D.O.

Proprietary Aspects: All of this Task.

Task 2, Part a: Progress to Date

The aim of this project was to determine if the demographics of the SWOG breast cancer clinical trials database over the last decade (by older age groups, race, socio-economic status or SES) are representative of the general population, and of women with breast cancer. Once studied, strategies to address any deficiencies identified were to be proposed. As outlined in the original proposal, we planned to employ the census-based and SEER-adjusted methodologies to determine the SES of study participants from zipcode of origin compared to US census data, and compare the age and racial mix of our national breast cancer clinical trials database to the SEER-adjusted US population.

Prior to beginning this task, it was necessary to refine our methodology. This was overseen by Dr. John Crowley, Statistical Center Director, and his associate biostatistician, Dorothy Rector, M.S. We conducted a major project which addressed gender, age, race and SES differences in non-sex-specific solid tumors. Based on our preliminary abstract (10), the modeling was refined and a near-final analysis presented at the Spring 1996 SWOG meeting. Therefore, Dr. Crowley determined that the methods were mature for application to Task 2a. Furthermore, a breast cancer epidemiologist (Dr. Polly Newcomb) was recruited by Dr. Crowley in May, 1996 to co-direct this project with Dr. Albain. She is based at the same facility as the

SWOG Statistical Center, which will facilitate her work with the database. We now plan, via a small proposal submitted to SEER by Dr. Newcomb, to obtain SEER zipcodes in order to also have the ability to compare the SES mix of the SWOG database to the SEER breast cancer population. Therefore, the project will be more meaningful than originally proposed. Dr. Newcomb is also coordinating Task 2b with Dr. Albain, so that the work for both parts of this task will proceed in parallel.

In the original proposal, we planned to wait until the database analysis was complete, and then initiate a prospective questionnaire and log system to discover the reasons for any accrual imbalance discovered. However, after some discussion, this part of the project was revised and initiated as a pilot study at two SWOG institutions (see details in Task 4a). Therefore, results from both aspects will be available at the same time and optimize future strategy formation for correction of any problems identified.

Task 2, Part b: Progress to Date

This aspect of Task 2 is based on the Intergroup trial SWOG 8814 (Appendix D), chaired by Dr. Albain, and its recently funded ancillary biomarkers trial 9445 (Appendix E), the latter a new initiative since the grant proposal. Postmenopausal patients with node- and receptor-positive disease were randomized among three arms: five years of tamoxifen alone, six cycles of CAF followed by five years of tamoxifen, or six cycles of CAF with concurrent tamoxifen for five years. This patient group may be the last of its kind (tamoxifen-only control arm), because with the broad recognition of the 1992 Oxford Overview findings, the trend in this country has been to use combined chemo-endocrine adjuvant therapy for this subset. In fact, this reality resulted in a marked slow-down of accrual (not anticipated at the time of the grant proposal), so that this trial did not complete accrual until August of 1995. Analysis of the complete demographic data from this United States and Canadian Intergroup trial on the 1468 patients was only recently feasible, and will be summarized in brief below. The majority of the planned analyses, with an expansion of the original proposal made possible by NCI's funding of our biomarker correlative study (Appendix E), will occur over the next one to two years. Due to the lengthened accrual time, mature survival results will not be available for correlation for one year.

The objective of Task 2b was to expand our study of older women with breast cancer through a focus on this clinical trial via the following analyses, distinct from the outcome endpoints of the main trial. The database was divided by narrow age categories for our exploratory analyses as well as for eventual survival correlations, and other interactions of age with study factors such as: prior exogenous hormones, co-morbid diseases, SES (using same zip code/census methods as above as well as correlation with SEER population SES), race, tumor size, receptor level, PgR status, S-phase, site of first relapse, competing cause of death, and late effects (flare of menopausal symptoms, osteoporosis, any cardiac toxicity, second malignancies, thromboembolic complications and dyspareunia). Total dose received and dose intensity for the two chemotherapy arms will be calculated and the toxicity spectrum analyzed. These dose results will be correlated between the tamoxifen alone vs. the two chemotherapy arms, and among the narrow age categories, race, and SES. The interactions of all these variables with prestudy characteristics (prior exogenous hormones, co-morbid diseases), tumor biology (size, number of positive nodes, receptor level, DNA S-phase and other factors to be measured in the new biomarkers study 9445 such as angiogenesis, HER-2/neu, p53, Ki67, HSP 27, and grade), long-term effects, and competing causes of death will be explored by multivariate modeling.

We can provide only preliminary demographic and treatment summary data as of this writing, with the rest of the above either just initiated or else planned over the next two years. 1,558 patients were registered, and eligibility has to date been confirmed for 1,468 (number to change as more forms are received). Approximately 60% of patients had 1-3 positive nodes and 20% of tumors were PgR negative. Less than 10% of patients had T3 tumors. Postmenopausal estrogen (specifics pending) was received by approximately 22% prior to breast cancer diagnosis. Forty-eight percent of the women listed co-morbid diseases on the Prestudy Form. Detailed determinations of co-morbid conditions and SES data are under analysis. 9.2% were African American, similar to the overall SEER-adjusted US population. The median age was 60 (range 33-89). By narrow age category, the numbers currently are < 50 (53, 3.6%); 50-54 (218, 14.9%); 55-59 (348, 23.7%); 60-64 (344, 23.4%); 65-69 (294, 20.0%), 70-74 (150, 10.2%); 75-79 (53, 3.6%); and 80+(7, 0.5%). Analyses of all demographic and tumor characteristics (above) by these narrow age categories are in progress at the time of this writing.

Analyses of tolerance to anthracycline-based adjuvant treatment in this postmenopausal population were initiated. One patient on the tamoxifen arm and 25 on the CAF arms discontinued tamoxifen early due to toxicity, whereas 71 patients on the CAF arms did not complete chemotherapy due to toxicities. Summary toxicity data was collected: There were three treatment related deaths. Forty-six percent of patients on the CAF followed by T arm, and 47% on the CAF + T arm had Grade 4 hematologic toxicities. Other grade 4 toxicities were not common, but included abdominal pain, diarrhea, vomiting and stomatitis. A comprehensive review of cardiac events is ongoing. The detailed toxicity analyses as originally proposed (above) were initiated and are in progress. The follow-up forms now coming in are being reviewed for late effects and other post-treatment, non-tumor-related events, as well as the usual follow-up for disease recurrence. Finally, the biomarker study funding was just received, so that age correlations with these important results will occur in the future.

In conclusion, once completed, Tasks 2a and 2b will provide both critical information regarding as well as new directions for 1) the care of elderly women with breast cancer on clinical trials, and 2) an understanding of those women of non-white races and/or those who are SES-disabled regarding any differences in their presentation, tolerance of therapy, and outcomes.

SECTION THREE

Original Statement of Work for Task 3: Determine why there is under-utilization of breast conservation in women on cooperative group trials.

- Part a.** Use logistic regression analyses to assess independent contributors to low lumpectomy rates.
- Part b.** Activate a prospective surgical options questionnaire study in patients, primary surgeons, and oncologists to evaluate multi-factorial contributions to surgical choice process.

Primary Collaborators: Allen Lichter, M.D., Stephanie Green, Ph.D., Laura Hutchins, M.D., Janet O'Sullivan, M.A., Laura Loll, M.S., and the CWH Lay Advocates.

Proprietary Aspects: The manuscript for Task 3a is in press as of this writing. Task 3b is proprietary data of the SWOG.

Task 3, Part a: Progress to Date

This project was initiated at the time of submission of the original proposal, and the initial analysis was published in Abstract form (11) and presented to the American Society of Clinical Oncology in May, 1994. With the start of the sabbatical, additional analyses were proposed and initiated. Successful completion of this project occurred with the recent acceptance of the final manuscript by the Journal of Clinical Oncology: "The influence of patient characteristics, socioeconomic factors, geography and systemic risk on the use of breast sparing treatment in women enrolled on adjuvant breast cancer studies: An analysis of two intergroup trials". (12) Rather than reiterating this complex analysis here, the entire manuscript is provided in Appendix F. For a summary of the methods and findings, the reader is referred to the Abstract on Page 2 of Appendix F. The conclusion of this unique retrospective analysis was that breast sparing therapy was utilized in the minority of women subsequently accrued to two national adjuvant breast cancer studies conducted at the time of the release of the NCI Consensus Conference directives, even though this patient cohort and their referring surgeons represented a highly select population. As implied by the manuscript title, above, multiple independent factors were associated with lower lumpectomy rates.

Task 3, Part b: Progress to Date

Based upon the results of the retrospective analysis of Task 3a (Appendix F), there was momentum to explore the feasibility of the activation of a prospective study of the multifactorial surgical choice process at cooperative group institutions, simultaneously in surgeons and patients. The two questionnaires were drafted via a multidisciplinary team of medical and radiation oncologists, surgeons, behavioral scientists and patient advocates and survivors. The study design went through several revisions, with joint involvement by the CWH and Breast Committees. The next step was a distribution of a summary of the study design and physician and patient questionnaires to all Group institutions. The aim of this poll was to ascertain if there was widespread endorsement of the feasibility of this type of study within the cooperative group structure, since the entire denominator of surgeons and patients must be available for each participating institution, and a complete geographical cross-section of institutions must be involved. There was a good return from the poll. Fourteen institutions agreed, and others requested more time to query investigators. Nevertheless, the needed broad geographic distribution was not present. It was decided by Group leadership and the CWH Advisory Board that the resources required to organize and mount such a trial in all geographic regions of the country would necessitate a major grant with intergroup participation, and that at present Group resources could not be dedicated to such an effort with no certainty that the majority of institutions could commit all their surgeons to the process. Thus, although it was concluded that a simultaneous study of both surgeon and patient bias was sorely needed, this type of project must be abandoned within the cooperative group structure. Of note, a similar experience was encountered by CALGB investigators in their independent attempt to initiate a broader study of this question. However, one CWH institution proceeded to obtain DOD funding for a local, population based study, which is ongoing. It is anticipated the widespread distribution of our findings with the upcoming publication of Task 3a will raise awareness among surgeons and

patients.

Finally, as a new initiative not proposed in the original grant, we recently performed an analysis of our current adjuvant trial database in order to assess the impact of the Consensus Statement, which was published toward the end of the accrual period for our retrospective analysis (Task 3a). Please refer to Appendix G for the table of "Percent Breast Sparing Surgery by Intergroup Adjuvant Study Number and Consecutive Year of Accrual, with respect to Patient Subgroup for Risk for Relapse". This Table adds the last two years of accrual of S8814 (Appendix D, Task 3a), as well as the first two years of accrual of the current node-negative Intergroup trial S9313, to the earlier results for S8814 and S8897 in Task 3a. The first observation made was that there clearly was a gradual increase in increased lumpectomy utilization in all subsets. The tests for time trend for all the S8897 and S8814 subsets were significant at $p \leq .001$, except it was $p=.01$ for the postmenopausal, N 4+, T 2-5 subset. The first year of accrual for S9313, 1994, showed a very similar percent in the subsets that overlapped the end of accrual for S8897 and S8814.

The second observation was that despite the overall rise in lumpectomy rates, in most subsets, postmenopausal patients continue to have lower lumpectomy rates, even within the same risk subgroup. Third, after 1994, there was no further significant increase in the percentage who received lumpectomy, perhaps indicating that either the maximum impact of the Consensus statement was achieved by that time, or that the "real" rates are now being observed, reflecting true patient choice. Nevertheless, physician bias and other factors may still be operative. Finally, this is almost certain based on the provocative findings in this and our initial analysis (12) regarding much lower rates for positive nodal status versus negative (data not known at the time of the surgical decision), despite the same tumor size. We plan to continue to monitor lumpectomy rates over the next two years to determine the potential impact of our publication and other national educational efforts across disciplines.

SECTION FOUR

Original Statement of Work for Task 4: Determine how to increase breast cancer clinical trial recruitment strategies and survivorship research in a cooperative group setting.

- Part a.** Complete development and activate research focus groups comprised jointly of patients, advocates, and CWH breast cancer investigators.
- Part b.** Finalize concepts and implement trials regarding breast cancer survivorship issues.

Primary Collaborators: Amy Langer, M.B.A., Sharon Green, M.H.S., Ellen Stovall, Michelle Melin, Debra Christie, M.B.A., Silvana Martino, D.O., Patricia Ganz, M.D., Carolyn Gotay, Ph.D., Wendy Stock, M.D., Marilyn Slovak, Ph.D., Cheryl Willman, M.D., Frederick Appelbaum, M.D., Ellen R. Gritz, Ph.D., John J. Crowley, Ph.D., Stephanie R. Green, Ph.D., Polly Feigl, Ph.D., Laura Loll, M.S., Janet O'Sullivan, M.A., Deborah Erwin, Ph.D., J. Wendall Goodwin, M.D., R.K. Potkul, M.D., Laura Hutchins, M.D., Antoinette Wozniak, M.D., Otis Brawley, M.D., Leslie Ford, M.D., Andrea Troxel, M.A., Eileen Sondak, Tika Beard, Peggy McCarthy and Peggy Michelson.

Proprietary Aspects: All of Task 4a and 4b, except the initial summary in Task 4a of Lay

Advocates Pilot Project evolution.

Task 4, Part a: Progress to Date

This project expanded and matured beyond that envisioned at the time of the grant submission, at which time the plan was to use a roundtable of lay survivors and advocates to advise the CWH Advisory Board on appropriate focus group research and study questions pertaining to survivor involvement in breast cancer clinical research and new study directions. While the latter indeed occurred, the process which evolved through the direct involvement of survivor and advocacy leadership was not that of focus group methodology, but instead, was the formation of a new standing subcommittee of the CWH, the Lay Advocates Steering Subcommittee. This Subcommittee was directly involved in all subsequent aspects of Task 4. Through this Subcommittee's efforts, the fully functional Lay Advocates Pilot Project received three years of funding under peer review from the National Action Plan on Breast Cancer. This funded grant is provided in full in Appendix H; the evolution of this project is now summarized, followed by specific research studies and concepts under development regarding recruitment to clinical trials (Task 4a) and breast cancer survivorship quality of life and late effects (Task 4b).

The CWH Chair polled national organizations for their interest in joining with the SWOG in an exploratory discussion of the potential for the formation of a pilot project of the involvement of cancer survivors and their advocates in Group activities. Leadership from the National Alliance of Breast Cancer Organizations, the National Breast Cancer Coalition, the National Coalition for Cancer Survivorship and the Y-Me National Organization for Breast Cancer Information and Support attended the inaugural meeting, along with representatives from the CWH, Breast Committee, Lung Committee, Cancer Control Research Committee, Statistical Center, and Operations Office. The lay leadership concurrently continued their involvement in the Group activities on the Lay Advisors/Advocates Implementation Committee as well as began active participation in various Working Groups and Committees for the Group. The following questions were discussed at the first meeting of this group: 1) How to better educate the cancer population at large in the nature and value of cancer clinical trials through the use of lay advisors/advocates? 2) What strategies could be adopted to solicit and incorporate lay input on various aspects of our clinical trials process on an ongoing basis? 3) How could cooperative groups best network with other organizations to optimize national education and implementation strategies for our clinical research studies? 4) Are there ways this lay advisor-cooperative group liaison could work to improve knowledge of and availability of clinical trials to underserved populations (eg: the majority of women with breast cancer, the elderly, minority groups)?

The group concluded that these questions would be best addressed on an ongoing basis by continued involvement of the lay leadership in the biannual meetings. However, to allow greater collaborative potential and to involve other lay experts and survivors, a three-year pilot project was designed for the Breast and the Lung Committees, with the hope of expanding to other Group Committees. The Lay Advisors/Advocates Implementation Committee met at the April 1994 meeting to formulate the procedures and job descriptions for two types of positions. Two persons (one for each type) were to be appointed to serve a three-year term on the Breast Committee, and two others were to sit on the Lung Committee. Potential appointees were to be of either sex with personal experience and interest in either breast or lung cancer research and survivorship concerns.

The first type of position was to be filled by a professional well versed and educated in either the scientific method and/or the clinical trials process. She/he was also to be currently

playing a key national or local patient advocacy role. This individual was, for example, to be a scientist, nurse, physician, data manager, statistician, public health professional, or a leader or other representative of a national or local lay cancer advocacy or survivors organization. She/he was also to be either a survivor of cancer, or close to a person living with the disease, or a leader of an advocacy or survivors group. The second position was to be for a "survivor representative at large", ie, a patient or member of the public who could speak directly to survivor concerns. Willingness to serve was more important than experience and scientific background was not required. However, past participation or experience with clinical trials was preferred.

Representation from and/or expertise concerning underserved populations was encouraged for both positions. All participants were to agree to the importance of mutual collaboration between the clinical cancer research and cancer advocacy/survivors communities. Participants were to agree to attend each Group meeting and were to be reimbursed for their travel. They were required to meet with the full Committee and the working group of their assigned Committee. They were also required to attend meetings of the Committee on Women's Health, the Lay Advisors/Advocates Committee, and the to join all conference calls pertaining to these committees between Group meetings. Members were to agree to serve as consultants to the Group and Committee Chairs on an ad hoc basis. Appointees were to serve as a channel to funnel suggestions of the survivors and advocacy communities to the cooperative groups.

A broad national mailing requesting nominations for these positions was sent in August, 1994. The Implementation Committee reviewed applications and selected finalists at the October 1994 meeting. A telephone interview subcommittee comprised of CWH and Breast Committee leadership and the lay advocates had extensive discussions with each finalist, and the ultimate appointees were chosen in the Spring of 1995 by unanimous decision, and announced by a national mailing. The implementation committee was dissolved and replaced by a permanent subcommittee named the Lay Advocates Steering Subcommittee. The Pilot Project appointees were added to this steering subcommittee, and were first present on site at the April 1995 Group meeting. An orientation manual was developed (Appendix H), which contained 1) The History and Evolution of the Southwest Oncology Group 2) the Southwest Oncology Group Organizational Structure, 3) Roster of the Committee on Women's Health Advisory Board, 4) Description of the Types of Studies conducted by Disease Committees and the CWH, 5) History of the Southwest Oncology Group Lay Advisors and Advocates Pilot Project, and 6) Glossary and Common Acronyms. A new Mentor Program was inaugurated under the leadership of the Chair of the Southwest Oncology Group Research Associates Committee, also a member of the CWH Advisory Board and a breast cancer survivor. This mentor program paired a "seasoned" CWH member with each new advocate at the various meetings each day, and held an informal "debriefing" session at the close of the April 1995 Group meeting with the advocates, the CWH Chair and the Mentor Chair.

The newly appointed participants in the Pilot Project, as well as the continuing permanent members of the Steering Committee, have since met regularly with the full Committee and the closed session working group of the Breast Committee at each Group meeting. They also attended open and closed meetings of the CWH and its Lay Advocates Steering Subcommittee and have joined all conference calls pertaining to these committees between Group meetings. They receive all active protocols and concepts of those under development, and are on all CWH and Disease Committee mailing lists.

The Lay Advocates Steering Subcommittee proposed research questions of mutual interest that would go forward as a partnership among the Cooperative Group, the Advocacy

Organization(s) and the primary granting agency, the NCI. These projects are summarized below in this Task as well as Task 4b. The reciprocity of all levels of this collaboration is vital to the success of the Pilot Project, as is already in evidence by the successful joint development new concepts and protocols and the early feedback from the lay leadership and new appointees.

One major research focus of regular discussion on site at meetings and by intervening telephone conferences was potential study designs to address barriers to accrual to clinical trials from a patient and physician perspective. Numerous models were discussed, and one final design was proposed as a pilot project by the CWH medical anthropologist, Dr. Deborah Erwin, and her colleague, CWH Advisory Board member Dr. Laura Hutchins. This study utilizes Patient Advocates for Clinical Trials (PACT) to inform women about breast cancer clinical trials at the University of Arkansas. Please refer to Appendix I for the complete project. It was funded by the Clinical Trials Working Group of the National Action Plan on Breast Cancer. In its first 6 months of funded activity, 19 survivors participated in the training sessions. A limited institution Group study will follow if the pilot study is completed successfully to address impact on accrual rates of underserved populations of breast and other cancer patients.

Another research concept regarding recruitment issues is in the early stages of pilot data collection at two CWH Advisory Board members' institutions, prior to the initiation of a Group study. The purpose of this pilot study of the Universities of Arkansas and Wayne State (Drs. Hutchins and Wozniak, respectively) is to demonstrate the feasibility of accessing the entire denominator of cancer patients at a given institution. A questionnaire was developed for this pilot study which will analyze both patient and physician reasons for non-accrual (to include protocol availability, eligibility and eventual accrual). Questions to study gender differences will be added for tumor sites other than breast and other sex-specific sites. The pilot study will involve all cancer types, with the intent to focus on specific disease sites such as breast and those with under-accrual of women in the follow-on Group study. This project will also dovetail with the work of Task 2a.

At the suggestion of Dr. Albain, Dr. Otis Brawley provided additional analyses of the minority CCOP database regarding gender differences in protocol availability, eligibility and accrual if eligible and patient and physician information for breast cancer. More women than men were ineligible for "other" reasons than prior treatment, poor performance status, comorbid diseases, second malignancies and abnormal laboratory findings. Men more often had poor performance status as the reason for ineligibility. More eligible men than women enrolled on trials overall, and patient refusal as the reason for non-accrual was more common in women than men. Patient refusal if eligible was very high in breast cancer (73.1% versus 16.7% for physician refusal). The above 2-institution pilot study will expand on the specific reasons for patient and physician refusal.

Consent document research was identified as a critical area of interest for both advocates and investigators. The consensus was that the process was a barrier to clinical trial participation for both patients and physicians. There will be an RFA forthcoming from the NIH for studies in this area. Therefore, Dr. Patricia Ganz, CWH Advisory Board and Lay Advocates Steering Subcommittee member convened a conference call which discussed research questions which would be feasible to address in the Group in anticipation of this RFA, to be developed over the next year.

A number of other concepts regarding breast cancer clinical trials accessibility and recruitment are under active development by the Lay Advisors Steering Subcommittee. These include the following: 1) A potential "SWOG Alumni Project" will be chaired by Ms. Langer and Ms. Green. This would create a national telephone "speakers" bureau of breast cancer survivors

who participated in a Group trial to be available for callers seeking one-on-one information on SWOG clinical trials. Breast Committee members will nominate patients for this program. A training program will be formalized. A pool of "anonymous" Breast Committee physicians could serve as a resource to answer specific protocol questions if needed. 2) Simple information pages on each breast adjuvant trial and eventually all Group trials will be developed for posting on the internet home pages of NABCO, NCCS and SWOG. 3) Y-ME is in the process of development of a formal curriculum on clinical trials for its national hot line volunteers. Dr. Albain spoke at the kickoff event in Chicago on: "Debunking the Myths of Clinical Trials" and the SWOG CWH members will serve as consultants to this project. The goal will be to provide callers with enough information to be able to intelligently interact with PDQ and 1-800-4-CANCER. Once in place, the program will be evaluated via a research project. It may provide a training venue for the SWOG Alumni Project, above. 4) An information booklet for women with metastatic breast cancer continues under development by Y-ME. Dr. Martino offered the Breast Committee members to provide feedback to Y-ME.

Task 4, Part b: Progress to Date

Due to the overwhelming success in the formation and ongoing operations of the Lay Advocates Steering Committee and Pilot Project (Task 4a, above), members were also involved from the start in the development of other breast cancer research activities of the CWH under Task 4b. Thus, a number of research projects were designed, developed and/or implemented which addressed cancer control and other survivorship questions. This activity also far exceeded the original vision of this sabbatical, and in large part attests to the feasibility and value of a partnership involvement with survivors and advocates in the breast cancer research process. These ongoing projects represent an definite expansion of the type of study conducted by the cooperative groups and demonstrate the possibilities once supplemental funding is secured (see Introduction). Dr. Albain directed the design and implementation of each of these programs in all details during her Sabbatical year. These important projects are named as follows, and the complete information for each is provided in the Appendix:

1. Appendix J. "Enhancing Well-Being During Initial Breast Cancer Recurrence". This project just received "Gold Standard Proposal" funding from the USAMRMC and will begin in the Fall, 1996. Co-investigators for this novel study include the breast cancer advocacy organization Y-Me, whose volunteers will be trained to deliver the intervention.
2. Appendix K. "A Phase III Trial of Placebo versus Megestrol Acetate 20 mg/day versus Megestrol Acetate 40 mg/day as Treatment for Symptoms of Ovarian Failure in Women Treated for Breast Cancer (SWOG S9626)". This cancer control study was approved by NCI/DCPC both for cancer control credits and supplemental funding.
3. Appendix L. "A Study of the Late Cardiac Effects of Two Different Adjuvant Chemotherapy Regimens in Women with Node Negative Breast Cancer Treated on S8897 (SWOG S9342)." This study became more vital with the recent inclusion of anthracyclines in all national adjuvant therapy trials for early breast cancer. Supplemental funding was secured from both DCT and DCPC of the NCI.
4. Appendices M and N. Prospective (SWOG S9630) and Cross-sectional (SWOG S9631)

studies with molecular correlates to address various aspects of the problem of endometrial abnormalities in women with breast cancer who are treated with adjuvant tamoxifen. These trials received a major grant from the NCI, with priority given to their development due to the recent information regarding the increased risk of endometrial cancer among these patients.

5. Appendix O. An IDEA grant proposal to the 7/17/96 USAMRMC Breast Cancer Program "Clonal Hematopoiesis as a Marker of Genetic Damage following Adjuvant Chemotherapy for Breast Cancer: A Pilot Study of the Southwest Oncology Group to Evaluate Incidence". This proposal was significantly revised after initial review and will now prospectively address the possible development of genetic precursors of treatment-related myelodysplastic syndrome and leukemia. This is in direct response to the report at the beginning of the sabbatical regarding an increased rate of M5 leukemia in an adjuvant trial with AC and G-CSF support. We await the upcoming review of this proposal.

CONCLUSIONS

The conclusions of each of the four Tasks were reviewed in each Section, above, and attest to Dr. Albain's success during this Sabbatical. She achieved the specific aims of each Task as well as the sabbatical's overarching goal of the development of a novel breast cancer research agenda for the Southwest Oncology Group Committee on Women's Health, distinct from the traditional treatment related trials of the national clinical cooperative groups. In the process, Dr. Albain expanded her national network of investigators and gained valuable experience in collaboration with a multi-disciplinary group of experts. These studies either have or will impact on the understanding, treatment and care of breast cancer survivors in a unique fashion complementary to treatment advances. Due to Dr. Albain's achievements during this year, continued funding has been secured for the CWH and specific projects, which will ensure the uninterrupted conduct and completion of this broad and expanded research agenda over the ensuing few years.

REFERENCES

1. Albain KS, Allred C, Clark G: Outcome and predictors of outcome in younger women with breast cancer: Are there age differentials? *Monogr Natl Cancer Inst* 16:35-42, 1994.
2. Allred DC, Clark GM, Fuqua SAW, Elledge RM, Hilsenbeck SG, Ravdin PM, Yee D, Chamness GC, Osborne CK: Overexpression of p53 in node-positive breast cancer. *Proceedings of ASCO* 15:103, 1995.
3. Albain KS, Allred DC, Clark GM: Interactions between very young age and prognostic factors for disease-free survival (DFS) in the presence or absence of adjuvant breast cancer therapy. *Proceedings of ASCO* 15: 1996.
4. Mansour EG, Gray R, Shatila A, Osborne CK, Tormey DC, Gilchrist KW, Cooper MR, Falkson G: Efficacy of adjuvant chemotherapy in high-risk node-negative breast cancer. An Intergroup Study. *N Engl J Med* 320:485-90, 1989.
5. Prioleau J, Schnitt SJ: p53 antigen loss in stored paraffin slides. *N Engl J Med (Letter)* 332:11521-22, 1995.
6. Albain KS, Green S, LeBlanc M, Rivkin S, O'Sullivan J, Osborne CK: Proportional hazards and recursive partitioning and amalgamation analyses of the Southwest Oncology Group node-positive adjuvant CMFVP breast cancer data base: A Pilot Study. *Breast Cancer Research and Treatment* 22: 273-284, 1992.
7. Wood WC, Budman DR, Korzun AH, Cooper MR, Younger J, Hart RD, Moore A, Ellerton JA, Norton L, Ferree CR, Ballow AC, Frei E, Henderson IC: Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. *N Engl J Med* 330:1253-9, 1994.
8. Muss HB, Thor AD, Berry DA, Kute T, Liu ET, Koerner F, Cirrincione CT, Budman DR, Wood WC, Barcos M, Henderson IC: c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. *N Engl J Med* 330:1260-6, 1994.
9. Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer: an overview of the randomised trials. *Lancet*. In Press, 1996.

10. Hutchins L, Rector D, Stotts C, Dahlberg S, Coltman CA, Albain K: Analysis of Southwest Oncology Group accrual for sex ratios and associated socioeconomic status factors. Proceedings of ASCO 13:188, 1994.
11. Lichter A, Green S, Albain K, Hutchins L, Martino S for the Southwest Oncology Group Radiotherapy, Women's Health, and Breast Committees: The influence of patient characteristics, socioeconomic factors, geography, and systemic risk on the use of breast sparing treatment in adjuvant breast cancer studies. Proceedings of ASCO 13:62, 1994.
12. Albain KS, Green SR, Lichter AS, Hutchins L, Wood WC, Henderson IC, Ingle JN, O'Sullivan J, Osborne CK, Martino S: The influence of patient characteristics, socioeconomic factors, geography, and systemic risk on the use of breast sparing treatment in women enrolled on Intergroup adjuvant breast cancer studies. J Clin Oncol. In Press, 1996.

APPENDIX A

Curriculum Vitae/Bibliography of Principal Investigator Kathy S. Albain, M.D.

July, 1996

CURRICULUM VITAE

Kathy S. Albain, M.D.

ADDRESSES: Home: 220 South Maple
Oak Park, Illinois 60302

Office: Loyola University Medical Center
Division of Hematology/Oncology
2160 South First Avenue
Cancer Center, Room 109
Maywood, Illinois 60153
Telephone: 708-327-3102
Facsimile: 708-327-3231
Internet: kalbain@wpo.it.luc.edu

DATE OF BIRTH: June 4, 1952

PLACE OF BIRTH: Monroe, Michigan

CITIZENSHIP: United States

MARITAL STATUS: Single

CHURCH: Grace Evangelical Lutheran Church and Senior Choir
River Forest, Illinois

EDUCATION:

1970 Monroe High School, Michigan; Co-valedictorian

1974 B.S. Wheaton College, Wheaton, IL, Summa Cum Laude.
Major: Chemistry; Minors: Music, Biology.
Research: Rates of dehydrohalogenation of perfluoralkyl-substituted iodoalkanes and alkenes and resulting products.

1978 M.D. University of Michigan Medical School, Ann Arbor, Michigan.

Residency:

1978-1981 Internal Medicine Resident
University of Illinois Medical Center, Chicago, IL.

Fellowship:

1981-1984 Fellow in Hematology/Oncology
The University of Chicago Hospitals and Clinics, Chicago, IL.

LICENSURE AND CERTIFICATION:

- 1979 Diplomate, National Board of Medical Examiners
- 1979- Illinois License #036-059349
- 1981 American Board of Internal Medicine #084230
- 1983 Subspecialty Certification in Medical Oncology, American Board of Internal Medicine #084230

ACADEMIC APPOINTMENTS:

- 1980-1981 Clinical Instructor in Medicine, University of Illinois Medical Center
- 1981-1984 Fellow, Department of Medicine, Section of Hematology/Oncology, The University of Chicago Medical Center
- 1984-1991 Assistant Professor of Medicine
Loyola University Chicago Stritch School of Medicine
Department of Medicine, Section of Hematology/Oncology
- 1991- Associate Professor of Medicine
Loyola University Chicago Stritch School of Medicine
Department of Medicine, Division of Hematology/Oncology

HOSPITAL APPOINTMENTS:

- 1978-1981 Resident Physician, The University of Illinois Chicago Hospitals and Clinics and West Side Veterans Administration Hospital, Chicago, IL.
- 1981-1984 Fellow, The University of Chicago Hospitals and Clinics, Chicago, IL.
- 1984- Attending Physician, Hines Veterans Administration Hospital, Hines, IL.
- 1984- Attending Physician, Loyola University Chicago Foster G. McGaw Hospital

AWARDS AND HONORS:

- 1973 Inductee, Scholastic Honor Society of Wheaton College, Wheaton, IL.
- 1974 Summa Cum Laude Graduate of Wheaton College, Wheaton, IL.

- 1981-1984 National Cancer Institute Fellowship Training Grant Recipient, Hematology/Oncology, The University of Chicago Medical Center
- 1992 Loyola University Medical Center Auxiliary Community Service Award
- 1995 Department of Defense Breast Cancer Special Sabbatical (see below)

MEMBERSHIP IN PROFESSIONAL SOCIETIES:

- 1977- Christian Medical and Dental Society
- 1979-1984 Associate, American College of Physicians
- 1983- International Association for the Study of Lung Cancer
- 1984- American Society of Clinical Oncology
- 1984- American College of Physicians
- 1985- American Federation for Clinical Research
- 1987- American Association for Cancer Research

NATIONAL CLINICAL RESEARCH, ADVISORY PANEL AND MAJOR COMMITTEE APPOINTMENTS:

- 1982-1984 Co-Investigator for the University of Chicago, National Surgical Adjuvant Breast and Bowel Project (NSABP)
- 1986- Member, Southwest Oncology Group
- 1986- Member, Breast Cancer Committee, Southwest Oncology Group
- 1986- Member, Breast Cancer Working Group, Southwest Oncology Group
- 1986- Member, Lung Cancer Committee, Southwest Oncology Group
- 1986- Member, Lung Cancer Working Group, Southwest Oncology Group
- 1989- Member, Gynecologic Cancer Committee and Working Group, Southwest Oncology Group
- 1990- Member, Sarcoma (Mesothelioma) and Brain Committees, Southwest Oncology Group
- 1992- Chair, Committee on Women's Health, Southwest Oncology Group
- 1993- Member, National Cancer Institute Intergroup Lung Cancer Working Cadre

- 1993-4 Clinical Trials Co-chair, Secretary of HHS National Breast Cancer Action Plan
- 1994- Member, National Cancer Institute Breast Cancer Intergroup Chairs Committee
- 1994- Member, Advisory Panel (Study Section), State of Illinois Breast and Cervical Cancer Research Fund
- 1995 Member, Program Committee, American Society of Clinical Oncology
- 1995- Member, Cancer Control Research Committee, and its Working Group and Behavioral and Health Outcomes Committee, Southwest Oncology Group
- 1995- Charter Member, National Institutes of Health Advisory Committee on Research in Women's Health
- 1995 Member, National Cancer Institute Breast Cancer Intergroup Committee on Correlative Sciences
- 1995- Member, Early Breast Cancer Trialists' Collaborative Group
- 1995- Member, Clinical Trials Working Group, Secretary of Health Donna E. Shalala's National Breast Cancer Action Plan
- 1995- Co-chair, Research Subcommittee, National Institutes of Health Advisory Committee on Research on Women's Health

CLINICAL RESEARCH - PRINCIPAL INVESTIGATOR OR STUDY COORDINATOR:

- 1982-1983 Principal Investigator, A Phase II trial of The University of Chicago Lung Cancer Group: Vindesine, etoposide and cisplatin in patients with previously treated, advanced stage, non-small cell bronchogenic carcinoma.
- 1984- Loyola/Hines VAH Principal Investigator for Southwest Oncology Group Lung Carcinoma Clinical Trials
- 1984- Loyola/Hines VAH Principal Investigator for Southwest Oncology Group Breast Carcinoma Clinical Trials
- 1986-1989 Primary Study Coordinator, Southwest Oncology Group Protocol #8605: Cyclophosphamide, ara-C infusion and vincristine for relapsed or refractory extensive small cell lung cancer: A phase II study
- 1987-1989 Principal Investigator, Loyola/Hines pilot study of cisplatin preceded by concurrent cytarabine and oral hydroxyurea in patients with advanced solid tumors.
- 1988-1992 Primary Study Coordinator, Southwest Oncology Group Protocol #8805: Neoadjuvant cisplatin and VP-16 plus concurrent chest and brain irradiation for patients with Stages IIIa and IIIb non-small cell carcinoma, A Phase II pilot.
- 1989-1991 Principal Investigator, Loyola/Hines pilot study of cisplatin preceded by concurrent

intravenous hydroxyurea and cytarabine.

- 1989-1992 Primary Study Coordinator, Southwest Oncology Group Protocol #8904: Phase II trial of piroxantrone in ovarian carcinoma.
- 1989- Primary Study Coordinator, Southwest Oncology Group Protocol #8814 (Intergroup): Phase III comparison of adjuvant chemoendocrine therapy with CAF and concurrent or delayed tamoxifen to tamoxifen alone in postmenopausal patients with involved axillary lymph nodes and positive receptors.
- 1989- Primary Study Coordinator, Southwest Oncology Group Protocol #8854 (Intergroup): Prognostic value of cytometry measurements of breast cancer DNA from postmenopausal patients with involved nodes and receptor positive tumors: a companion protocol to SWOG #8814.
- 1991- Primary Study Coordinator, Southwest Oncology Group Protocol #9019: A Phase III, randomized comparison between chemotherapy plus radiotherapy, and the same chemotherapy plus radiotherapy together with surgery for selected stage IIIA (positive mediastinal nodes) and selected stage IIIB (no malignant effusion) non-small cell lung cancer.
- 1992- Primary Study Coordinator, Southwest Oncology Group Protocol #9143: A Phase II study of cisplatin preceded by a 12-hour continuous infusion of concurrent hydroxyurea and cytosine arabinoside (Ara-C) for patients with untreated, malignant mesothelioma.
- 1992- Primary Study Coordinator, Southwest Oncology Group Protocol #9148: A Phase II study of cisplatin preceded by a 12-hour continuous infusion of concurrent hydroxyurea and cytosine arabinoside (Ara-C) for patients with untreated, extensive stage small cell and non-small cell lung carcinoma.
- 1993- Co-Study Coordinator, Southwest Oncology Group Protocol #9149: A Phase II study of cisplatin preceded by a 12-hour continuous infusion of concurrent hydroxyurea and cytosine arabinoside (Ara-C) for adult patients with malignant glioma.
- 1993- Co-Study Coordinator, Southwest Oncology Group Protocol #9342: A study of the late cardiac effects of two different adjuvant chemotherapy regimens in women with node negative breast cancer treated on SWOG-8897.
- 1994- Principal Study Coordinator, NCI High Priority (1995 Designation) Intergroup Protocol #0139 (SWOG-9336, RTOG, ECOG, CALGB, NCCTG): A phase III comparison between concurrent chemotherapy plus radiotherapy, and concurrent chemotherapy plus radiotherapy followed by surgical resection for stage IIIA(N2) non-small cell lung cancer.
- 1994- Co-Study Coordinator, Southwest Oncology Group Protocol #9445: Prognostic factor panel to predict preferred therapy for node positive postmenopausal breast cancer Patients
- 1995- Co-Study Coordinator, Southwest Oncology Group Protocol #9504: Phase II trial of concurrent cisplatin/VP-16 and radiotherapy followed by consolidation taxotere in stage IIIB non-small cell lung cancer.
- 1995- Co-Study Coordinator, Southwest Oncology Group Protocol #9626: A Phase III trial of placebo versus megestrol acetate 20 mg/day versus megestrol acetate 40 mg/day as

treatment for symptoms of ovarian failure in women treated for breast cancer.

- 1995- Co-Study Coordinator, Southwest Oncology Group Protocol #9631: A cross-sectional study to estimate the incidence of endometrial pathology in women receiving tamoxifen on SWOG-8814 and SWOG-8897.
- 1995- Co-Study Coordinator, Southwest Oncology Group Protocol #9630: A phase III placebo-controlled trial of low-dose progestin as potential chemoprevention of endometrial abnormalities in women with early breast cancer receiving adjuvant tamoxifen.
- 1996- Senior Investigator, Southwest Oncology Group Committee on Women's Health Department of Defense Gold Standard Award Research Project: "Enhancing Well-Being During Breast Cancer Recurrence".

OTHER PROFESSIONAL POSITIONS AND ASSIGNMENTS:

- 1982-1984 Co-Investigator, Multidisciplinary Lung Cancer Staging and Research Group, The University of Chicago and Michael Reese Hospital Medical Centers
- 1985-1991 Coordinator, Annual Breast Cancer Screening Program, Senior Center of La Grange, Illinois
- 1986- Chairperson of the Lung Cancer Multidisciplinary Staging and Research Group, Loyola University Medical Center and Hines Veterans Administration Hospital
- 1986-90 Loyola Medical School Representative to the American Federation of Clinical Research
- 1987- Member, Medical Advisory Board, Y-Me National Breast Cancer Organization
- 1991- Co-director, Loyola University Medical Center Multidisciplinary Breast Care Center
- 1993- Member, Oncology Medical Advisory Board, Eli Lilly and Company
- 1994 Clinical Research Planning Group, Secretary of Health Donna E. Shalala's National Breast Cancer Action Plan
- 1994- Director, Loyola University Medical Center Multidisciplinary Lung Cancer Evaluation Center

Invited Journal Manuscript Reviewer:

Cytometry

Breast Cancer Research and Treatment

Cancer Research
 Journal of Clinical Oncology
 Cancer
 Chest

Loyola Standing Committees:

Quality Assurance Committee (1986-1991)
 Resident Evaluation Committee, Department of Medicine (1986-1992)
 Loyola Community Nursing Medical Advisory Board (1986-1993)
 Loyola University Medical Center Hospice Task Force (1992-1994)

GRANTS:

1988-1993 Co-Investigator: Combination chemotherapy regimens designed to inhibit DNA repair in resistant human tumors treated with alkylating agents or platinum compounds. Bristol-Myers Research Grant Program. \$1,000,000.

1989 Clinical Trial Support Grant, SquibbMark Company, \$3000.00.

1990 Clinical Research Grant, UpJohn Company, \$3000.00.

1991 Clinical Research Grant, UpJohn Company, \$5000.00.

1992 Principal Investigator: "Southwest Oncology Group Committee on Women's Health Lung Cancer, Smoking, and Women Ancillary Studies". Office of Research on Women's Health/National Cancer Institute Joint Initiative 92-1 ("Women's Health Issues"), \$50,000 (subcontract to Southwest Oncology Group Statistical Center).

1993-95 Principal Investigator: "Southwest Oncology Group Committee on Women's Health Lung Cancer and Women Ancillary Studies - Continuation and Expansion of 1992 award. Office of Research on Women's Health/NCI Joint Initiative, \$50,000.

1993-1998 Committee Chair and Principal Investigator: Southwest Oncology Group Women's Health Initiative. National Cancer Institute, approved with excellent merit; funded for five years (5% salary support).

1994-95 Principal Investigator: "Implementation of the Southwest Oncology Group Committee on Women's Health Research Agenda: A Special Sabbatical for the Chairperson", \$100,000 (CY 1995).

- 1995- Co-principal Investigator: "Trials to study and prevent endometrial pathology in breast cancer patients receiving tamoxifen". NCI Special RFA, contract to Southwest Oncology Group (subcontract to Loyola Oncology Institute), \$400,000.

TEACHING EXPERIENCE:

- 1978 Instructor Physical Diagnosis, University of Michigan Medical School
- 1980-1981 Instructor in Medicine, University of Illinois Hospitals and Clinics
- 1983-1984 Junior Medical Student Lectureship in Hematology/Oncology, The University of Chicago Hospitals and Clinics
- 1984- Loyola Medical Student Advisor
- 1984- Annual Second Year Medical Student lectures, Loyola University Chicago Stritch School of Medicine:
 Medical Pharmacology (Antineoplastic agents subsection)
 Organ Systems (Hormone Dependent Malignancies)
- 1984- Annual Third Year Medical Student Responsibilities, Loyola University Chicago Stritch School of Medicine
 Case Discussion Seminars on Breast and Lung Carcinoma
 Case Checking, Medical Oncology
- 1984- Internal Medicine Housestaff and Hematology/Oncology Fellows teaching responsibilities, Loyola University Medical Center and Hines Veterans Administration Hospital
 Lecturer, Medical Grand Rounds and Hematology/Oncology Divisional Grands Rounds and Journal Club
 Internal Medicine Board Review Course Lectures in Breast and Lung Carcinomas
 Chair, weekly Multidisciplinary Loyola-Hines Lung Cancer Patient Teaching Conference
- 1984- Attending Physician Responsibilities, Loyola University Medical Center and Hines Veterans Administration Hospitals:
 Inpatient Medical Oncology Service
 Inpatient Hematology Service
 Inpatient Medical Oncology Consultation Service

- 1992- Supervisor, Hematology/Oncology Fellows' Rotation in Loyola University Cancer Center Multidisciplinary Breast Care Center
- 1994- Supervisor, Hematology/Oncology Fellows' Rotation in Loyola University Cancer Center Multidisciplinary Lung Cancer Evaluation Clinic
- 1994- Supervisor, Internal Medicine Residents' Outpatient Rotation in the Loyola University Cancer Center Breast Care Center

SELECTED INVITED LECTURES AND PRESENTATIONS:

- 1987 Wheaton College Scholastic Honor Society Symposium
- 1987- Local Chapters Lecturer, Y-Me National Organization for Breast Cancer Support and Information
- 1988 Second Annual Coleman/Fannie May Candies Foundation Cancer Research Conference: Modulation of cisplatin resistance by cytarabine and hydroxyurea.
- Illinois Cancer Council Annual Symposium: Review of Breast Cancer Growth Factors and Oncogenes
- Alexian Brothers Medical Center Breast Cancer Conference: Clinical Trials Update
- Illinois Nurses' Association Breast Cancer Conference: Review of Adjuvant Trials
- 1989 American Cancer Society Early Breast Cancer Conference: Current Adjuvant Therapy Recommendations
- Group W Cable TV of Chicago Program on Breast Cancer Screening
- Bristol-Myers Squibb National Symposium on modulation of cisplatin resistance: Results of first Loyola/Hines Pilot Study with cisplatin, cytarabine and hydroxyurea (see above for full description)
- 1990 Oak Park, Illinois Women's Cancer Symposium: Update on Breast Cancer
- Southwest Oncology Group Plenary Session: A presentation of the SWOG extensive non-small cell master analysis
- Bristol Myers Squibb Hydroxyurea Symposium: A presentation of results of the two Loyola/Hines pilot studies of cisplatin, cytarabine, and hydroxyurea
- MacNeal Memorial Hospital Grand Rounds: New Lung Cancer Treatment Strategies

- 1991 Presbyterian Medical Center of San Francisco Minisymposium on Combined Modality Therapy of Stage III Non-Small Cell Lung Cancer

National Cancer Institute Decision Network: Presentation of results of Loyola/Hines pilot trials of cisplatin, hydroxyurea, and cytarabine

Workshop Leader and Speaker for the Midwest Conference on AIDS, Oak Park, Illinois: Stresses of Terminal Illnesses.

Southwest Oncology Group Plenary Session: Presentation of Protocol # 8805 results (see above for description of trial)

Y-Me National Organization for Breast Cancer Information and Support National Conference on Issues and Controversies in Breast Cancer: A Review of Past and Present Adjuvant Breast Cancer Trials

Mercy Memorial Medical Center of St. Joseph, Michigan Annual Oncology Symposium: Lung Cancer Update.

Copley Memorial Hospital of Aurora, Illinois: Update on new lung cancer treatment approaches.

Loyola Department of Nursing Greater Chicago Symposium on "Perspectives on Women with Cancer": Breast Cancer Review and Update.

University of California at San Diego Symposium on Management Strategies in Early Lung Cancer: Combined Modality Induction in Non-small Cell Lung Cancer.

- 1992 Oak Park (IL) Hospital Multidisciplinary Conference: Update on Locally Advanced Lung Cancer.

David L. Rike Cancer Center (Dayton, Ohio) Lung Cancer Symposium: Multidisciplinary Management of Non-small Cell Lung Cancer.

Sacred Heart Cancer and Research Center Lung Cancer Symposium (Spokane, WA): Combined Modality Therapy of Locally Advanced Lung Cancer.

Saint Louis University Cancer Symposium on Controversies in the Treatment of Early Breast and Gynecologic Cancers: Node-negative Breast Cancer: Indications for Adjuvant Therapy and Future Directions.

Illinois Cancer Center Symposium on Issues of Cancer Management in Women and Minorities: Women's Health Issues in Cancer Research.

University of Colorado Lung Cancer Symposium on Innovations in Multimodality Therapy for Lung Cancer: Combined Modality and Neoadjuvant Treatment of Stage IIIA and IIIB Non-small Cell Lung Cancer.

Loyola University Chicago Breast Cancer Imaging in the 90's: Medical Oncology Approaches to Early Breast Cancer.

Southwest Oncology Group Data Managers Plenary Session: Review of new SWOG lung cancer research initiatives and strategies for quality control.

University of Pennsylvania Cancer Center Symposium on New Developments in Cancer Therapy with Focus on Women's Health Keynote speech: Cancer and Women: the Problem.

National Cancer Advisory Board Subcommittee on Women's Health: Presentation of new Southwest Oncology Group Women's Health Initiative.

Office of Research on Women's Health of the National Institutes of Health: Presentation of Southwest Oncology Group Committee on Women's Health.

- 1993 National Cancer Institute Symposium on Strategies for Future Research in Younger Women with Breast Cancer: Predictors of Outcome in Younger Women with Breast Cancer.

Kishwaukee Medical Center Breast Cancer Conference: Prognostic Factors in Breast Cancer.

Southwest Oncology Group Committee on Women's Health Spring Educational Symposium: A Review of Breast Cancer Data Bases Regarding Outcome Predictors in Young Women with Breast Cancer.

Visiting Professor, University of Arizona Cancer Center: Presentation of p53 Abnormalities and Other Adverse Prognostic Factors in Young Women with Early Stage Breast Cancer.

Presentation of Intergroup trial, National Lung Cancer Intergroup Working Cadre meeting.

Invited Participant, National Cancer Institute DCPC Strategy Session on the national research agenda for the hormonal treatment of menopausal symptoms in women with breast cancer.

Plenary Session, San Antonio International Breast Cancer Symposium: p53 Abnormalities and Other Adverse Prognostic Factors in Young Women with Early Stage Breast Cancer.

Plenary Session, The Secretary of Health (DHHS) Conference to Establish a National Breast Cancer Action Plan.

- 1994 Intergroup stage IIIA(N2) lung cancer trial presentation, NCI Intergroup Lung Working Cadre meeting.

Speaker, annual Columbus Cancer Symposium: "New directions in the adjuvant therapy of breast cancer."

Co-Chairs meetings, National Breast Cancer Action Plan

Panelist, NCI extramural review of national lumpectomy data.

Chair: "New approaches to adjuvant therapy of early breast cancer" and speaker ("Evaluating new tamoxifen data") at National Cancer Institute Workshop "An Appraisal of Clinical Research for the Treatment of early Breast Cancer"

Invited speaker, Special Focus Panel at the national meeting of Radiological Society of North America (RSNA): "Breast Cancer in Younger Women: Controversies in Diagnosis and Treatment"

- 1995 Visiting Professor in Lung and Breast Cancer, University of California at Davis
- Speaker, Combined Modality Therapy of Non-small Cell Lung Cancer, Chicago, IL
- Symposium speaker, Breast Cancer in Young Women, Joliet, Illinois.
- Visiting Professor, Fred Hutchinson Cancer Research Center, Seattle, WA
- Invited Participant, Fourth Main Meeting of the Early Breast Cancer Trialists Collaborative Group, Oxford, United Kingdom
- Speaker, Grand Rounds of the Rush Cancer Institute, Chicago, IL.
- 1996 Speaker, Loyola University Chicago Oncology Institute Translational Research Seminar Series: "Beyond Efficacy: Evaluating Tamoxifen's Role in Breast Cancer Survivors", Maywood, IL
- Speaker, United States-Japan Lung Cancer Summit: "Combined Modality Therapy followed by Surgery in Locally Advanced Non-small Cell Lung Cancer"
- American Cancer Society Chicago Regional Symposium Speaker: Update on Research in Women's Health
- Speaker, Pittsburgh/Medical College of Pennsylvania Frontiers in Oncology: "Multimodality Therapy of Stage III Non-small Cell Lung Cancer"
- Keynote Address, International Association for the Study of Lung Cancer Workshop: "Status of Combined Modality Therapy Including Surgery for Non-small Cell Lung Cancer"
- Speaker, Indiana University Cancer Center Perspectives in Breast Cancer: "Update on Adjuvant Chemotherapy" (upcoming)
- Perelman Visiting Professor Lectureship, Cancer Center of Akron: "Perspectives on the Status of Adjuvant Therapy for Breast Cancer" (upcoming)
- Speaker, Case Western University Ireland Cancer Center Conference on the Management of Thoracic Malignancies: "Multimodality treatment of Stage III Non-small Cell Lung Cancer" (upcoming)

OTHER RECENT OR CURRENT EXTRAMURAL POSITIONS:

- Board of Directors, Wheaton College Alumni Association
- Board of Directors, Wheaton College Scholastic Honor Society
- Advisory Board, Career Development Network, Wheaton College
- Medical Student Mentor Program, Christian Medical/Dental Society
- Board of Worship, Grace Evangelical Lutheran Church

ORIGINAL REPORTS:

1. Brace NO, **Albain KS**, Mayforth RD, Miller JA: The effect of conjugation on hydrogen iodide and hydrogen fluoride elimination from 1-(F-alkyl)-4-iodo-1-pentene to 5-(F-butyl) pentadienes and further to 1-fluoro-1-(F-propyl)-1,3,5-hexatrienes. *J Org Chem* 55:5252-5259, 1990.
2. **Albain KS**, LeBeau MM, Vardiman JW, Golomb HM, Rowley JD: Development of a dysmyelopoietic syndrome in a hairy cell leukemia patient treated with chlorambucil: Cytogenetic and morphologic evaluation. *Cancer Genetics and Cytogenetics* 8:107-115, 1983.
3. **Albain KS**, Ultmann JE: Development of aggressive large cell lymphoma of the ileum following long-term cyclophosphamide therapy for breast carcinoma. *Am J Med* 75:882-886, 1983.
4. **Albain KS**, Bitran JD, Golomb HM, Hoffman PC, Skosey C, Noble S, Blough RR: Trial of vindesine, etoposide and cisplatin in patients with previously treated, advanced stage, non-small cell bronchogenic carcinoma. *Cancer Treat Rep* 68:413-415, 1984.
5. Hoffman PC, **Albain KS**, Bitran JD, Golomb HM: Current concepts in small cell carcinoma of the lung: *Ca-A Cancer Journal for Clinicians* 34:3-15, 1984.
6. **Albain KS**, True LD, Golomb HM, Hoffman PC, Little AG: Large cell carcinoma of the lung: Ultrastructural differentiation and clinical-pathologic correlations. *Cancer* 56:1618-1623, 1985.
7. Vardiman JW, LeBeau MM, **Albain KS**, Larson RA, Jacobs R, Rowley JD: Myelodysplasia: A comparison of therapy-related and primary forms. *Ann Biol Clin* 43:372-375, 1985.
8. Bitran JD, Golomb HM, Hoffman PC, **Albain KS**, Evans R, Little AG, Purl S, Skosey C: Protochemotherapy in non-small cell lung carcinoma: An attempt to increase surgical resectability and survival. A preliminary report. *Cancer* 57:44-53, 1986.
9. LeBeau MM, **Albain KS**, Larson RA, Vardiman JW, Davis EM, Blough RR, Golomb HM, Rowley JD: Clinical and cytogenetic correlations in 63 patients with therapy-related myelodysplastic syndromes and acute nonlymphocytic leukemia: Further evidence for characteristic abnormalities of chromosome nos. 5 and 7. *J Clin Oncol* 4:325-345, 1986.
10. **Albain KS**, Hoffman PC, Bitran JD, Golomb HM, DeMeester TR, Little AG, Raghavan VT, Blough RR, Skosey C: Pleural involvement in stage III MO non-small cell bronchogenic carcinoma: A need to differentiate subtypes. *Am J Clin Oncol (CCT)* 9:225-261, 1986.

11. Jacobs RH, Greenburg A, Bitran JD, Hoffman PC, **Albain KS**, Desser R, Potkul L, Golomb HM: A ten year experience with combined modality therapy for stage III small cell lung carcinoma. *Cancer* 58:2177-84, 1986.
12. Swinnen LJ, Barnes DM, Fisher SG, **Albain KS**, Fisher RI, Erickson LC: 1- β -D-arabinofuranosylcytosine and hydroxyurea production of cytotoxic synergy with cis-diamminedichloro-platinum (II) and modification of platinum-induced DNA interstrand crosslinking. *Cancer Res* 49:1383-89, 1989.
13. **Albain KS**: Adjuvant chemotherapy and endocrine therapy for node-positive and node-negative breast carcinoma. *Clin Obstet Gynecol* 32:835-857, 1989.
14. **Albain KS**, LeBeau MM, Ullirsch R, Schumacher H: Implication of prior treatment with drug combinations including inhibitors of topoisomerase II in therapy-related monocytic leukemia with a 9;11 translocation. *Genes, Chromosomes and Cancer* 2:53-58, 1990.
15. **Albain KS**, Crowley JJ, LeBlanc M, Livingston RB: Determinants of improved outcome in small cell lung cancer: an analysis of the 2,580-patient Southwest Oncology Group data base. *J Clin Oncol* 8:1563-74, 1990.
16. **Albain KS**, Swinnen LJ, Erickson LC, Stiff PJ, Fisher RI: Cisplatin preceded by concurrent cytarabine and hydroxyurea: a pilot study based upon an *in vitro* model. *Cancer Chemotherapy and Pharmacology* 27:33-40, 1990.
17. Goodman GE, Crowley JJ, Livingston RB, Rivkin SE, **Albain KS**, McCulloch JH: Treatment of limited small cell lung cancer with concurrent etoposide/cisplatin and radiotherapy followed by intensification with high-dose cyclophosphamide: a Southwest Oncology Group Study. *J Clin Oncol* 9: 453-457, 1991.
18. **Albain KS**, Crowley JJ, Livingston RB: Long-term survival toxicity in small cell lung cancer: expanded Southwest Oncology Group experience. *Chest* 99:1425-32, 1991.
19. Stiff PJ, McKenzie RS, Potempa LD, **Albain KS**, Koch D, Braud E, Bansal VK, Weidner MK, Lanzotti VJ, Chun HG, Johnson C, Fisher RI: A Phase I trial of high dose diaziquone and autologous bone marrow transplantation: An Illinois Cancer Council study. *J Clin Oncol* 9: 1487-94, 1991.
20. **Albain KS**, Crowley JJ, LeBlanc M, Livingston RB: Survival determinants in extensive stage non-small cell lung cancer: The Southwest Oncology Group Experience. *J Clin Oncol* 9:1618-26, 1991.

21. **Albain KS**, Green S, LeBlanc M, Rivkin S, O'Sullivan J, Osborne CK: Proportional hazards and recursive partitioning and amalgamation analyses of the Southwest Oncology Group node-positive adjuvant CMFVP breast cancer data base: A Pilot Study. *Breast Cancer Research and Treatment* 22: 273-284, 1992.
22. **Albain KS**, Swinnen LJ, Erickson LC, Stiff PJ, Fisher SG, Fisher RI: Cytotoxic synergy of cisplatin with concurrent hydroxyurea and cytarabine: Summary of an *in vitro* model and the initial clinical pilot experience. *Semin Oncol* 19: 102-109, Suppl 9 (June), 1992.
23. **Albain KS**: Induction therapy followed by definitive local control for stage III non-small cell lung cancer: a review, with a focus on recent trimodality trials. *Chest* 103:43S-50S, 1993.
24. Rusch VW, **Albain KS**, Crowley JJ, Rice T, Lonchyna V, McKenna R, Griffin B, Livingston RB, and Benfield J: Surgical resection of stage IIIa and stage IIIb non-small cell lung cancer after concurrent chemoradiotherapy: a Southwest Oncology Group trial. *J Thorac Cardiovasc Surg* 105:97-106, 1993.
25. **Albain KS**, Crowley JJ, Hutchins L, Gandara D, O'Bryan RM, Von Hoff DD, Griffin B, and Livingston RB: Predictors of survival following relapse or progression of small cell lung cancer: Report of Southwest Oncology Group (SWOG) study #8605 and an analysis of the SWOG recurrent disease data base. *Cancer* 72:1184-91, 1993.
26. Budd GT, Green S, Osborne CK, **Albain K**, Dressler L, Rivkin S, O'Bryan R, Margolin K, Hutchins LF: Recent and planned Southwest Oncology Group trials in operable breast cancer. *Canadian J Oncol* 3(Suppl 2):47-53, 1993.
27. **Albain KS**, Allred C, Clark G: Outcome and predictors of outcome in younger women with breast cancer: Are there age differentials? *J National Cancer Inst Monographs* 16:35-42, 1994.
28. Locker GY, Kilton L, Khandekar JD, Lad TE, Knop RH, **Albain K**, Blough R, French S, Benson AB III: High-dose aminothiadiazole in advanced colorectal cancer: an Illinois Cancer Center phase II trial. *Investigational New Drugs*, In Press.
29. Rusch VW, **Albain KS**, Crowley JJ, Rice TW, Lonchyna V, McKenna R, Stelzer K, Livingston RB: Neoadjuvant therapy: a novel and effective treatment for stage IIIB non-small cell lung cancer. *Annals of Thoracic Surgery* 58:290-5, 1994.
30. Expert Panel's report on the NCI's audit and analysis of NSABP Protocol B-06. Bethesda, Md.: National Cancer Institute, December 12, 1994.

31. **Albain KS**, Liu PY, Hantel A, Poplin EA, O'Toole RV, Wade JL, Barlogie B and Alberts DS: A phase II trial of piroxantrone in advanced ovarian carcinoma after failure of platinum-based chemotherapy: Southwest Oncology Group study 8904. *Gynecologic Oncology* 57:407-11, 1995.
32. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of the randomized trials. *N Engl J Med* 333:1444-55, 1995.
33. **Albain KS**, Rusch VW, Crowley JJ, Rice TW, Turrisi AT, Weick JK, Lonchyna VA, Presant CA, McKenna RJ, Gandara DR, Miller TP, Taylor SA, Stelzer KJ, Beasley KR and Livingston RB: Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA(N2) and IIIB non-small cell lung cancer: Mature results of Southwest Oncology Group phase II study 8805. *J Clin Oncol* 13:1880-92, 1995.
34. **Albain KS**, Green SR, Lichter AS, Hutchins L, Wood WC, Henderson IC, Ingle JN, O'Sullivan J, Osborne CK, Martino S: The influence of patient characteristics, socioeconomic factors, geography, and systemic risk on the use of breast sparing treatment in women enrolled on Intergroup adjuvant breast cancer studies. *J Clin Oncol*. In Press, 1996.
35. Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer: an overview of the randomised trials. *Lancet*. In Press, 1996.

Abstracts: (*Indicates published elsewhere as full manuscript)

1. ***Albain KS**, et al: Development of a dysmyelopoietic syndrome in a hairy cell leukemia patient treated with chlorambucil: Cytogenetic and morphologic evaluation. Proceedings of American Association for Cancer Research 23:118, 1982. (Presented)
2. ***Albain KS**, LeBeau MM, Rowley JD, Golomb HM and Vardiman JW: Secondary acute nonlymphocytic leukemia and dysmyelopoietic syndrome in 46 patients: Clinical and Cytogenetic correlations. Clinical Research 30:770a, 1982 and Blood 60(Suppl. 1):119a, 1982. (Presented)
3. ***Albain KS**, et al: Trial of vindesine, etoposide and cisplatin in patients with previously treated, advanced stage, non-small cell bronchogenic carcinoma. Proceedings of ASCO 2:189, 1983.
4. ***Albain KS**, et al: Pleural involvement in stage III MO non-small cell bronchogenic carcinoma: A need to differentiate subtypes. Clinical Research 31:741a, 1983 (Presented) and, Proceedings of ASCO 3:254, 1984.
5. Pearson MG, Ultmann JE, Golomb HM, Raghavan VT, Miller JB, Lester EP, **Albain KS** and Daly K: A comparison of palliative therapy versus four drug combination chemotherapy in state III and IV non-Hodgkins lymphomas with favorable histologies. Clinical Research 30:71a, 1982.
6. ***Albain KS**, True L, Golomb H, and Little A: Large cell carcinoma of the lung: Ultrastructural differentiation and clinical-pathologic correlations. Proceedings, American Association for Cancer Research 25:48, 1984. (Presented)
7. **Albain KS**, LeBeau MM, Vardiman JW, Rowley JD, Golomb HM and Ultmann JE: Secondary acute nonlymphocytic leukemia and dysmyelopoietic syndrome: A model of leukemogenesis with implications in the primary treatment of lymphomas. Second International Conference on Malignant Lymphomas, Lugano, June, 1984. (Invited abstract, plenary session)
8. *Bitran J, Golomb H, Hoffman P, **Albain KS**, Little A, Kozloff M, Evans R, Purl S and Skosey C: Neoadjuvant chemotherapy in non-small cell lung cancer (NSCLC) stage III MO (T3N2): An attempt to increase surgical resectability. Proceedings of ASCO 4:175, 1985.
9. Hoffman PC, Bitran JD, Golomb HM, **Albain KS** and Skosey CA: Do high dose cisplatin regimens add to the therapy of metastatic non-small cell lung cancer? Proceedings of ASCO 4:185, 1985. (Presented)
10. Jacobs RH, Bitran JD, **Albain KS**, Golomb HM, and Hoffman PC: A pilot study of cisplatin and 5-fluorouracil infusion in previously treated patients with stage III carcinoma of the lung. Clinical

Research 33:853A, 1985.

11. Toth J, Franklin WA, DeSombre ER, Joseph L, **Albain KS**, Fisher RI, Folk F and Orfei E: Immunohistochemical localization of estrogen receptor and proliferating antigen (Ki-67) in normal, benign and malignant human breast tissue. Presented: International Cancer Congress, 1986.
12. *Swinnen LJ, Barnes DM, **Albain KS**, Fisher SG, Fisher RI and Erickson LE: 1- β -D arabinofuranosylcytosine and hydroxyurea produce cytotoxic synergy with cis-diamminedichloroplatinum (II) and modifications in platinum-induced DNA interstrand crosslinking. Proceedings of AACR 29:473, 1988. (Presented)
13. ***Albain KS**, Crowley J, Livingston R: Prognostic factors in limited small cell lung cancer reconsidered: Southwest Oncology Group studies. Proceedings of ASCO 8:225, 1989. (Presented)
14. ***Albain KS**, Swinnen LJ, Erickson LC, and Fisher RI: Cisplatin preceded by concurrent cytarabine (Ara C) and hydroxyurea (HU) for refractory or advanced solid tumors: a Phase I trial based upon an in vitro model. Proceedings of AACR 30:275, 1989. (Presented)
15. *Stiff P, Weidner M, Potempa L, **Albain KS**, Bansal V, Braud E, Koch D, and Chun H: Phase I trial of high dose aziridinybenzoquinone (AZQ) with autologous bone marrow transplantation. Proceedings of ASCO 8:83, 1989. (Presented)
16. ***Albain KS**, Crowley J, LeBlanc M, and Livingston R: Does cisplatin-based therapy improve survival in extensive non-small cell lung cancer? Southwest Oncology Group studies. Proceedings of ASCO 9:227, 1990. (Presented)
17. ***Albain KS**, Green S, Rivkin S, and Osborne K: Age <35 years is an adverse prognostic feature in premenopausal node-positive breast cancer patients in Southwest Oncology Group studies. Proceedings of ASCO 9:35, 1990.
18. ***Albain KS**, Rusch V, Crowley J, Griffin B, Beasley K, and Livingston RB: Concurrent cisplatin, VP-16, and chest irradiation followed by surgery for stages IIIa and IIIb non-small cell lung cancer: A Southwest Oncology Group study (#8805). Proceedings of ASCO 10:836, 1991. (Presented)
19. Locker G, Kilton L, Khandekar D, Shevrin D, **Albain K**, Blough R, Watkins A, Tuteur D: High dose aminothiodiazole (ATDA) in advanced colorectal adenocarcinoma: An Illinois Cancer Council phase II study. Proceedings of ASCO 10:138, 1991.
20. Lad T, Mullane M, Swedler R, Kilton L, Johnson P, **Albain K**, Blough R, Weidner L: Phase II trial of didemnin-B in non-small cell lung cancer. An Illinois Cancer Council study. Proceedings of

ASCO 10:258, 1991.

21. ***Albain K**, Rivkin S, Green S, LeBlanc M, and Osborne K: A recursive partitioning and amalgamation analysis of the Southwest Oncology Group Node (+) adjuvant CMFVP data base: four distinct prognostic groups are described by ER and number of nodes. Proceedings of ASCO 11:57, 1992. (Presented)
22. ***Albain KS**, Allred DC, Clark GM: Age < 35 is associated with high % S-phase, abnormal p53, and adverse breast cancer outcome. Proceedings San Antonio International Breast Cancer Symposium: Breast Cancer Research and Treatment 27:131, 1993. (Presented, Plenary Session)
23. ***Albain K**, Rusch V, Crowley J, Turrisi A, Rice T, Livingston R: Concurrent cisplatin/etoposide plus chest radiation followed by surgery for stages IIIA(N2) and IIIB non-small cell lung cancer: completed analysis of SWOG-8805. Proceedings of ASCO 13:337, 1994. (Presented)
24. Schilder LE, **Albain KS**, Hantel A, Philpot T, Rossof AH: Phase I trial of taxol, ifosfamide, cisplatin (TIC) in patients with solid tumors. Proceedings of ASCO 13, 404, 1994.
25. Hutchins L, Rector D, Stotts C, Dahlberg S, Coltman CA, **Albain K**: Analysis of Southwest Oncology Group accrual for sex ratios and associated socioeconomic status factors. Proceedings of ASCO 13:188, 1994.
26. *Lichter A, Green S, **Albain K**, Hutchins L, Martino S for the Southwest Oncology Group Radiotherapy, Women's Health, and Breast Committees: The influence of patient characteristics, socioeconomic factors, geography, and systemic risk on the use of breast sparing treatment in adjuvant breast cancer studies. Proceedings of ASCO 13:62, 1994. (Presented)
27. Schilder LE, **Albain KS**, Hantel A, Philpot T, Rossof AH: Phase I trial of taxol, ifosfamide, and cisplatin (TIC) in patients with solid tumors. Proceedings of ASCO 14: , 1995. (Presented)
28. **Albain KS**, Allred DC, Clark GM: Interactions between very young age and prognostic factors for disease-free survival (DFS) in the presence or absence of adjuvant breast cancer therapy. Proceedings of ASCO 15: 1996. (Presented)
29. Flaherty L, Unger J, Liu PY, **Albain KS**, Sondak V: Gender differences and independent predictors of survival in patients with metastatic malignant melanoma. Proceedings of ASCO 15: 1996. (Presented)

APPENDIX B

Summary data from presentation to the American Society of Clinical Oncology in May 1996: "Interactions between very young age and prognostic factors for disease-free survival (DFS) in the presence or absence of adjuvant breast cancer therapy." Kathy S. Albain, M.D., D. Craig Allred, Ph.D., and Gary M. Clark, Ph.D.

The following unpublished data summary is proprietary information.

BACKGROUND

- Young women with breast cancer have the worst survival if matched with similarly staged older cohorts in epidemiologic studies.
- Women <35 years of age had more adverse prognostic factors and worse outcomes than older patients in our initial study (*Monogr Natl Cancer Inst* 16:35, 1994).
- The present study incorporates:
 - longer follow-up (median = 5 years)
 - adjuvant therapy data
 - new debris-stripping algorithm for S-phase
 - additional analyses of p53 abnormalities
 - models of interactions among young age, adverse prognostic factors and treatment

OBJECTIVES

1. Validate that very young women have poor clinical outcomes.
2. Correlate very young age and other prognostic factors with clinical outcomes among women who received:
 - a. No adjuvant therapy
 - b. Chemotherapy \pm endocrine therapy (N+)
 - c. Endocrine therapy alone (N+)
3. Identify very young women with good clinical outcomes who do not need adjuvant therapy.

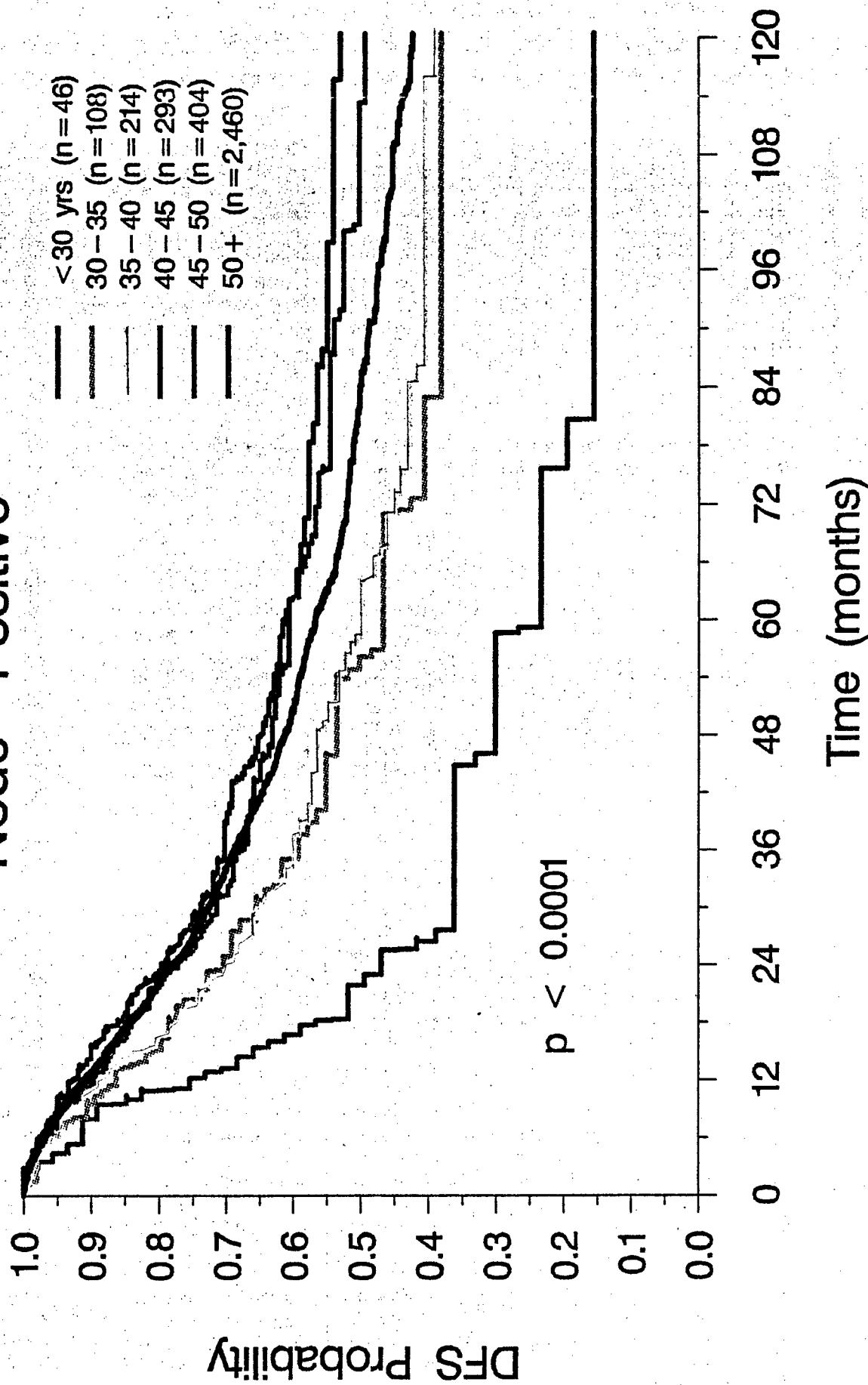
METHODS

1. Early stage breast cancer (T₁₋₃ N₀₋₁)
2. Frozen tumor specimens large enough for biochemical ER assays
3. Age categories: <30, 30-35, 35-40, 40-45, 45-50, >50
4. Prognostic factors: # positive nodes, tumor size, ER, PgR, DNA ploidy, S-phase fraction, p53
5. Survival analyses: univariate - Kaplan-Meier curves; multivariate - Cox models

PATIENT CHARACTERISTICS

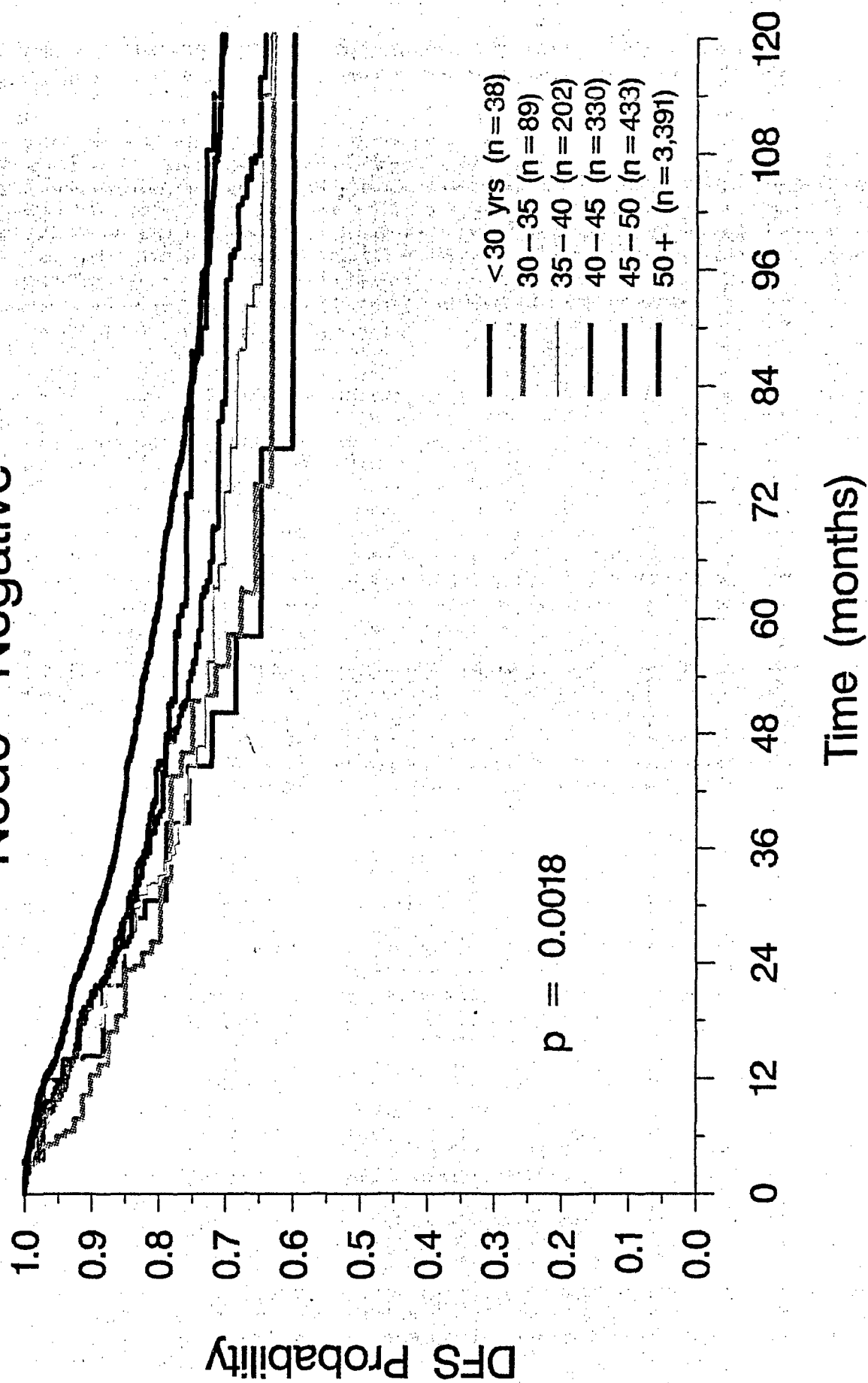
	All Pts	Pts with p53 and S-phase
Total	6,477	1,019
Age <35 (<30)	233 (70)	40 (11)
No adjuvant Tx	3,122	350
No adjuvant Tx, <35	81	0
N+, chemotx ± endotx	1,434	368
N+, endotx only	726	195

Disease Free Survival Node – Positive



Disease Free Survival

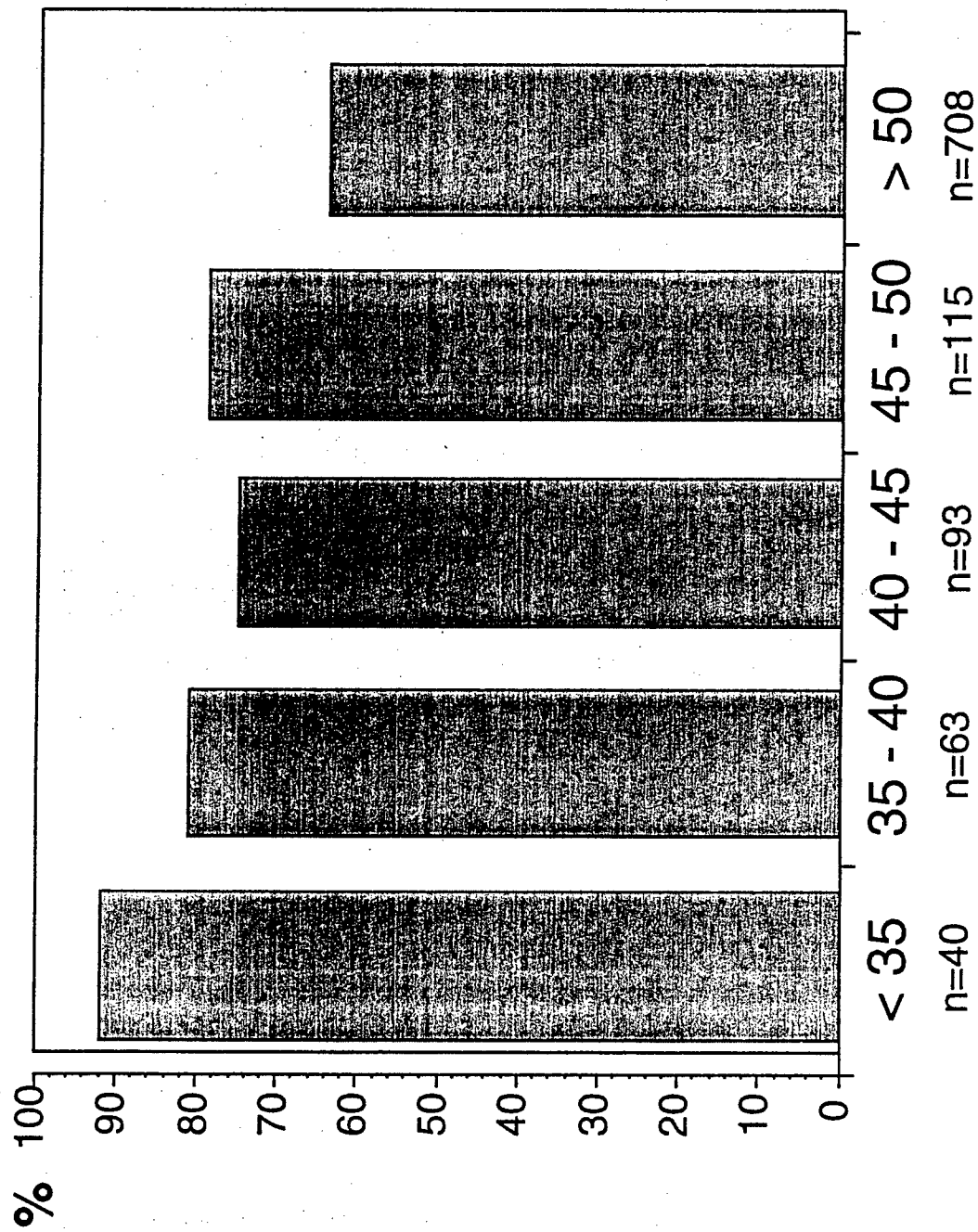
Node - Negative



ADVERSE PROGNOSTIC FACTORS AND VERY YOUNG AGE

- **Positive lymph nodes**
(0 vs. >0, <4 vs. 4+, <10 vs 10+)
- **ER-negativity, PgR-negativity**
- **T3 tumors**
- **High S-phase fraction**
- **Abnormal p53 expression**

% High S-Phase and/or Abnormal p53



SIGNIFICANT PREDICTORS OF DISEASE-FREE SURVIVAL

	All Pts	Pts with p53 and S-phase
No adjuvant tx	N, T, age<35	N, T, p53, S
N+, chemotx ± endotx	N, T, age<30	N, T
N+, endotx only	N, PgR, T, age 30-35	N, T, p53, age 35-40
Age <35	N	N, S, p53

N = sqrt (# positive nodes)

T = sqrt (tumor size)

S = log (S-phase fraction)

p53 = abnormal p53 expression

IDENTIFICATION OF VERY YOUNG WOMEN WHO DO NOT NEED ADJUVANT THERAPY

- 233 women <35 years of age
- # positive nodes was the only significant predictor of adverse outcome
- No subset could be identified with 5-year disease-free survival > 70%
 - N₀: 66% ± 5% (n=108)
 - N₀ no Tx: 64% ± 7% (n=65)
 - N₄₊: 24% ± 6% (n=73)

CONCLUSIONS

1. Young age is an independent adverse factor regardless of treatment category.
2. Most very young patients have high S-phase and/or p53+ tumors.
3. p53+ and/or high S-phase is associated with poor outcome.
4. p53 not a strong predictor of outcome in the presence of chemotherapy.
5. No subsets among very young women have very good prognosis.
6. Cannot analyze complex interactions among very young age, S-phase, p53, treatment without large numbers of patients.

APPENDIX C

Representative Email Correspondence with Statisticians Richard Gray and Michael Clarke of the Early Breast Cancer Trialists Collaborative Group: Ongoing Analyses of the Young Age Subset for the Year 15 International Overview.

The following correspondence is proprietary information

To: grayr, clarkem
Date: Saturday, November 11, 1995 4:12 pm
Subject: EBCTCG

Dear Richard and Mike,

At your request in your October letter, I again reviewed all the materials given to us at the meeting, and would suggest the following additional analyses, in follow-up to ongoing discussions regarding additional analyses in the subset of very young women, in particular in context of what you have already done. Richard, you suggested I send more specific ideas to you in keeping with the types of analyses feasible in the overview.

- a. The chemoendo question is critical to sort out in greater detail, because although the overall additive effect was impressive, it is not clear that all subsets benefit from the combination (eg: no benefit adding tam to chemo in any receptor subset under age 50!). Many of us are concerned the chemoendo combo is now being employed indiscriminately in the community (and even on some cooperative group trials). Thus, it would be very important to see the following:
 - percent reduction of annual odds chemo vs nil by age under vs over 50 (we only have chemotam vs tam)
 - percent reduction of annual odds chemo vs nil and chemotam vs tam by ER poor vs ER positive (overhead was shown but not included book or in packet mailed after meeting)
 - percent reduction annual odds chemo vs. nil and chemotam vs. tam by the four main age/receptor categories as was done for tam vs nil and tamchemo vs chemo (ie under 50 receptor poor, under 50 receptor positive, over 50 receptor poor, over 50 receptor pos.)
- b. In addition, if at all possible, then break down the two under 50/receptor categories into under 40 and 40-50 and do same four major categories (tam vs nil, tamchemo vs chemo, chemo vs nil, chemotam vs tam). Would just do for receptor pos and receptor poor and leave unknowns or borderline out.
- c. Explore what happens (as Richard and I discussed at the meeting) with an under 30 and 30-40 grouping for the main ovarian ablation or not, tamoxifen or not and chemo or not questions. Do in both node positive and node negative groups.

It is especially important to look at the very young age question because it is striking to see the data as you presented it for the under 40 group only (I made a slide of just this age group from the analyses already done): There was no benefit to ablation (perhaps most had cytotoxics), tamoxifen had only borderline recurrence reduction and NO survival benefit, with only chemo showing strong benefit.

Hopefully by at least expanding the chemoendo analyses as above in b. (and checking the 30-40 and under 30 group), we will learn much more. NONE of the individual trials or even cooperative group data bases I am working with have large enough samples of the very young women to look at treatment effect in detail. I believe these analyses, unlike some of those I proposed to you in August, are quite doable with this type of sample.

Thank you very much.

Kathy Albain

From: Kathy Albain
To: internet:grayr@vax.ox.ac.uk
Date: Wednesday, May 29, 1996 2:18 pm
Subject: ovarian ablation draft

Dear Richard,

Attached are my comments on the ablation draft. They will be faxed as well in the am with the response cover sheet.

Regards,
Kathy

Files: F:\USER\KALBAIN\WP51\ABLATION

Comments on Draft Ovarian Ablation Manuscript.

1. From the fourth line of Methods on it is a little confusing in the wording (although I understand, reader may not): "... versus no such adjuvant treatment that began recruiting before 1990. In practice, however, all the trials reviewed here began before 1980, and all involved surgical or radiotherapeutic ablation." Might be best to bring forward to this point the sentences from later on which clarify that LHRH trials are not yet in this overview, and also point out the ablation vs nil and the ablation in presence of cytotoxics distinction.

2. In the Results, could you go back to some of the data shown in Oxford which was deleted from this manuscript for the women under 40 and 40-49? As written, the reader concludes that ablation works for all women under 50. I do not think we can say that yet. Quoting the figures shown on your overhead at Oxford (and included in the packet mailed after the meeting), the overall percent reduction in annual odds of recurrence and of mortality was NOT significantly reduced by ablation in women under 40, whereas it was so for women 40-49. Now, of course the problem may be that many of the women under 40 may have been exposed to cytotoxics. THEREFORE, could you do the following analysis: look at the group of ablation vs nil (no cytotoxics) by age under 40 and 40-49. Depending on what is found, it would be important to add survival curves to the manuscript as was done for nodes (figure 3 was the two node categories in absence of cytotoxics; thus, add a figure 4 for the 2 premenopausal age categories in absence of cytotoxics, ablation vs not).

3. Then, the Discussion section should address this same issue about whether the data support ablation for ALL premenopausal women, or whether instead the presence of cytotoxics obscures a true estimate of benefit in the women under 40. Again, this is critical because "under 50" includes those done with childbearing versus those who still wish to do so.

Respectfully submitted,

Kathy Albain

APPENDIX D

Selected Pages of Southwest Oncology Group Protocol S8814: "Phase III Comparison of Adjuvant Chemoendocrine Therapy with CAF and Concurrent or Delayed Tamoxifen to Tamoxifen Alone in Postmenopausal Patients with Involved Axillary Lymph Nodes and Positive Receptors. Intergroup Trial INT-0100 (Southwest Oncology Group, Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, North Central Cancer Treatment Group, National Cancer Institute of Canada.

Principal Study Coordinator: Kathy S. Albain, M.D.

Co-Study Coordinators for the SWOG: C. Kent Osborne, M.D., Allen S. Lichter, M.D., Chester J. Herman, M.D., Ph.D., Harold V. Gaskill, M.D., Stephanie J. Green, Ph.D. (see following page for coordinators from other Groups)

The following protocol is proprietary information and is a privileged communication for investigational use only

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY
Revised 7/15/90
Revised 3/1/91
Revised 10/1/91

SWOG-8814
INT-0100
May 15, 1989
Revised 3/1/92
Revised 2/1/94

SOUTHWEST ONCOLOGY GROUP

**PHASE III COMPARISON OF ADJUVANT CHEMOENDOCRINE THERAPY WITH CAF AND
CONCURRENT OR DELAYED TAMOXIFEN TO TAMOXIFEN ALONE IN POSTMENOPAUSAL
PATIENTS WITH INVOLVED AXILLARY LYMPH NODES AND POSITIVE RECEPTORS
INTERGROUP (SWOG, ECOG, CALGB, NCCTG, NCIC)**

	<u>Page</u>
SCHEMA	3
1.0 OBJECTIVES.....	4
2.0 BACKGROUND.....	4
3.0 DRUG INFORMATION.....	8
4.0 STAGING CRITERIA.....	12
5.0 ELIGIBILITY CRITERIA	12
6.0 DESCRIPTIVE FACTORS/STRATIFICATION/RANDOMIZATION	14
7.0 TREATMENT PLAN.....	15
8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS.....	24
9.0 STUDY CALENDAR.....	27
10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS.....	30
11.0 STATISTICAL CONSIDERATIONS	30
12.0 DISCIPLINE REVIEW.....	31
13.0 REGISTRATION GUIDELINES.....	31
14.0 DATA SUBMISSION SCHEDULE	32
15.0 DISTRIBUTION OF MATERIALS FOR ANALYSIS	33
16.0 SPECIAL INSTRUCTIONS	34
17.0 ETHICAL AND REGULATORY CONSIDERATIONS	34
18.0 BIBLIOGRAPHY	39
19.0 MASTER FORMS SET.....	43
20.0 APPENDICES.....	54

**PARTICIPANTS: ALL GROUP, CCOP AND CGOP MEMBERS OF THE SOUTHWEST ONCOLOGY
GROUP, ECOG, CALGB, NCCTG AND NCIC**

STUDY COORDINATORS (SOUTHWEST ONCOLOGY GROUP):

Kathy S. Albain, M.D. (Medical Oncology)
Loyola University
Stritch School of Medicine
Building 54, Room 046
2160 South First Avenue
Maywood, IL 60153
Phone: 708/216-5005

Allen S. Lichter, M.D (Radiation Therapy)
Department of Radiation Oncology
University of Michigan
Room B2C490, Box 0010
1500 E. Medical Center Drive
Ann Arbor, MI 48109
Phone: 313/936-4301

C. Kent Osborne, M.D. (Medical Oncology)
Department of Medicine
Division of Oncology
University of Texas Health
Science Center
7703 Floyd Curl Drive
San Antonio, TX 78284
Phone: 210/567-4777

Chester J. Herman, M.D., Ph.D. (Pathology)
Director, Anatomic Pathology
Grady Memorial Hospital
80 Butler Street, SE
Atlanta, GA 30335
Phone: 404/616-4123

M176/mkp

Harold V. Gaskill, M.D. (Surgery)
University of Texas Health Science Center
Department of Surgery
7703 Floyd Curl Drive
San Antonio, TX 78284
Phone: 512/567-5750

Stephanie J. Green, Ph.D (Biostatistics)
Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street
Seattle, WA 98104-2092
Phone: 206/667-4623

STUDY COORDINATORS (ECOG-4188)

Charles D. Cobau, M.D. (Medical Oncology)
Flower Hospital
5200 Harroun Rd.
Sylvania, Ohio 43560
Phone: 419-473-3564.

Barbara Fowble, M.D. (Radiation Therapy)
Hospital of the University of Pennsylvania
Department of Radiation Therapy
3400 Spruce St.
Philadelphia, PA 19104
Phone: 215/662-4000

Kennedy Gilchrist, M.D.
University of Wisconsin
Clinical Science Center
Room K4-536
600 Highland Ave.
Madison, WI 53792
Phone: 608/263-5353

STUDY COORDINATORS (NCCTG-883051)

James N. Ingle, M.D.
Mayo Clinic
Rochester, MN 55905
Phone: 507/284-2511

Donald I. Twito, M.D.
Billings Clinic
P.O. Box 35100
Billings, MT 59107
Phone: 406/256-2500

Paula J. Schumberg, M.D. (Radiation Oncology)
Mayo Clinic
Rochester, MN 55905
Phone: 507/284-3551

AGENTS:

Adriamycin (NSC-123127)
Cyclophosphamide (NSC-26271)
5-Fluorouracil (NSC-19893)
Thiotepa
Tamoxifen (NSC-180973)

STUDY COORDINATORS (CALGB-9194)

Ellis Levine, M.D.
Roswell Park Cancer Institute
Dept. of Medicine
Elm and Carlton Streets
Buffalo, NY 14263
Phone: 716/845-4440
FAX: 716/845-3423

Jay R. Harris, M.D.
50 Binney Street
Boston, MA 02115
Phone: 617/735-2345

I. Craig Henderson, M.D.
Chief, Medical Oncology
University of California, San Francisco
Moffitt-Long Hospitals, UCSF Medical Center
505 Parnassus Avenue, Room M1286
Box 1270
San Francisco, CA 94143-1270

Donald A. Berry, Ph.D.
Phone: 919/286-7774

STUDY COORDINATORS (NCIC-MA.9)

Kathy Pritchard, M.D.
Head, Div. of Medical Oncology
Toronto Bayview Regional Cancer Center
Sunnybrook Health Science Centre
2075 Bayview Avenue
North York, Ontario M4N 3M5075
Phone: 416/480-4616

Lois Shepherd, M.D.
Physician Coordinator
NCIC - Clinical Trials Group
Queens University
82-84 Barrie Street
Kingston, Ontario K7L 3N6
Phone: 613/545-6430

Michael Brundage, M.D. (Radiation Oncologist)
NCIC-Clinical Trials Group
Queens University
82-84 Barrie Street
Kingston, Ontario K7L 3N6
Phone: 613/545-6430

SCHEMA

	R	Arm I Tamoxifen x 5 years
	A	
<u>Stratification:</u>	N	
- 1-3, vs. ≥ 4 positive nodes	D	Arm II
- Interval between surgery * and randomization ≤ 6 weeks vs > 6 weeks	O	Intermittent CAF x 6 courses followed by tamoxifen x 5 years
	M	
- PgR+ (ER+ or-) vs PgR- (ER+)	I	
	Z	Arm III
	E	Intermittent CAF x 6 courses with concurrent tamoxifen x 5 years

* The date of definitive surgery is date of either mastectomy or axillary dissection for patients who had lumpectomy.

INTERGROUP ADJUVANT BREAST CANCER PRESTUDY

Amended Data: Yes, mark amended items.

Coord Gp Pt. No. _____ Coord Gp Study No. _____ Pt. No. _____ Study No. _____

Patient's Name _____ Social Security No. --

Group _____ Institution _____ Affiliate (if applicable) _____

Physician _____ Hospital Number _____

INSTRUCTION: If parts of dates are unknown, enter "-1" in boxes.

PATIENT CHARACTERISTICS

Date of birth -- (M,D,Y)

Race White Black Other Unknown

Actual weight kg

Actual height cm

Actual body surface area m²

Performance status
0 - Fully active
1 - Symptoms but ambulatory and able to do light work
2 - No work but self care and active > 50% of waking hours
3 - Limited self care, confined to bed or chair > 50% of waking hours
4 - Completely disabled

Concurrent chronic disease No Yes

If Yes, specify: _____

Chronic medications No Yes

If Yes, specify: _____

Prior exogenous hormones No Yes

Hormones _____

Date stopped (M,D,Y)

Current menopausal data

Prior hysterectomy No Yes Unk

If "Yes", date (M,D,Y)

Prior bilateral ovariectomy No Yes Unk

If "Yes", date (M,D,Y)

Date last menses (M,D,Y)

FSH value (if required - see protocol) (mU/ml)

Laboratory _____

Laboratory standard cut off for premenopause (mU/ml)

DISEASE CHARACTERISTICS

Date of Histologic Diagnosis of Primary (M,D,Y)

Location of Primary Multicentric (more than one distinct lesion) No Yes

(Check all involved areas)
RIGHT QUADRANT LEFT
 inner upper
 inner lower
 outer upper
 outer lower
 central

Size of Lesion (longest diameter) If multiple lesions, use largest.

Clinical (physical exam) cm

Pathologic cm

Clinical Characteristics

Skin infiltration No Yes Unk
Inflammatory No Yes Unk
Fixation to chest wall No Yes Unk
Skin ulceration No Yes Unk

Pathologic Characteristics

Dermal lymphatic invasion No Yes Unk
Involvement pectoral fascia/muscle No Yes Unk
Margins free (gross) No Yes Unk
Margins free (microscopic) No Yes Unk

Axillary Nodes

Pathological

Infraclavicular nodes involved No Yes Unk

Number of nodes removed: } Use 98 if many, NOS; -1 if unknown

Number of nodes positive:

Extranodal extension into axillary fat No Yes Unk

Clinical

Arm edema before surgery No Yes Unk

Suspicious palpable nodes No Yes Unk

Fixed/matted nodes No Yes Unk

INTERGROUP ADJUVANT BREAST CANCER PRESTUDY

Amended Data: Yes, mark amended items.

Coord Gp Pt. No. _____ Coord Gp Study No. _____ Pt. No. _____ Study No. _____

Patient's Name _____
 (L) (F) (M)

INSTRUCTION: If parts of dates are unknown, enter "-1" in boxes.

PRIOR TREATMENT -- Related to This Cancer

PRIOR SURGERY

Procedure #1 _____ Code*

Date - - (M,D,Y)

Procedure #2 _____ Code*

Date - - (M,D,Y)

Procedure #3 _____ Code*

Date - - (M,D,Y)

*Code

- 1 - Aspiration cytology
- 2 - Incisional biopsy
- 3 - Excisional biopsy
- 4 - Tumorectomy/lumpectomy
- 5 - Wide excision
- 6 - Segmental/partial mastectomy/quadrantectomy
- 7 - Total mastectomy
- 8 - Modified radical mastectomy
- 9 - Radical mastectomy
- 10 - Other

If codes 4 through 7 or 10 are used, was an axillary node dissection or node sampling done?

No Yes

Date of Dissection or Sampling - - (M,D,Y)

Notes:

PRIOR RADIATION THERAPY

No Yes

First Dose - - (M,D,Y)

Last Dose, Including Boost - - (M,D,Y)

Sites Irradiated:

- Breast No Yes
- Chest wall No Yes
- Axilla No Yes
- Internal mammary nodes No Yes
- Supraclavicular nodes No Yes
- Other No Yes

If yes, specify _____

PRIOR TAMOXIFEN

No Yes

Start date - - (M,D,Y)

Stop date - - (M,D,Y)

Notes:

**ADJUVANT BREAST CANCER
FOLLOW UP FORM PRIOR TO RECURRENCE**

SWOG Study No.

Assigned Treatment Arm _____

SWOG Pt. No. Patient's Name _____ (L,F,M)

Institution / Member _____ Physician _____ Hospital No. _____

Groups other than SWOG: Group Name/Study No./Pt No. _____ / _____ / _____

Instructions: Complete and submit within two weeks of every follow up evaluation until recurrence and within two weeks after the first recurrence. At first recurrence a Notice of Recurrence form must also be submitted. If the patient cannot be contacted, submit this form at protocol specified follow up intervals. Append additional page for Notes if necessary. All dates are MONTH, DAY, YEAR. Indicate an unknown part of a date with a horizontal line drawn across the appropriate boxes.

Date of last contact or death: - - Status: Alive Dead

Complete this section if patient contact was unsuccessful.

Follow Up Methods used: (Check all that apply)

- Contacted patient's referring or family physician
- Checked tumor registries
- Wrote or phoned patient's relative / friend
- Requested death certificate from last known state of residence
- Other, specify: _____

Date of last attempted contact:

- -

Complete the remainder of this form if patient contact was successful.

Tamoxifen since last form?

No Yes, dose: _____

If patient has discontinued tamoxifen and this has not been reported, specify date:

and reason: - -

If patient has received non-protocol treatment for breast cancer since the last form, specify in Notes.

Breast cancer assessment since last form

0-Not done or not required 1-Neg 2-Equiv 3-Pos

Physical exam	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chest X-Ray	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chest CT	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Liver / Abdomen CT	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bone scan	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mammogram	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
CBC / labs,	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

specify all abnormal values _____

Other _____

Long term effects assessment

(do not code if no change from last form)

9-Unk 0-No 1-Yes

Cardiac disease

Osteoporosis

Thromboembolic disease

Menstrual/menopausal changes

Date LMP, if registered as pre - -

Dyspareunia

Pregnancy (outcome if yes)

Other significant condition

Has the patient developed a new breast primary, other new malignancy, or myelodysplastic syndrome since last follow up? No Yes (Submit Notice of Second Malignancy)

Notes:

BY: _____ DATE: _____

NOTICE OF RECURRENCE/RELAPSE

Amended data: Yes, mark amended items in red

Disease Committee _____

SWOG Study No.

SWOG Pt. No.

Patient Name _____ (L.F.M)

Institution/Member _____ Physician _____

Groups other than SWOG: Group Name/Study No./Pt.No. = _____ / _____ / _____

INSTRUCTIONS:

Submit this form and follow-up flowsheet within 4 weeks of knowledge of first disease recurrence/relapse; if recurrence is detected at death, also submit the NOTICE OF DEATH.

Do not submit this form if an OFF TREATMENT NOTICE citing "progression or relapse" as the reason off treatment has been submitted for this patient and study number.

First date recurrence/relapse established: - - (M,D,Y)

Indicate all site(s) of recurrence/relapse, the means of detection for each site, and the date the test was performed.

SITE	METHOD	DATE
<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/>

Subsequent therapy planned?

No Yes, specify: _____ Unknown

Notes:

BY: _____

DATE: _____

**ADJUVANT BREAST CANCER
POST RECURRENCE FOLLOW UP FORM**

SWOG Study No.

SWOG Pt. No. Patient's Name _____ (L,F,M)

Institution / Member _____ Physician _____ Hospital No. _____

Groups other than SWOG: Group Name/Study No./Pt No. _____ / _____ / _____

Instructions: After recurrence, complete and submit every six months until death. If the patient cannot be contacted, submit at protocol specified follow up intervals. All dates are MONTH, DAY, YEAR. Indicate an unknown part of a date with a horizontal line drawn across the appropriate boxes.

Date of last contact or death: - - Status: Alive Dead

Complete this section if patient contact was unsuccessful.

Follow Up Methods used: (Check all that apply)

Date of last attempted contact:

- -

- Contacted patient's referring or family physician
- Checked tumor registries
- Wrote or phoned patient's relative / friend
- Requested death certificate from last known state of residence
- Other, specify: _____

Complete the remainder of this form if patient contact was successful.

Code treatments and outcomes since last form.

Treatment	Start Date	Stop Date	* Best Response	New sites of disease at time of progression
	<input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/>		
	<input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/>		
	<input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/>		

* Best Response: 1=CR 2=PR 3=Response, NOS 4=Stable 5=Progressive disease 6=Not applicable 9=Unknown

Has the patient developed a new breast primary, other new malignancy, or myelodysplastic syndrome since last follow up form? No Yes (Submit Notice of Second Malignancy)

Notes:

NOTICE OF SECOND MALIGNANCY

SWOG Study No.

SWOG Pt. No. Patient Name _____ (L,F,M)

Groups other than SWOG: Group Name/Study No./Pt No. _____ / _____ / _____

Amended data: Yes, mark amended items in red.

INSTRUCTIONS: Report any malignancy of a new histologic type or any malignancy of a previous type which is judged to be a new primary. Do not report recurrences on this form.
NOTE: If available, submit pathology report documenting the second malignancy along with this form. Refer to the protocol regarding sample submission instructions for second malignancies.

Type (site, histology) of second malignancy: _____

Date of First Pathologic Diagnosis - - (M,D,Y)

Notes:

BY: _____

DATE: _____ SWOG 06-29-90 SW124

INTERGROUP HORMONE RECEPTOR ASSAY FORM

Coordinating Group Study No. _____ Coordinating Group Patient No. _____

Patient Name _____ (L) _____ (F) _____ (M) Pt. No. _____ Study No. _____

Group _____ Institution _____ Affiliate (if applicable) _____

Physician _____ Hospital No. _____

Amended data: Yes, mark amended items in red.

Instructions: Complete 1 column for each type of hormone assay and each site for which an assay was performed. Send a copy of the laboratory report for each assay. All dates are MONTH, DAY, YEAR.

Hormone assay 1-estrogen 2-progesterone 7-other, specify on line 9-unknown	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Site of tissue sample 1-primary breast 2-nodes (specify if not axilla) 7-other lesion, specify on line 9-unknown	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date sample obtained	<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>
Interpretation of assay result 1-negative 2-positive 3-borderline 9-unknown	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Actual value reported (round to nearest whole number)	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Units 1-femtomoles /mg cytosol protein 7-other, specify on line 9-unknown	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Assay technique 1-dextran coated charcoal 2-sucrose density gradient 3-immunocytochemical 7-other, specify on line 9-unknown	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date of assay	<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>
Name of laboratory				
Address				

Notes:

INVESTIGATOR: _____

DATE: _____

SWOG 12-02-91 SW041

INTERGROUP BREAST FLOW SHEET

Amended Data: Yes, mark amended items in red.

Coord Group Patient No. _____ Coord Group Study No. 8814 Page _____

Patient's Name _____ (L,F,M) Patient No. _____ Study No. _____

Group _____ Institution _____ Affiliate (if applicable) _____

Physician _____ Hospital Number _____

Protocol Treatment	Date 19 (Mo./Day)	/	/	/	/	/	HT _____ cm	
	Cycle/Day	/	/	/	/	/	BSA _____ m ²	
	Record actual dose. If modified or not given, explain.							Remarks (R ₁ , R ₂ , R ₃ , etc. and date)
	Cyclophosphamide							
	Adriamycin							
	5-FU							
Tamoxifen								
Other Therapy	Radiation (cgy)							
	Transfusions (red cells/platelets)							
	Antibiotics							
	Antiemetics							
	Other, specify:							
Patient Status	Performance status							
	Weight (kg)							
	Temperature							
	Blood pressure (sys/diastolic)							
Abnormalities/Toxicities (Grade 1-5) Circle reactions due to Protocol Therapy	Nausea/Vomiting	/	/	/	/	/		
	Diarrhea/Stomatitis	/	/	/	/	/		
	Infection							
	Granula/thrombocytopenia	/	/	/	/	/		
	Cardiac dysrhythmia/CHF	/	/	/	/	/		
	Weakness							
	Hemorrhage cystitis							
	Hot flashes/Alcpecia	/	/	/	/	/		
	Other, specify:							
Laboratory Values Refer to Protocol Test Schedule	HGB (GMS)							
	Platelets (x 1000)							
	WBC (x 1000)							
	Granulocytes							
	Normals							
	CA (mg%)							
	Creatinine (mg%)							
	SGOT (units)/LDH	/	/	/	/	/	/	
	FSH							
	Alk Phos							
	Bilirubin							
Urinalysis								
Evaluation X-ray / Scan *	Chest X-ray / Bone X-ray *	/	/	/	/	/	* X-rays / Scans + positive - negative ND not done IF POSITIVE, DESCRIBE IN REMARKS	
	Scan: Bone / Brain / Liver *	/	/	/	/	/		
	Mammogram R*/L*	/	/	/	/	/		
	CT: Head / Chest / Abdomen *	/	/	/	/	/		

INTERGROUP BREAST CANCER OFF TREATMENT NOTICE and NOTICE of DEATH Amended data: Yes, mark amended items.

Coordinating Group Study No. _____ Coordinating Group Patient No. _____

Patient Name _____ (L) _____ (F) _____ (M) Pt. No. _____ Study No. _____

Group _____ Institution _____ Affiliate (if applicable) _____

Physician _____ Hospital No. _____

INSTRUCTIONS: Fill out applicable side(s) and submit at times specified in the protocol. All dates are MONTH, DAY, YEAR.

OFF TREATMENT NOTICE

STEP

Date off treatment step. See protocol for definition of step.

First date of progression, death, or decision to discontinue therapy: --

Reason off treatment step. Check one only.

- 1-Treatment completed per protocol.
- 2-Complications or toxicity, medically required, specify:

- 3-Pt. refused due to complications or toxicity, specify:

- 4-Patient withdrawal or refusal for reasons other than complications or toxicity, specify:

- 5-Progression or relapse
- 6-Death (complete next column)
- 7-Other complicating disease, specify:

- 8-Other, specify:

Date of last administration of protocol therapy (this step): --

NOTICE OF DEATH

Date of death --

Cause of death. See codes below. Code no more than one as primary cause.

- Toxicity from protocol treatment, if 2, 3 or 4 specify:

- Non-cancer and non-treatment related causes, if 2, 3, or 4 specify:

- Due to breast cancer
- Due to other cancer, specify primary sites:

Codes: 1 = No 2 = Primary cause
 3 = Contributory 4 = Possible
 9 = Unknown

Autopsy done? No Yes

Death information obtained from: (check all that apply)

- Autopsy
- Medical Record / Death Certificate
- Physician
- Relative or friend
- Other, specify:

Notes:

APPENDIX E

Southwest Oncology Group Protocol S9445: "Prognostic Factor Panel to Predict Preferred Therapy for Node Positive Postmenopausal breast Cancer Patients (CAF vs Tamoxifen)." A Companion Protocol to S8814 (Appendix D)

Study Coordinators: Peter Ravdin, M.D., Ph.D., Kathy S. Albain, M.D., D. Craig Allred, Ph.D., Deborah E. Powell, M.D., Stephanie J. Green, Ph.D., James N. Ingle, M.D., Nancy Davidson, M.D.

Funded by a supplemental grant to the Southwest Oncology Group Breast Tumor Bank from the National Cancer Institute.

The following protocol is proprietary information and is a privileged communication for investigational use only

SOUTHWEST ONCOLOGY GROUP

**PROGNOSTIC FACTOR PANEL TO PREDICT PREFERRED THERAPY FOR NODE POSITIVE
POSTMENOPAUSAL BREAST CANCER PATIENTS (CAF vs TAMOXIFEN)**

(A COMPANION PROTOCOL TO **SWOG-8814** (INT-0100, CALGB-9194,
ECOG-4188, NCCTG-883051, NCIC-MA.9)

ANCILLARY

	<u>Page</u>
1.0 OBJECTIVES	2
2.0 BACKGROUND	2
3.0 ELIGIBILITY CRITERIA.....	5
4.0 PROCEDURES/SAMPLE SUBMISSION REQUIREMENTS.....	6
5.0 STATISTICAL CONSIDERATIONS	6
6.0 REGISTRATION GUIDELINES	7
7.0 DATA SUBMISSION SCHEDULE	8
8.0 ETHICAL AND REGULATORY CONSIDERATIONS	8
9.0 BIBLIOGRAPHY	9
10.0 MASTER FORMS SET.....	12

PARTICIPANTS: ALL SOUTHWEST ONCOLOGY GROUP, CCOP AND CGOP MEDICAL
ONCOLOGISTS AND PATHOLOGISTS; AND NCCTG

STUDY COORDINATORS:

Peter M. Ravdin, M.D., Ph.D. (Medical Oncology)
University of Texas Health Science Center
Division of Oncology
Department of Medicine
7703 Floyd Curl Drive
San Antonio, TX 78284-7884
Telephone: 210/567-4770

D. Craig Allred, Ph.D. (Pathology)
University of Texas Health Sci. Center
Department of Pathology
7703 Floyd Curl Drive
San Antonio, TX 78284-7884
Telephone: 210/567-4091

Kathy S. Albain, M.D. (**SWOG-8814** Coordinator)
Loyola University Medical Center
Cancer Center, Room 109
2160 South First Avenue
Maywood, IL 60153-5589
708/327-3102 or 708/216-8000 (pager)

Deborah E. Powell, M.D. (Pathology)
University of Kentucky
College of Medicine
Department of Pathology
800 Rose Street, CC452
Lexington, KY 40536-0093

Stephanie J. Green, Ph.D. (Biostatistics)
Janet O'Sullivan, M.A.
Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street, MP-557
Seattle, WA 98104-2092
Telephone 206/667-4623

NCCTG STUDY COORDINATOR:
James N. Ingle, M.D. (Medical Oncology)
Mayo Clinic
200 First Street, SW
Rochester, MN 55905

ECOG STUDY COORDINATOR:
Nancy Davidson, M.D.
Johns Hopkins Oncology Center
Breast Cancer Laboratory
422 North Bond Street
Baltimore, MD 21231

M374/mb



February 1, 1995

*SWOG Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street MP557
Seattle, WA 98104-2092
Patient registration (206) 667-4623*

SWOG Patient No.	
Treatment No.	
Other Group Patient No.	
Other Group Name	

Investigator No.		<u>PATIENT NAME</u> (last,first,middle)	
Investigator		Patient's sex and race	
Institution		Patient's birthdate	
Date of IRB approval		Patient's Soc. Sec. No.	
Date of informed consent		Patient's zip code	
Projected start date of treatment		Method of payment	

SWOG 9445 (NCCTG 95-30-51, ECOG S9445) Prognostic Factor Panel to Predict Preferred Therapy for Node Positive Postmenopausal Breast Cancer Patients (CAF vs Tamoxifen) (A Companion Protocol to SWOG 8814 [INT-0100, CALGB-9194, EST-4188, NCCTG-883051, NCIC-MA.9]).

Eligibility Checklist

Each of the questions in the following two sections must be answered appropriately for a patient to be considered eligible for registration. The checklist should be entirely filled out and should be referred to during the phone registration. A copy must be submitted with the prestudy form and initial flow sheet.

Criteria for Eligibility (All responses must be Yes)

Yes No

- ___ ___ 1. Is the patient registered for SWOG-8814 (EST-4188, CALGB-9194, NCCTG-883051, INT-0100)?
- ___ ___ 2. Are paraffin blocks from the original primary breast tumor available? (Note: If blocks have been submitted for SWOG-8854 and not yet returned, it is not necessary to retrieve blocks before registering to SWOG-9445. Blocks will be transferred from Loyola to San Antonio after registration to SWOG-9445.)

Descriptive Factors

1. Fixation procedure. (Please indicate method: _____)

Note: Please also specify the fixation procedure and how long it was fixed on the specimen submission form.

1.0 **OBJECTIVES**

The overall objective of this study to correlate a panel of markers with clinical outcome and responsiveness to adjuvant therapy of node positive post menopausal breast cancer patients who participated in Southwest Oncology Group protocol **SWOG-8814** (EST-4188, CALGB-9194, NCCTG-883051, NCIC-MA.9, INT-0100) "Phase III comparison of adjuvant chemotherapy with tamoxifen and CAF in node-positive breast cancer patients". The most important initial objective of this study is to confirm the results of the CALGB study, CALGB-8541, which suggested that c-erbB-2 expression (as detected by immunohistochemistry) is a strong predictor of the efficacy of CAF-based adjuvant chemotherapy. The assumption is that the relationship of erbB-2 to tamoxifen efficacy is the same as the relationship of erbB-2 to low dose CAF efficacy. In addition, the study also plans to take advantage of access to an abundant number of specimens obtained from a large Phase III trial, **SWOG-8814**, to explore whether other markers, or combinations of markers, might be useful in predicting responsiveness to CAF or tamoxifen-based adjuvant therapy.

The specific objectives of this proposal include the following:

- 1.1 To evaluate if c-erbB-2 can allow the discrimination of node positive breast cancer patients who markedly benefited from adjuvant therapy with CAF (those with over-expressed c-erbB-2) from patients who did not obtain additional benefit from dose intensive CAF (those with low c-erbB-2 expression).
- 1.2 To measure a panel of prognostic factors (histologic and nuclear grade, estrogen and progesterone receptors, c-erbB-2, p53, Ki67, flow cytometrically determined DNA index and S-phase), angiogenesis, hsp27 (heat shock protein 27), nuclear and histologic grading, and immunohistochemically measured estrogen and progesterone receptors on node positive postmenopausal breast cancer patients.
- 1.3 To test the association of the factors listed above with biological and clinical features, including recurrence, survival, and apparent efficacy of CAF chemotherapy in patients entered on the Southwest Oncology Group-coordinated intergroup protocol, **SWOG-8814** (INT-0100), "Phase III Comparison of Adjuvant Chemoendocrine Therapy with CAF and Concurrent or Delayed Tamoxifen to Tamoxifen Alone in Postmenopausal Patients with Involved Axillary Lymph Nodes and Positive Receptors".
- 1.4 To cut and store additional sections to allow the evaluation of markers that are mechanistically interesting but in the early development stage in breast cancer prognostic work which may be identified within the next 2-3 years, to be analyzed for prognostic significance and impact on the apparent benefit obtained by adjuvant CAF.

2.0 **BACKGROUND**

The major objective of this proposal is to attempt to confirm the results of the CALGB study, CALGB-8541, which suggested that c-erbB-2 expression (as detected by immunohistochemistry) is a strong predictor of the responsiveness of node positive patients to CAF-based adjuvant chemotherapy. (1) The proposal also plans to take advantage of the planned processing of cooperative group specimens (obtained to answer the central c-erbB-2 hypothesis) to explore whether other markers, or combinations of markers, might be useful in predicting responsiveness to CAF-based adjuvant therapy.

The observations made in CALGB-8541 are not ready for application into practice without replication and confirmation. There are several important caveats. First, it should be noted that the total number of patients is small. Given that only about 1/3 of the patients have high c-erbB-2 levels, the results in the high c-erbB-2 patient subsets by treatment are based on approximately 50 patients per subset; and, given that the number of events in the first 3 years is relatively small, the results can be seen to be based on relatively little information.

The inclusion of a biologically and clinically diverse population (both pre and post menopausal as well as both ER+ and ER- patients) in CALGB 8541 is another limitation of the use of materials of patients from CALGB 8541 for evaluating whether c-erbB-2 allows improved prediction of whether a patient will respond to CAF. Patients from SWOG-8814 are more homogeneous, all being N+, post-menopausal, and ER+. In this patient population a critical question is whether patients should receive tamoxifen alone or in addition to adjuvant chemotherapy. The results of the CALGB study suggest that c-erbB-2 determinations may help may this decision.

The result of the CALGB trial is also in strong contrast to the results of the Ludwig and ECOG trials. (2, 3) In both these studies, high c-erbB-2 levels were associated with relative resistance to the CMF-based chemotherapy, with the greatest benefits of CMF seen in patients with low levels of c-erbB-2. These results are in contrast to the CALGB trial, where the greatest benefits to CAF were seen in patients with high levels of c-erbB-2.

The question of whether c-erbB-2 could be used to predict whether a patient might benefit from CAF-based chemotherapy is one of major importance. The most appropriate trial for attempting to develop supporting evidence of this result appears to be the Southwest Oncology Group protocol, SWOG-8814 (INT-0100). This trial will accrue 1,400 node-positive, postmenopausal ER+ patients who are randomized between 1) tamoxifen alone for 5 years, 2) CAF and concurrent tamoxifen and then tamoxifen for 5 years, and, 3) CAF and then tamoxifen for 5 years. This trial could therefore be viewed basically as a trial with all patients getting tamoxifen (particularly if the concurrent arm is ignored where CAF/tamoxifen confounding interactions may occur), with patients randomized to either no chemotherapy or CAF.

If this study does confirm the CALGB results (that patients with high levels of c-erbB-2 expression benefit substantially from adjuvant CAF, but that women with low levels of c-erbB-2 do not), the results may have major medical and economic importance. In the United States each year there are approximately 30,000 postmenopausal women who are diagnosed as having node positive, ER+ breast cancers. If SWOG-8814 shows that, on average, such women benefit more from CAF plus tamoxifen than from tamoxifen alone, the standard of care in this population will change to treating such women with more than the current standard of tamoxifen to a more toxic and expensive regimen CAF followed by tamoxifen. If, however, the results of this study show that the benefit of the high dose CAF is restricted to patients who have high expression of c-erbB-2, as suggested in CALGB-8541, the more toxic and expensive therapy need only be given to about 1/3 of these women (only those with high expression of c-erbB-2), sparing many women the additional toxicity of CAF. Given an estimate of \$6,000 for a course of adjuvant CAF, the national health cost savings may be on the order of \$120 million per year.

It seems reasonable to also explore the impact on the efficacy of adjuvant CAF of other prognostic markers. For example, the CALGB-8541 study also found that S-phase was predictive for treatment responsiveness, although less so than c-erbB-2. This result may be due to the known correlation between c-erbB-2 and S-phase or other markers of high proliferative rate. (4,5) Other markers have been suggested as predictors of treatment sensitivity. In an era in which nearly all subgroups of breast cancer patients have been shown to benefit from adjuvant therapy (although for many of these groups the absolute benefit is small), it is increasingly important to use prognostic markers to predict the outcome of treated patients, in particular, the relative responsiveness to different treatment regimens. (6) Because these questions are as yet not broadly explored, we are also proposing to measure a broad panel of prognostic markers including the following: classical markers (histologic and nuclear grading, immunohistochemical ER and PgR); markers that may be involved with the proliferative state (PCNA, p53); provocative new markers (e.g., for angiogenesis); and, a marker associated with resistance to doxorubicin (heat shock protein 27). We also propose to bank sectioned material to allow rapid exploration of additional markers and hypotheses in the future.

A number of additional markers might be of particular interest that have been implicated in treatment resistance including topoisomerase II and BCL-2.

c-erbB-2

c-erbB-2 (also referred to as HER-2/neu) is a transmembrane receptor for a peptide ligand. Several investigators have shown that both c-erbB-2 amplification and expression are important predictors of early recurrence in node-positive breast cancer. (7) Concurrent studies are currently being conducted in node negative trial SWOG-8897 (INT-0102) and also have been conducted in the analysis of c-erbB-2 in material from the paraffin embedded blocks for the intergroup node negative study coordinated by ECOG (EST-1180, SWOG-8294, INT-0011). (3)

P53

p53 is a tumor suppressor gene that plays a role in the regulation cell passage through the cell cycle. A mutation of the gene can result in functional inactivation of the protein, a longer half life, and accumulation of the protein in the cell. (8) This abnormal accumulation can be detected by IHC. In a pilot study of 700 node negative patients, those patients without p53 staining (normal for p53 by IHC) had a significantly better disease-free survival and overall survival than those over-expressing p53. This study also showed in multivariate analysis that both S-phase and p53 (although strongly correlated) were both independent statistically significant predictors of outcome. (9,10) Thor and colleagues also found p53 to be a strong independent predictor of disease-free survival in both N+ and N- patients. (11) Neither of these studies included cooperative group patients with uniform treatment, so that it was impossible to assess whether p53 made the cells more sensitive or resistant to therapy. There are several rationales as to why p53 expression might perturb drug sensitivity. The simplest rationale is that p53 seems to participate in the regulatory cell cycle process that may be important to cellular repair of damage. (12,13) Thus, aberrant p53 may allow cytotoxic drugs to inflict greater damage on cells, making them more sensitive to chemotherapy. Cells with normal expression of p53 might therefore be more therapy resistant. On the other hand, if aberrancies in p53 were associated with only a minor difference in treatment sensitivity, but a greatly enhanced proliferative rate, then there might be no apparent effect of p53 on drug sensitivity, or even an apparent resistance to therapy for cells over-expressing p53.

Angiogenesis

The degree of angiogenesis associated with breast cancer has been shown in some studies to be a powerful predictor of patient outcome. (14 - 16) There have been no studies to date to suggest how this factor might relate to treatment outcome; thus, its inclusion in the list of factors to be measured is speculative. Rationales for why it might be important, including higher mitotic rates in vascular tumors, different growth factor milieu, etc., may be proposed. Given that the SWOG-8814 patient population contains both a hormonal therapy alone arm and a chemotherapy plus tamoxifen arm, this study at the very least will help delineate the importance of this factor in node-positive patients receiving these types of therapies. The methodology previously described by others of IHC staining for factor VIII will be used to help quantitate microvessels for study. (15)

Ki67

Ki67 has been widely used as a marker for cell proliferation. There are studies which suggest that this marker is of value in defining prognosis. (17 - 20) Additional markers of this general class, including those detected by PCNA and M1B1, are available. Of this class of markers, Ki67 has been generally found to be the most useful (although the investigators in this proposal have had some experience with all three mentioned above). (17) The marker Ki67 will be utilized to assess its efficacy as an IHC measure of cell proliferation. Studies have suggested that such a marker might be of value in measuring relative drug sensitivity following observations of an apparent effect of S-phase on drug sensitivity. (21 - 23)

Heat Shock Protein 27

It has been demonstrated *in vitro* culture systems that heat shock protein 27 (hsp27) strongly modulates the sensitivity of breast cancer cells to doxorubicin. (24, 25) In an initial study in node negative breast cancer patients, the investigators found that a related protein, hsp70, strongly correlated with disease-free survival; however, in this population, too few patients had received an Adriamycin-based chemotherapy to assess the effects of heat shock proteins on doxorubicin *in vivo*. (26) The patient tumor material in SWOG-8814 would be ideal for assessing this question. Previous study results, therefore, support the possibility that the proposed study will find that hsp27 is a predictor of treatment resistance.

Flow Cytometry

DNA flow cytometry has been utilized extensively for evaluating the prognosis of breast cancer patients. (27-29) S-phase has been shown by these investigators to be a strong predictor of treatment outcome in both node positive and node negative breast cancer patients. The effect of S-phase on adjuvant chemotherapy with doxorubicin-based regimens has not been specifically investigated in previous studies, due to the heterogeneous nature of the existing data base and the lack of analysis of trial results in which a doxorubicin-based regimen was used. The results of the CALGB study 8541 is provocative, in that not only c-erbB-2 but also S-phase was predictive of the degree of efficacy of adjuvant CAF. The analysis of patients in SWOG-8814 should prove to confirm or refute these results.

Histologic and Nuclear Grading

Several combined and histologic grading systems have been described and shown to have prognostic significance in breast carcinomas. (30 - 33) All of these take into account the architectural arrangement of the cells, the degree of nuclear differentiation, and the mitotic rate. If mitotic rate as measured by S-phase is a predictor of efficacy of CAF-based chemotherapy, the mitotic rate as measured by in histologic grading systems might then be highly expected to also be a predictor; in fact, flow cytometry-measured mitotic rate might possibly be a better predictor than that measured by S-phase, given the uncertain number of normal cells in a DNA flow cytometry. Some studies have recognized that patients who seemed to have the greatest apparent sensitivity to adjuvant chemotherapy were those with poor nuclear grade. (34 - 36) It should be noted that investigators in this proposal are examining the predictive value of grading systems and microscopically determined mitotic rate estimates in their work with the Intergroup node negative study (SWOG-8897). Insights from this other study will be directly applied to the work with SWOG-8814.

Estrogen and Progesterone Receptors

The proposed study plans to measure IHC staining for ER and PgR to examine the potential impact of these factors on treatment sensitivity to CAF. Although patients will already have ER and PgR measured by biochemical assays, because of the decrease in the average size of breast tumors, it is anticipated that an increasing number patients in the future will have ER and PgR only measured by IHC, and therefore that studies to be relevant to these patients should have steroid receptors measured by the IHC technique.

3.0 ELIGIBILITY CRITERIA

- 3.1 Only paraffin blocks from patients who were participants in SWOG-8814 (EST-4188, CALGB-9194, NCCTG-883051, INT-0100) (irrespective of eligibility) will be eligible for use in this study.
- 3.2 The paraffin blocks from the original primary breast tumor must be available.

- 3.3 All paraffin blocks, irrespective of fixation procedure will be evaluated; however, the fixation procedure must be indicated, since it could interfere with the assays.

4.0 PROCEDURES/SAMPLE SUBMISSION REQUIREMENTS

- 4.1 This protocol does not involve treatment, but only submission of paraffin embedded material from the primary breast cancer.

- 4.2 Within 30 days of registration the following materials are to be submitted (to the address noted in Section 4.3). If the blocks have been submitted for SWOG-8854, registration and submission of the Eligibility Checklist for SWOG-9445 will prompt transfer of the blocks from Loyola to San Antonio.

- a. One representative paraffin block containing tissues for the original mastectomy specimen.

The block is to be placed in a "locking plastic bag." (please do not wrap the block in gauze.) The bag is to be labeled with the patient name, SWOG-9445, and the Southwest Oncology Group patient number as well as the registering group name, study number and patient number (if a non-Southwest Oncology Group institution).

- b. One copy of the Specimen Submission Form with the top half completed should be included, with the information regarding the fixation procedure entered onto the form, and (if at all possible) a copy of the Pathology Report.
- c. Pack the sealable bag in a padded envelope;
- d. Pack the padded envelope in a Federal Express mailer.
- e. Prepaid, pre-addressed Federal Express Airbills, along with padded envelopes and mailers for shipment can be requested by contacting Virginia Boucher (phone 210-567-6823, FAX 210-567-6687; e-mail virginia@oncology.uthscsa.edu).
- f. The outer container must be marked as "BIOHAZARD".

ECOG Institutions:

A memo will be sent to the institutions by the ECOG Pathology Coordinating Office listing patients who were previously registered to E4188 (SWOG-8814) and cases for which blocks have been previously submitted for E1189 (SWOG-8854) and are currently being stored at the ECOG Pathology Coordinating Office. If blocks are in storage at the ECOG Pathology Coordinating Office, follow the Registration Guidelines in Section 6.0 and submit a Southwest Oncology Group Specimen Submission Form and a copy of the pathology report.

- 4.3 Materials noted in Section 4.2 will be sent to (for Southwest Oncology Group and NCCTG institutions):

Ms. Virginia Boucher
Department of Medicine/Oncology
University of Texas Health Science Center
7703 Floyd Curl Drive
San Antonio, TX 78284

ECOG institutions will send the materials noted in Section 4.2 to the ECOG Pathology Coordinating Office:

ECOG Coordinating Center
Frontier Science
Attn: Pathology
303 Boylston Street
Brookline, MA 02146-7648

The ECOG PCO will log in the materials and route them to the University of Texas Health Science Center. After the blocks are sectioned, they will be returned to the ECOG Coordinating Center in a timely fashion for tissue banking. A copy of the completed Southwest Oncology Group Specimen Submission Form will be sent to the ECOG Study Coordinator and to the ECOG Coordinating Center by the ECOG Pathology Coordinating Office. The submitting pathologist should be informed that the blocks will not be returned unless requested.

- 4.4 Approximately 4 50-micron and 20 3-micron sections will be cut from each block.

The 3-micron sections for IHC will be considered to be of highest priority and these will be cut before the 50-micron sections for flow cytometry.

- 4.5 Specimen Submission Form will be completed at the University of Texas Health Science Center, and will be sent from the University of Texas to the Statistical Center as well as to the ECOG Pathology Coordinating Office.

5.0 STATISTICAL CONSIDERATIONS

The main hypotheses in this study concern the prognostic value of c-erbB-2 positivity and high S-phase fraction, especially as these might effect the therapeutic value of CAF. Specifically, patients will be studied who are c-erbB-2 positive (approximately 25% of the total) and alternately, those with high S-phase fraction (a defined level above the median of the sample) to see whether,

in these subgroups, patients receiving CAF followed by tamoxifen (Arm II of the trial, **SWOG-8814**) have a better survival outcome than those receiving tamoxifen alone (Arm I of the trial).

By December 1994, the protocol **SWOG-8814** will have accrued its projected goal of 880 patients (this study's design will utilize only two of the three arms of the protocol initially; the third arm of concurrent CAF and tamoxifen will be excluded), randomized over five years in a 3:2 ratio between CAF followed by tamoxifen and tamoxifen alone. This group of patients has a median survival of approximately 7.5 years, as specified in the design of the protocol. Assuming good compliance with sample submission and usability, there will be at least 2.5 years of follow-up on about 220 c-erbB-2 positive patients by July 1997, when the start of the statistical analysis is planned. This sample size is sufficient to detect a halving of the hazard ratio in the CAF arm as opposed to the tamoxifen alone arm (86% power for a one-sided 5% log rank test). With 660 patients who are c-erbB-2 negative, there is 68% power to detect a hazard ratio of 3/4, and 90% power for a ratio of 2/3. Approximately 450 patients will have S-phase fraction above or below the median, which would give 77% power to detect a hazard ratio of 2/3. Cox regression modeling will be performed to adjust these comparisons for other prognostic factors

Other exploratory analyses will also be performed, using the c-erbB-2, S-phase and the other panel markers being measured, as well as other prognostic factors and treatment group. Samples from all three arms of the study (I, II and III) will be used for this. In particular, an attempt will be made to define combinations of factors which lead to especially good or especially poor prognoses. One statistical technique to be utilized is recursive partitioning, which has been adapted for use with censored survival data. (37, 38) This technique lends itself well to situations where combinations of factors are used to form a few prognostic groups, and incorporates internal cross-validation to improve the reproducibility of the results. However, in contrast to the confirmatory nature of the main hypotheses discussed above, these analyses are inherently exploratory, and will need to be confirmed by others before they are widely accepted.

Neither CALGB 8541 nor **SWOG-8814** are mature studies at this point. Thus the hypotheses to be tested may change before the analysis of results from **SWOG-9445**. Whenever possible the results of **SWOG-9445** will be used to prospectively confirm positive results from CALGB 8541 and other studies. This will involve, whenever possible, a standardization of reagents, and a clear statement of a *prospective* hypothesis *before* the prognostic marker results are coupled to treatment outcome data for analysis. Thus, before an analysis of the prognostic or predictive significance of a marker takes place the Statistical Center, CTEP and the Study Coordinator will exchange formal written correspondence agreeing on the prospective hypothesis to be tested before the clinical outcome data is combined with the prognostic marker results for the analysis. A statement about the prospective hypothesis and whether it was confirmed or refuted will be included in the subsequent publications about that given marker.

6.0 REGISTRATION GUIDELINES

6.1 Registration

- a. Southwest Oncology Group: Patients must be registered on this protocol by telephoning the Southwest Oncology Group Statistical Center at 206/667-4623, 6:30 a.m. to 5:00 pm Pacific time, Monday through Friday, except holidays.
- b. NCCTG: A signed 310 form(s) is to be on file at the NCCTG Randomization Center before patient entry.

To register a patient, call the NCCTG Randomization Center at 507/284-4130 8:00 a.m. to 4:30 p.m. Central Time, Monday through Friday. The NCCTG Randomization Center will verify eligibility by completing the Eligibility Checklist

and will call the Southwest Oncology Group Statistical Center, Monday through Friday 6:30 a.m. to 4:30 p.m. Pacific Time to register the patient.

c. **ECOG:**

A signed HHS 310 Form must be on file at the ECOG Coordinating Center before an ECOG institution may enter patients. These will be submitted to ECOG Coordinating Center, Frontier Science, ATTN: IRB, 303 Boylston Street, Brookline, MA, 02146-7648.

To register eligible cases, the investigator will telephone the Randomization Desk at the ECOG Coordinating Center at (617) 632-2022, Monday - Friday, between the hours of 9:00 am and 5:30 p.m. ET to allow time to call the Southwest Oncology Group that same day. ECOG members should not call Southwest Oncology Group directly. The following information will be requested: A) Protocol Number; B) Investigator Identification (including institution and/or affiliate name and investigator's name); C) Patient Identification (including patient's name or initials, chart number, social security number and demographics [sex, birth date, race, nine-digit zip code and method of payment]); D) Pathology Block number(s) of the primary breast tumor; E) Eligibility Verification. Patients must meet all the eligibility requirements listed in Section 3.0. The randomization specialist will verify eligibility by asking questions from the checklist, and will also verify IRB approval. The ECOG Randomization Desk will then contact the Southwest Oncology Group Statistical Center to enter the patient after which the ECOG Coordinating Center will contact the institution to relay the sequence numbers for that patient. The Southwest Oncology Group will forward a confirmation of registration to the ECOG Randomization Desk for routing to the ECOG participating institution.

- 6.2 At the time of registration, the caller must be prepared to answer every question on the eligibility checklist.
- 6.3 The caller must also be prepared to provide the date of institutional review board approval for this study. Patients will not be registered if the IRB approval date is not provided or is > 1 year prior to the date of registration.

7.0 DATA SUBMISSION SCHEDULE

Southwest Oncology Group members and CCOPs must submit two copies of all data forms directly to the Statistical Center in Seattle. CGOPs must submit (number of copies to be determined by the Group Member) copies of all forms to their Group Member institution for forwarding to the Statistical Center.

NCCTG members will send 2 copies of all forms to the NCCTG Operations Office for forwarding to the Southwest Oncology Group Statistical Center. Include the Southwest Oncology Group patient number and protocol number on all forms as well as the NCCTG patient number and protocol number.

ECOG Institutions

The original data forms as listed should be submitted at the required intervals to:

ECOG Coordinating Center
Frontier Science
Attn: Data
303 Boylston Street
Brookline, MA 02146-7648

Include the Southwest Oncology Group and ECOG study and patient number. The ECOG Coordinating Center will forward the forms to the Southwest Oncology Group Statistical Center.

7.1 WITHIN 14 DAYS OF REGISTRATION:

Submit the following: Eligibility Checklist

7.2 WITHIN 30 DAYS OF REGISTRATION:

Specimen Submission Form and Pathology Report with the paraffin block. These materials need only be sent to the laboratory in San Antonio, Texas (as described in Section 4.0). The laboratory will forward the Specimen Submission Form to the Statistical Center after processing.

8.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with the Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

As only existing pathological specimens will be studied, informed consent need not be obtained as described by the Federal Regulatory guidelines (Federal Register Vol. 56, No. 117, June 18, 1991, part 101 b4) and the Office for Protection from Research Risks Reports: Protection of Human Subjects, Code of Federal Regulations 45 CFR 46 (46.101.b5).

Institutional Review

As only existing pathologic material will be studied and involves no more than minimal risk, this protocol may be reviewed by the institutional review board through an expedited review procedure as described by the Code of Federal Regulations 45 CFR 46 (46.110.b) and Federal Register Vol. 56, No. 117, Section 110, June 18, 1991.

9.0 BIBLIOGRAPHY

1. Muss HB, Thor A, Berry DA, et al. c-erbB-2 expression and S-phase activity predict response to adjuvant therapy in women with node positive early breast cancer. Proc Ann Meet Am Soc Clin Onc 11:A88, 1993.
2. Gusterson BA, Gelber RD, Goldhirsch A, et al. Prognostic importance of c-erbB-2 expression in breast cancer. J Clin Onc 10:1049-1056, 1992.
3. Allred DC, Clark GM, Tandon AK, Molina R, Tormey DC, Osborne CK, Gilchrist KW, Mansour EG, Abeloff M, Eudey L, et al. HER-2/neu in node-negative breast cancer: prognostic significance of overexpression influenced by the presence of in situ carcinoma. J Clin Onc 10(4):599-605, 1992.
4. Barnes DM, Meyer JS, Gonzalez JG, Gullick WJ, Mills RR. Relationship between c-erbB-2 immunoreactivity and thymidine labeling index in breast cancer in situ. Br Ca Res Tr 18:11-17, 1991.
5. Kallionemi OP, Holli K, Visakorpi T, Koivula T, Hein HH, Isola JJ. Association of c-erbB-2 protein over-expression with high rate of cell proliferation, increased risk of visceral metastasis and poor long-term survival in breast cancer. Int J Cancer 49:650-655, 1991.
6. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. Lancet 339:1-15, 71-85, 1992.
7. Molina R, Ciocca DR, Tandon AK, et al. Expression of HER-2/neu oncoprotein in human breast cancer. Anticancer Res 12:1965-1971, 1992.
8. Levine AJ, Momand J, Finlay CA. The p53 suppressor gene. Nature 351:453-456, 1991.
9. Allred DC, Clark GM, Brown RW, Fuqua SAW, Elledge R, Chamness GC, McGuire WL. Mutation of P53 is associated with increased proliferation and early recurrence in node-negative breast cancer. Proc Ann Meet Am Soc Clin Onc 11:A45, 1992.
10. Allred DC, Clark GM, Elledge R, Fuqua SA, Brown RW, Chamness GC, Osborne CK, McGuire WL. Association of p53 protein expression with tumor cell proliferation rate and clinical outcome in node-negative breast cancer. JNCI 85(3):200-6, 1993.
11. Thor A, Edgerton D, Moore L, Chun-Chen H, Smith HS. Overexpression of P53 in primary human breast cancer. Proc Ann Meet Am Soc Clin Onc 11:A56, 1992.
12. Kuerbitz SJ, Plunkett BS, Walsh WV, Kastan MB. Wild type p53 is a cell cycle checkpoint determinant follow irradiation. Proc Natl Acad Sci 89:7491-7495, 1992.
13. Lane DP. p53, guardian of the genome. Nature 358:15-17, 1992.
14. Weidner N, Folkman J, Pozza F, Bevilacqua P, Allred EN, Moore DH, Meli S, Gasparini G. Tumor angiogenesis: a new significant and independent prognostic indicator in early stage breast carcinoma. JNCI 84:1875-1887, 1992.
15. Weidner N, Semple JP, Welch WR, Folkman J. Tumor angiogenesis and metastasis - correlation in invasive breast carcinoma. NEJM 324:1-8, 1991.
16. Bosari S, Lee AK, DeLellis RA, Wiley BD, Heatley GJ, Silverman ML. Microvessel quantitation and prognosis in invasive breast carcinoma. Human Pathology 23:755-761, 1992.

17. Hilsenbeck SG, Brown RW, Allred DC, Clark GM, McGuire WL. Ki67 and flow cytometry provide complementary prognostic information in node-negative breast cancer. *Proc Ann Meet Am Soc Clin Oncol* 11:A52, 1992.
18. Bouzubar N, Walker KJ, Griffiths K, Ellis IO, Elston CW, Robertson JF, Blamey RW, Nicholson RI. Ki67 immunostaining in primary breast cancer: pathological and clinical associations. *British Journal of Cancer* 59(6):943-7, 1989.
19. Locker AP, Birrell K, Bell JA, Nicholson RI, Elston CW, Blamey RW, Ellis IO. Ki67 immunoreactivity in breast carcinoma: relationships to prognostic variables and short term survival. *European Journal of Surgical Oncology* 18(3):224-9, 1992.
20. Leonardi E, Girlando S, Serio G, Mauri FA, Perrone G, Scampini S, Dalla Palma P, Barbareschi M. PCNA and Ki67 expression in breast carcinoma: correlations with clinical and biological variables. *Journal of Clinical Pathology* 45(5):416-9, 1992.
21. Remvikos Y, Beuzeboc P, Zajdela A, Voillemot N, Magdelenat H, Pouillart P. Correlation of pretreatment proliferative activity of breast cancer with response to cytotoxic chemotherapy. *JNCI* 81:1381.
22. Sulkes A, Livingston RB, Murphy WK. Triated thymidine labeling index and response in human breast cancer. *JNCI* 62:153-515, 1979.
23. O'Reilly SM, Camplejohn RS, Rubens RD, Richards MA. DNA flow cytometry and response to preoperative chemotherapy for primary breast cancer. *Eur J Cancer* 28:681-683, 1992.
24. Ciocca DR, Fuqua SAW, Lock Lim S, et al. Response of human breast cancer cells to heat shock and chemotherapeutic drugs. *Cancer Research* 52: 3648-3654, 1992.
25. Oesterreich C, Weng CN, Qiu M, Hilsenbeck SG, Osborne CK, Fuqua SAW. The small heat shock protein hsp27 is correlated with growth and drug resistance in human breast cancer cell lines. *Cancer Research*, in press.
26. Ciocca DR, Clark GM, Tandon AK, Fuqua SAW, Welch WJ, McGuire WL. Heat shock protein hsp70 in patients with axillary lymph node-negative breast cancer: prognostic implications. *JNCI* 85: 570-574, 1993.
27. Clark GM. Applicability of flow cytometry in breast cancer. *Annals of the New York Academy of Sciences* 677:379-83, 1993.
28. Dressler LG, Eudey L, Gray R, Tormey DC, McGuire WL, Gilchrist KW, Clark GM, Osborne CK, Mansour EG, Abeloff MD. Prognostic potential of DNA flow cytometry measurements in node-negative breast cancer patients: preliminary analysis of an intergroup study (INT-0076). *Monographs - National Cancer Institute* (11):167-72, 1992.
29. Clark GM, Mathieu MC, Owens MA, Dressler LG, Eudey L, Tormey DC, Osborne CK, Gilchrist KW, Mansour EG, Abeloff MD, et al. Prognostic significance of S-phase fraction in good-risk, node-negative breast cancer patients. *Journal of Clinical Oncology* 10(3):428-32, 1992.
30. Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer. *Br J Cancer* 11:359-377, 1957.
31. Scarff RW, Torioni H. Histological typing of tumors. *Geneve WHO*:13-20, 1968.
32. Elston CW. Grading of invasive carcinoma of the breast. In: *Diagnostic Histopathology of the Breast*. Page EL and Anderson TJ eds. Churchill Livingstone pp 300-311, 1987.

33. Fisher ER, Redmond C, Fisher B. Histologic grading of breast cancer. In: Pathology Annual Sommers, SC and Rosen PP, eds. Appleton-Century-Crofts 5:239-251, 1980.
34. Fisher ER, Redmond C, Fisher B. Pathologic findings for the National Surgical Adjuvant Breast Project. Relationship of chemotherapeutic responsiveness to tumor differentiation. Cancer 51:181-191, 1983.
35. Fisher B, Fisher ER, Redmond C. Ten year results from the NSABP clinical trial evaluating the use of L-phenylalanine mustard (L-Pam) in the management of primary breast cancer. J Clin Onc 4: 929-941, 1986.
36. Reiner A, Sponza J, Reiner G, et al. Estrogen receptor analysis on biopsies. Am J Pathol 125:443-449, 1986.
37. LeBlanc M, Crowley J. Relative risk trees for censored survival data. Biometrics 48:411-425, 1992.
38. LeBlanc M and Crowley J. Survival trees by goodness of split. J Amer Stat Asso 88:457-467, 1993.

SPECIMEN SUBMISSION FORM

SWOG Study No.

Protocol Step

SWOG Pt. No.

Patient's Name _____ (L.F.N)

Institution / Member _____ Disease _____

Physician _____

Contact Person at Institution _____ Telephone No. _____

Groups other than SWOG: Group Name/Study No./Pt. No. _____ / _____ / _____

Amended data: Yes, mark amended items in red.

INSTRUCTIONS: All dates are MONTH, DAY, YEAR. Indicate an unknown part of a date with a horizontal line drawn across the appropriate boxes. Check protocol for submission details.

SPECIMEN

Type of Specimen: (check only one)

- 1- Tubes of blood
- 2- Tubes of bone marrow
- 3- Tubes of serum
- 4- Tissue, specify site(s): _____
 check one: 1- fresh
 2- frozen
 3- paraffin embedded
- 5- Slides,
 type and number: _____
- 6- Karyotype(s), number: _____
- 7- Other, specify: _____

Date specimen collected: - -

Time specimen collected: :
(24 hour time)

REASONS FOR SPECIMEN SUBMISSION

(Check all that apply)

- Status Treatment Study No.
- Prestudy specimen
- Complete remission/response specimen
 (Will patient be registered on a SWOG study for adjuvant therapy?
 No Yes Unknown)
- Relapse/recurrence specimen
 (Will patient be registered on a SWOG study for relapsed/recurrent disease?
 No Yes Unknown)
- Other specimen, specify: _____

By: _____ Date: _____

Notes from submitting institution:

For Central Laboratory Use Only

Note -- Central Laboratory: complete and return form to SWOG Statistical Center

Central laboratory identification number:

Date specimen received: - -

Time specimen received: :
(24 hour time)

Condition of specimen:

- 1- usable as received
- 2- not usable as received; adequate submission
- 3- not usable as received; inadequate submission

By: _____ Date: _____

Notes from central laboratory:

APPENDIX F

Manuscript In Press, Journal of Clinical Oncology: "The Influence of Patient Characteristics, Socioeconomic Factors, Geography and Systemic Risk on the Use of Breast Sparing Treatment in Women Enrolled on Adjuvant Breast Cancer Studies: An Analysis of Two Intergroup Trials." KS Albain, et al.

The following manuscript in press is proprietary information, pending publication in 1996.

Journal of Clinical Oncology

The Official Journal of the American Society of Clinical Oncology

EDITOR-IN-CHIEF

George P. Canellos, MD
454 Brookline Avenue
Suite 28
Boston, MA 02115
(617) 632-5150
FAX (617) 632-5152

May 14, 1996

MANAGING EDITOR

Deborah A. Whippen
454 Brookline Avenue
Suite 28
Boston, MA 02115
(617) 632-5150
FAX (617) 632-5152
E-mail daw%cec%dfci@rhys.
dfci.harvard.edu

Kathy S. Albain, M.D.
Associate Professor of Medicine
Division of Hematology/Oncology
Loyola University Medical Center
2160 South First Avenue
Maywood, IL 60153

ASSOCIATE EDITORS

Martin D. Abeloff, MD
The Johns Hopkins Oncology Center
600 N Wolfe Street
Room 157
Baltimore, MD 21287

Stephen A. Cannistra, MD
Dana-Farber Cancer Institute
44 Binney Street
Dana 910A
Boston, MA 02115

Lawrence H. Einhorn, MD
Indiana University Hospital
550 N University Blvd
Room 1730
Indianapolis, IN 46202-5265

Allen S. Lichter, MD
University of Michigan
Medical Center
Department of Radiation Oncology
1500 E Medical Center Drive
Room B2C490, Box 0010
Ann Arbor, MI 48109

Joseph V. Simone, MD
Huntsman Cancer Foundation & Institute
University of Utah
Building 533, Room 4130
Salt Lake City, UT 84112

Glenn D. Steele, Jr, MD, PhD
The University of Chicago
Division of Biological Sciences
5841 South Maryland Avenue
MC 1000
Chicago, IL 60637-1470

Robert C. Young, MD
Fox Chase Cancer Center
7701 Burholme Avenue
Philadelphia, PA 19111

Dear Dr. Albain:

I am pleased to inform you that your revised paper, "The Influence of Patient Characteristics, Socioeconomic Factors, Geography and Systemic Risk on the Use of Breast Sparing Treatment in Women Enrolled on Adjuvant Breast Cancer Studies: An Analysis of Two Intergroup Trials" (MS#1-95-06-45-R), has been accepted for publication.

You will be contacted shortly regarding the handling of your accepted paper.

Thank you for giving us the opportunity to publish your paper in the *Journal of Clinical Oncology*.

Sincerely yours,

Martin D. Abeloff

Martin D. Abeloff, M.D.
Associate Editor

MDA:ehr
enclosure

THE INFLUENCE OF PATIENT CHARACTERISTICS, SOCIOECONOMIC FACTORS,
GEOGRAPHY AND SYSTEMIC RISK ON THE USE OF BREAST SPARING TREATMENT IN
WOMEN ENROLLED ON ADJUVANT BREAST CANCER STUDIES:
AN ANALYSIS OF TWO INTERGROUP TRIALS

By Kathy S. Albain, M.D.¹, Stephanie R. Green, Ph.D.², Allen S. Lichter, M.D.³,
Laura F. Hutchins, M.D.⁴, William C. Wood, M.D.⁵, I. Craig Henderson, M.D.⁶,
James N. Ingle, M.D.⁷, Janet O'Sullivan, M.A.², C. Kent Osborne, M.D.⁸
and Silvana Martino, D.O.⁹

¹Loyola University Chicago Medical Center, Maywood, IL

²Southwest Oncology Group Statistical Center, Seattle, WA

³University of Michigan Medical Center, Ann Arbor, MI

⁴University of Arkansas for Medical Sciences, Little Rock, AK

⁵Emory University School of Medicine, Atlanta, GA

⁶University of California at San Francisco, CA

⁷Mayo Clinic, Rochester, MN

⁸University of Texas Health Science Center at San Antonio, TX

⁹The Westlake Comprehensive Cancer Center, Westlake Village, CA

This investigation was supported in part by Department of the Army Research Grant DAMD17-94-J-4220 (KSA) and the following PHS Cooperative Agreement grant numbers awarded by the National Cancer Institute, NIH, DHHS: CA-20319, CA-04920, CA-37981, CA-35431, CA-22433, CA-12644, CA-42028, CA-58416, CA-35281, CA-13612, CA-04919, CA-35090, CA-35176, CA-58686, CA-58861, CA-46113, CA-32734, CA-46282, CA-58882, CA-35128, CA-27057, CA-45450, CA-35261, CA-46136, CA-28862, CA-35192, CA-12213, CA-58348, CA-16385, CA-58658, CA-46441, CA-58723, CA-45377, CA-35119, CA-42777, CA-58415, CA-35178, CA-52757, CA-52654, CA-52650, CA-35200, CA-35262, CA-35117, CA-45807, CA-46368, CA-58348, CA-45461, CA-52772, CA-25224.

Address for Editorial Correspondence:

Kathy S. Albain, M.D.
Associate Professor of Medicine
Division of Hematology/Oncology
Loyola University Medical Center
2160 South First Avenue
Maywood, IL 60153
Telephone: 708-327-3102
Facsimile: 708-327-3231

Address for Reprints:

Southwest Oncology Group Operations Office (S8814/S8897)
14980 Omicron Drive
San Antonio, Texas 78245-3217

(Note to Editor: Please **DO NOT** send editorial correspondence or proofs to reprint address.)

Running Head: Breast sparing treatment in Intergroup trials

ABSTRACT

PURPOSE: To investigate the frequency of breast sparing treatment among breast cancer patients subsequently enrolled in national cooperative group studies of adjuvant chemotherapy as a function of geographic locale, risk of systemic relapse and other factors.

PATIENTS AND METHODS: A database was formed of 5,172 patients randomized on two intergroup trials (one, node-negative; the other, postmenopausal, receptor positive, node-positive). Lumpectomy rates by study, within study-defined risk strata, and across geographic regions of the country, with adjustment for study factors, were analyzed. Significant predictors of lower lumpectomy usage were then determined in multivariate analyses which included these variables: disease characteristics (tumor size, nodal status, number of positive nodes, and systemic risk strata [low vs uncertain vs high] for node-negative patients based on tumor size and receptor status); patient characteristics (age, menopausal status, race), geographic region descriptors; and socioeconomic indicators (rural or urban location, educational level, income) based on zipcode of residence.

RESULTS: Breast conservation rates were 30% in the node-negative and 15% in the node-positive trials, with a wide geographic variation within each study (14-49% and 9-31%, respectively). Lumpectomy use declined with increasing tumor size in both the node-negative and node-positive groups, and did not exceed 40% even for tumors of 1cm or less with negative nodes. With increasing risk of systemic relapse, frequency of lumpectomy declined (rates for five strata in order of increasing systemic risk: 41%, 33%, 24%, 18%, and 11%) even though these strata were not known at time of the surgical decision. A logistic model confirmed the joint significance of geographic region and systemic risk. An exploratory model which adjusted for all important variables identified significant predictors of lower lumpectomy use: positive nodes;

many positive nodes, increased systemic risk; tumor size ≥ 2.0 cm; older age; South, Central or non-New England regions; and either lack of college degree or lower income levels.

CONCLUSION: Breast sparing therapy was utilized in the minority of women subsequently accrued to two national adjuvant breast cancer studies at the time of the release of the NCI Consensus Conference directives, even though this patient cohort and their referring surgeons represented a highly select population. Although multiple concrete factors were independent predictors of lower lumpectomy rates, further research into how both patients and their physicians approach the mastectomy vs. lumpectomy decision is needed.

INTRODUCTION

Breast conserving therapy was declared preferable to mastectomy for the majority of women with stage I and II breast cancer at the 1990 National Cancer Institute (NCI) Consensus Development Conference on the Treatment of Early Breast Cancer, and in the subsequently published Consensus Statement.¹ At the time of that recommendation, a number of investigators undertook studies to determine the frequency with which women in the United States received breast conservation versus the more traditional mastectomy approach.²⁻⁶ Collectively, these studies documented that a minority of American women were treated with non-mastectomy techniques: approximately 30% nationwide, and less than 15% of the Medicare population. A marked geographic variation of four to five-fold in the use of breast sparing therapy was described across regions of the country for the same stage of disease. To a variable degree, some of these studies addressed other potential influences on the surgical choice such as patient characteristics, tumor-related prognostic variables, socioeconomic status, and physician and/or patient bias.

These investigations concentrated on women who were treated in the mid-1980's, prior to or just at the time of the NCI Consensus Conference. Most of these data represented a broad cross-section of medical practice from unselected patient databases such as Medicare insurance claims, tumor registries, and the Surveillance, Epidemiology and End Results (SEER) program.²⁻⁶ We hypothesized that due to the high profile status of this issue at the release of the mandate of the Consensus Conference, increased rates of breast conservation would first be detected among certain select populations of women with stage I and II disease. One such group possibly would be those women enrolled by medical oncologists on state-of-the-art national clinical trials of adjuvant therapy, since their referring surgeons might be expected to be well aware of and endorse the NCI Conference recommendations. We anticipated that high rates of non-

mastectomy therapy would be observed in this select population.

Therefore, this investigation of rates of breast conservation was initiated by the Committee on Women's Health and the Radiation Therapy Committee of the Southwest Oncology Group (SWOG). A database of over 5,000 women randomized after surgery onto two of the recent national intergroup adjuvant studies was analyzed. Our objectives were to 1) determine the rates of breast conservation versus mastectomy overall for each study, and for the defined prognostic strata in each trial; 2) analyze rates of breast sparing therapy across geographic regions of the country to learn if previously described variability occurred in this select patient population; and 3) explore whether there is prediction of surgical option after adjustment for other factors by patient characteristics such as age or menopausal status, disease-related prognostic variables (tumor size, nodal status, and other risk factors for relapse), geographic region, and socioeconomic characteristics.

PATIENTS AND METHODS

Patient Database

The database consisted of women enrolled on two intergroup adjuvant breast cancer trials administratively directed by the SWOG. Other members of the breast cancer intergroup at the time of conduct of these trials included the Cancer and Acute Leukemia Group B (CALGB), the Eastern Cooperative Oncology Group (ECOG), the North Central Cancer Treatment Group (NCCTG), and the National Cancer Institute of Canada (NCI-C). Canadian patients were enrolled on one of the two trials, but were excluded from this database due to the absence of zipcode and census data required for determination of geographic region and socioeconomic status identifiers (see below).

The first study was S8814 (INT 0100), which opened in May, 1989 and completed accrual

in August, 1995. All members of the intergroup participated. Eligible patients were postmenopausal, with involved axillary lymph nodes and tumors with positive hormonal receptors (estrogen and/or progesterone). Primary tumor sizes of T1, T2, or T3 were allowed if a mastectomy was performed, but size eligibility was restricted to T1 or T2 if breast conserving therapy was used. Following primary surgery, patients were randomized to one of three treatment arms: 1) tamoxifen alone; 2) cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) plus concurrent tamoxifen; or 3) CAF followed by tamoxifen. The tamoxifen duration was five years in each arm. The stratification factor of 1-3 positive nodes versus 4 or more involved nodes was applied at randomization.

The second trial in this database was S8897 (INT 0102), which opened in July, 1989 and closed February, 1993. The CALGB and ECOG were co-participants with the SWOG. The eligibility requirements were negative axillary nodes, any menopausal and receptor status, and the same tumor size criteria as outlined above for S8814. Three prognostic risk groups defined the pre-randomization strata: low, uncertain, and high. The low risk category included tumors too small for biochemical hormone receptor analysis while the high risk subset was comprised of tumors ≥ 2.0 cm, or receptor-negative disease of any size. Patients whose tumors were < 2.0 cm and receptor-positive were assigned to the uncertain risk group, with their subsequent treatment assignment directed by the results of flow cytometry. Tumors with diploid DNA content and an S-phase fraction of less than 4.4%, or aneuploid with an S-phase fraction of less than 7% were grouped with the low risk patients, as were patients with tumor size of 1 cm or less with S-phase fraction unknown due to insufficient amount of tumor. All other DNA results indicated an adverse prognostic potential, so these patients were assigned to the high risk group. Low risk patients were observed without systemic therapy, whereas high risk patients were randomized to CAF vs CAF plus tamoxifen vs CM(methotrexate)F vs CMF plus tamoxifen.

The intergroup strove to maximize participation in both trials from patients who received breast conservation. Since there was no firm consensus as to whether breast radiation should be delivered before or after a course of adjuvant chemotherapy,⁷ either sequence was acceptable according to institution or physician preference, as long as day 1 of chemotherapy was given within 12 weeks of definitive surgery. Guidelines for the delivery of radiation were written broadly to cover the entire spectrum of recognized radiation techniques. Because of the perceived investigator burden of reporting radiation data on numerous forms and the expense of mailing copies of simulation and portal films, radiation oncologists were not required to submit copies of port films, simulator films or other dosimetric information.

Variables in the Database

The variables available for analysis of their potential association with the type of primary surgical treatment rendered prior to entry are shown in Table 1. These variables were drawn from disease or patient characteristics, geographic region and socioeconomic factors. The five disease variables were related to the risk of systemic recurrence as defined by the strata of the study or the prestudy tumor size. Since patients with T3 tumors were ineligible for breast conservation, all analyses in this database were restricted to patients with T1 and T2 tumors. Table 1 also lists four patient characteristics related to two age cutpoints (≥ 40 , ≥ 65), race and menopausal status. For the analyses of possible geographic variation of breast conserving therapy, the country was divided into nine regions (Figure 1) as utilized by the American Hospital Association⁴ and the National Cancer Data Base.² United States zipcode information from randomization records was used to categorize the patients into these nine regions. The three geographic variables in Table 1 were derived for the multivariate analyses from different condensations of the nine regions and are defined in detail in the Table footnote (South vs North, Central vs Coastal, and New England vs all others). The two regions that extended from

North to South (Pacific and Mountain) were assigned to the North subgroup for this analysis.

Individual socioeconomic data were not available in the intergroup database. Thus, in order to explore the possible contribution of socioeconomic status to surgical choice, identifiers derived from the zipcode of residence were used instead.⁸ The zipcode information was combined with 1990 census data to derive variables for median income in zipcode of residence (<\$25,000; <\$50,000), percent rural in zipcode of residence, and educational level (percent without college degree in zipcode of residence).

Statistical Methods

The percentages of patients who received breast conserving therapy were determined for each study, and within study, for each of the nine geographic regions. The lumpectomy rates were also analyzed within tumor size subsets in each study, in the two nodal strata of S8814 and the three prognostic risk strata of S8897. A major objective was to determine if regional variation in use of breast sparing therapy would be identified in this select group of patients. Thus, geographic differences were tested both with chi-squared tests for contingency tables⁹ within studies S8814 and S8897 and with a logistic model⁹ of the geographic variables North vs South and Central vs Coastal, adjusted for the two studies and their strata. The number of positive nodes (1-3 versus 4 or more) for S8814 and the three prognostic risk groups (low, uncertain, high) for S8897 were investigated in this primary logistic analysis since these were the major stratification factors for the studies. In fact, these strata defined a sequence of increasing risk of relapse.

A secondary objective identified at the start of this analysis was to determine if markers of systemic risk of relapse were predictive of the surgical choice after adjustment for other potential influencing factors. Using the disease characteristics of Table 1, the following variables were constructed for additional multivariate modeling: low risk node-negative vs all others, node

positive or high risk node-negative vs all others, node-negative or positive, and four or more positive nodes vs all others. Exploratory logistic modeling was then done using all variables in Table 1, incorporating the socioeconomic factors and patient characteristics along with the disease and geographic region variables. The model was first applied to the entire database, and then additional modeling was done within each of the major risk strata defined by the studies. As with any exploratory analyses, results are not definitive unless confirmed in other studies. Furthermore, although we have reported p-values of $<.05$, only smaller p-values ($<.005$) should be considered of particular interest in view of the many tests performed.

RESULTS

Primary Analyses

The overall rates of breast conservation for each study and within each of the nine geographic regions are depicted in Table 2. Of the 4,174 women accrued to the node-negative trial (S8897) with known zipcodes and T1 or T2 tumors, 30% (95% confidence intervals 28-31%) had a lumpectomy plus breast irradiation. The rate of breast conserving therapy was only 15% (95% confidence intervals 13-17%) for the 998 women entered on the node-positive trial with known zipcodes and T1 or T2 lesions.

There were statistically significant geographic variations in the rates of breast conserving therapy in each study (Table 2). Within the node-negative trial, the range of lumpectomy rates was from 49% of the New England registrants to 14% of the East South Central patients (X^2 , 8 degrees of freedom $p <.0001$). This range for the node-positive study was from 31% of the patients from New England to 8% of the women who resided in the Mountain region (X^2 , 8 degrees of freedom $p =.013$).

The lumpectomy percentage varied according to primary tumor size in each study: in the

node-negative study, breast conservation was performed in 35% vs 20% for T1 vs T2 tumors; the rates were 20% vs 10%, respectively, in the node-positive trial. Table 3 provides additional size breakdowns within the T1 category for each study. Patients with tumors of 1.0 cm or less and negative lymph nodes had the greatest chance of having a lumpectomy (38%), whereas only 10% of those women with positive nodes and tumors of 2.0-5.0 cm had a lumpectomy. Even among those women with negative nodes and primary tumors 0.5 cm or less, the rate of breast conservation was only 38% (Table 3).

Although not known at the time of the decision regarding type of definitive surgery, the prognostic factors of systemic relapse as defined by the risk strata for each study (see Methods) were strongly associated with the lumpectomy rate. The greater the systemic risk of relapse, the lower the use of breast conservation. These data are summarized in Table 4. In the node-positive trial, 18% (95% confidence intervals 15-21%) of the 1-3 positive node stratum received breast sparing treatment, whereas only 11% (95% confidence intervals 8-14%) of the women with 4 or more positive nodes were so treated ($p=.002$). This trend of less usage of lumpectomy if more nodes were positive was also observed within most geographic regions. For example, in the New England region, 37% of the 1-3 positive node subset had breast conservation, but this rate was only 19% for the 4 or more positive node group. Similarly, in the West North Central region, the breast conservation rates were 13% and 5%, respectively, for the two node subsets; or, in the East North Central region, the rates were 17% and 9%, respectively. Overall, seven of the nine geographic regions had lower lumpectomy usage in the stratum with four or more positive nodes compared to the 1-3 positive node subset. Table 4 also depicts the significant differences of lumpectomy rates across the systemic the risk strata in the node-negative trial: 41% of the low risk subset had a lumpectomy compared to 33% of the uncertain risk and 24% of the high risk groups ($p<.0001$).

A logistic regression model was applied to the combined dataset of both trials to test the association of lumpectomy use with geographic region and systemic risk strata. Two regional variables (North vs South and Coastal vs Central) were used, adjusted only for the study-defined systemic risk variables (low, uncertain and high risk node-negative and 1-3 or 4 or more positive nodes). There were two significant findings in this analysis. First, disease variables associated with risk of systemic disease were predictive of rates of lumpectomy utilization after adjustment for geographic locale; breast conservation was decreased, in general, as a function of increasing risk of systemic relapse. The second significant finding in this multivariate model was that breast conservation rates varied across geographic region after adjustment for the systemic risk variables. Lumpectomy rates were generally highest in North Coastal regions, lowest in South Central, and intermediate in the other two geographic regions, regardless of risk strata. However, not all of the differences in the observed rates of breast conservation were explained by this simple model which incorporated only the two elements of study-defined strata of systemic risk of relapse and variables defined by geographic region. Thus, exploratory models were applied which incorporated multiple variables.

Exploratory Analyses

Table 5 depicts the results of an exploratory model applied to the combined study database in which all available variables were tested for potential influence on rates of breast conservation. Predictors of lower lumpectomy percentages after adjustment for other significant factors were: four or more positive nodes, positive nodes in general (vs negative), not low risk node-negative, tumors ≥ 2.0 cm, age ≥ 65 , age ≥ 40 , residence in South or Central regions, residence anywhere but New England, and lack of college degree. The log-odds ratios and their 95% confidence intervals for each of these significant predictors of lower lumpectomy rate are shown in Table 5. The other six available variables from Table 1 were not important predictors

in this overall model (Table 5). Of note, due to the way the model was parameterized, the insignificance of the combined variable "node-positive or high risk node-negative" but the strong significance of "not low risk node-negative" implied that the probabilities of lumpectomy use for the uncertain risk and the high risk node-negative patients of S8897 were similar after adjustment for other variables.

Four exploratory logistic models using all appropriate variables were next considered in each of the study-defined systemic risk strata (low, uncertain, and high-risk node-negative; node-positive). These separate models were analyzed because the patients in these strata were managed differently, so that specific selection biases might have been at work in each. It is also possible that various factors had different degrees of influence on lumpectomy use depending on the systemic risk status of the patients. Although there was some shifting of the importance of related variables across the subsets, the results from one risk stratum model to another were remarkably similar to the overall model discussed above and shown in Table 5. For example, the disease characteristics significant in the overall model that were also applicable to each subset remained significant in the subset models. Tumor size of ≥ 2.0 cm was an important predictor in the applicable strata of high risk node-negative and node-positive subsets (only T1 tumors were included in the low and uncertain risk strata by definition; see Methods). Thus, with respect to disease-related variables, the data support the interpretation that the greater the risk of systemic dissemination, the lower the use of breast sparing treatment.

Consistent results across the four exploratory models applied to the risk strata were also observed for variables representing patient characteristics, geographic region and socioeconomic status indicators, similar to the findings in the overall model (Table 5). With respect to patient-related variables, race was not an independent factor in any model, whereas older age was a strong predictor of lower breast conservation rates in all node-negative risk subsets. In addition,

age ≥ 40 predicted lower lumpectomy usage in the high-risk node-negative subset. However, the node-positive model found no significant age effect. Only the factor age ≥ 65 was applicable (this trial was restricted to postmenopausal patients) and it was not significant ($p = .22$). Nor was menopausal status significant after adjustment for age in any of the models. Geographic region variables were also important in every risk subset after adjustment for all other factors. Residence in either South, Central and/or non-New England regions were significant predictors of lower rates of breast conservation in each model. Finally, after adjustment for other variables, one of the socioeconomic status indicators predicted lower lumpectomy usage in each model. For the overall model (Table 5) and the models for low and high-risk node-negative patients, the lack of college degree variable was an independent predictor, whereas in the uncertain risk node-negative and node-positive models, one of the variables indicating lower annual income was predictive of less lumpectomy usage.

DISCUSSION

This analysis documented low lumpectomy rates in a highly select population of women who subsequently gave informed consent to participate in a randomized national adjuvant treatment study. Only 35% of those with T1N0 disease, 20% of the T2N0 subset, and 15% of the T1-2N1 group had breast conserving therapy. In fact, these frequencies were very similar to breast conservation rates reported in other analyses of less highly selected United States populations.²⁻⁶ In contrast, a recent analysis from London, England, showed that breast conservation was performed in 90% of stage I and 68% of stage II cases.¹⁰ The disappointing results of the present analysis ran counter to our initial hypothesis that this patient population and its treating surgeons might have been among the first to benefit from and/or apply the directives of the high-profile release of the NCI Consensus Conference findings in 1990. Furthermore, despite the select nature of this population, we observed remarkably similar

geographic variability within each study as noted by others in previous reports.²⁻⁴ This finding suggests that at the time of conduct of these trials, wide regional differences in both the definition and acceptance of the optimal surgical approach were operative even among surgeons who referred their patients to clinical trials and among those women who agreed to participate in such studies.

Several study-specific factors perhaps influenced the observed frequency of breast conservation in this analysis over and above the previously reviewed explanations for low national rates and geographic variability.²⁻⁶ First, patients had to be willing to be randomized to a chemotherapy arm (node-positive or high risk node-negative) or to be assigned to no adjuvant treatment (low risk node-negative). Women and their physicians may have considered breast conservation enough of a departure from traditional breast cancer therapy such that the addition of a clinical trial to this regimen was less likely to be accepted. This would therefore skew participation in these studies towards those who received a mastectomy. Second, the chemotherapy in both of these trials was started within 12 weeks of the definitive breast surgery. While this is a generous time allotment, some institutions elected the option to deliver breast radiotherapy prior to beginning systemic chemotherapy. Since the time to plan and administer this treatment was included in the 12 week interval, some patients with lumpectomy treatment may have been excluded from study participation because they could not complete their radiation and be registered on study within the 12 week time limit. Finally, the time required to complete the full course of radiotherapy may have been prohibitive for women who lived some distance from an approved radiation facility.

We observed marked variation in rates of breast conservation by tumor size, nodal status and risk of systemic relapse. These findings were highly significant after adjustment for all other factors in multivariate models and were not examined in this fashion in previous studies of

national usage patterns. Within either the node-negative or node-positive studies, the frequency of breast conservation was lower if the primary tumor was 2.0 cm or greater, and this was a significant predictor after adjustment for all other factors. Certainly others described lower lumpectomy rates for T2 versus T1 tumors, or for stage II vs stage I disease.^{2,5,6,10} However, our findings within the T1N0 presentations were particularly noteworthy: even for tumors 0.5 cm or small, only 38% had breast conservation. There are many reasons a tumor might not be acceptable for a lumpectomy.¹¹⁻¹⁶ Certainly it is well-recognized that conservation therapy for larger T2 lesions may not yield good cosmesis in smaller breasts, and to some degree a lower lumpectomy frequency in T2 vs T1 disease would be expected. However, our findings of very low rates in T1a lesions is more difficult to reconcile. It is possible that even though the tumor was T1a in size, there may have been multifocality, extensive in situ or invasive disease at margins, widespread suspicious calcifications in other areas of the breast, or underlying collagen vascular disease. In one series, 47% of patients evaluated were unsuitable for breast conserving therapy, including approximately 15-20% of the patients with T1 lesions.¹⁶ Nevertheless, even with these reasons factored into the equation, the low lumpectomy rates observed in this study for T1a tumors are of great concern.

An intriguing result of this analysis was the significant decrease in frequency of breast conservation as the risk of systemic relapse increased across the study-defined strata (Table 4). Specifically, for the five strata of increasing risk from low to uncertain to high risk node-negative, and then from 1-3 to 4 or more nodes positive, the respective lumpectomy rates were 41%, 33%, 24%, 18% and 11%. These prestudy strata retained predictive significance in the multivariate model after adjustment for other factors. Of the variables which defined the risk strata or otherwise predicted increased risk of relapse, only tumor size and receptor levels were known prior to the decision regarding type of definitive surgery. Node status, number of nodes positive,

and the DNA results were not available until later (unless experimental prognostic factors were obtained outside study guidelines by the local institution). Thus, none of these five risk strata were definable at the time of the surgical choice, yet were highly predictive of whether or not a lumpectomy had been performed. Speculations as to the reason(s) for this previously unreported finding follow, using nodal status as the example.

Lumpectomy utilization was lowest in the node-positive subsets, and decreased as a function of number of positive nodes. This interesting finding could not be explained by tumor size associations with node positivity, as the result persisted even within the smallest tumor sizes. One explanation would be that a subset of patients with clinically suspicious nodes were more frequently recommended to have mastectomies based on extreme conservatism on the part of the surgeon. Or, for those with clinically negative axillae, perhaps the presence of adverse prognostic factors such as high S-phase fraction and/or abnormal p53 or HER2/neu were known to surgeons and thus served as surrogates for possible node-positivity. Although the presence of involved nodes (either microscopic, non-fixed or matted) is clearly not an accepted indication to avoid breast conservation, it remains an oft-quoted reason given by many surgeons. In fact, several studies have indicated that the risk of an in-breast failure actually decreases in patients who have received chemotherapy in addition to radiation.¹⁷⁻¹⁹ Thus, there is little medical reason to avoid breast conserving treatment in node-positive breast cancer (or in those patients with surrogate prognostic factors for greater chance of positive nodes). This is especially the case when one considers that the risk of systemic recurrence far exceeds the risk of an in-breast failure.²⁰

This analysis identified other factors which significantly influenced the type of definitive surgery, after adjustment for other contributing variables. Older age and an indicator of socioeconomic status (either educational level below college degree or lower income level) were

important predictors of lower lumpectomy frequencies. These observations are consistent with other reports regarding age,^{3-5, 21-23} education,^{4,5} and income.^{4,5} Neither race, urban vs rural residence nor menopausal status were significant predictors in this analysis, although others have reported important associations among these factors.³⁻⁵ There are other critical factors that may influence the surgical choice which are unfortunately unavailable in the intergroup database. These include type of hospital (medical school, teaching affiliate, inner city, community, etc), volume of breast cancer cases by the surgeon, physician density in area of residence, presence of an on-site radiation facility, the distance of the patient from the radiation facility, ability to travel daily to radiation treatments and formal geriatrics services.

Perhaps the most important contributors to the surgical decision are those many intangibles associated with physician biases and choice^{20,24-27} and with patient choice,^{16,24,28-32} each of which are irretrievable from a cooperative group database but are fertile ground for prospective research. Some surgeons in this country suggest that mastectomy yields an optimal medical result and will bias the surgical choice presentation accordingly. Or, lumpectomy may not be presented as the preferred option out of a belief that survival is equivalent, but instead is presented only because the surgeon believes a choice must be offered. Many women undergo significant psychological stress when the physician does not indicate the preferred option. Also, some physicians believe that there is a trade-off between preservation of the breast and fear that the cancer will recur, with lumpectomy patients enduring greater insecurity for the rest of their lives.²⁴ In this context, the manner in which the treatment choice is presented can influence the patient's decision substantially. However, three trials showed no difference in the fear of recurrence between women treated by the two approaches.^{24,30-32} Furthermore, even when medically appropriate and properly presented, breast conservation may simply not be right for a given patient in her eyes. In two studies, 31-55% of patients did not choose lumpectomy

as their best option despite a careful presentation.^{16,28} Thus, it is uncertain what figure should represent the "appropriate" lumpectomy frequency. But, in our view, the rates observed in the present study are unacceptably low.

In summary, breast sparing therapy was utilized in the minority of women who subsequently chose to participate in national intergroup adjuvant trials conducted at the time of the NCI Consensus Conference. Lumpectomy frequencies varied significantly by geographic region of the country and decreased with increasing risk of systemic disease, with increasing size of the primary tumor, with older age, and with lower educational levels. All these variables had an independent contribution to the surgical choice. Although the NCI Consensus Conference declared breast conservation to be the preferred option for women with early breast cancer, the clinical practice pattern among surgeons who referred women to these clinical trials did not reflect this mandate. With the steady development of multidisciplinary centers specializing in the treatment of breast diseases, women are increasingly evaluated by a team of breast cancer specialists prior to undertaking primary therapy. In this fashion, unfounded biases against breast conserving therapy should diminish so that the conservation option will be presented as the preferred treatment. It is hoped that the lumpectomy rates for the women enrolled in the current generation of intergroup adjuvant trials will reflect this change. Then, prospective attention to the multiple other factors influencing the patient's choice can be given.

REFERENCES

1. NIH Consensus Development Conference Statement: Treatment of Early Stage Breast Cancer. JNCI 11:1-6, 1992
2. Osteen RT, Steele G, Jr., Menck HR, Winchester DP: Regional differences in surgical management of breast cancer. Ca Cancer J Clin 42:39-43, 1992
3. Nattinger AB, Gottlieb MS, Veum J, et al: Geographic variation in the use of breast-conserving treatment for breast cancer. N Engl J Med 326:1102-7, 1992
4. Farrow DC, Hunt WC, Samet JM: Geographic variation in the treatment of localized breast cancer. N Engl J Med 326:1097-1101, 1992
5. Lazovich DA, White E, Thomas DB, Moe RE: Underutilization of breast-conserving surgery and radiation therapy among women with stage I or II breast cancer. JAMA 266:3433-8, 1991
6. Swanson GM, Satariano ER, Satariano WA, Osuch JR: Trends in conserving treatment of invasive carcinoma of the breast in females. Surg Gynecol Obstet 171:465-71, 1990
7. Recht A, Come S, Harris J: Integration of conservative surgery, radiotherapy and chemotherapy for patients with early-stage breast cancer. Semin Radiat Oncol 2:107-15, 1992

8. US Department of Commerce: Census of Population and Housing. U.S. Department of Commerce, Washington, D.C., 1990
9. Cox D: The analysis of binary data. London: Methuen & Co Ltd, 1970
10. McCarthy M, Bore J: Treatment of breast cancer in two teaching hospitals: a comparison with consensus guidelines. *Eur J Cancer* 27:579-82, 1991
11. McCormick B: Invasive breast carcinoma: Patient selection for conservative management. *Semin Radiat Oncol* 2:74-81, 1992
12. Teixidor HS, Chu FC, Kim YS, Levin TL: The value of mammography after limited breast surgery and before definitive radiation therapy. *Cancer* 69:1418-23, 1992
13. Leopold KA, Recht A, Schnitt SJ, et al: Results of conservative surgery and radiation therapy for multiple synchronous cancers of one breast. *Int J Radiat Oncol Biol Phys* 16:11-16, 1989
14. Winchester DP, Cox JD: Standards for breast-conservation treatment. *Ca Cancer J Clin* 42:134-62, 1992
15. Fleck R, McNeese MD, Ellerbroek NA, et al: Consequences of breast irradiation in patients with pre-existing collagen vascular diseases. *Int J Radiat Oncol Biol Phys*

17:829-33, 1989

16. Wolberg WH, Tanner MA, Romsaas EP, et al: Factors influencing options in primary breast cancer treatment. *J Clin Oncol* 5:68-74, 1987
17. Fisher B, Anderson S, Redmond C, et al: Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 333:1456-61, 1995.
18. Fisher B, Wickerham DL, Deutsch M, et al: Breast tumor recurrence following lumpectomy with and without breast irradiation: an overview of recent NSABP findings. *Semin Surg Oncol* 8:153-60, 1992
19. Rose MA, Henderson IC, Gelman R, et al: Premenopausal breast cancer patients treated with conservative surgery, radiotherapy and adjuvant chemotherapy have a low risk of local failure. *Int J Radiat Oncol Biol Phys* 17:711-7, 1989
20. Fisher B, Ore L: On the underutilization of breast-conserving surgery for the treatment of breast cancer [editorial]. *Ann Oncol* 4:96-8, 1993
21. Chu J, Diehr P, Feigl P, et al: The effect of age on the care of women with breast cancer in community hospitals. *J Gerontol* 42:185-90, 1987
22. Greenfield S, Blanco DM, Elashoff RM, Ganz PA: Patterns of care related to age of

- breast cancer patients. *JAMA* 257:2766-70, 1987
23. Mor V, Masterson-Allen S, Goldberg RJ, et al: Relationship between age at diagnosis and treatments received by cancer patients. *J Am Geriatr Soc* 33:585-9, 1985
 24. Lasry JC, Margolese RG: Fear of recurrence, breast-conserving surgery, and the trade-off hypothesis. *Cancer* 69:2111-5, 1992
 25. Liberati A, Apolone G, Nicolucci A, et al: The role of attitudes, beliefs, and personal characteristics of Italian physicians in the surgical treatment of early breast cancer. *Am J Public Health* 81:38-42, 1991
 26. Belanger D, Moore M, Tannock I: How American oncologists treat breast cancer: an assessment of the influence of clinical trials. *J Clin Oncol* 9:7-16, 1991
 27. Tarbox BB, Rockwood JK, Abernathy CM: Are modified radical mastectomies done for T1 breast cancers because of surgeon's advice or patient's choice? *Am J Surg* 164:417-20, 1992
 28. Fallowfield LJ, Hall A, Maguire GP, Baum M: Psychological outcomes of different treatment policies in women with early breast cancer outside a clinical trial. *British Med J* 301:575-80, 1990
 29. Whelan T, Levine M, Gafni A, et al: Breast irradiation postlumpectomy: Development

and evaluation of a decision instrument. *J Clin Oncol* 13:847-53, 1995

30. Schain W, Edwards BK, Gorrell CR, et al: Psychosocial and physical outcomes of primary breast cancer therapy: mastectomy vs excisional biopsy and irradiation. *Breast Cancer Res Treat* 3:377-82, 1983
31. Kemeny MM, Wellisch DK, Schain WS: Psychosocial outcome in a randomized surgical trial for treatment of primary breast cancer. *Cancer* 62:1231-7, 1988
32. Kiebert GM, de Haes JC, van de Velde CJ: The impact of breast-conserving treatment and mastectomy on the quality of life of early-stage breast cancer patients: a review. *J Clin Oncol* 9:1059-70, 1991

Acknowledgment

The authors thank the following members of the Southwest Oncology Group Advocates Steering Committee for their support of and input in this project: Tika Beard, Sharon L. Green, Amy S. Langer, Peggy McCarthy, Michelle Melin, Peggy Michelson, Eileen Sondak, and Ellen L. Stovall.

Table 1. Variables Available for Study of Association with Rate of Breast Conservation

CATEGORY	VARIABLE
Disease Characteristics (yes vs no)	≥ 4 positive nodes ≥ 1 positive node node-positive or high risk node-negative ¹ not low risk node-negative ¹ tumor size ≥ 2 cm
Patient Characteristics (yes vs no)	age ≥ 65 years age ≥ 40 years postmenopausal non-white
Geographic Region ²	South (vs North) Central (vs Coastal) Not New England (vs New England)
Socioeconomic Characteristics ³	percent without college degree percent rural median income $< \$25,000$ (yes vs no) median income $< \$50,000$ (yes vs no)

¹ High and low risk node-negative subsets were defined as strata by the study and are explained in the patient population section of the Methods.

² South = West South Central plus East South Central plus South Atlantic and North = all other regions; Central = Mountain plus West South Central plus West and East North Central and Coastal = all other regions. Regions are defined in Figure 1.

³ Determined based on zipcode of residence using census-based methodology (see Methods).

Table 2. Rate of Breast Conservation within Study Across Geographic Regions

Region of the U.S.A.	Number Patients Node-Negative (S8897)	Percent Lumpectomy ¹ (95% confidence intervals)	Number Patients Node-Positive (S8814)	Percent Lumpectomy ² (95% confidence intervals)
East North Central	1160	29% (26-31)	269	14% (10-18)
East South Central	120	14% (8-20)	40	13% (4-27)
Middle Atlantic	547	37% (33-41)	118	21% (14-29)
Mountain	152	26% (19-33)	48	8% (2-20)
New England	251	49% (43-55)	62	31% (20-44)
Pacific	462	36% (32-41)	112	18% (11-25)
South Atlantic	582	29% (25-32)	100	14% (8-22)
West North Central	578	22% (19-26)	148	9% (5-14)
West South Central	322	21% (17-26)	101	10% (4-16)
Total	4,174	30% (28-31)	998	15% (13-17)

¹p-value for difference across regions < 0.0001

²p-value for difference across regions = 0.013

Table 3. Rate of Breast Conservation within Study by Tumor Size

Tumor Size	Percent Lumpectomy Node-Negative (total patients S8897)	Percent Lumpectomy Node-Positive (total patients S8814)
≤ 0.5 cm	38% (261)	17% (6)
> 0.5-1.0 cm	38% (817)	32% (74)
> 1.0 - 2.0 cm	33% (1645)	18% (382)
> 2.0 - 5.0 cm	20% (1421)	10% (523)

Table 4. Rate of Breast Conservation as a Function of Prognostic Risk Category

Risk Category ¹	Percent Lumpectomy ² (95% confidence intervals)
Node-positive trial (S8814)	
1-3 nodes	18% (15-21)
4 or more nodes	11% (8-14)
Node-negative trial (S8897)	
Low risk	41% (37-45)
Uncertain risk	33% (30-36)
High risk	24% (22-26)

¹Study-defined strata, see Methods

²p-values for differences across risk strata: S8814, p = .002; S8897, p < .0001

**Table 5. Predictors of Lower Rates of Breast Conservation
P-Values and Estimates of Log-odds Ratios for all Patients in a Logistic Regression Model**

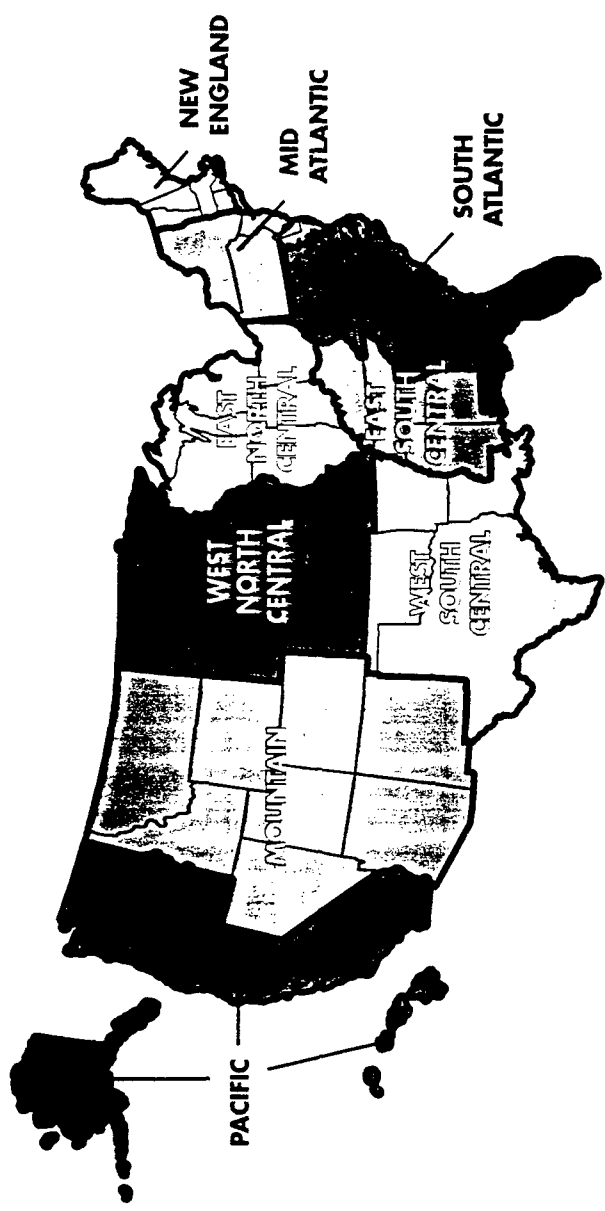
Characteristic	Variable	P-Value	Log-Odds Ratio Estimates (95% confidence intervals)
Disease	≥ 4 (+) nodes	.03	- .43 (-.81 to-.04)
	≥ 1 (+) node	.004	- .35 (-.58 to-.11)
	node (+) or high risk node (-)	ns	(- .06)
	not low risk node (-)	.0008	- .32 (-.50 to-.13)
	tumor size ≥ 2 cm	.0001	- .67 (-.81 to-.52)
Patient	non-white	ns	(-.11)
	age ≥ 65	.0001	-.42 (-.60 to-.23)
	age ≥ 40	.0003	-.35 (-.54 to-.16)
	postmenopausal	ns	(-.25)
Geographic Region	South	.0001	- .35 (-.53 to-.18)
	Central	.0001	- .33 (-.50 to-.16)
	Not New England	.001	- .46 (-.75 to-.18)
Socioeconomic¹	percent without college degree	.0001	- 1.6 (-2.10 to-1.18)
	percent rural	ns	(- .14)
	median income < \$25,000.	ns	(- .20)
	median income < \$50,000.	ns	(- .01)

ns = not significant after adjustment for the important variables; estimates in parentheses were obtained after adjustment for important variables.

¹Using zipcode of residence and U.S. census data (see Methods).

Figure Legend

Figure 1. The nine geographic regions used in this study. Patients were assigned to a region based on the zipcode of residence.



APPENDIX G

Table from Recent Analysis of Percent Breast Sparing Treatment by Southwest Oncology Group Study, Risk Subset and Year. Kathy S. Albain, M.D., Stephanie Green, Ph.D. and Laura Loll, M.S. for the Committee and Women's Health and Breast Committee.

The following table is proprietary information.

Table of Percent Breast Sparing Surgery by Intergroup Adjuvant Study Number and Consecutive Year of Accrual, with Respect to Patient Subgroup for Risk for Relapse

Pt subgroup	Stno	89	90	91	92	93	94	95
pre, N-, <2	8897	20%	33%	38%	46%	61%		
	9313						57%	57%
post, N-, <2	8897	27%	23%	32%	41%	46%		
	9313						56%	50%
pre, N-, 2-5	8897	12%	15%	29%	33%	37%		
	9313						43%	42%
post, N-, 2-5	8897	3%	11%	18%	23%	32%		
	9313						38%	35%
pre, 1-3, <2	9313						47%	51%
post, 1-3, <2	8814	9%	21%	23%	35%	41%	35%	
	9313						36%	38%
pre, 1-3, 2-5	9313						23%	34%
post, 1-3, 2-5	8814	3%	6%	12%	24%	22%	32%	
	9313						27%	24%
post, 4+, <2	8814	13%	9%	13%	11%	39%	25%	
post, 4+, 2-5	8814	4%	5%	12%	16%	20%	31%	

Legend: Pre, Premenopausal; Post, Postmenopausal; N-, negative axillary nodes; 1-3 or 4+, number of positive axillary nodes; < 2 or 2-5, tumor size in cm.

BLANK

APPENDIX H

Southwest Oncology Group Committee on Women's Health Advocates and Survivors Partnership Pilot Project Grant Application.

Funded by the National Action Plan on Breast Cancer.

Aspects of the following grant application that address research objectives and plans of the SWOG constitute proprietary information.



NATIONAL ACTION PLAN ON BREAST CANCER
A Public/Private Partnership

October 25, 1995

RECEIVED IN

OCT 30 1995

OPERATIONS OFFICE

Charles Coltman Jr., M.D.
Southwest Oncology Group
14980 Omicron Drive
San Antonio, TX 78245-3217
REFERENCE: OWII #00163 and 00213

CO-CHAIRS:

Susan J. Blumenthal, MD, MPA
Deputy Assistant Secretary
for Health (Women's Health)
Assistant Surgeon General

Frances M. Visco, Esq.
President
National Breast Cancer Coalition

PHS Office on Women's Health
U.S. Department of Health
and Human Services
200 Independence Avenue, SW
Room 730B
Washington, DC 20201
Telephone: 202-401-9587
Facsimile: 202 401-9590

Dear Applicant:

Congratulations on your successful application for funding under the National Action Plan on Breast Cancer (NAPBC). The NAPBC received over 600 applications in response to the NAPBC Request for Applications and Grant Supplement Program Announcement published in April 1995. All applications were reviewed for technical merit followed by a programmatic review by NAPBC Working Groups and the NAPBC Steering Committee. Of the many excellent applications received, approximately 16% received funding. The total funding in 1995 for NAPBC-supported grants and supplements was \$8.8 million.

We are very pleased that your application was funded. We will be following the progress of all NAPBC-supported grants and look forward to hearing more about the goals and accomplishments of your project. Thank you for your efforts and contributions to the fight against breast cancer and your dedication to eliminating this disease.

Sincerely,

Susan J. Blumenthal, M.D., M.P.A.
Co-Chair, NAPBC
Deputy Assistant Secretary for Health
(Women's Health)
Assistant Surgeon General

Frances M. Visco, Esq.
Co-Chair, NAPBC
President
National Breast Cancer Coalition

**Southwest Oncology Group Committee on Women's Health Advocates and Survivors
Partnership Pilot Project**

PROPOSAL OBJECTIVES AND SPECIFIC AIMS

The purpose of this application to the National Action Plan on Breast Cancer (NAPBC) is to provide an administrative supplement to the parent five-year grant of the Southwest Oncology Group (CA-32102) for development of one specific component of its Committee on Women's Health (CWH) research agenda. In companion proposals, administrative supplements to the CWH Chair and to the Group Statistical Center are requested to further the two main objectives of these programs pertinent to the NAPBC: 1) develop and implement ongoing CWH research activities in the NAPBC Priority Area of **Clinical Trials Accessibility and Barriers**; and, in parallel, 2) develop and expand the organization and partnership research agenda of the model CWH Lay Advocates and Survivors Pilot Project (NAPBC Priority Area of **Consumer Involvement**). For the last two years, the Group Chair has been endorsing and carrying the Advocates program as an "unfunded mandate" of NCI's directive and CWH's intent to pilot a model of consumer involvement in the clinical trials process for the national cooperative groups. Therefore, this proposal has ONE SPECIFIC AIM: to request funding for the conduct of the Pilot Project initiated in April 1995.

BACKGROUND AND SIGNIFICANCE

History of the Southwest Oncology Group and Formation of the Committee on Women's Health

The Southwest Oncology Group is a national cooperative group funded for a five-year cycle (current cycle, 1993-1997) by the National Cancer Institute (NCI) to conduct therapeutic, women's health and cancer control and prevention clinical trials. Its History, Organization, Notice of Award and Peer Review Comments are provided in Appendices 1-4. In 1994, 17,184 patients were involved in therapeutic, women's health and cancer control research, using protocols developed by the membership of the Group with consistent policies concerning human subjects (Appendix 5). It is a standing policy of the Group to include eligible patients of both sexes and all races and ethnicities in its clinical trials. For example, accrual of the Southwest Oncology Group Breast Cancer Committee in 1994 totaled 1,412 patients, the majority of whom were enrolled in eight NCI-sponsored randomized Phase III trials. This accrual included 74% (1046/1412) Caucasian patients, 9% (128/1412) African-Americans, 4% (53/1412) Hispanics and 13% (185/1412) miscellaneous other races.

At the Fall 1991 Group biannual meeting, the Committee on Women's Health (CWH) was considered as a potential new Group initiative to complement the treatment-related activities of the Breast Committee and to address other non-therapeutic aspects of women's health and cancer throughout the Group. Dr. Kathy Albain was appointed CWH Chair, based on her involvement in the activities of the Breast and Lung Committees (see Biographical Sketch and Appendix 6), which represent the most common and most deadly cancers in women. Dr. Albain formed a consortium of Group leaders and national experts, and developed a CWH organizational plan, research agenda and grant proposal. Dr. Albain presented this new initiative as part of the Group's Competitive Renewal Application in 1992. The NIH (NCI) awarded the Group five years of CWH activity at a level of "Excellent" merit (Appendices 3, 4, 7). The CWH Chair was approved at 5% effort, two trips to the biannual Group meetings and consultant costs (2 per year). In its Competitive Renewal Application (independently but concurrently submitted with the Group application to the NCI), the Group Statistical Center's request for a new statistician to support CWH activities was not approved. Following announcement of new award, the CWH Chair presented its research agenda to the National Cancer Advisory Board, to the NIH Office of Research on Women's Health and to other cooperative group chairs. The NCI Director announced that if successful, the CWH would serve as a model for the development of such programs in other cooperative groups.

Organization of the CWH

The organizational goals of the CWH as outlined in the 1992 Group Competitive Renewal were successfully enacted. Now at the midpoint of the third year of the five-year award, the CWH has matured and is fully functional. The CWH Advisory Board (Appendix 8) was formed with an External Panel of national experts in women's health and advocacy leadership (non-Group members) and an Internal Advisory Board. The CWH Advisory Board has expertise not only in clinical trials research, but also in lay advocacy issues, epidemiology and public health, behavioral science, medical anthropology, psycho-oncology, quality of life, cancer control, and sex differences research. This composition of the Board enables ongoing "cross-committee" internal communication and collaboration within the Group; the formation of external partnerships with advocates, survivors and other public and private organizations; and, positions the CWH to respond to RFAs from multiple sources (NCI, National Action

Plan on Breast Cancer, Department of Defense, Office of Research on Women's Health, etc.). The collaborations between the CWH Chair and the Breast and Cancer Control Committee Chairs have been especially productive.

Committee membership has grown to 130 active members and boasts multidisciplinary breadth and depth: medical, radiation, gynecologic and surgical oncologists; nurse oncologists and research nurses; pathologists; Ph.D.s in biostatistics, epidemiology, psychology, and medical anthropology; Masters-level experts in statistics, public health, business, and teaching; data managers; liaisons from the NIH (NCI and ORWH); and representatives of various lay advocacy organizations (Appendices 8 and 9; also, see Methods, below for narrative). This membership includes representatives of all Group Committees, the Statistical Center, and the Operations Office (Executive Officer plus others). Underserved populations also have expert representation among the CWH members: Spanish-American, African-American, Native Americans, Native Alaskans, and Native Hawaiians.

The CWH is charged with the development of concepts and protocols for the incorporation in the menus of the Disease and Cancer Control Committees. The CWH Chair and the Statistical Center Director have therefore worked closely to develop a productive collaboration. New CWH concepts are jointly reviewed, followed by the assignment of a statistician on an ad hoc basis (whenever possible, since the CWH was not awarded a Committee Statistician). The conference call mechanism is also essential to the efficient completion of many CWH concepts, and allows the CWH Chair to utilize broad multi-committee expertise and leadership during study development and to effectively incorporate external partners in study development. The types of studies conducted by the CWH and the Breast Committee are complementary, and enhance the non-competitive and fruitful collaboration of these Committees (Appendix 10).

Mission of the Committee on Women's Health and Progress to Date

It is important to emphasize the uniqueness of the CWH in the Group, as well as within the national cooperative group structure in general. Furthermore, it is critical to note that a large proportion of the CWH breast cancer and advocacy research agendas previously approved by the CWH Advisory Board and currently either under development or activation are in significant accord with the recently announced priority areas of the NAPBC. The purpose of the CWH is best summarized by its four-part mission: 1) to educate the Group at large in issues concerning women's health and cancer; 2) to generate ideas for new research questions (different from the standard treatment protocol, yet complementary) and bring them to fruition as concepts and protocols in the Group's Disease and Cancer Control Research Committees; 3) to utilize the vast Group data base as a valuable bank and research tool; and, 4) to assist the Group in incorporating cancer survivors and advocates in the clinical trials process.

The CWH educational process is detailed in Appendix 11, with areas applicable to the NAPBC Priorities highlighted in bold. All of these activities significantly preceded announcement of the six priority areas. The CWH scientific and research goals are defined by the Focus Areas and Specific Research Objectives contained in the original 5-year proposal in the 1992 Competitive Renewal, with the Objectives revised for the recent Year Three continuation award and Group Scientific Retreat (Appendix 12). All but two of these 11 Objectives preceded but are now endorsed as priorities by the NAPBC. Despite its two-year existence, CWH scientific activities have generated two published manuscripts, four abstracts (two selected for slide presentations), and one submitted manuscript (Appendix 13). In addition, a number of concepts have matured to the point of external funding, protocol approval, or active development (Appendix 13). The CWH has led the way in the Group in its utilization of the large breast cancer data bank. Many of these projects are currently underway as part of a Department of Defense Award to the CWH Chair to further the Breast Cancer Research Agenda of the CWH (Appendix 13). Finally, the maturation and early successes of the Group-Lay Advocates Partnership Pilot Project (See Methods, below) led to this request for authentication through a consistent funding source.

Therefore, this supplemental grant will enable the CWH Chair and the Advocates participating in the program (described below) to focus on the agendas of their partnership and research interests by removing the uncertainty of the project's "unfunded mandate" status. Furthermore, it is clear that this program was consistent with the parent grant's objectives when the CWH was proposed as a new initiative in 1992, antedating the current directives to incorporate consumers in clinical research. The significance of this type of supplemental application, together with the evidence that it will bear fruit, can be underscored in several ways. First, the CWH and its Lay Advocates/Advisors Steering Subcommittee already have a successful track record on practical and scientific levels. Second, the CWH Chair is now positioned in several arenas to move CWH external partnership activities forward (appointments of the CWH Chair first to the Co-chairs Committee of the NAPBC and currently its Clinical Trials Working Group, to the NIH Advisory Committee on Women's Health, to the Advisory Boards of national advocacy organizations, and to the cooperative group "Intergroup Breast Chairs Committee"). And third, the CWH Chair in partnership with the Statistical Center and advocacy community is currently mid-way

through a one-year model of CWH-sponsored clinical research and administrative activities under a peer-reviewed Department of Defense "Special Sabbatical".

DESIGN AND METHODS

Evolution of the Southwest Oncology Group Committee on Women's Health Lay Advocates and Survivors Partnership: Formation of the Steering Committee and Initiation of the Pilot Project

To fulfill one of the major objectives proposed by the CWH at the time of its initial funding (Appendix 12), national advocacy organizations were polled for their interest in joining with the Southwest Oncology Group (Group) in an exploratory discussion of the potential for the formation of a pilot project of the involvement of cancer survivors, their advocates and advisors in Group activities. Leadership from the National Alliance of Breast Cancer Organizations, the National Breast Cancer Coalition, the National Coalition for Cancer Survivorship and the Y-Me National Breast Cancer Organization attended the inaugural organizational meeting in October, 1993. They joined representatives from the Group's CWH, Breast Cancer Committee, Lung Cancer Committee, Cancer Control Research Committee, Statistical Center, and Operations Office. As a result, the Lay Advisors/Advocates Implementation Subcommittee was formed (Appendix 9). Subsequently, the lay leadership has continued their involvement in Group activities on this subcommittee, as well as via active participation in various other Working Groups and Committees for the Group (Appendices 8, 11). They played a vital role in several CWH and Breast Committee concepts, and a number of collaborative ventures with the SWOG and their organizations are under development (discussed below). At the April 1995 Group meeting, this lay leadership team joined with CWH members to form the Lay Advocates/Advisors Steering Committee, a permanent CWH subcommittee replacing the Implementation Committee, on which they were granted long-term member status.

Prior to this, the following questions were initially considered by the Implementation Subcommittee: 1) How to better educate the cancer population at large in the nature and value of cancer clinical trials through the use of lay advocates/advisors? 2) What strategies could be adopted to solicit and incorporate lay input on various aspects of our clinical trials process on an ongoing basis? 3) How could cooperative groups best network with other organizations to optimize national education and implementation strategies for our clinical research studies? 4) Are there ways this lay advisor-cooperative group liaison could work to improve knowledge of and availability of clinical trials to underserved populations (e.g., the majority of women with breast cancer, the elderly, minority groups)?

The Implementation Subcommittee decided that these questions should optimally be addressed on an ongoing basis by the development of a full partnership that would require a continued and consistent involvement of the lay leadership in the biannual meetings over time. This plan was approved. However, to allow greater collaborative potential and to involve other lay experts and survivors, a three-year pilot project was designed for two types of lay positions, each of the two to participate in a Disease Committee (e.g., Breast Cancer Committee) and the Committee on Women's Health, with the hope of eventually expanding the program to other Group Disease Site Committees. The Implementation Committee formulated the procedures and job descriptions for the two types of positions. These were circulated and approved through a joint review by CWH members and Advocates.

In summary, two persons (one for each type of position) would be appointed to serve a three-year term on the Breast Cancer Committee (chosen as the first pilot disease site based on the strength of its national advocacy movement), and two others will sit on the Lung Committee (chosen as the second pilot site because despite being the most common cause of cancer death in men and women, lung cancer advocacy and survivors concerns are in their infancy). Lay appointees to the Lung Cancer Committee will also have concurrent responsibilities in the breast cancer research agenda of the CWH. Appointees could be of either sex and must have personal experience and interest in women's health issues and either breast or lung cancer research and survivorship concerns.

The first type of position ("Position A") was to be filled by a professional, well-versed and educated in either the scientific method and/or the clinical trials process. She/he must also currently be playing a key national or local patient advocacy role. This individual could, for example, be a scientist, nurse, physician, data manager, statistician, public health professional, or a leader or other representative of a national or local lay cancer advocacy or survivors organization. She/he must also be either a survivor of cancer, or close to a person living with the disease, or a leader of an advocacy or survivors group. The second position ("Position B") was to be for a "survivor representative at large", i.e., a patient or member of the public who can speak directly to survivor concerns. Willingness to serve was considered more important than experience, and scientific background is not required. However, past participation or experience with clinical trials was preferred. Representation from and/or expertise concerning underserved populations was encouraged for both positions. All participants were to agree to the importance of mutual collaboration between the clinical cancer research and cancer

advocacy/survivors communities, and to maintain the ethical and confidentiality standards of the Southwest Oncology Group.

A broad national mailing (Appendix 14) requesting nominations for these positions resulted in applications from many sources. The finalists were chosen at the Fall 1994 meeting of the Implementation Committee, and were interviewed subsequently by telephone. The appointees were then chosen by unanimous decision of the interview subcommittee, comprised of CWH and Advocacy leadership, and announced by a second national mailing (Appendix 15). The Pilot Project was initiated at the Spring 1995 Group meeting. An orientation manual was developed, which contained 1) The History and Evolution of the Southwest Oncology Group (Appendix 1), 2) the Southwest Oncology Group Organizational Structure (Appendix 2), 3) Roster of the Committee on Women's Health Advisory Board (Appendix 8), 4) Description of the Types of Studies conducted by Disease Committees and the CWH (Appendix 10), 5) History of the Southwest Oncology Group Lay Advisors and Advocates Pilot Project (this section), and 6) Glossary and Common Acronyms (16). A new Mentor Program developed under the leadership of the Chairs of the Southwest Oncology Group Data Managers and Nursing Committees, both members of the CWH Advisory Board. This mentor program was inaugurated at the Spring 1995 meeting for the new Pilot Project appointees. This program paired a "seasoned" CWH member with each new advocate at the various meetings each day, and held an informal "debriefing" session at the close of the Group meeting with the advocates, the CWH Chair and the Mentor Chair.

The newly appointed participants in the Pilot Project, as well as the continuing permanent members of the Steering Committee, attend each Group meeting and are reimbursed for their travel and accommodations by the Southwest Oncology Group Operations Office. This proposal, if funded, will supplement this aspect of the project. They meet with the full Committee and the closed session working group of their assigned Committee. They also attend open and closed meetings of the CWH and its Lay Advocates/Advisors Steering Subcommittee (on which they are members), and they join all conference calls pertaining to these committees between Group meetings. They received all active protocols and concepts under development, and will be on all CWH and Disease Committee mailing lists. Members will serve as consultants to the Group and Committee Chairs on an ad hoc basis. One advocate was recently placed on the Group Data Monitoring Committee by the Group Chair. All advocates will serve as a channel to funnel suggestions of the survivors and advocacy communities to the cooperative groups.

Finally, at the Spring 1995 meeting, the Lay Advocates/Advisors Steering Committee proposed research questions of mutual interest that would go forward as a partnership among the Cooperative Group, the Advocacy Organization(s) and the primary granting agency, the NCI. These projects are outlined in greater detail below. External networks will be expanded and solidified in order to promote cooperative group activities among the lay survivors population, and vice versa. Participation of CWH members in the national meetings of the various lay advocacy and survivors organizations is also planned. The reciprocity of all levels of this collaboration is vital to the success of the Pilot Project, as is already in evidence by joint development new concepts and protocols and the early feedback from the lay leadership and new appointees.

The Evolving "Partnership in Research Agenda" of the CWH Members and the Lay Advocates and Advisors.

- A. A number of clinical trials and projects underway in Breast Cancer by the CWH, Breast and Cancer Control Research Committees already have received valuable input from the Advocates. Some examples include of these prospective studies currently either under development or activation include:
 - 1) multi-variable assessment of the breast surgery choice from patient's and surgeon's view;
 - 2) two clinical trials assessing frequency of tamoxifen-induced endometrial damage and its chemoprevention;
 - 3) frequency of subclinical congestive heart failure in women five and ten years after standard anthracycline-based chemotherapy;
 - 4) prospective placebo-controlled trial of menopausal symptom reduction; and,
 - 5) prospective study of post-chemotherapy DNA damage as a potential precursor to myelodysplasia and leukemia.
- B. In addition, lay advocates and advisors will participate jointly with CWH members in the development of a prospective limited institution pilot study of reasons and barriers for non-accrual to randomized cooperative group trials from a patient and physician perspective. These survivors with breast cancer will otherwise be eligible for a Group trial. The denominator (of all patients at that institution, who is eligible versus not) will also be known in order to access all potentially eligible patients.
- C. A project to develop targeted accrual strategies based on Group data analyses regarding under-represented subsets of breast cancer survivors will be initiated in partnership with CWH lay advocates and advisors.
- D. An exciting development is recent activation of two very popular concepts in which the lay advocacy organizations will directly collaborate in the conduct of the research: 1) pilot phase and follow-on randomized prospective study of a directed telephone intervention at time of first recurrence (Y-Me

survivors to be trained to deliver the intervention), and 2) development and pilot study of utility of study-specific clinical trials Fact Sheets (in partnership with NABCO). This will create a "clearinghouse" of study-specific Clinical Trial Fact Sheets which will be available for both consumers and for gatekeeper physicians, as both experience barriers with respect to lack of understanding about clinical trials. The format of these simple, succinct sheets will provide information at a stage before the user might be referred to NCI's PDQ system, or could stand alone for patients at lower income levels. The program then will be piloted among the advocacy organizations and selected gatekeeper physicians affiliated with target Group institutions.

- E. The CWH Chair and Advisory Board and Advocates will serve as consultants and advisors to the University of Arkansas pilot feasibility study training breast cancer survivors previously on a clinical trial to be "witness counselors" to women first considering a clinical trial. The pilot study is being designed in collaboration with the CWH, and will chose counselors for training of low, middle and upper incomes and of African-American and Caucasian race. The CWH will perform a limited institution prospective trial of the successful pilot model to determine if accrual will be enhanced.
- F. The CWH Advisory Board with the lay advocates and survivors will design prospective consent document research to develop better "non-barrier-producing" models while still preserving intent to inform. Several concepts under discussion include: 1) a determination of frequency of non-accrual solely due to the consent, 2) the possibility of different model consents for the various types of information seekers, 3) the potential need for differences in model language between the sexes, and 4) limited institution pilot study of physician and patient responses to current breast cancer intergroup trials, including those with deliberately overlapping eligibility.
- G. The CWH members and advocates will study the feasibility and the objectives of an 800 number at the Southwest Oncology Group for use by the national organizations, consumers and gatekeepers which will complement rather than duplicate information available on 1-800-4-CANCER. This will be implemented under separate funding.
- F. An educational program in "clinical trials" will be jointly designed and conducted by CWH members and advocates for Hot-Line volunteers in partnership with Y-Me National Breast Cancer Organization. The aim is to develop a model that can be utilized by other national and local hot lines and volunteer organizations.

SUMMARY JUSTIFICATION OF SUPPLEMENTAL FUNDING REQUESTS

This proposal clearly fulfills the intents of the RFA (Appendix 17) to a) supplement a research program consistent with the objectives of an eligible, federally-funded parent grant and b) directly addresses the priorities of the NAPBC. In this case, the Group's parent grant expires in December 1997, so that there is ample time remaining for the conduct of this pilot proposal. And, two of the Priority Areas are part and parcel of this CWH research agenda, Consumer Involvement and Clinical Trials Accessibility/Barriers. As an original Action Plan Co-Chair for Clinical Research and a current member of the Clinical Trials Working Group, the CWH Chair and her advisors (several of whom also are involved in Action Plan leadership - see Cover Letter for disclosures) were most careful to keep this proposal true to the heart of the NAPBC. Conversely, it was gratifying to see that so many of the early concepts of the CWH are in fact consistent with the Action Plan's target areas.

It is important to emphasize that this proposal does not duplicate any other Group or CWH funding sources. Therefore, as detailed in the Budget section, the current proposal requests that the Pilot Project be fully funded for all travel costs incurred by the three permanent Steering Committee members (Ms. Langer, Ms. Green, Ms. Stovall) and the four new Pilot Project Appointees (Ms. Beard, Ms. Sondak, Ms. McCarthy and Ms. Michelson) for the duration of the parent grant. In addition, we request reimbursement for 6 CWH/Advocates conference calls per year remaining in the parent grant. The CWH Chair, Dr. Kathy Albain, expends intensive effort on this project, but will not request funding in this proposal.

In summary, this proposal represents the "coming of age" of the CWH from its official start 2.5 years ago. Indeed, it currently represents a functioning and novel model of successful three-way partnership activities among academic- and community-based cooperative group breast cancer trialists, the advocacy community and various federal agencies (NCI, ORWH, DOD). It is fully anticipated that at the end of the proposal year, many concepts will be fully competitive independently in the next round of NAPBC funding.

Southwest Oncology Group Advocates and Survivors Partnership Pilot Project

APPENDICES

Due to the nature of this supplemental application, the following Appendices are supplied in lieu of standard references. A full listing of references pursuant to the formation and design of the research program of the Committee on Women's Health are provided in the parent competitive renewal grant application. (Funded CY 1993-1997)

1. The History and Evolution of the Southwest Oncology Group
2. Southwest Oncology Group Organizational Structure
3. Notice of Award for Five-Year Competitive Renewal of the Southwest Oncology Group, 1993-1997
4. Initial peer review comments for parent Southwest Oncology Group Competitive Five-Year Renewal 1993-1997
5. Southwest Oncology Group Policies Regarding Human Subjects
6. Selected National Clinical Research Studies and Major Grants of the Chair of the Southwest Oncology Group Committee on Women's Health
7. Abstracted peer review approval of new Southwest Oncology Group Initiative on Women's Health from parent Southwest Oncology Group Competitive Five-Year Renewal and Current Year Three Award
8. Organizational Structure of the Advisory Panel and Board of the Southwest Oncology Group Committee on Women's Health
9. Southwest Oncology Group Committee on Women's Health Lay Advocates/Advisors Implementation Committee Participant List
10. Lay Advisors/Advocates Pilot Project Orientation Manual "Types of Studies" (Committee on Women's Health and Breast Committee)
11. Southwest Oncology Group Committee on Women's Health Educational Symposia and Presentations (April 1992-April 1995)
12. Committee on Women's Health Focus Areas and Research Objectives
13. Publications, Abstracts and Selected Funded or Approved Active or Pending Projects of the Southwest Oncology Group Committee on Women's Health
14. Letter of Request for Applications to the Southwest Oncology Group Lay Advocates/Advisors Pilot Project
15. Announcement Letter of Appointees to the Southwest Oncology Group Lay Advocates/Advisors Pilot Project
16. Lay Advisors/Advocates Pilot Project Orientation Manual "Glossary and Acronyms"
17. "General Provisions for the National Action Plan on Breast Cancer Omnibus Public Health Service Administrative Supplements"

The History & Evolution of the Southwest Oncology Group

The following history of the Southwest Oncology Group was prepared to document significant events and achievements of the Group over the past thirty-eight years, as well as to chart its evolution into the multidisciplinary adult cancer cooperative organization represented today.

The 1950's

In 1955, the National Cancer Institute formed a Clinical Studies Panel. During one of its early meetings, it was suggested that the study of leukemia would advance more expeditiously if investigators joined to collaborate on clinical trials through a "cooperative group" mechanism. Precedence for this proposed action had already been established by the collaboration of Veterans Administration hospitals investigating tuberculosis. Two of the initial cooperative groups formed in 1955 were the Acute Leukemia Group A and the Acute Leukemia Group B. These groups later became Cancer and Leukemia Group B (CALGB), with the addition of solid tumor investigations. Also initiated in 1955 was the Eastern Solid Tumor Group, which consisted of a five member east coast consortium to investigate the relative activities of the available nitrogen mustards. This group later evolved into the present-day Eastern Cooperative Oncology Group (ECOG).

The Southwest Cancer Chemotherapy Study Group (SWCCSG) began one year later in 1956 as a pediatric oncology group under the direction of Grant Taylor, M.D., a pediatric oncologist at M.D. Anderson Hospital and Cancer Center in Houston, Texas. Soon after its inception, this group grew to include clinical activities with medical oncology, and, in 1958 extended its membership to include investigators evaluating adult malignancies. This action was at the direction of the National Cancer Institute (NCI), which had multiple chemotherapy agents available requiring clinical evaluation. The Group then consisted of the following member institutions:

- University of Arkansas
- Baylor University
- University of Texas Medical Branch at Galveston
- M.D. Anderson Hospital and Cancer Center, Houston
- Southwestern at Dallas
- Tulane University

Seven Veterans Administration institutions were also members in the following cities: Dallas, Houston, Little Rock, New Orleans (two institutions), Oklahoma City and Washington, D.C. The pediatric and adult divisions then functioned as two separate entities with separate administrative bodies.

The 1960's

During the first half of the sixties, the adult division of the Southwest Cancer Chemotherapy Study Group was slowly beginning to increase its activities in cooperative clinical cancer trials. The early trials focused on liquid cancers (leukemia and myeloma). The adult division then established a Solid Tumor Committee which began developing trials for all solid tumor malignancies. Study development at that time was based on the availability of new agents rather than the present scientific prioritization of group committees and advisory groups.

Also in 1969, a formal document, the Constitution and Bylaws, was adopted by the Group which provided for a single Executive Committee as the governing body of the Group. The Group Chairman was then responsible directly to the Executive Committee. During this time, the Groups members grew to include membership from former participants in the Midwest Cancer Chemotherapy Study Group.

The 1970's

The 1970's brought many changes to the organization of the Group. In 1971, the original Constitution and Bylaws was replaced by a Constitution which provided for two divisions of the Group, Adult and Pediatric, each with its own executive committee. In the spring of 1973, the large Solid Tumor Committee was disbanded and six separate disease study committees were instituted in the Adult Division of the Group.

The Southwest Cancer Chemotherapy Study Group was formally renamed in June of 1973, as "**The Southwest Oncology Group**". At this time, the constitution was again revised to establish stringent performance criteria for the evaluation of its institutions and members. At the end of 1973, two new Standing Committees were established for Radiotherapy and Immunology-Immunotherapy. The composition of the Group continued to change, with the addition of Standing Committees for Surgery and Pathology.

In 1976 the NCI activated the Cancer Control Program (later renamed the **Cooperative Group Outreach Program, or CGOP**). This program was developed by the Division of Cancer Prevention and Control (DCPC) at the National Cancer Institute. It was designed to involve physicians outside the university medical centers, and included groups or individual physicians who were interested in participating in studies for cancer management and control. This new Cancer Control CGOP Program was developed around the member institutions so that there was a geographic relationship and close communication between the Principal Investigator at the member institution and his or her CGOP affiliates. By the end of 1976 there were 29 participating CGOP affiliates in this program. The objectives of this program were: 1) to make state-of-the-art cancer management available to cancer patients in the community; 2) to involve a wider segment of the community in clinical research than is possible through the existing cooperative group programs; 3) to enhance recruitment of patients from community hospitals into appropriate protocols; and 4) to evaluate the transfer of new patient care technology to the community. These four objectives still serve as the function of the CGOP outreach program today under the auspices of the cooperative groups.

In 1977, the Southwest Oncology Group adopted the pilot study concept, and new guidelines were developed to monitor these studies. Pathology review was established in a limited number of disease committees including: breast, genitourinary, gynecological, leukemia, myeloma, lung, lymphoma, sarcoma and pediatric solid tumors.

In 1978, the New Agents and Pharmacology Committee was reorganized. The Adult Division of the Southwest Oncology Group began to meet twice a year; a year later, the Pediatric Division also began semi-annual meetings. The Constitution and Bylaws were again amended to reflect an attendance requirement of one meeting every two years for all Group members.

The 1980's

In 1980, the Southwest Oncology Group still consisted of two separate Adult and Pediatric Divisions. Later that year, the pediatric division sought independent status, and formed the Pediatric Oncology Group (POG), housed in St. Louis.

In January of 1981, Dr. Barth Hoogstraten announced his intention to step down as Chairman of the Group. **Dr. Charles A. Coltman, Jr.** was elected in March of 1981, and the Operations Office was relocated to its current home city of San Antonio, Texas. Shortly after his election, a transition team was appointed to advise Dr. Coltman on organization problems within the Group and to identify potential solutions. Their deliberations resulted in the replacement of the Group Executive Committee by a Board of Governors which would consist of funded Principal Investigators and representatives of Discipline Committees. The focus for scientific efforts and administrative responsibility then shifted to the Disease Committees of the Group. On May 28, 1981, a meeting of the Southwest Oncology Group Principal Investigators was held in Dallas, Texas, which resulted in the ratification of the transition team's recommendations.

Several new committees were subsequently formed and included Medical Oncology, Quality Assurance, Statistical Center Users, Human Tumor Cloning Subcommittee of New Agents and Pharmacology, Clinical Pharmacology Subcommittee of New Agents and Pharmacology, Pharmacy

Subcommittee of New Agents and Pharmacology and the Nurses Committee. Later in this period, the Data Managers Committee was formed whose purpose is to assure excellent quality of data. A Bone Marrow Transplantation Committee was also formed in order to effectively evaluate transplantation trials in the Group.

During 1983, the **Community Clinical Oncology Program (CCOP)** began with similar objectives as the CGOP program. CCOP affiliates submit applications directly to NCI through DCPC, naming the Group as their research base. Primary focus for these new members involved the investigation of cancer control research questions. The Southwest Oncology Group initially served as the research base for 18 CCOP institutions. The Board of Governors amended the Constitution and Bylaws to integrate these participants into a full relationship with the Group, both scientifically and administratively. In the first three months of participation, the CCOP members entered a total of 206 patients to Group cancer clinical trials.

A Quality Control Program was developed in conjunction with the new CCOP program. This program was centered in the Operations Office. The stringent review of CCOP data by the Quality Control system resulted in unparalleled quality of data from the institutions. In the fall of 1983, the first Data Manager/Nurse Oncologist Training Course was held in Chicago to educate the new participants in administrative and scientific policies and procedures of the Group.

The major change to occur in the early 1980's was the relocation of the Statistical Center from Houston, Texas, to the Fred Hutchinson Cancer Research Center in Seattle, Washington under the direction of newly appointed Group Statistician, **John J. Crowley, Ph.D.** The present Statistical Center began functioning on October 1, 1984. Over the ensuing years, the Statistical Center has developed into the finest statistical resource in existence, as evidenced by the quality of their work, the level of scientific and intellectual interchange and their total commitment to excellence.

Scientific activities continued to increase and necessitated the establishment of a Protocol Allocation policy to limit protocol activations to a number which was manageable for statistical and financial resources of the group. Presently, the Group has from 100 - 125 active trials at any given time.

In 1985, the Group began preparations for the Competitive Renewal Application, due two years later in February of 1987. The exhaustive efforts by Group members resulted in an unprecedented award of five years of funding, with the approval of several new scientific endeavors. These new funded programs included the Leukemia Biology Program, the Central Lymphoma Immunophenotyping Laboratory and the Flow Cytometry Program.

During the 1980's, the CCOP program grew steadily. As a result of the increased efforts in cancer control activities the Group developed a Cancer Control Research Committee, headed by Dr. Frank Meyskens. Also formed during this time was the Developmental Biologics Committee, and Developmental Therapeutics Committee (previously named New Agent & Pharmacology).

The year 1987 initiated the development of the **Group Newsletter**. The quarterly newsletter serves to inform Group and non-Group members of Southwest Oncology Group activities.

The following year, 1988, led to two major membership changes which significantly affected the Southwest Oncology Group. The first initiative was the **Urologic Cancer Outreach Program (UCOP)**, which was designed to recruit new urologists into the Group, fund data management for current urologists and increase total accrual to genitourinary trials. The second initiative, the **High Priority Program**, was designed by the National Cancer Institute and serves to increase accrual to NCI-designated high priority clinical trials. This program recruited new unfunded members to join the Southwest Oncology Group and accrue patients to selected trials designated as "high priority" by the NCI.

In 1989, Dr. Coltman was reelected for four more years as Chairman of the Group.

The 1990's

A major emphasis of the Southwest Oncology Group in the 1990's is the recruitment of women and minority patients to all cancer treatment and control research trials. In June 1990, the Southwest

Oncology Group expanded its CCOP membership to include seven new institutions, which have access to a minority population of 50% or greater of new cancer patients. The **Minority-based CCOPs (MBCOPs)** will provide valuable research data and findings to address and resolve specific concerns regarding the prevention and treatment of cancer in these populations. In a further effort to increase minority representation in cancer research, the Group responded to the Cancer Therapy Evaluation Program's initiative to increase minority accrual to clinical trials (**CTEP Minority Initiative Program**). Of the institutions originally participating in this program, two were universities with significant black populations.

The Southwest Oncology Group also recognized a critical need to address the special clinical research concerns of minority groups, as well as to generate research of specific importance to minorities. A new subcommittee of the Cancer Control Research Committee, the **Minority Research Subcommittee**, was formed to address these specific issues within the Group. An initial working group meeting of this subcommittee was held.

Another new initiative in 1990 was the development and utilization of a **Race/Ethnicity Questionnaire**, originally developed by the Southwest Oncology Group for use by institutions participating in the CTEP Minority Initiative program. This form was later distributed to all Group institutions for use during all patient registrations and enables the Group to evaluate the participation of women and minorities in Group clinical trials.

A new Standing Committee, formally named the **Stomatology Committee**, was added to the Group in 1990. This committee will address issues in oral complications of chemotherapy through the provision of dental consultation to ongoing Group protocols, as well as the development of protocols related to the study of these issues in clinical trials research.

At the Spring 1991 Group Meeting the Group Chairman disclosed the accrual crisis facing the Group. He illustrated the severe lack of fiscal resources available to support the Statistical Center given our rapidly increasing accrual, projected to reach over 11,000 patient registrations by the end of 1991. An announcement was made that there would be an immediate cap on accrual, holding the patient registrations at 6,451, which was the level of annualized accrual to Phase II and Phase III clinical trials reached on March 2, 1991. This action would resolve the immediate crisis, with a long term solution being the creation of a non-profit foundation, which would enable the Group to tap private philanthropists for financial support. The Board of Governors accepted and unanimously endorsed the motion to form a Southwest Oncology Group Foundation.

Dr. Mace L. Rothenberg was introduced at this same meeting as the Group's new Executive Officer, devoting 50% effort to the Group.

The Fall 1991 Group Meeting saw the creation of what is now known as the **Committee on Women's Health**, which was formed to address the specific concerns regarding the participation of women in Group clinical trials and activities. The Committee was formally designated as a Group Standing Committee in February 1992 under the leadership of Dr. Kathy S. Albain.

The Group submitted its Competitive Renewal Application to NCI on February 1, 1992 to request funding for the next five years. At the request of the NCI, this application included budget requests and progress reports for four membership programs previously supported through separate grant awards: the CGOP, CTEP Minority Initiative, High Priority, and UCOP programs as well as several newly-formed Tumor Biology Subcommittees.

In 1992, in response to increased clinical trials within the Group involving agents for which the NCI does not hold Investigational New Drug (IND) documentation, a new position was created within the Operations Office. The IND Coordinator is responsible for the collection of regulatory documentation, the creation and maintenance of an IND database, and the submission of IND applications to the Food and Drug Administration (FDA) for Group-held INDs.

The Operations Office moved to its new building located at the Texas Research Park on November 16, 1992. A Grand Opening ceremony for the 11,000 square foot facility and the neighboring Institute for Drug Development was held on December 4, 1992.

In October 1993 the Southwest Oncology Group launched the first large-scale prevention trial for prostate cancer. Under the Prostate Cancer Prevention Trial (PCPT), a double-blinded study designed to test whether taking the drug finasteride will prevent prostate cancer, 18,000 men will be enrolled at over 220 sites located throughout the United States. They will be divided randomly into two groups; half will take one finasteride tablet per day for seven years and half will take a placebo. All men in the trial will have a prostate biopsy at the end of seven years to determine whether they have developed prostate cancer. Also participating in the inter-group study are the Cancer and Leukemia Group B (CALGB), the Eastern Cooperative Oncology Group (ECOG) and NCI-Designated Cancer Centers. After one year, the PCPT is well on its way to reaching its accrual goal of 18,000 randomized participants with 15,713 men enrolled in the study and 10,485 randomized (*as of September 28, 1994*).

The Southwest Oncology Group will continue to strive for excellence in cancer research efforts. This goal may only be accomplished with the dedication and commitment of each Southwest Oncology Group member, whether it is physician, nurse, data manager or administrative personnel. We join the National Cancer Institute, in the cooperative effort to achieve a significant reduction in the deaths from cancer by the year 2000.

Adapted from the Official Southwest Oncology Group History 4/3/95

SOUTHWEST ONCOLOGY GROUP ORGANIZATIONAL STRUCTURE

The Southwest Oncology Group has evolved since its inception in 1956 into an adult multi-disease, multi-modality clinical research organization. This organization has grown to include 33 Full Member Institutions, 22 Community Clinical Oncology Program (CCOP) institutions, including 5 Minority-Based CCOPs, 31 Urologic Cancer Outreach Program (UCOP) members, 22 High Priority program members and a network of approximately 1,422 Cooperative Group Outreach Program (CGOP) investigators at 308 affiliate hospitals. In addition, 17 Group institutions also participate in the CTEP Minority Initiative program, which serves to enhance minority accrual in cancer clinical trials. More than 4,000 investigators, representing all research modalities, are members of the Group and actively participate in the registration of patients to cancer treatment and cancer control and prevention protocols. In addition, the Southwest Oncology Group coordinates a large intergroup chemoprevention trial, the Prostate Cancer Prevention Trial (PCPT), which is a randomized, double-blind, placebo-controlled trial involving the accrual of approximately 18,000 healthy men, ages 55 and older, to study the efficacy of finasteride in the prevention of prostate cancer. More than 235 PCPT institutional sites affiliated with the Southwest Oncology Group and two other cooperative groups participate in this trial. Close interaction between all components of the Group assures optimal performance by Group members and rapid completion of scientifically sound and innovative cancer clinical trials.

An Organizational Chart of the Southwest Oncology Group is provided on the following page. The Board of Governors is the governing body of the Group. In addition to the Group Chairman, Charles A. Coltman, Jr., M.D., the Board consists of the Group Executive Officers, Associate Chairman, Group Biostatistician, Principal Investigators of member institutions (Member and CCOP) funded by NCI, and representatives, including Chairs, of all Discipline Committees.

The Group Chairman is elected by the Board of Governors and is the presiding officer of the Group. Charles A. Coltman, Jr., M.D. has held the position of Group Chairman since his election in 1981. Dr. Coltman is responsible for the guidance and supervision of all Group activities, as well as the administrative activities of the Operations Office.

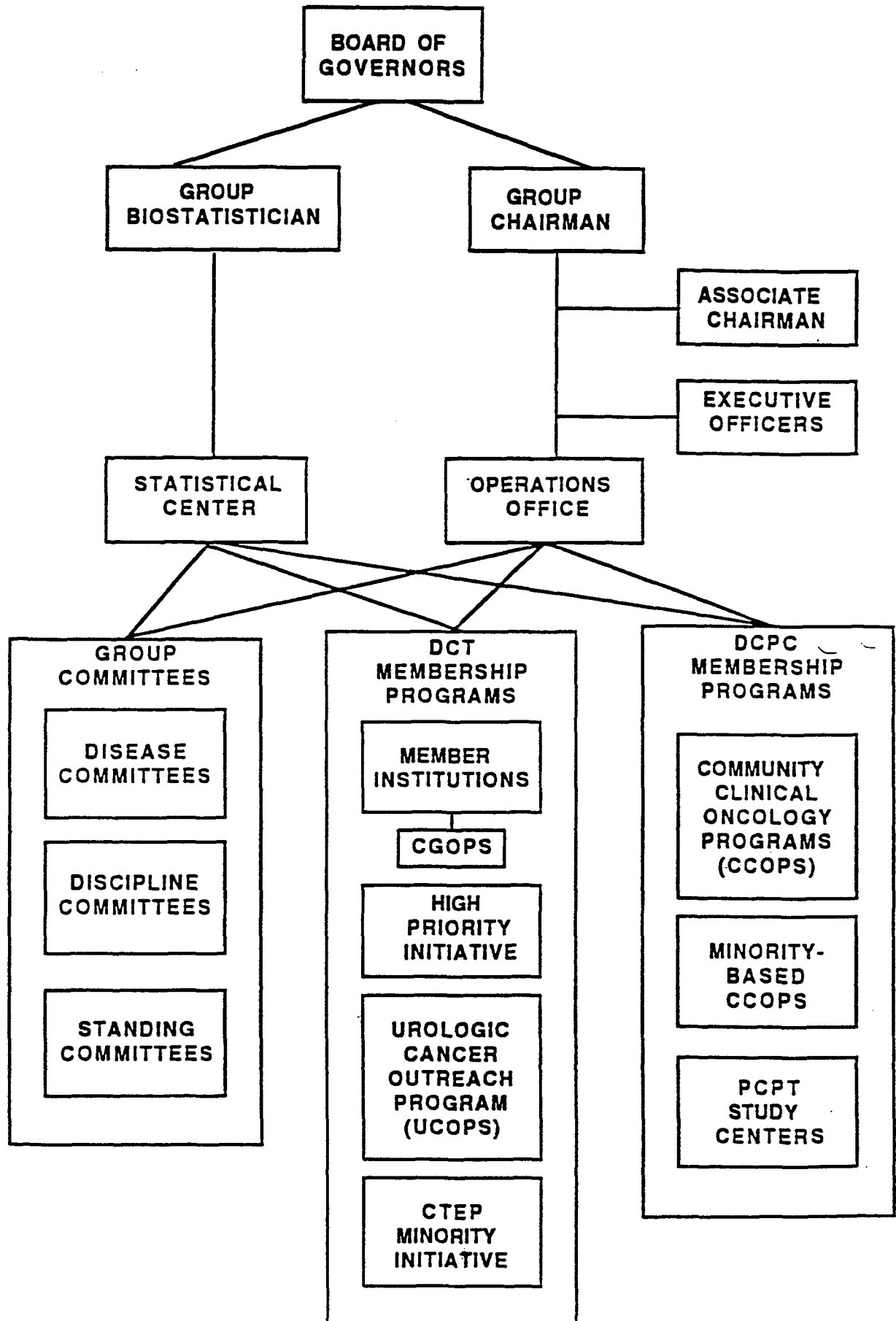
The Associate Chairman is a Senior Investigator in the Group, and must be housed in an institution other than that of the Group Chairman. Laurence H. Baker, D.O. (University of Michigan) has served as the Associate Chairman since 1981. Responsibilities of the Associate Chairman include providing advice and consultation to the Group Chairman, as well as the assumption of control of the Group during the absence of the Group Chairman, pending election of a new Group Chairman.

The Executive Officers of the Group are appointed by the Group Chairman, and are responsible for providing scientific and administrative consultation and assistance to the Chairman, Disease/Discipline Chairs and Study Coordinators. Mace L. Rothenberg, M.D. serves as the Executive Officer. Geoffrey R. Weiss, M.D. and Noburo Oishi, M.D. serve as the Associate Executive Officers. Executive Officers assist the staff of the Operations Office in protocol development, and maintain close communication with the Clinical Therapy Evaluation Program at the NCI regarding research directions and goals of the Group.

The Group Biostatistician directs the Statistical Center, and maintains close communications with Group Chairman and Board of Governors. John J. Crowley, Ph.D. has served as the Group Biostatistician since 1984, and is responsible for statistical design, quality control and analysis of all Group science.

The Operations Office of the Southwest Oncology Group is directed by the Group Chairman, Charles A. Coltman, Jr., M.D., and is the liaison between the National Cancer Institute and the Group membership. The Operations Office, located in San Antonio, Texas since 1981, ensures the accurate and timely transfer of information and guidelines pertinent to successful conduct of cooperative clinical oncology trials. Major responsibilities include the day-to-day administration, management and communications of Group activities, maintenance of Group membership, publications and records, and coordination of all Group meetings. The Quality Assurance Program, ADR Program and the IND Program are coordinated from this office. In addition, the Operations Office is responsible for the development and administration of all Group cooperative agreements and financial affairs.

SOUTHWEST ONCOLOGY GROUP ORGANIZATION



The Statistical Center of the Southwest Oncology Group is directed by the Group Biostatistician, John J. Crowley, Ph.D., and is located at the Fred Hutchinson Cancer Research Center in Seattle, Washington. Statisticians at the Statistical Center are each assigned to at least one Disease and/or Discipline Committee. All protocols of the Southwest Oncology Group are reviewed by these statisticians for feasibility, experimental design, and the appropriate number of patients needed to answer the research objectives. Statisticians also perform analyses of study results for the semi-annual Report of Studies, as well as for Data Monitoring Committees and publications. Data Coordinators register and randomize patients on protocols, review patient data forms for consistency, completeness and quality, as well as assisting in study monitoring. Computer programmers maintain the Center's hardware and software, and develop new software as needed to accomplish the Center's objectives. Administrative and clerical tasks are carried out by the Project Coordinator and by secretaries and data entry operators.

The Disease Committees consist of 12 disease/disease site committees. The Disease Committees are responsible for defining scientific programs and priorities, protocol development and review, and reports and publications generated by Committee members.

The 12 Disease Committees and their respective Chairmen are as follows:

<u>Committee</u>	<u>Chair</u>	<u>Medical Specialty</u>
Brain Tumor Committee	S. Clifford Schold, M.D., Chair Robert Morantz, M.D., Vice-Chair William T. Sause, M.D., Vice-Chair	Medical Oncology Surgical Oncology Radiation Therapy
Breast Cancer Committee	Silvana Martino, D.O., Chair Allen S. Lichter, M.D., Asso. Chair	Medical Oncology Radiation Oncology
Gastrointestinal Cancer Committee	John S. Macdonald, M.D., Chair	Medical Oncology
Genitourinary Cancer Committee	E. David Crawford, M.D., Chair Mario Eisenberger, M.D., Vice-Chair	Surgical Oncology Medical Oncology
Gynecological Cancer Committee	David S. Alberts, M.D., Chair Edward V. Hannigan, M.D., Co-Chair Mace L. Rothenberg, M.D., Co-Chair	Medical Oncology Surgical Oncology Medical Oncology
Head and Neck Cancer Committee	David E. Schuller, M.D., Chair John F. Ensley, M.D., Co-Chair	Surgical Oncology Medical Oncology
Leukemia Committee	Frederick Appelbaum, M.D., Chair David R. Head, M.D., Vice-Chair	Medical Oncology Pathology
Lung Cancer Committee	Robert B. Livingston, M.D., Chair Thomas W. Rice, M.D., Vice-Chair	Medical Oncology Surgical Oncology
Lymphoma Committee	Richard I. Fisher, M.D., Chair Thomas P. Miller, M.D., Co-Chair	Medical Oncology Medical Oncology
Melanoma Committee	Vernon K. Sondak, M.D., Chair Laurence E. Flaherty, M.D., Vice-Chair	Surgical Oncology Medical Oncology
Myeloma Committee	Sydney E. Salmon, M.D., Chair Barthel Barlogie, M.D., Vice-Chair	Medical Oncology Medical Oncology

Sarcoma Committee

Stanley P. Balcerzak, M.D., Chair
 Karen Antman, M.D., Co-Chair
 James R. Ryan, M.D., Vice-Chair

Medical Oncology
 Medical Oncology
 Surgical Oncology

The seven Discipline Committees serve to ensure quality control of data within each respective discipline, to develop and conduct educational programs for the Group, and to provide scientific input to the Disease Committees in the development of Group research protocols, with respect to consistency of treatment description and current state-of-the-art treatment regimens.

The seven Discipline Committees and their Chairs are listed below:

Cytogenetics Committee	R. Ellen Magenis, M.D., Chair
Data Managers Committee	Debra W. Christie, R.R.A., Chair Beth MacCracken, Co-Chair
Nurse Oncologist Committee	Jeanne Parzuchowski, R.N., Chair
Pathology Committee	Cecilia Fenoglio-Preiser, M.D., Chair
Radiotherapy Committee	Jeffrey D. Forman, M.D., Chair
Stomatology Committee	Francis G. Leveque, D.D.S., Chair Mark M. Schubert, D.D.S., Vice-Chair
Surgery Committee	E. Carmack Holmes, M.D., Chair

The eight Standing Committees of the Southwest Oncology Group provide administrative support of specific scientific activities within the Group on a continuing basis, and closely interact with both the Disease and Discipline Committees. Included in the eight Standing Committees is the Committee on Women's Health, chaired by Kathy S. Albain, M.D. The responsibilities of this committee include the evaluation and enhancement of the accrual of women to Group trials, the determination of special concerns regarding women's health issues which can be addressed in the cooperative group setting, and acting as a direct liaison with women's health groups, such as the Office of Research on Women's Health (ORWH).

The eight Standing Committees of the Southwest Oncology Group and their Chairmen include the following:

Board of Governors	Charles A. Coltman, Jr., M.D., Chair
Bone Marrow Transplantation Committee	Karl G. Blume, M.D., Chair Elizabeth J. Shpall, M.D., Co-Chair
Cancer Control Research Committee	Frank L. Meyskens, M.D., Chair Gary E. Goodman, M.D., Vice-Chair
Committee on Women's Health	Kathy S. Albain, M.D.
Cooperative Group Outreach Program (CGOP) Committee	James K. Weick, M.D.
Developmental Therapeutics Committee	Mace L. Rothenberg, M.D., Chair
Membership Committee	John H. Saiki, M.D., Chair

The Headquarters Offices (Operations Office and Statistical Center) are in constant contact through electronic mail, phone and FAX to ensure a high quality cooperative effort in all administrative and scientific activities of the Group. In addition, yearly Summit Meetings involving the Group Chairman, Group Biostatistician, Executive Officers, Deputy Directors, and key staff personnel from both Headquarters Offices offer rich opportunities to present and address areas of concern and/or new strategies regarding Group resources and research directions. The successful collaboration between these two offices has resulted in continued streamlining of office procedures and protocol development, and meticulous ongoing performance evaluations of the Group's Committees and membership-at-large.

SOUTHWEST ONCOLOGY GROUP POLICIES REGARDING HUMAN SUBJECTS

In 1994, 17,184 patients were involved in therapeutic, women's health and cancer control research, using protocols developed by the membership of the Southwest Oncology Group. All patients on therapeutic research protocols have histologically proven cancer or premalignant diagnoses. Specific inclusion/exclusion criteria are developed for each research protocol, and specific treatment procedures/correlative study analyses are also detailed in the protocols. It is a standing policy of the Southwest Oncology Group to include eligible patients of both sexes and all races and ethnicities in all Group clinical trials, except as restricted by specific disease site (e.g., prostate, gynecological). There are no specific exclusions related to sex, race or ethnic background. The conduct of the trial at multiple institutions through a large cooperative group such as Southwest Oncology Group further ensures broad-based demographic and geographic inclusion in these studies. An ongoing monitor of sex, race, age and socioeconomic status of study participants is being developed by the Committee on Women's Health.

The recruitment of subjects and the consent procedures are standardized throughout the Southwest Oncology Group. Physician members at Member Institutions, Community Clinical Oncology Programs (CCOPs) and Cooperative Group Outreach Programs (CGOPs), in the routine care of patients with cancer, identify individual patients who meet the eligibility criteria for the therapeutic, women's health and cancer control research protocols. The Operations Office, which functions as the administrative arm of the Southwest Oncology Group, develops a model informed consent form which is included with each protocol. This consent form is reviewed and considered along with the protocol during its approval by the National Cancer Institute. The potential medical, psychological and/or social risks vary according to the specific protocol. The risks to subjects are reasonable when the potential benefits to the subjects are examined. The potential benefits of the therapeutic agent and the follow-up evaluation are considered carefully by the disease committees and study coordinators in the development of the protocols. In every instance, the anticipated benefit outweighs the risk of harm to the patients as a result of participation in the protocol.

The model informed consent form and protocols are submitted by each individual institution involved in the therapeutic and cancer control research studies to their Institutional Review Board and independently reviewed by this Board. The elements of the consent form can be individually modified by that Institutional Review Board to satisfy the institutional needs.

**SELECTED NATIONAL CLINICAL RESEARCH STUDIES AND MAJOR GRANTS EITHER WRITTEN,
DESIGNED AND CONDUCTED, OR, PRINCIPALLY ORGANIZED BY
SOUTHWEST ONCOLOGY GROUP COMMITTEE ON WOMEN'S CHAIR KATHY S. ALBAIN, M.D.**

- Principal Study Coordinator: Southwest Oncology Group Protocol #8605: Cyclophosphamide, ara-C infusion and vincristine for relapsed or refractory extensive small cell lung cancer. A phase II study.
- Principal Study Coordinator: Southwest Oncology Group Protocol #8805: Neoadjuvant cisplatin and VP-16 plus concurrent chest and brain irradiation for patients with Stages IIIa and IIIb non-small cell carcinoma. A phase II pilot study .
- Principal Study Coordinator: Southwest Oncology Group Protocol #8904: Phase II trial of piroxantrone in ovarian carcinoma.
- Principal Study Coordinator: Southwest Oncology Group Protocol #8814 (Intergroup): Phase III comparison of adjuvant chemoendocrine therapy with CAF and concurrent or delayed tamoxifen to tamoxifen alone in postmenopausal patients with involved axillary lymph nodes and positive receptors.
- Principal Study Coordinator: Southwest Oncology Group Protocol #8854 (Intergroup): Prognostic value of cytometry measurements of breast cancer DNA from postmenopausal patients with involved nodes and receptor positive tumors (a companion protocol to SWOG-8814).
- Principal Study Coordinator: Southwest Oncology Group Protocol #9019: A Phase III, randomized comparison between chemotherapy plus radiotherapy, and the same chemotherapy plus radiotherapy together with surgery for selected stage IIIA (positive mediastinal nodes) and selected stage IIIB (no malignant effusion) non-small cell lung cancer.
- Principal Study Coordinator: Southwest Oncology Group Protocol #9143: A Phase II study of cisplatin preceded by a 12-hour continuous infusion of concurrent hydroxyurea and cytosine arabinoside (Ara-C) for patients with untreated, malignant mesothelioma.
- Principal Study Coordinator: Southwest Oncology Group Protocol #9148: A Phase II study of cisplatin preceded by a 12-hour continuous infusion of concurrent hydroxyurea and cytosine arabinoside (Ara-C) for patients with untreated, extensive stage small cell and non-small cell lung carcinoma.
- Principal Study Coordinator: Intergroup Protocol #0139 (SWOG-9336, RTOG 93-08): A phase III comparison between concurrent chemotherapy plus

radiotherapy, and concurrent chemotherapy plus radiotherapy followed by surgical resection for stage IIIA(N2) non-small cell lung cancer. **(Awarded National Cancer Institute High Priority Status)**

Co-Study Coordinator: Southwest Oncology Group Protocol #9342: A study of the late cardiac effects of two different adjuvant chemotherapy regimens in women with node negative breast cancer treated on SWOG-8897. **(Funding request pending)**

Co-Study Coordinator: Southwest Oncology Group Protocol #9445: Prognostic factor panel to predict preferred therapy for node positive postmenopausal breast cancer patients: a companion study to SWOG-8814. **(Awarded supplemental funding by NCI)**

Co-Study Coordinator: Southwest Oncology Group Protocol #9504: Phase II trial of concurrent cisplatin/VP-16 and radiotherapy followed by consolidation taxotere in stage IIIB non-small cell lung cancer.

Co-Study Coordinator: Southwest Oncology Group (Intergroup) Protocol #95XX: Cross-sectional study of endometrial abnormalities in women on the tamoxifen arms of SWOG-8814 and SWOG-8897 for durations of 1, 2, 3, 4 or 5 years. **(Awarded supplemental funding by NCI)**

Co-Study Coordinator: Southwest Oncology Group Protocol #95XX: Prospective phase III placebo-controlled trial of cyclical low-dose progestin for chemoprevention of endometrial abnormalities in postmenopausal women with node-negative receptor positive breast cancer who are beginning five years of adjuvant tamoxifen. **(Awarded supplemental funding by NCI)**

Co-Study Coordinator: Southwest Oncology Group Protocol #95XX: Placebo-controlled phase III study of low dose progestins (six potential dose levels) to ameliorate menopausal symptoms in breast cancer survivors. **(Awarded supplemental funding by NCI)**

Principal Investigator: "Implementation of the Southwest Oncology Group Committee on Women's Health Breast Cancer Research Agenda: A Special Sabbatical for the Chairperson." **(Granted maximum award through initial US Army Breast Cancer Research Program, January 1995 through December 1995).**

INITIATIVE ON WOMEN'S HEALTH AT THE OO

DESCRIPTION: SWOG is making efforts to include women in its study protocols. Overall SWOG 1990 and 1991 female accruals were 54 and 55 percent, respectively. Only their UCOP accruals were significantly less than these frequencies (eight and 37 percent). They have taken steps to address cancer problems unique to women. The latter is illustrated in the plenary session of the SWOG Oct. 1991 meeting, entitled "Women's Health Issues: Focus on Breast Cancer." They also have initiated a SWOG Women's Task Force which is to address participation of women in group clinical trials and activities.

In the current grant application SWOG is applying for separate funding for an "Initiative on Women's Health." They have mounted a program which focuses on evaluation and enhancement of the accrual of women to group trials, determination of special concerns regarding women's health which can be addressed in a cooperative group, and acting as a liaison with women's health groups. Specific aims of the initiative are: a). To develop strategies to assess the representation of women on group studies, including the elderly, minorities, and underserved and create a standard demographic, descriptive and follow-up data "repository" for use in all group studies.

b). To utilize the Statistical Center data base for multivariate analyses to explore interactions of age, race, and socioeconomic status with other variables in cancers unique to or more prevalent or serious in women, as well as to explore gender differences in relation to the important variables for those cancers which affect both men and women.

c). To facilitate transfer into clinical trials of laboratory advances in areas of genetics, tumor markers, tumor biology, and new treatments, with special attention to gender-related ancillary issues. This will be done in collaboration with disease-specific and Cancer Control Research Committees.

d). To collaborate with the Cancer Control Research Committee in the design and conduct of studies to address issues pertaining to women (in particular, those related to high-risk smoking behavior) and generate analyses including gender related questions.

e). To facilitate the investigation and implementation of novel group initiatives in areas pertaining to lay representation in the development of studies of women's issues in cancer research, patient-care based studies,

recruitment of the underserved, patient education, physician outreach, and technology transfer.

f). To continue preliminary activities to educate the group regarding the development and organization of the Women's Task Force and its associated research aims and efforts, and to implement feasibility studies to prioritize specific efforts of this new research mechanism. Specific strategies by which to accomplish the specific aims are being developed for implementation and include educational activities, collaborative efforts with Disease Committees, and development of research in targeted areas of study.

CRITIQUE: This is an admirable beginning to the study of health care of women as regards to cancer. The Committee is only formed in Oct, 1991, and has already outlined many areas of possible investigation. The question is whether they can investigate these many areas simultaneously, and if not, what would their priorities be? It is recommended that this Committee take the lead in obtaining prevalence rates of women affected by diseases being studied in SWOG protocols to facilitate protocol accrual rates of women to reflect actual prevalence rates. It is noted that the Committee's membership does not include gynecologists whose perspective should obviously be included. The Committee is encouraged to assume educational and leadership roles in efforts to develop research questions addressing mechanisms to improve the percentage of organ-sparing primary treatment options (it is noted that the lumpectomy vs. mastectomy rate of patients entering SWOG breast cancer protocols is low).

RECOMMENDATION: The Initiative on Women's Health component is recommended for the five years requested and at a level of excellent merit. Activities related to Cancer Control would fall under the purview of DCPC. Demonstration projects should undergo critical re-evaluation during this five-year interval.

BUDGET: Delete Melone (-\$6,800). Reduce Albain to five percent \$5,222, consultants to only one and domestic travel to two trips per year (\$2,000).

**ORGANIZATIONAL STRUCTURE OF THE
ADVISORY PANEL AND BOARD, SWOG COMMITTEE ON WOMEN'S HEALTH**

Kathy S. Albain, M.D., Chairperson

External (non-Southwest Oncology Group members) Advisory Panel:

Amy Langer, M.B.A.	Executive Director National Alliance of Breast Cancer Organizations (NABCO) Permanent Member, Lay Advisors/Advocates Steering Committee
Ellen Stovall	Executive Director National Coalition for Cancer Survivorship (NCCS) Permanent Member, Lay Advisors/Advocates Steering Committee
Sharon Green, M.H.S.	Executive Director Y-Me National Breast Cancer Organization (Y-Me) Permanent Member, Lay Advisors/Advocates Steering Committee
Tika Beard	Director of Genetic Education, Myriad Genetics Expertise in patient-physician relationship in context of genetic testing for inherited cancer risk Breast Cancer Advocate; Position A, three-year term
Eileen Sondak	Educator and expert in business communications Breast Cancer Survivor and participant in a clinical trial Position B, two-year term
Peggy McCarthy	Executive Director Alliance for Lung Cancer Advocacy, Support, and Education (ALCASE) Expert in development and marketing of user-friendly breast cancer educational materials (eg: "Breast Cancer? Let Me Check My Schedule") Breast and Lung Cancer Advocate; Position A, three-year term
Peggy Michelson	Founder of Wellness Community of Greater St. Louis Breast and Lung Cancer Advocate; Position B, two-year term
Iris J. Schneider Assistant Director for Program Operations and Planning, NCI	NIH (NCI) liaison Co-chair NIH Advisory Committee on Women's Health Issues
Leslie Ford, M.D.	Liaison, Division of Cancer Prevention and Control National Cancer Institute
Vivian Pinn, M.D.	Director, Office of Research on Women's Health National Institutes of Health
Otis Brawley, M.D.	Liaison, Division of Cancer Prevention and Control National Cancer Institute

Carrie Hunter, M.D. Liaison, Office of Research on Women's Health
National Institutes of Health

Jeffrey Abrams, M.D. Liaison, Division of Cancer Treatment
National Cancer Institute

Ruthann Giusti, MD Liaison, Division of Cancer Treatment
National Cancer Institute

Ross Prentice, Ph.D. Biostatistician
Fred Hutchinson and expert in women's health;
Cancer Research Center Chair, National Women's Health Initiative

Thomas Moon, Ph.D. Epidemiologist and Biostatistician
Professor of Epidemiology Expertise in behavior interventions and health
Director, Arizona Disease education in underserved populations
Prevention Center, U. Ariz.

Internal Advisory Board: (Members of the Southwest Oncology Group):

John Crowley, Ph.D. Statisticians for Lung, Breast, and Cancer Control Research Committees,
Stephanie Green, Ph.D. and/or actively involved in data base multivariate analyses
Polly Feigl, Ph.D.
Steve Dahlberg, M.S.
Carol Moinpour, Ph.D.
Dorothy Rector, M.S.
Michael Le Blanc, Ph.D.
(Committee Statisticians)

C. Kent Osborne, M.D. Southwest Oncology Group Committee Chairs for Breast, Gynecology,
David Alberts, M.D. Lung and Cancer Control Research
Robert Livingston, M.D.
Frank Meyskens, Jr., M.D.
Silvana Martino, D.O.

Debra Christie, MBA, RRA Brings unique focus and expertise to Advisory Board due to
University of Mississippi personal experience with breast cancer and participation in a SWOG
Cancer Research & Registry clinical trial.
Chair, SWOG Data Managers
Committee; Advocates Mentor
Program Chair

Mace Rothenberg, M.D. Operations Office Liaison to Committee on Women's Health
Executive Officer
Southwest Oncology Group
Co-Chair, Gynecologic Cancer Comm.

Dana Sparks, M.A.T. Head Protocol Coordinator, Breast and Women's Health Committees
Southwest Oncology Group Lay Advisors/Advocates Steering Committee liaison for Operations
Operations Office Office; liaison for educational and clearinghouse research development with
lay advisors' organizations

Karen Antman, M.D. National expert in breast cancer clinical research and in public policy
and advocacy
Professor of Medicine and
Chief, Division of Oncology
Columbia Univ. Cancer Center
SWOG Sarcoma Committee Chair,
Breast Committee Working Group

Patricia Ganz, M.D., MPH National expert in quality of life and survivors research
Director, Division of
Cancer Control
UCLA Comprehensive Cancer Center
Chair, SWOG Cancer Control
Behavioral and Health Outcomes
Subcommittee; Breast Committee

Ellen R. Gritz, Ph.D. Nationally recognized expert in smoking trends and behavior
interventions in women vs. men and in adherence issues
Chair, Department of
M.D Anderson Cancer Center
Behavior Science,
Co-Chair, SWOG Cancer Control
Behavioral and Health Outcomes
Subcommittee

Gary Clark, Ph.D. Biostatistician with national recognition for work with early
breast cancer prognostic factor data bases, multiple multivariate
methodologies, validation sets.
Professor of Biostatistics
Division of Oncology
UTHSA, San Antonio

Allen Lichter, M.D. National expert on breast cancer radiation issues
Professor and Chair
Department of
Radiation Oncology
University of Michigan

Carolyn Gotay, Ph.D. Psychologist/Cancer Prevention and Control Program in Native Hawaiians;
expertise in behavioral interventions
Associate Researcher
Univ. of Hawaii Cancer Center

Deborah O. Erwin, Ph.D. Medical Anthropologist, expertise in Education and Outreach Programs
in underserved populations
Assistant Professor
Univ. of Arkansas Cancer Center

Susan Love, M.D. Expert breast surgeon and author
National Breast Cancer Coalition
Director, UCLA Breast Center

Laura Hutchins, M.D. Chair of Intergroup node-negative adjuvant breast trial; major
interest and expertise in Group-wide data base strategies to
study accrual trends in underserved
Professor of Medicine
Arkansas Cancer Research Ctr.
SWOG Breast Committee
and Working Group

Elizabeth J. Shpall, M.D. Expertise in novel therapeutic approaches in breast and ovarian
 Univ. of Colorado Cancer Ctr. cancer; active interest in access issues
 SWOG Bone Marrow Transplant,
 Gynecology Working Groups,
 and Breast Committee

Sharon Wilczynski, M.D., PhD Basic research interests re: HPV, cervical cancer; also screening
 Department of Pathology efforts based on basic science innovations
 Director of Cytology
 City of Hope Medical Center
 Chair, SWOG Gyn Pathology

Claudia Wilson, M.D. Expertise in public education and awareness programs in breast cancer
 SUNY Health Science Center and materials culturally relevant to Latin Americans
 at Brooklyn

Brian Issell, M.D. Research interest in cancer control efforts in Native Hawaiian women;
 University of Hawaii NCI-UO1
 Director, Cancer Research
 Center of Hawaii
 SWOG Cancer Control Comm.

June Strickland, RN, Ph.D. Expert in inductive studies involving cancer problems in Alaskan native
 Cancer Info. Service, FHCRC and Hispanic women; study chair for novel SWOG breast screening trial
 SWOG Cancer Control Research involving underserved populations.
 Committee, Minorities
 subcommittee

Edward DeAntoni, Ph.D. Expertise in developing breast and cervical cancer screening programs
 Assistant Professor of for State of Colorado (linking with American Cancer Society) and the CDC
 Epidemiology and Urology
 University of Colorado
 SWOG GU subcommittee for
 Cancer Control

Joseph Chu, MPH, M.D. Clinical epidemiologist, interest in cervical cancer chemoprevention
 University of WA, Seattle
 Fred Hutchinson CRC
 SWOG GYN Executive Comm.

Thomas Budd, M.D. Breast Cancer Working Group member and study chair
 Medical Breast Service
 Cleveland Clinic

Mary Daly, M.D., Ph.D. Expert in high breast and ovarian cancer risk studies
 Associate Director,
 Cancer Control Science
 Fox Chase Cancer Center

Wendall Goodwin, M.D. Breast and Cancer Control Research Working Groups; Study Chair for pilot
 Principal Investigator trial of treatment of premature menopause in breast cancer survivors
 Ozarks Regional CCOP

Edith Perez, M.D.
Mayo Clinic

Minority breast cancer programs;
translational research using high dose tamoxifen

Jeanne Parzuchowski, MSN
Chair, Nursing Oncology
Committee

Expertise in focus group and outreach methodologies

Dorothy Coleman, R.N.
Clinical Coordinator
Cancer Research Center
SWOG Nursing Committee

Actively involved in broad spectrum of initiatives to bring state of the art cancer-related interventions to the Native Hawaiian, elderly, and other disadvantaged and underserved women; research interest consent document modifications

Bertie Ford, MS, RN, ONS
Ohio State University
SWOG Breast Cancer and
Nursing Committees

Interest/expertise in sexuality, sexual function, and fertility.

Lisa Trif, RN
Columbia River CCOP
Portland, OR
SWOG Cancer Control and
Nursing Committees

Chair of current Cancer Control Research Committee initiative to evaluate education programs to increase cervical cancer screening practices in Latin American women; also interest in inductive studies regarding cultural barriers to interventions in women, and in gender differences in toxicity severity.

**Committee on Women's Health
Lay Advisors & Advocates Implementation Committee
Participant List**

Kathy S. Albain, M.D.

Chair, Southwest Oncology Group Committee on Women's Health
Member, Breast, Lung and Gyn Committee Working Groups

Debra W. Christie, M.B.A., R.R.A.

Chair, Southwest Oncology Group Data Managers Committee
Committee on Women's Health Advisory Board

Charles A. Coltman, Jr., M.D.

Chairman, Southwest Oncology Group

John J. Crowley, Ph.D.

Director, Southwest Oncology Group Statistical Center

Debroah O. Erwin, Ph.D.

Medical Anthropologist, University of Arkansas Cancer Center
Committee on Women's Health Advisory Board

Lesile Ford, M.D.

Division of Cancer Prevention and Control, National Cancer Institute

Patricia Ganz, M.D.

Chair, Behavioral and Health Outcomes CCRC Subcommittee
Committee on Women's Health Advisory Board; Breast, CCRC Working Groups

Carolyn Gotay, Ph.D.

Psychologist, Cancer Prevention and Control Program, Univ. of Hawaii Cancer
Research Center; Committee on Women's Health Advisory Board

Sharon Green, M.H.S.

Executive Director, Y-Me National Breast Cancer Organization

Ellen Gritz, Ph.D.

Chair, Southwest Oncology Group Behavioral and Health Outcomes CCRC Subcommittee
CCRC and Committee on Women's Health Advisory Boards

Amy Langer, M.B.A.

Executive Director, National Alliance of Breast Cancer Organizations (NABCO)

Susan Love, M.D.

Committee on Women's Health Advisory Board; Breast Working Group
National Breast Cancer Coalition

Silvana Martino, D.O.

Chair, Southwest Oncology Group Breast Committee
Committee on Women's Health Advisory Board

Mary McCabe, R.N., B.A.

Clinical Trials Specialist, National Cancer Institute

Carol Moinpour, Ph.D.

Southwest Oncology Group Statistical Center
Committee on Women's Health and CCRC Advisory Boards

Jeanne Parzuchowski, M.S.N.

Chair, Southwest Oncology Group Nurse Oncologist Committee

Mace L. Rothenberg, M.D.

Executive Officer, Southwest Oncology Group; co-chair GYN Committee

Dana Sparks, M.A.T.

Head Protocol Coordinator, Southwest Oncology Group (Committee on Women's Health,
Breast, Gyn Committees and Working Groups)

Ellen Stovall

Executive Director, National Coalition for Cancer Survivorship

TYPES OF STUDIES

Committee on Women's Health

Groupwide data base projects - These projects utilize the vast amount of information on all patients entered to Southwest Oncology Group studies, housed in the computer files of the Statistical Center. Examples include analyses of women enrolled on Group trials (compared to frequency of men), of underserved populations on breast and ovarian cancer studies, and of the utilization of lumpectomy on recent Intergroup trials. The purpose of these types of studies is to point out areas for improvement and to generate new ideas for Group study.

Trials for breast cancer survivors - The concepts generated and developed for these studies are then carried out in the Breast Cancer Committee. Examples are current trials addressing the use of Megace to treat symptoms of menopause in women with early breast cancer, three trials to study the effects of tamoxifen on the uterus and to prospectively ameliorate tamoxifen-induced stimulation of the endometrium (uterine lining), and a concept to investigate the use of breast conservation.

Trials for lung cancer survivors - The concepts generated and developed for these studies are then carried out in the Lung Cancer Committee. One example is a current treatment trial using tamoxifen to overcome resistance to the commonly used lung cancer treatment, cisplatin. Equal numbers of men and women will be studied. Also, a smoking intervention study in male and female lung cancer survivors is under development.

Novel Group initiatives in women's health and cancer - The Lay Advisors/Advocates Pilot Project was a proposal "on paper" in this category and is now a reality. There are many other concepts in the early stage of development, such as several ideas for collaborative projects with the lay advocates' organizations represented on the Steering Committee. In addition, there are plans to potentially develop an intervention study in women with first recurrence of breast cancer, to use survivors as "witnesses" to women considering a clinical trial, and to design a study to better understand why women and/or their physicians refuse to participate in clinical trials.

(Note also that many of the Committee on Women's Health projects are not only designed in collaboration with Disease Committees such as the Breast and Lung Cancer Committees, but also are done in conjunction with the Cancer Control Research Committee.)

TYPES OF STUDIES

Breast Cancer Committee

Adjuvant Studies - Adjuvant studies are studies of treatment following surgical removal of the tumor (either by mastectomy or lumpectomy). Adjuvant studies are usually very large, and are usually performed in collaboration with other cooperative groups (intergroup studies). The treatment involved in adjuvant studies may further be divided by patient characteristics such as menopausal status, tumor size (before removal), tumor spread (to regional lymph nodes), number of involved lymph nodes, prior therapy and estrogen and progesterone receptor status*. Although the primary tumor has been removed, adjuvant studies are performed to prevent the cancer from returning. Depending on the degree of risk associated with the patient characteristics, adjuvant treatment may range from five years of oral tamoxifen, to high dose chemotherapy, to bone marrow transplantation.

Advanced Disease Studies - Advanced disease studies are for patients whose cancer has recurred or progressed after or during adjuvant treatment, or whose disease is metastatic at diagnosis. These studies may include development of new chemotherapy agents or combinations of agents, and/or bone marrow transplantation.

Ancillary Studies - Ancillary studies are companions to treatment protocols. Many ancillary studies are tissue collection studies which allow examination of tumor tissue in the laboratory for the identification of information for future study.

Quality of Life Studies - Quality of Life studies are performed to help determine the effects of treatment on the patients' daily lives. Quality of Life studies ask for the patient's point of view in determining the potential benefit of a particular treatment.

Additional Studies - The Breast Cancer Committee is committed to working with the Committee on Women's Health to identify new areas of study relating to gender issues in treatment decisions, side effects and outcomes.

*ER and PgR (estrogen receptors and progesterone receptors): Proteins that have the ability to bind their respective hormones and also to DNA. Primary breast tumors that express ERs, PgRs or both are less likely to recur than tumors that do not express these proteins.

Southwest Oncology Group Committee on Women's Health
EDUCATIONAL SYMPOSIA AND PRESENTATIONS
April 1992-April 1995

The following topics were formally presented to the Southwest Oncology Group membership at biannual Group meetings under the sponsorship of the Committee on Womens Health since its inception. **NB:** Subjects which directly addressed one of the six National Action Plan on Breast Cancer high priority areas are **highlighted in bold**.

1. An overview of gender differences in cancer incidence, mortality, treatment effects and outcome, **proposing strategies for research regarding targeted approaches to women with cancer versus men.**
2. Smoking trends, behavior interventions in women vs. men and gender-specific adherence issues pertaining to smoking.
3. **Barriers to cancer care in women in general and in underserved populations of women and elderly women, with input from lay advisors and advocates.**
4. **Strategies for addressing cancer risk counseling in a clinical trial setting.**
5. Review of outcome differences by sex in melanoma.
6. Mechanisms of tamoxifen interaction with chemotherapy.
7. Breast cancer outcome in the very young woman, including need for **targeted national data base repositories, analyses and research** for this subset.
8. Initial results of the CWH group-wide demographic data base analyses of accrual trends by sex and socioeconomic status using novel census-based methodology (overall, and by geographic region and by disease). **Proposal of next phase of this project: study of the large Southwest Oncology Group Breast Cancer database to determine if there is under-representation in general and by geographic region of any age, race or SES subset.**
9. Overview of cancer survivorship research and issues (late effects, gender-specific differences). **Focus on fear of late effects as barrier to clinical trials participation with input from lay advisors and advocates..**
10. Review of quality of life research methods pertinent to survivorship research in cooperative group studies in **partnership with lay advisors and advocates.**

11. **Summary of problems and strategies to overcome such regarding the accrual and retention of women in trials.**
12. **Review of factors which influence the use of breast sparing treatment in women who subsequently enroll on adjuvant breast cancer studies, with joint proposal from members and lay advocates for a prospective study.**
13. **Minisymposium by national lay advocates leadership providing an overview of activities of national survivors' organizations and proposal of concepts for research partnerships with the Southwest Oncology Group Committee on Women's Health.**
14. **Summary of research regarding the ethical and social implications in testing for genetic predisposition to breast cancer and challenges facing the cooperative groups in considering this area as a potential research venue.**
15. **Controversies surrounding the exclusion of pregnant women from participation in clinical trials: joint Group/Advocates minisymposium. Mandate formulated requesting reconsideration of restrictions and forwarded to the NCI.**
16. **Symposium on new data on secondary myelodysplasia and leukemia in breast cancer survivors treated with adjuvant chemotherapy with or without growth factors, tamoxifen and radiation. Overview of latest technical advances available for potential prospective study of early DNA damage in these women. Formulation of proposal to develop a Southwest Oncology Group-based national repository of samples from women enrolled on new generation adjuvant trials. Joint input from Group members and Lay Advocates.**

COMMITTEE ON WOMEN'S HEALTH FOCUS AREAS and RESEARCH OBJECTIVES

**A New Initiative of the Southwest Oncology Group
Approved with Excellent Merit, NCI/NIH Competitive Renewal 1/1993-12/1997**

- FOCUS AREA A:** Exploratory Group-wide data base strategies regarding women's health issues, and ongoing monitoring of accrual demographics.
- FOCUS AREA B:** Cancers and related issues either unique to or more prevalent or serious in women.
- FOCUS AREA C:** Cancers and related issues with differences between sexes in risk, incidence, demographics, response, survival, or late effects.
- FOCUS AREA D:** Potential new Group initiatives in the public health arena as pertains to cancer aspects of women's health research.

Specific Research Objectives

(Objectives as revised 10/94 for Continuation Years Three-Five, 1/95-12/97)

1. Monitor representation of women on Group studies in non-gender specific cancers and of underserved populations of women in breast and gynecologic cancers.
2. Investigate, create, and pilot a Group-wide demographic data "repository" and/or prospective trial to study and address reasons for under-accrual defined under Objective 1 and to propose strategies for overcoming identified barriers.
3. Develop a close collaboration with the Cancer Control Research Committee in concept development and trial design and conduct for novel women's health studies outside the normal treatment oriented protocols. Insure that such studies or analyses address women's health issues and/or include gender-related questions
4. Generate concepts for prospective study using retrospective data base analyses, in collaboration with the Breast Cancer and other disease-specific Committees.
5. Collaborate with the Breast Cancer and other disease-specific Committees in trials addressing prevention and/or control of sequelae of treatment, especially those which result in patient fear and create barriers to potential trial participation and/or significantly alter quality of life.
6. Facilitate transfer of laboratory advances in genetics, early markers, tumor biology, and new treatments into clinical trial, collaborating with the Breast Cancer and other disease-specific Committees. Expand the use of banks and repositories among the Group's nationwide network of investigators.

7. Use data base analyses to assess gender aspects in relation to high-risk behavior, and to demographic, prognostic, and treatment variables.
8. Devote significant effort to the problem of the female smoker.
9. Develop and pilot novel approaches to technology transfer, and to the improvement of access to care and recruitment of the underserved.
10. Design and implement a working model for the involvement of survivors and their advocates in the cooperative group process.
11. Develop educational activities for Committee and Group members regarding women's health issues in cancer clinical research.

**PEER-REVIEWED PUBLICATIONS, ABSTRACTS AND
SELECTED FUNDED, APPROVED OR PENDING ACTIVE PROJECTS OF THE
SOUTHWEST ONCOLOGY GROUP COMMITTEE ON WOMEN'S HEALTH**

Publications

Albain KS, Green S, LeBlanc M, Rivkin S, O'Sullivan J, Osborne CK: Proportional hazards and recursive partitioning and amalgamation analyses of the Southwest Oncology Group node-positive adjuvant CMFVP breast cancer data base: A Pilot Study. *Breast Cancer Research and Treatment* 22: 273-284, 1992.

Albain KS, Allred C, Clark G: Outcome and predictors of outcome in younger women with breast cancer: Are there age differentials? *J National Cancer Inst Monographs* 16:35-42, 1994.

Lichter AS, Green SR, Albain KS, Hutchins L, Martino S, Osborne CK: The influence of patient characteristics, socioeconomic factors, geography, and systemic risk on the use of breast sparing treatment in women enrolled on Intergroup adjuvant breast cancer studies. Submitted.

Abstracts

Albain K, Rivkin S, Green S, LeBlanc M, and Osborne K: A recursive partitioning and amalgamation analysis of the Southwest Oncology Group Node (+) adjuvant CMFVP data base: four distinct prognostic groups are described by ER and number of nodes. *Proceedings of ASCO* 11:57, 1992. (Presented)

Albain KS, Allred DC, Clark GM: Age < 35 is associated with high % S-phase, abnormal p53, and adverse breast cancer outcome. *Proceedings San Antonio International Breast Cancer Symposium: Breast Cancer Research and Treatment* 27:131, 1993. (Presented, Plenary Session)

Hutchins L, Rector D, Stotts C, Dahlberg S, Coltman CA, Albain K: Analysis of Southwest Oncology Group accrual for sex ratios and associated socioeconomic status factors. *Proceedings of ASCO* 13:188, 1994.

Lichter A, Green S, Albain K, Hutchins L, Martino S for the Southwest Oncology Group Radiotherapy, Women's Health, and Breast Committees: The influence of patient characteristics, socioeconomic factors, geography, and systemic risk on the use of breast sparing treatment in adjuvant breast cancer studies. *Proceedings of ASCO* 13:62, 1994. (Presented)

Selected Funded or Approved Active Committee on Women's Health Projects

Cross-sectional study of endometrial abnormalities in women on the tamoxifen arms of SWOG-8814 and SWOG-8897 for durations of 1, 2, 3, 4 or 5 years. (Awarded supplemental funding by NCI)

Prospective phase III placebo-controlled trial of cyclical low-dose progestin for chemoprevention of endometrial abnormalities in postmenopausal women with node-negative receptor positive breast cancer who are beginning five years of adjuvant tamoxifen. (Awarded supplemental funding by NCI)

Placebo-controlled phase III study of low dose progestins (six potential dose levels) to ameliorate menopausal symptoms in breast cancer survivors. (Awarded supplemental funding by NCI)

Selected Pending Committee on Women's Health Studies

A study of the late cardiac effects of two different adjuvant chemotherapy regimens in women with node negative breast cancer treated on SWOG-8897. (Funding request pending)

A prospective study of physician and patient variables influencing choice breast surgery option in a cooperative group setting.

Phase III randomized study to assess the impact of usual care versus a concentrated telephone counseling intervention in breast cancer survivors at the time of their first recurrence.

A prospective limited institution study of "pathway to accrual or not" targeting various SES-described populations in order to address strategies to overcome barriers to accrual in women with breast cancer.

A limited institution prospective pilot study of the potential impact on recruitment through the use of a lay health educator ("witness") previously enrolled on a breast cancer clinical trial.



Southwest
Oncology Group
A National Clinical Research Group

August 31, 1994

Dear Colleague:

This is to solicit nominations for membership in the Southwest Oncology Group Lay Advisors and Advocates pilot program. Since 1993, the membership of the Southwest Oncology Group and leaders of national cancer survivors and advocacy organizations have been meeting together to discuss the optimal way to incorporate the expertise and insight of lay advisors and advocates in the clinical cancer research process. We are now ready to initiate a three-year pilot project in two of our disease Committees (Breast Cancer and Lung Cancer).

Attached are job descriptions for the two types of positions which were formed. Two persons (one for each type) will be appointed to serve a three-year term on the Breast Committee and two others will sit on the Lung Committee. All will attend the meetings of the Committee on Women's Health as well. Thus, potential appointees may be of either sex and should have personal experience and interest in either breast or lung cancer research and survivorship concerns.

Please circulate the job descriptions and forward your nominations to the Operations Office (Attn: Dana B. Sparks, M.A.T.) by September 30, 1994. Include a letter of nomination which summarizes the nominee's qualifications for either position A or position B. Also attach a *curriculum vitae* or resume and two letters of reference for each potential candidate. The selection committee (comprised of Southwest Oncology Group members and lay advisors and advocates) will meet in October to review all applications and finalize the appointments. Once selected, members will receive information regarding the orientation, mentoring and debriefing process which will be enacted on site at the upcoming Spring Group meeting.

Thank you very much for your interest and support of this exciting project.

Sincerely,

Dana Sparks to Kathy Albain
Kathy S. Albain, M.D.

Chair, Committee on Women's Health

Charles A. Coltman
Charles A. Coltman, M.D.

Chair, Southwest Oncology Group

Distribution List:

Southwest Oncology Group Committee Chairs & Co-Chairs
Committee on Women's Health
Breast Working Group
Lung Working Group
Samuel Broder, M.D. - Director, NCI
Bruce Chabner, M.D. - NCI
Michael Friedman, M.D. - NCI
Vivian Pinn, M.D. - ORWH
Carrie Hunter, M.D. - ORWH
Iris J. Schneider, M.A. - NCI
Ruthann Guisti, M.D. - DCT
Susan Blumenthal, M.D., M.P.A. - OWH, HHS

Leslie G. Ford, M.D. - DCPC
Otis Brawley, M.D. - DCPC
Frances Visco, Esq. - NBCC
Amy Langer, M.B.A. - NABCO
Sharon Green, M.H.S. - Y-Me
Michelle Melin - Y-Me
Ellen Stovall - NCCS
Deborah Collyar - BCA
Zora Cramer Brown - BCRC
Peggy McCarthy - SBLCAS
Kay Dickerson, Ph.D.



Southwest
Oncology Group
A National Clinical Research Group

September 20, 1994

TO: Executive Director, Susan G. Komen Foundation

FROM: Kathy S. Albain, M.D. - Chair, Southwest Oncology Group Committee on Women's Health

RE: Enclosed materials

Enclosed please find a letter asking for nominations for membership in our Lay Advisors and Advocates Pilot Program. We apologize for inadvertently omitting your group from our distribution list. We certainly hope that you will be able to participate in this exciting venture. If you are unable to meet the deadline of September 30th for submission of applications, we will certainly be willing to grant your group a limited extension.

If you have further questions, please do not hesitate to contact either myself (Kathy S. Albain, M.D. (708/327-3102) or Dana B. Sparks, M.A.T. (210/677-8808). Again, please accept our apologies.

PC/dbs

enclosures

cc: Charles A. Coltman, Jr., M.D.
Dana B. Sparks, M.A.T.
Marjorie A. Godfrey

Southwest Oncology Group
Lay Advisors and Advocates Pilot Project
Job Descriptions

POSITION A

This representative must be a professional well versed and educated in either the scientific method and/or the clinical trials process. She/he must also currently be playing a key national or local patient advocacy role. This individual may, for example, be a scientist, nurse, physician, data manager, statistician, public health professional, or a leader or other representative of a national or local lay cancer advocacy or survivors organization. She/he must also be either a survivor of cancer, or close to a person living with the disease, or a leader of an advocacy or survivors group. Representation from and/or expertise concerning underserved populations will be encouraged.

POSITION B

This representative should be a "survivor representative at large", ie, a patient or member of the public who can speak directly to survivor concerns. Willingness to serve is more important than experience and scientific background is not required. However, past participation or experience with clinical trials is preferred. Representation from and/or expertise concerning underserved populations will be encouraged.

REQUIREMENTS COMMON TO EITHER POSITION A OR B

Participants agree to the importance of mutual collaboration between the clinical cancer research and cancer advocacy/survivors communities.

Term of membership will be three years, with a staggered replacement.

Participants will attend each Group meeting and will be reimbursed for their travel. They will meet with the full Committee and the working group of their assigned Committee. They will also attend meetings of the Committee on Women's Health and join all conference calls pertaining to these committees between Group meetings.

Members will serve as consultants to the Group and Committee Chairs on an ad hoc basis.

Appointees will serve as a channel to funnel suggestions of the survivors and advocacy communities to the cooperative groups.

All agree to maintain the ethical and confidentiality standards of the Southwest Oncology Group.



April 11, 1995

Dear Colleague:

Thank you for your overwhelming response to our letter of August 31, 1994 requesting nominations for the Southwest Oncology Group Lay Advisors and Advocates pilot program. The Lay Advisors Steering Committee of the Committee on Women's Health (comprised of Group members and national lay advocacy group leadership) screened the applications, all of which nominated highly qualified individuals. The ten finalists were then interviewed individually by conference call. The final selections were made by a subcommittee of the Steering Committee. We are please to announce the following appointments:

Ms. Tika Beard	3-year term, Position A Breast Cancer and Women's Health Committees
Ms. Eileen Sondak	2-year term, Position B Breast Cancer and Women's Health Committees
Ms. Peggy McCarthy	3-year term, Position A Lung Cancer and Women's Health Committees
Ms. Peggy Michelson	2-year term, Position B Lung Cancer and Women's Health Committees
Ms. Patricia Barr	Alternate Breast Cancer Committee Position A
Ms. Marilyn Freedman	Alternate Breast Cancer Committee Position B

We are also pleased that Ms. Debbie Christie, Chair of the Southwest Oncology Group Data Managers Committee and member of the Steering Committee, will lead a new "Mentors Project". This program will facilitate the assimilation of our new members into the Group process. Ms. Dana B. Sparks (Protocol Coordinator) is completing a new Orientation Packet to the Group, geared to non-investigators, which also will be piloted with this project.

On a sad note, we offer our deepest condolences to the family, colleagues and friends of Dr. Marti Nelson, who died of breast cancer since her application to this project. She was one of the ten finalists.

The appointees are all highly qualified and we are certain they will contribute greatly to our Group and its scientific endeavors. In addition to their assigned Committees, they will also attend other selected Committees according to their interest and expertise. Please join us in welcoming them at our upcoming Group Meeting in Phoenix.

Sincerely,

Dana Sparks for Dr. Albain

Kathy S. Albain, M.D.
Chair, Committee on Women's Health

Charles A. Coltman, Jr.
Charles A. Coltman, Jr., M.D.
Chair, Southwest Oncology Group

PC/dbs

Distribution List:

Tika Beard
Eileen Sondak
Peggy McCarthy
Peggy Michelson
Patricia Barr
Marilyn Freedman
Southwest Oncology Group Chairs and Co-Chairs
Committee on Women's Health
Breast Working Group
Lung Working Group
Edward Sondik, M.D. - NCI
Michael Friedman, M.D. - NCI
Susan Blumenthal, M.D., M.P.A.

Leslie Ford, M.D. - NCI, DCPC
Otis Brawley, M.D. - NCI, DCPC
Barbara Rimer - Chair, NCAB
Susan Nayfield, M.D. - NCI
Frances Visco, Esq. - NBCC
Amy Langer, M.B.A. - NABCO
Sharon Green, M.H.S. - Y-Me
Ellen Stoval - NCCS
Nancy Evans - BCA
Zora Cramer Brown - BCRC
Nancy Brinker - the Kohman Foundation
Dana B. Sparks, M.A.T.
Marjorie A. Godfrey

GLOSSARY

ACTIVATION: The decision by a Group/Institution to open a study for patient entry (which occurs after CTEP approval).

ACTIVATION AMENDMENT: An amendment sent to CTEP detailing any protocol change which occurs after CTEP approval and prior to local activation. Examples: the study is approved by CTEP with recommendations which are incorporated prior to activation; these changes must be listed and submitted to CTEP as an Activation Amendment.

ADR: Adverse Drug Reaction - An "alarming" ADR is any serious, fatal, or life-threatening clinical experience in a patient which is thought to be drug related. It must be reported immediately to the drug sponsor. "Other" ADR's are reported if that effect has not been described previously.

AMENDMENT: Changes to the protocol which directly affect patient care or treatment; these changes usually constitute a change in the treatment plan, dosage modifications or study parameters. Examples of amendments include an increase or decrease in the dose of a drug and addition or deletion of a study parameter. Justification for the amendment is required; amendments sometimes require NCI approval. The amendment date appears in the upper right-hand corner of amended protocol pages. Amendments may require IRB review.

APPROVAL: CTEP approves the protocol in writing when the science and informed consent are acceptable, the IRB documentation is on file (not applicable to Groups), and the drugs to be supplied are specified by the Drug Management and Authorization Section. If recommendations are specified, CTEP expects an "Activation Amendment" to indicate any changes to the approved document.

CANCER CENTER: An institution which is designated by NCI as a comprehensive or clinical cancer center and is eligible to conduct IND drug studies.

CCIRC: Cancer Clinical Investigations Review Committee - The committee which is responsible for peer reviews of Group Competing applications (Site Visit).

CCOP: Community Clinical Oncology Program - CCOP is a cooperative agreement supported program which provides support to community-based oncologists to participate in clinical trials sponsored by the clinical cooperative groups and/or cancer centers. Each CCOP is expected to enter a minimum of 50 patients per year on NCI-approved research protocols.

CGOP: Cooperative Group Outreach Program - Membership program for small physician consortiums or individual MDs requiring affiliation with full member institutions.

CLINICAL BROCHURE: This document contains all relevant information about the drug, including animal screening, preclinical toxicology, and detailed pharmaceutical data. Also included, if available is a summary of current knowledge about pharmacology and mechanism of action and a full description of the clinical toxicities.

CLINICAL COOPERATIVE GROUPS: Cancer clinical cooperative groups are composed of investigators who join together to develop and implement common protocols. The distinguishing characteristic of cooperative groups is the central operations and statistical offices which support the administrative requirements of the research and perform central data collection and analysis.

CLINICAL TRIALS MONITORING SERVICE: The Theradex organization receives, reviews, and performs data management service on individual patient case report forms for Phase I and some Phase II NCI investigational drug studies.

CLOSED: The decision by a Group, Institution, or NCI to close a study to new patient entries; previously entered patients will continue treatment.

COMPLETED: The study is closed and no patients are being treated or followed for data collection.

CTEP: Cancer Therapy Evaluation Program, DCT, NCI

CTEP LETTER: Newsletter which announces the approval of new drugs for clinical trials and other drug development information.

DCPC: Division of Cancer Prevention and Control - NCI division which funds cancer control research and CCOP program.

DCT: Division of Cancer Treatment, NCI

DHHS: Department of Health and Human Services.

DRUG ACCOUNTABILITY RECORD FORM: Form used to maintain records of disposition of NCI investigational drugs. NIH Form-2564.

DMAS: Drug Management and Authorization Section, IDB, CTEP.

DRAS: Drug Regulatory Affairs Section, RAB, CTEP, DCT, NCI.

DRUG MONITOR: A physician in IDB assigned to coordinate the clinical development of specific IND drugs.

DTP: Developmental Therapeutics Program, DCT, NCI.

FDA: Food and Drug Administration, DHHS

FD-1573: Also referred to as a "Statement of Investigator," it is a requirement of section 505(i) of the Food, Drug, and Cosmetic Act and §312.1 of Title 21 CFR, that an investigator complete this form as a condition for receiving and conducting clinical studies involving investigational drug(s). It includes the investigator's training and experience and provides for legal certifications.

HHS 596: Protection of Human Subjects Assurance/ Certification/ Declaration. An HHS Form 596 is the form used by an institution with a Cooperative Oncology Group (COG) assurance to document the initial and annual re-review of protocols by its Investigational Review Board (IRB).

HIGH PRIORITY PROGRAM (HI PRI): - Unfunded institutions which can accrue only to Hi Pri studies (studies designated by NCI as High Priority).

ICS: Investigator's Contribution Sheet

IDB: Investigational Drug Branch, CTEP, DCT, NCI

IND: Investigational New Drug Application - The IND is the legal mechanism under which experimental drug research is performed in the United States. An IND is submitted to the Food and Drug Administration in order to receive an exception from premarketing approval requirements so that experimental clinical trials may be conducted.

INVESTIGATOR: Any physician who assumes full responsibility for the treatment and evaluation of patients on research protocols as well as the integrity of the research data.

LOI: The Letter of Intent is an investigator's declaration of interest in conducting a Phase II trial with a specific investigational drug in a particular disease. Approval of the LOI by CTEP commits an investigator to submit a protocol within a specified timeframe.

MULTIPLE PROJECT ASSURANCE (MPA): Is a formal written agreement with the Office of Protection from Research Risks (on behalf of the Secretary of HHS) and an institution which conducts or supports a large amount of HHS sponsored research involving human subjects, the MPA specifies how the institution will implement the HHS regulations at 45 CFR 46.

NCAB: National Cancer Advisory Board

NCI: National Cancer Institute, NIH, DHHS.

NDA: New Drug Application is the formal process by which the FDA makes the drug generally available to patients and physicians for specific medications.

NEW DRUG STUDY GROUP: A group of highly qualified clinical researchers at an institution approved by IDB to participate in NCI's drug development program.

NIH: National Institutes of Health, DHHS.

OPRR: Office for Protection from Research Risks, NIH.

OFFICIALLY FILED: At the time of CTEP approval, the protocol document, the informed consent, or amendment is placed in the "approved" PIO file and is distributed to the Clinical Trials Monitoring Services, the Food and Drug Administration, and/or PDQ.

PDQ: The Physician Data Query is an on-line data base which makes state-of-the art treatment information, directory information, and protocol information available to primary care physicians. This data base is maintained by the International Cancer Research Data Base Branch, International Cancer Information Center, NCI.

PIO: The Protocol and Information Office, CTEP, DCT manages the protocol and amendment review process and maintains the official record of all NCI sponsored protocols as well as voluntary protocols for PDQ.

PHS: Public Health Service, DHHS.

PO1: Funding Mechanisms for Program Project Grants (PPGs) (investigator initiated).

PRC: The CTEP Protocol Review Committee reviews and approves all studies involving DCT investigational drugs, cooperative group, or CCOP credit.

PRINCIPAL INVESTIGATOR (PI): Name of physician who has organizational and fiscal responsibility for the use of federal funds to conduct a plan of research which frequently includes several clinical trials, i.e., Contract PI, Group Chairman, RO1/POI PI, etc.

PROTOCOL CHAIRMAN: see Study Coordinator

QACS: Quality Assurance and Compliance Section, RAB, CTEP, DCT, NCI

QUALITY ASSURANCE: The monitoring of a clinical trial to assure the quality of the data which supports scientific conclusions.

RAB: Regulatory Affairs Branch, CTEP, DCT, NCI, NIH.

RESEARCH BASE: An institution or cooperative group which assumes a broad range of responsibilities and functions for the support of clinical trials conducted under its name. It supports the investigator in developing, organizing, implementing, and analyzing clinical trials. It assumes responsibility for the quality of the research, both in concept and execution, and has an important role in assuring patient safety.

REVISIONS: Administrative changes to a protocol which do not affect patient care or patient treatment. Examples of revisions include change of study coordinator, addition or deletion of a participating institution, or correction of an error. The revision date appears in the upper right hand corner of revised protocol pages.

REA: Request for Applications - NCI sends down a request for studies dealing with their priority research areas that they have specifically put money aside for funding if high quality applications are received and approved.

RO1: Funding mechanism for new research proposals (investigator initiated).

SINGLE PROJECT ASSURANCE (SPA): Is a formal written agreement with the Office of Protection from Research (on behalf of the Secretary of HHS) and an institution which has a Multiple Project Assurance and conducts a HHS - sponsored research project, the SPA specifies how the institution will implement the HHS regulations a 45 CFR 46.

SPONSOR: An organization or individual who assumes legal responsibilities for supervising or overseeing clinical trials with investigational agents.

STUDY COORDINATOR: The scientific coordinator of the study who is responsible for developing and monitoring the study as well as analyzing, reporting, and publishing its results.

TEMPORARILY CLOSED: The decision by a Group, Institution, or NCI to stop patient entry pending study evaluation.

UCOP: - Urologic Cancer Outreach Program - Institutions which accrue to GU studies only to increase urologic surgeon's participation in the Group.

1/31/95

DRUG LIST

All drug names used in text should be lower case except trademarked names and acronyms such as: 10-EdAM, 5-FUDR, Roferon-A, Ara-C, AT-125, AZQ, BCG, BCNU, CBDCA, CCNU, CHIP, Cytosan, DCF-Pentostatin, DHAC, DHAD, DTIC, Adriamycin, VP-16, r-GIFN, G-CSF, GM-CSF, IL-2, Intron A, L-asparaginase, m-AMSA, MGBG, RU-486, Stelazine, TCAF, VM-26, Wellferon, Decadron, Depo-Provera, Matulane, Myleran, Nolvadex and Oncovin.

If drug names are used separately (not in text) they should be capitalized.

10-EdAM (*Edatrexate)
5-Azacytidine
5-Fluorouracil (5-FU)
6-Mercaptopurine
6-Thioguanine
*13-cis retinoic acid (Isotretinoin) (Accutane®)
Accutane® (*13-cis retinoic acid) (Isotretinoin)
*Acivicin (AT-125)
*Actinomycin-D (Dactinomycin)
*Acyclovir (Zovirax®)
*Adriamycin® (Doxorubicin)
Allopurinol
*All trans retinoic acid (Trentinoin)
*Alpha Interferon (Roferon®)
*Altretamine (Hexalen®)
*Amonafide (Nafidimide)
Ara-C (*Cytosine Arabinoside)
AT-125 (*Acivicin)
AZT (*Zidovudine)
AZQ
Bactrim® (*Trimethoprim sulfa)
BCG Connaught
BCG Tice
BCNU
*Beta-Carotene (Vitamin A)
Bleomycin
Bropirimine
*Busulfan (Myleran®)
*Carboplatin (CBCDA)
Casodex®
CBCDA (*Carboplatin)
CCNU
Chlorambucil
Ciprofloxacin hydrochloride
Cisplatin
*Cyclophosphamide (Cytosan®)
Cyclosporine
*Cytosine Arabinoside (Ara-C)
Cytosan® (*Cyclophosphamide)
Dacarbazine (*DTIC)
Dactinomycin (*Actinomycin-D)
Daunomycin
*Deoxycoformycin (DCF) (Pentostatin)
Decadron® (*Dexamethasone)
Depo-Provera®
*Dexamethasone (Decadron®)

DHAC
 DHAD (Dihydroxyanthracenedione, *Mitoxantrone)
 *Didanosine (ddl) (Videx®)
 Didemnin-B
 Dihydroxyanthracenedione (DHAD, *Mitoxantrone)
 Diphenhydramine
 *Dipyridamole (Persantine)
 *Docetaxel (Taxotere®)
 Doxorubicin (*Adriamycin)
 *DTIC (Dacarbazine)
 *Edatrexate (10-EdAM)
 Eldesine (*Vindesine)
 *Erythropoitin (Procrit®)
 Etoposide (*VP-16) IV
 *Etoposide (VP-16) PO
 Fazarabine
 Fenretinide (4-HPR)
 *Filgrastim (G-CSF) (Neupogen®)
 *Finasteride (Proscar®)
 Fludarabine Phosphate
 Flutamide
 Folinic Acid (*Leucovorin calcium)
 Gallium nitrate
 G-CSF (*Filgrastim) (Neupogen®)
 *GM-CSF (Immunex) (Sargromostim) (Leukine®)
 Hexalen® (*Altretamine)
 Hydroxyurea
 Ifosfamide
 IL-2 (*Interleukin-2)
 IL-3 (*Interleukin-3)
 IL-4 (*Interleukin-4)
 IL-6 (*Interleukin-6)
 Interferon Alpha 2b (*Intron A)
 *Interleukin-2 Cetus (IL-2 Cetus)
 *Interleukin-2 (Hoffman-LaRoche) (IL-2)
 *Intron A (interferon Alpha-2b)
 Isotretinoin (*13-cis retinoic acid) (Accutane®)
 L-Asparaginase
 *Leucovorin Calcium (Folinic Acid)
 Leukine® (*GM-CSF) (Sargromostim)
 Leuprolide Acetate (Lupron®)
 Levamisole
 Melphalan
 Merbarone
 Mesna
 Methotrexate
 *MGBG (Methyl-GAG)
 *Mifepristone (RU-486)
 Mitomycin-C
 *Mitoxantrone (DHAD, Dihydroxyanthracenedione)
 Myleran® (*Busulfan)
 Navelbine® (*Vinorelbine tartrate)
 Neupogen® (*Filgrastim) (G-CSF)
 Nafidimide (*Amonafide)
 Nolvadex (*Tamoxifen)
 Oncovin® (*Vincristine)
 Ormaplatin

*Paclitaxel (Taxol®)
PALA
Pentostatin (*Deoxycofomycin) (DCF)
*Pentoxifyline (Trental®)
Persantine (*Dipyridamole)
Pibenzimol
Piroxantrone
PIXY 321
Prednisone
Procrit® (*Erythropoietin)
Proscar® (*Finasteride)
*Pyrazoloacridine (PZA)
Roferon® (*Alpha Interferon)
RU-486 (*Mifepristone)
Stelazine® (*Trifluoperazine Hydrochloride)
Suramin
Taxol® (*Paclitaxel)
Taxotere® (*Docetaxel)
*Tamoxifen (Nolvadex®)
TCAR (*Tiazofurin)
*TCN-P (Tricyclic nucleoside 5'-phosphate)
Tetraplatin
Thiotepa
*Tiazofurin (TCAR)
*Teniposide (VM-26)
Topotecan
Trental® (*Pentoxifyline)
*Trifluoperazine Hydrochloride (Stelazine®)
*Trimethoprim sulfa (Bactrim®)
Verapamil
Videx® (*Didanosine) (ddl)
Vinblastine Sulfate
*Vincristine (Oncovin®)
*Vindesine (Eldesine)
Vitamin A (*Beta-Carotene)
VM-26 (*Teniposide)
*VP-16 (Etoposide) IV
VP-16 (*Etoposide) PO
Wellferon (Burroughs-Wellcome Interferon)
*Zidovudine (AZT)
Zoladex
Zovirax® (*Acyclovir)

* Stars are placed by the preferred name of the drug for use in protocols.

**ACRONYMS USED WITHIN THE
SOUTHWEST ONCOLOGY GROUP (SWOG)**

ACRONYMS ASSOCIATED WITH THE NATIONAL CANCER INSTITUTE (NCI):

ADR:	Adverse Drug Reactions
CCIRC:	Cancer Clinical Investigations Review Committee
CIB:	Clinical Investigations Branch
COG:	Cooperative Oncology Group
CTEP:	Cancer Therapy Evaluation Program
DCPC:	Division of Cancer Prevention and Control
DCT:	Division of Cancer Treatment
DHHS:	Department of Health and Human Services
DMAS:	Drug Management and Authorization Section
DRAS:	Drug Regulatory Affairs Section
FDA:	Food and Drug Administration
IDB:	Investigational Drug Branch
IND:	Investigational New Drug Application
IRB:	Institutional Review Board
LOI	Letter of Intent
MPA:	Multiple Project Assurance
NIH:	National Institute of Health
OPRR:	Office for Protection from Research Risks
PIO:	Protocol and Information Office
PDQ:	Physician Data Query
QACS:	Quality Assurance and Compliance Section
RAB:	Regulatory Affairs Branch
RFA:	Request for Application

OTHER COOPERATIVE GROUPS:

BTCG:	Brain Tumor Cooperative Group
CALR:	Cancer and Leukemia Research
CCSG:	Children's Cancer Study Group
ECOG:	Eastern Cooperative Oncology Group
EORTC:	European Organization for Research on Treatment for Cancer
GOG:	Gynecologic Oncology Group
IRS:	Intergroup Rhabdomyosarcoma Study
MAOP:	Mid-Atlantic Oncology Program
NCOG:	Northern California Oncology Group
NSABP:	National Surgical Adjuvant Project for Breast and Bowel Cancer
NWTSG:	National Wilms' Tumor Study Group (NWTSG)
NCCTG:	North Central Cancer Treatment Group
POG:	Pediatric Oncology Group
RTOG:	Radiation Therapy Oncology Group

MEMBERSHIP PROGRAMS:

MEM:	Full Group Members
CGOP:	Cooperative Group Outreach Program
CCOP:	Community Clinical Oncology Program
UCOP:	Urologic Cancer Outreach Program
HIPRI:	High Priority Program
PCPT:	Prostate Cancer Prevention Trial
SPEC:	Special Membership

**ACRONYMS USED WITHIN THE
SOUTHWEST ONCOLOGY GROUP (SWOG)
ROSTER DATABASE**

INVESTIGATOR TABLE:

PI:	Principal Investigator
COPI:	Co-Principal Investigator
PART:	Participant

SPECIALITY TABLE:

MO:	Medical Oncologist
P:	Pathologist
RT:	Radiotherapist
S:	Surgeon

DISCIPLINE TABLE:

CARDI:	Cardiology
GASTRO:	Gastrointestinal
GO:	Gynecologic Oncology
GYN:	Gynecology
HEM:	Hematology
IM:	Internal Medicine
NEUR:	Neurology
ONC:	Oncology
ORTH:	Orthopedics
OSTEO:	Osteopathy
OTOL:	Otolaryngology
PATH:	Pathology
PS:	Plastic Surgery
SC:	Scientific Consultant
SM:	Special Member
STAT:	Statistics
SURG:	Surgery
THOR:	Thoracic
UROL:	Urology

DISEASE COMMITTEES:

BRAIN:	Brain Tumor Committee
BREAST:	Breast Cancer Committee
GI:	Gastrointestinal Cancer Committee
GU:	Genitourinary Cancer Committee
GYN:	Gynecologic Cancer Committee
HN:	Head and Neck Cancer Committee
LEUK:	Leukemia Committee
LUNG:	Lung Cancer Committee
LYMPH:	Lymphoma Committee
MELAN:	Melanoma Committee

MYELO: Myeloma Committee
SARC: Sarcoma Committee

TUMOR BIOLOGY SUBCOMMITTEES:

TBBRNSUB: Brain Tumor Biology Subcommittee
TBBRTSUB: Breast Tumor Biology Subcommittee
TBGISUB: Gastrointestinal Tumor Biology Subcommittee
TBGUSUB: Genitourinary Tumor Biology Subcommittee
TBSYNSUB: Gynecologic Tumor Biology Subcommittee
TBHNSUB: Head and Neck Tumor Biology Subcommittee
TBLEUSUB: Leukemia Tumor Biology Subcommittee
TBLNGSUB: Lung Tumor Biology Subcommittee
TBLYMSUB: Lymphoma Tumor Biology Subcommittee
TBMELSUB: Melanoma Tumor Biology Subcommittee
TBMYLSUB: Myeloma Tumor Biology Subcommittee
TBSARSUB: Sarcoma Tumor Biology Subcommittee

DISCIPLINE COMMITTEES:

CYTOGEN: Cytogenetics Committee
DM: Data Managers Committee
NURSE: Nurse Committee
PATH: Pathology Committee
RT: Radiotherapy Committee
SURG: Surgery Committee
STOMAT: Stomatology Committee

PATHOLOGY SUBCOMMITTEES:

PBMTSUB: Bone Marrow Transplant Pathology Subcommittee
PBRNSUB: Brain Pathology Subcommittee
PBRSTSUB: Breast Pathology Subcommittee
CYTOM: Cytometry Subcommittee
PGISUB: Gastrointestinal Cancer Pathology Subcommittee
PGUSUB: Genitourinary Cancer Pathology Subcommittee
PGYNSUB: Gynecologic Cancer Pathology Subcommittee
PHNSUB: Head and Neck Cancer Pathology Subcommittee
PIMMUNO: Immunological Markers Pathology Subcommittee
PLEUKSUB: Leukemia Pathology Subcommittee
PLUNGSUB: Lung Cancer Pathology Subcommittee
PLYMSUB: Lymphoma Pathology Subcommittee
PMELSUB: Melanoma Pathology Subcommittee
PMOLBIO: Molecular Biology Pathology Subcommittee
PMYELSUB: Myeloma Pathology Subcommittee
PSARCSUB: Sarcoma/Mesothelioma Pathology Subcommittee

STANDING COMMITTEES:

BOG Board of Governors
BMT: Bone Marrow Transplant Committee
CCR: Cancer Control Research Committee
COMMWH: Committee on Women's Health
CGOP: Cooperative Group Outreach Program Committee
DEVTHE Developmental Therapeutics

MEM:
QA:

Membership
Quality Assurance

2/1/95

• 95.04.14 Notice

GENERAL PROVISIONS FOR THE NATIONAL ACTION PLAN ON BREAST CANCER
OMNIBUS PUBLIC HEALTH SERVICE (PHS) ADMINISTRATIVE SUPPLEMENTS

NIH GUIDE, Volume 24, Number 14, April 14, 1995

P.T.

Keywords:

National Cancer Institute

PROGRAM GOALS AND SCOPE

The National Action Plan on Breast Cancer (NAPBC) is a public-private partnership created to eliminate the epidemic of breast cancer. The Public Health Service's Office on Women's Health, which coordinates the implementation of the NAPBC, will offer approximately \$2 million in FY 1995 for supplemental awards of up to \$100,000 (direct costs) for a period of one year. These administrative supplements are offered to enable currently federally funded investigators to address one or more of six high priority areas for breast cancer research and outreach activities that were derived from the "Proceedings of the Secretary's Conference to Establish a National Action Plan on Breast Cancer," held in December 1993.

Any currently funded investigator-initiated PHS research and outreach grants relevant to breast cancer is eligible for an administrative supplement under this announcement including those funded by any PHS entity, NIH Institute, Center or Division (ICD). Contracts are not eligible for this supplement program. Since this announcement concerns administrative supplements for the National Action Plan on Breast Cancer, foreign or domestic applications with an international component are not eligible.

The six priority areas for administrative supplements are: information dissemination, national biological resource bank, consumer involvement, breast cancer etiology, clinical trials accessibility, and breast cancer susceptibility genes issues.

Applicants must address one or more of the six priority areas below. Within each priority area, examples of issues which may be addressed are, but not limited to, the following:

INFORMATION DISSEMINATION: Develop innovative tools, approaches and

strategies to disseminate information to and facilitate communication between scientists, consumers and practitioners about breast cancer, breast cancer clinical trials, and breast health using state-of-the-art information technologies (e.g. computer systems, interactive videos, CD-ROM, and/or the Information Superhighway).

NATIONAL BIOLOGICAL RESOURCE BANK: Establish biological resource banks to ensure a national resource of well characterized and documented biological materials for multiple areas of breast cancer research. Examples of possible topics include, but are not limited to, a survey of existing tissue banks, the inclusion of other biological tissues (cell lines, lymphocytes, etc.) in biological banks, use of new technologies to facilitate the collection of pertinent background data on samples, and cooperative participation in the National Biological Resource Bank activities to increase the availability of samples to investigators across the country. In addition, studies to investigate the ethics of using biological specimens in research are of interest.

CONSUMER INVOLVEMENT: Ensure consumer involvement at all levels in the development and implementation of public health and service delivery programs, research studies, and outreach efforts. Involve advocacy groups and women with breast cancer in setting research priorities and in patient education.

BREAST CANCER ETIOLOGY: Expand the scope and breadth of biomedical, epidemiological, and behavioral research activities related to the etiology of breast cancer. Priority areas for projects include the effects of radiation and electromagnetic fields, chemicals and hormones, lifestyle factors, viruses, and gene-environment interactions.

CLINICAL TRIALS ACCESSIBILITY: Make clinical trials more widely accessible to women with breast cancer and women who are at risk for breast cancer. Identify barriers to participation in clinical trials and develop strategies to overcome these barriers through outreach to consumers and clinicians, through better understanding of the decision making process for women and their physicians, through reduction of economic constraints, etc.

BREAST CANCER SUSCEPTIBILITY GENES ISSUES: Address the health needs and ethical, legal, and policy issues of individuals carrying breast cancer susceptibility genes. Recommend and test interventions for consumers, health care providers, and at-risk patient groups, which will lead to the development of a comprehensive plan for these groups.

It is especially important to note that all requests for supplements

MUST be within the scope of the parent grant. The parent grant can deal with breast cancer, other cancers, other diseases, or any of the above six priority areas.

Program directors for individual grants must be contacted for questions on the consistency of the proposed supplemental project's aims with the parent project. The parent award must have a minimum of one year remaining (end date no sooner than September 30, 1996) in the project from the time the supplement is awarded. This will ensure that results of the activities under the administrative supplement can be incorporated into a competing continuation application of the parent award at the discretion of the Principal Investigator.

Direct costs of the supplement can represent no more than 25 percent of the current year total direct costs, not to exceed \$100,000 direct cost maximum.

APPLICATION PROCEDURES

Principal Investigators requesting supplements (regardless of parent ICD) should use a standard PHS-398 (rev. 9/91) Face Page and Budget; no more than five single-spaced pages of text addressing specific aims, background and significance, research design and methods; and a list of pertinent references (not included in the five page limit). In addition, the following material is required: a copy of the official initial peer review comments for the parent grant (e.g. summary statement or the equivalent); the most current Notice of Grant award; biographical sketches (page FF of PHS-398 or equivalent) of all relevant project staff. All requests must be signed by the appropriate institutional officials as well as the Principal Investigator.

Budget requests for less than \$50,000 direct costs need only indicate personnel time and effort total dollars requested; budgets in excess of \$50,000 must provide categorical listings as required in PHS Form 398 instructions.

Investigators funded by PHS entities outside of the National Cancer Institute may be required to provide additional budgetary information or be subject to additional conditions or limitations consistent with the general policies and practices of the specific units holding the parent award. Individuals will be notified of such issues by their administrative contact if an award is contemplated.

Submit by the receipt date of June 14, 1995 a signed, typewritten original of the request and 4 signed, exact copies, in one package to:

Office on Women's Health, USPHS
Hubert Humphrey Building, Room 730-B
200 Independence Avenue, S.W.
Washington, DC 20201
Telephone: (202) 690-7650
FAX: (202) 690-7172

At the same time, an exact copy of the application MUST be submitted directly to the Program Director of the PHS funding component responsible for the funding of the parent grant. The name of the program director and awarding official should be on the notice of award for the parent grant that is sent directly to principal investigators and institutional business offices. If there is any question about who or where to send this copy, applicants should call the agency directly for the information prior to mailing the copy. A copy of this announcement should be included with your request for a supplement. Failure to do so may exclude the request from the competition.

In case your program director is not familiar with the NAPBC competition, they should be referred to one of the individuals listed below for more information.

EVALUATION AND FUNDING PROCEDURES

Requests for Omnibus Administrative Supplements will be evaluated and ranked by a process involving representatives of Federal agencies including DHHS, outside consultants, and the PHS Office of Women's Health.

The evaluation will be made against the following general criteria: originality of proposed activity, scientific and technical significance of the proposed study as related to the six high priority areas, appropriateness and adequacy of the experimental approach and methodology to carry out the activity, development of public and private partnerships, the potential of the project to develop successful programs during the one year supplement period (i.e. qualifications of project team, resources, data quality and management plans), and appropriateness of the proposed budget and activities to the parent award.

Applicants are encouraged to address the needs of women who may have been generally underserved in research and outreach projects. Special consideration will be given to proposed activities that emphasize the following:

- o Implementing partnerships with public and private sector groups,

- o Including breast cancer consumer/advocacy groups in the design, conduct and evaluation of clinical/outreach/research strategies,
- o Testing new, innovative designs for ongoing research or outreach studies,

The information and initial evaluation will be forwarded to appropriate PHS program directors for review to ensure that the proposed activities are compatible with and within the scope of the objectives and aims of the parent project. Requests will also be reviewed for the appropriateness of funds requested and for potential overlap with other current support.

Applications must be submitted by June 14, 1995. Successful supplements will be funded no later than September 30, 1995. Approximately 20-30 supplements will be awarded from this program.

The Public Health Service's Office on Women's Health coordinates the implementation of the NAPBC. Funding for the NAPBC is administered by the National Cancer Institute (NCI). Approved Administrative Supplements will be funded directly from the NCI (if the parent grant is a NCI grant); or through a co-funding or interagency agreement between NCI and other PHS entities.

INQUIRIES

For additional information about this initiative, interested and eligible investigators should contact:

Susan J. Blumenthal, M.D., M.P.A.
Deputy Assistant Secretary for Health (Women's Health)
Co-Chair, National Action Plan on Breast Cancer
ATTN: Suzanne G. Haynes, Ph.D. (etiology; consumer involvement)
Cheryl L. Marks, Ph.D. (clinical trials; information dissemination)
Debbie Saslow, Ph.D. (breast cancer susceptibility genes; tissue bank)
Office on Women's Health, USPHS
Hubert Humphrey Building, Room 730-B
200 Independence Avenue, S.W.
Washington, DC 20201
Telephone: (202) 401-9587
FAX: (202) 401-9590

or

Susan M. Sieber, Ph.D.
Deputy Director
Division of Cancer Etiology

National Cancer Institute
Building 31, Room 11A03
Bethesda, MD 20892
Telephone: (301) 496-5946
FAX: (301) 496-1297

Direct inquiries regarding fiscal matters to:

William G. Wells
Section Chief
Grants Administration Branch
National Cancer Institute
Executive Plaza South, Suite 243
6120 Executive Boulevard
Bethesda, MD 20892-7150
Telephone: (301) 496-7800, Extension 250
FAX: (301) 496-8601

Since program directors in agencies outside of NCI may be unfamiliar with this program, they are encouraged to contact one of the above individuals for more information.

APPENDIX I

Body of Southwest Oncology Group Committee on Women's Health Initiated Pilot Study: "Using Role Models to Inform Women About Breast Cancer Clinical Trials"

Principal Investigator: Deborah O. Erwin, Ph.D.

Funded in full 9/30/95-9/29/97 by the National Action Plan on Breast Cancer

The following grant proposal is proprietary information

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. **DO NOT EXCEED THE SPACE PROVIDED.**

This proposal poses a novel recruitment method designed to overcome some of the sociocultural barriers experienced by women as they consider the clinical trials process by applying the results and theories of outreach and health behavior research. The goal of the study is to investigate the feasibility of overcoming sociocultural barriers to clinical trials participation for breast cancer patients through the systematic use of survivors serving as role models. The specific aims of the research are 1) to develop a recruitment and training program to instruct breast cancer survivors from various cultural backgrounds who were also clinical trial participants, to serve as role models and assist in the information and accrual process; 2) to develop a systematic approach for the role models to contact women eligible for clinical trial participation in order to discuss the process, experiences, and potential benefits of participation; and 3) to evaluate the feasibility of using these methods at the institutional and cooperative group level. It is hypothesized that training culturally appropriate cancer survivors as role models to contact prospective breast cancer clinical trial participants will improve the accrual process for patients, increase the number of patients participating, alleviate physician constraints, and provide a systematic mechanism for applying this process and model to other clinical research settings. Based on prior outreach research, this study will recruit a minimum of six breast cancer survivors, one each from lower, middle and upper income African American and caucasian backgrounds to serve as role models. These survivors will be trained to talk with other women about their experiences as clinical trial participants, and the benefits and problems of that experience. The study will investigate two methods of contacting patients - direct/person-to-person and telephone. Qualitative and quantitative evaluation of the two-year study will be based on encounter surveys, focus group discussions, participation outcome measures, and process evaluation, such as attrition, staff evaluations, and qualitative ethnographic notes. The proposed study is the initial, single institution phase of a planned two-phase study which will investigate the survivor model prospectively in a cooperative group setting.

Name <u>Deborah O. Erwin</u>	Degree(s) <u>PhD</u>	Social Security No. <u>431-08-9121</u>
Position Title <u>Asst. Prof/Assoc Dir Ed</u>	Date of Birth (MM/DD/YY) <u>01/26/54</u>	Role on Project <u>Principal Investigator</u>
Organization <u>University of Arkansas for Medical Sciences (UAMS)</u>		Department <u>Surgery</u>
Name <u>Laura Hutchins</u>	Degree(s) <u>MD</u>	Social Security No. <u>587-70-1279</u>
Position Title <u>Professor</u>	Date of Birth (MM/DD/YY) <u>02/03/52</u>	Role on Project <u>Medical Oncologist</u>
Organization <u>University of Arkansas for Medical Sciences (UAMS)</u>		Department <u>Hematology/Oncology</u>
Name <u>Suzanne Klimberg</u>	Degree(s) <u>MD</u>	Social Security No. <u>515-60-9027</u>
Position Title <u>Assistant Professor</u>	Date of Birth (MM/DD/YY) <u>06/24/54</u>	Role on Project <u>Surgical Oncologist</u>
Organization <u>University of Arkansas for Medical Sciences (UAMS)</u>		Department <u>Surgical Oncology</u>
Name <u>Jeana Naile</u>	Degree(s) <u>BS</u>	Social Security No. <u>431-45-3706</u>
Position Title <u>Director of Clinical Research & Data Management</u>	Date of Birth (MM/DD/YY) <u>01/16/65</u>	Role on Project <u>Data Management</u>
Organization <u>University of Arkansas for Medical Sciences (UAMS)</u>		Department <u>Hematology/Oncology</u>
Name <u>Karen Mack</u>	Degree(s) <u>BSN</u>	Social Security No. <u>432-11-8933</u>
Position Title <u>Nurse Practitioner</u>	Date of Birth (MM/DD/YY) <u>12/11/55</u>	Role on Project <u>Clinical Trial Coordinator</u>
Organization <u>University of Arkansas for Medical Sciences (UAMS)</u>		Department <u>Hematology/Oncology</u>
Name <u>Diane Foster</u>	Degree(s) <u>AD</u>	Social Security No. <u>429-17-6844</u>
Position Title <u>Registered Nurse</u>	Date of Birth (MM/DD/YY) <u>10/24/58</u>	Role on Project <u>Patient Resource</u>
Organization <u>University of Arkansas for Medical Sciences (UAMS)</u>		Department <u>Medical Oncology</u>
Name <u>Maureen Colvert</u>	Degree(s) <u>RNP</u>	Social Security No. <u>487-52-1424</u>
Position Title <u>Nurse Practitioner</u>	Date of Birth (MM/DD/YY) <u>1/10/50</u>	Role on Project <u>Surgical Coordinator</u>
Organization <u>University of Arkansas for Medical Sciences</u>		Department <u>Surgical Oncology</u>

RESEARCH PLAN

The goal of this study is to investigate the feasibility of overcoming sociocultural barriers to clinical trial participation for breast cancer patients through the systematic use of breast cancer survivors serving as role models. It is proposed that a minimum of six cancer survivors, one each from a lower income, middle income, and well educated/higher income African American and Caucasian cultural group, be recruited and trained to act as role models.

1. SPECIFIC AIMS

The following objectives are proposed:

- 1) To develop a recruitment and training program to instruct breast cancer survivors from various cultural backgrounds, who were also clinical trial participants, to serve as role models and assist in the information and accrual process.
- 2) To develop a systematic approach for the role models to contact women eligible for clinical trial participation in order to discuss the process, experiences, and potential benefits of participation.
- 3) To evaluate the feasibility of using these methods at the institutional and cooperative group level.

In general, it is hypothesized that training culturally appropriate cancer survivors as role models who will contact prospective breast cancer clinical trial participants will improve the accrual process for patients, increase the number of patients participating, alleviate physician constraints, and provide a systematic mechanism for applying this process and model to other clinical research settings.

1.1 Research Questions:

- 1) Can former clinical trial participants work within the health care setting to routinely and systematically assist in the recruitment of new patients to clinical trials?
- 2) Is a telephone contact method as effective as a direct, in-person contact method?
- 3) How culturally similar do the women need to be to be effective as role models? (i.e., Do racial, economic, education, and age variables all have to be the same? Or are some of these factors more important?)
- 4) How much role model and staff training and preparation is necessary to initiate this model in a single institution?
- 5) Can a model be developed for study in the cooperative group setting?

2. BACKGROUND AND SIGNIFICANCE

The proposed research will directly address the RFA priority area of "Clinical Trials accessibility" by piloting a strategy to address and overcome some of the barriers for women by providing them with culturally sensitive experiential information. It also includes consumer involvement by breast cancer survivors in the design, implementation, and analysis of the study. The concept for this proposal was developed with guidance from the Southwest Oncology Group (SWOG) Committee on Women's Health (CWH) which includes advocates and survivors, as well as health care professionals. This proposal is the initial, single institution phase of a two-phase study. The second phase will be to conduct a second trial of the survivor model prospectively in the SWOG cooperative group setting. (See letter of support.) Although this study is to be piloted only on clinical trials related to female breast cancer, successful strategies could also be applied to trials for other types of cancer in the future.

National data suggest that African Americans and Hispanics are often underrepresented in clinical trials.⁽¹⁻²⁾ In addition to the National Cancer Institute, there has been increased concern in the cooperative group setting, like SWOG and the National Surgical Adjuvant Breast and Bowel Project (NSABP), about adequate representation of women, minorities, and underserved patients in the clinical trial process. Dr. Hutchins' report on these data for SWOG⁽³⁾ indicate some sites, such as colo-rectal and bladder cancer, could benefit by greater accrual of women. Increasing access to clinical trials provides the best available care for the individual patient and the greatest benefit for all breast cancer patients through the research results of the randomized clinical trial process. Therefore, there is a need to explore methods for overcoming barriers for breast cancer patients. Including survivors in the process is a natural way to ensure consumer involvement.

2.1 Barriers to Accrual

Reasons for lack of accrual and participation include accessibility and treatment cost problems due to low socioeconomic status,⁽⁴⁻⁶⁾ lack of bilingual or culturally sensitive staff,^(4,7,8) perceived efficacy of investigational programs or trials,⁽¹⁾ lack of protocol availability for minorities related to lower eligibility/late diagnosis,⁽⁹⁻¹⁰⁾ lack of community involvement and support,⁽²⁾ and difficulties related to poverty, such as hopelessness, powerlessness, and survival priorities.⁽⁵⁾

Some of these barriers may be specific to a particular ethnic group or gender; others are most closely related to poverty. And although there is no quantitative data, the SWOG CWH has suggested that there are also specific difficulties in the recruitment of well-educated, higher income women for clinical trials (CWH Board Meeting, April 1995). The experiences of the investigators for the proposed study have indicated that a general lack of information, misinformation, and many misconceptions regarding the clinical trial experience tend to make the subject psychosocially uncomfortable for many patients and their families to consider. In addition, physicians often experience time and sociocultural constraints that inhibit communication with many patients.

Nationally, endeavors to provide more information and increase participation in clinical trials have included the development and use of an NCI patient education booklet⁽¹¹⁾ and use of the Cancer Information Service (CIS) to increase public awareness. Unfortunately, these efforts employ mechanisms which are not well-suited to lower income, less educated minority populations.⁽¹²⁻¹⁵⁾ Less educated populations cannot read and comprehend a clinical trials booklet designed for a ninth grade or higher reading level.⁽¹⁴⁻¹⁷⁾ And there are significant credibility problems which hamper the use of the CIS by African Americans. Evaluation of the CIS system revealed that for African Americans, "spokespersons must be chosen carefully."⁽¹⁵⁾

Institutional efforts to increase enrollment of minorities and women into clinical trials have had limited success rates.^(4,7,8) These efforts often required the employment of additional staff and multilingual data managers to more closely meet the cultural backgrounds of the patient population. This demonstrates the need to address cultural diversity of patients and provide for one-on-one encounters with patients. The proposed project will study the feasibility of having survivors provide some of these services in a culturally sensitive way.

2.2 The UAMS Clinical Trial Experience

The Arkansas Cancer Research Center(ACRC) at the University of Arkansas for Medical Sciences (UAMS) serves as a statewide and regional referral center for cancer patients. In 1993, 116 (10%) of all new patients were breast cancer patients, and in 1994, ACRC treated 145 (11%) new breast cancer patients. Annually, approximately 20% of the breast cancer patients are African American. This referral pattern reflects the state population which is 17% African American and less than 1% Asian or Hispanic.

UAMS was a founding member of SWOG in 1959, has been an active member of SWOG for the past 11 years, and has ranked in the top 10% of institutions in accruals to clinical trials. Currently, over 80 SWOG protocols, 3 NSABP protocols, and 10 outside drug trials are approved by the UAMS Institutional Review Board and open for patient accrual. In 1994, UAMS enrolled 26 of 145 breast cancer patients on a breast cancer trial. Of the breast cancer patients enrolled in clinical trials at UAMS over the past 11 years, 49% had private insurance (or Medicare supplemented by private insurance), 8% were covered by Medicaid only, 6% had no insurance at all, and 5% received Medicare only (39% were enrolled before method of payment was recorded).

2.3 Strategies and Theories for Access and Accrual

There is ample evidence that social relationships influence health by facilitation of health promoting behaviors.^(18,19) For example, the social norms for many African Americans, particularly in rural areas, often delay seeking health care. They may rely on relatives, spiritualists, and healers instead of health care professionals.⁽²⁰⁻²³⁾ Although poverty and its subsequent barriers are beyond the scope of a health care facility like UAMS to ameliorate, numerous other cultural and social barriers can be addressed.

The proposed research explores the feasibility and requirements for initiating a novel recruitment method designed to overcome barriers experienced by women as they consider the clinical trials process. The research design is based upon the theoretical framework of a successful outreach program for increasing cancer screening in the rural Mississippi Delta areas of eastern Arkansas, which is co-directed by Dr. Erwin, and some informal testing of patient-to-patient contacts by Dr. Hutchins.

The outreach model, the Delta Witness Project™, recruits, trains, and promotes African American breast and cervical cancer survivors as role models and lay health advisors through rural churches and community settings. (See Appendix A). These women speak out about the need for breast self-examination, clinical breast exams, screening mammography, and Pap tests.⁽²⁴⁾ Results from the pilot project indicate that this program is an effective method to reach minority women, and current survey analysis of 221 women demonstrates a significant increase in the practice of breast self-examination and mammography.^(24,25)

The theoretical basis for the outreach project includes communication strategies and models for behavior change which address many of the same barriers which apply to clinical trial accrual. For example, low income and low literacy populations have not been adequately reached with traditional health communication strategies designed for the general public.

To be effective, messages must meet the needs of individuals at all literacy levels and cultural backgrounds. For individuals who read poorly, the setting needs to be peer-oriented⁽²⁶⁾ and focused on perceiving information concretely and on processing information actively.⁽²⁷⁾ Messages must regard all styles of learning and both brain hemisphere preferences. Both achievement and attitude are affected positively when learning styles and left and right brain preferences are addressed.⁽²⁸⁾ Many individuals without formal educational backgrounds are right-brained processors who learn best from demonstrated instructions in an open-ended setting that includes emotional judgements.^(27,29) Cancer survivors can provide these experiential, right-brain, personal messages.

Important predictors of behavior are related to cognitive and sociocultural models such as health beliefs,⁽³⁰⁾ health locus of control,⁽³¹⁾ social relationships,⁽¹⁹⁾ and social norms.⁽²⁰⁾ In cancer screening and education, projects that use direct education (in-person, small groups, one-on-one or tailored messages) with culturally sensitive methods are the most effective cues to action for addressing health beliefs.^(12,18,21,32) It is hypothesized that these direct education methods by women survivors to women patients, as peers from similar cultural backgrounds, will provide a meaningful message which can help patients address and overcome the emotional, social, and experiential issues and barriers involved in the clinical trial process.

With respect to minorities, recent information about outreach programs and the knowledge gap between Caucasians and African Americans indicates that there is a credibility problem related to the transfer of information to underserved populations. Freimuth reports that in the African American population, there is a "preference for ordinary African American people who had experienced and overcome a problem," which is the basis of the Witness Project™ model.⁽¹⁵⁾

Although the Witness Project™ is designed for reaching African American women, we suggest that this "role model" method may be effective for recruitment of all women to clinical trials. It is hypothesized that this type of initiative, involving women from various cultural backgrounds to speak to potential trial participants, is likely to address the social and cultural issues of credibility, empowerment, perceived efficacy, language, and community support.

Another program which has been used to help women negotiate the health care system and obtain appropriate care is the Patient Navigator program developed at New York's Harlem Hospital by Dr. Harold Freeman and his staff (personal communication, 1993-1994). This model includes trained lay advisors on the staff of the hospital who are assigned to work with screening and newly diagnosed patients to assure their follow-up care is accomplished in a timely and culturally sensitive manner and that they do not become lost to the system because of lack of resources or psychosocial difficulties. This effort to meet the needs of a multicultural and underserved patient population also utilizes a personal intervention approach.

3. PRELIMINARY STUDIES

3.1 The Witness Project

Since 1989, Dr. Erwin has co-directed an education research project within the African American and lower income communities in Arkansas. Based upon professional training in medical anthropology, together with a colleague in health education, Dr. Erwin developed the intervention known as the Witness Project™. This is an educational program in which rural and lower income African American women who have had early stage breast or cervical cancer tell about their experiences to encourage and educate other women about the importance of early detection.⁽²⁴⁾ The role models "witness" by talking about their cancer experiences, stressing the importance of early detection, and answer questions about their personal experiences, fears, and concerns. The witness education session addresses the fears and beliefs many women hold about cancer, demonstrates that the diagnosis of cancer is neither a death sentence nor a punishment, and provides the participants with accurate, personal information about cancer and early detection and treatment methods. The program is designed to empower women to prioritize their own health care needs and to counter the fear and fatalism so often found among minority and lower income populations. The program addresses important cultural, educational and theoretical parameters.⁽³³⁻³⁵⁾ Program activities include dramatic relief (i.e., story-telling), consciousness raising ("You can help take care of yourself." "This could happen to you."), and environmental re-evaluation ("Cancer is a problem for African Americans."), processes suggested by the transtheoretical theory regarding behavior change.⁽³³⁻³⁶⁾

Initial qualitative research to develop the Witness Project™ included focus groups, key informant interviews, and participant observation by Dr. Erwin. The research includes qualitative assessments and quantitative surveys with 450 primarily African American women from intervention and control counties in eastern Arkansas. These counties are in the heart of the Lower Mississippi Delta, an area characterized by extreme poverty, (20.9% poverty rate and per capita income of \$10,192 in 1988), and a wide variety of social ills. Results have demonstrated that the project is culturally sensitive, accepted and supported by African American church

groups and communities.⁽²⁴⁾ As mentioned above, current analysis also demonstrates a significant positive behavior change for breast self-examination and mamography.⁽²⁵⁾ As 45% of the participants have less than a 12th grade education, and 52% reported annual incomes under \$10,000, this intervention is making a significant impact on an underserved population which has not responded to traditional methods to increase early detection.

Dr. Erwin is currently expanding the project by establishing the Witness Instructional Training (WIT) program to recruit and train over 100 women in 21 counties to provide local Witness Projects™ in their communities (NCI funding, July 1995). This training program includes a culturally appropriate training curriculum, descriptive videotape, and implementation manual for establishing the outreach intervention nationwide. Preliminary research and educational programming demonstrate the ability of the principal investigator to develop culturally sensitive intervention methods for reaching underserved and minority women. Dr. Erwin has demonstrated effectiveness in using qualitative research methods to design and plan cancer education projects from the pilot phase through research, implementation, and dissemination.

3.2 Experience of the Key Personnel

Pertinent to the specific aims of this proposal, Dr. Erwin has been a member of the SWOG CWH since 1993. In this capacity, she worked with Dr. Hutchins to examine mechanisms for evaluating gender and minority representation on trials. She has been assigned the task of developing a behavioral concept to aid accrual to clinical trials. The proposed research is a direct result of the work on this committee. Outcomes and results from this feasibility study will be the foundation for development of a SWOG protocol concept for targeted institutions with deficiencies in accrual of underserved women, as well as a measure of the contribution of the model to the patient's accrual experience and consent process. (See Letter of Support.)

Dr. Hutchins has been actively involved in SWOG since 1983 and has registered significant numbers of patients on trials as evidenced by 13 publications of SWOG trials. Her largest clinical trial experience has been as principal investigator of the last intergroup, node-negative adjuvant breast cancer trial that accrued more than 4,000 patients. A large proportion of her clinical practice is the treatment of breast cancer patients.

Dr. Klimberg has been actively involved in SWOG since 1992, sitting on the Breast, CWH, and Cancer Control Research Committees. She is chairman for a prospective trial concept to study the under-utilization of breast conservation surgery. Dr. Klimberg is principal investigator on a series of local trials which are supported by a Career Development Award from the American Cancer Society and Scherring Corporation. As her practice is dedicated solely to breast disease, she sees a majority of ACRC's breast cancer patients.

In the area of data management, Jeana Naile directs the ACRC clinical research and data management office (CRDM). She brings 8 years of data management experience to this project, as a former clinical research associate for UAMS and as a data coordinator for the SWOG Statistical Center at the Fred Hutchinson Cancer Research Center in Seattle, WA. She serves on the board of directors for the Society of Clinical Research Associates and has been certified by

that organization as a CRA. In her position, she is responsible for coordinating approximately 100 active protocols with 300 patients entered annually.

Ms. Mack, RNP, OCN, and Ms. Foster, RN, are experienced oncology nurses from the medical and surgical oncology clinics at ACRC. They have extensive experience talking to and instructing patients regarding clinical trials and the treatment process. Ms. Colvert, RNP, OCN, is breast service coordinator for the UAMS department of surgical oncology. She has clinical and research experience and is active in the local oncology nursing society, SWOG, and the Susan G. Komen Breast Cancer Foundation.

3.3 Pilot Experience

Dr. Hutchins has incorporated the conceptual components of the Witness Project™ in an informal fashion to aid patients who are considering participation in a particularly strenuous treatment regimen for melanoma. Three patients who participated in the trial were asked by Dr. Hutchins if they would consider talking to other patients about the protocol experience. The survivors were enthusiastic about this opportunity and the patients responded positively. Dr. Hutchins now routinely asks prospective participants if they would like to talk with a survivor who has completed the trial. If the patient is interested, this contact is accomplished through telephone calls initiated by the survivor. Although there is no rigorous data for these informal contacts, Dr. Hutchins indicates that the encounter has been helpful for the prospective patients, the survivors, and the physician. Moreover, she has found the melanoma survivors to be enthusiastic about being able to help other patients.

This experience serves as an informal pilot for the proposed study and provides some guidance for training patients to counsel other patients, as well as initial evidence for the usefulness of this model. In addition, testing the two methods of contact (direct, in-person or telephone) are the results of combining the effective properties of the Witness Project™ and Dr. Hutchins' experience with the melanoma patients.

Based on past experience, the investigators anticipate that direct, in-person contacts by role models may be the most effective method (particularly for minority or low income patients), but it may also be the most costly and inconvenient. In addition, it may not be feasible in a regional referral center, so there is a need to explore the possibilities of telephone contacts or some combination of the two. Therefore, the design will include two methods. An opportunity to evaluate and revise the methods (using focus groups and encounter forms) will occur four times during the intervention phase of the two-year plan. Working with the staff and role models, new or different contact methods will be developed and initiated if the proposed methods prove to be unfeasible.

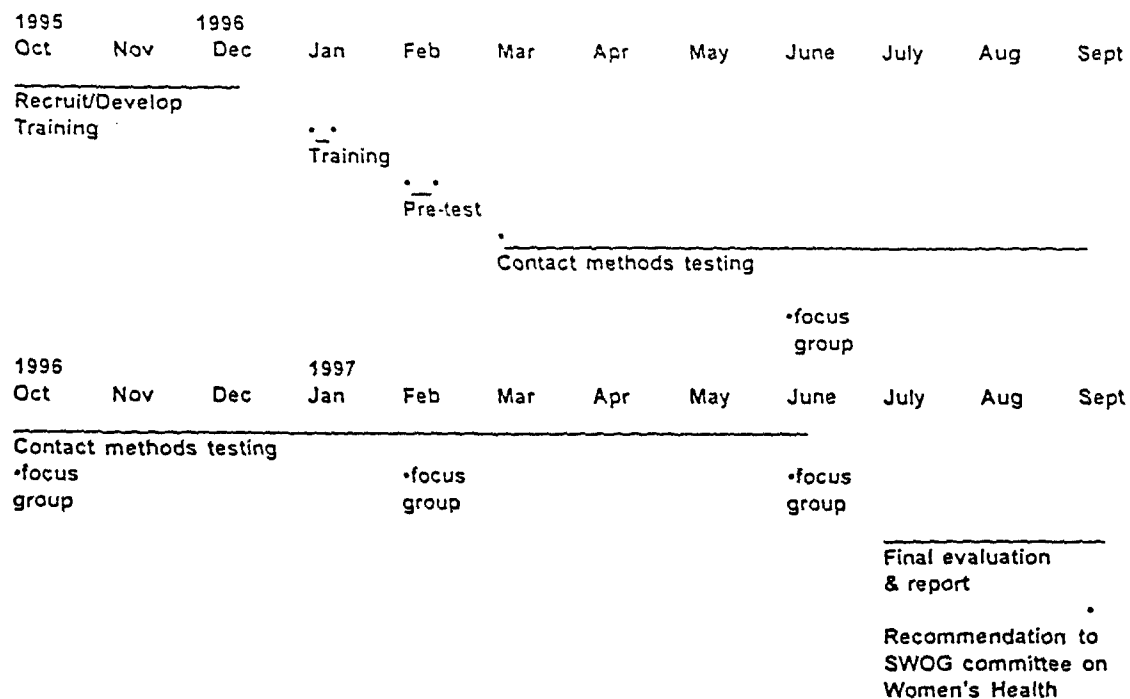
4. RESEARCH DESIGN AND METHODS

4.1 Program Overview

During the two years of this feasibility study, we propose to recruit a minimum of six of 97 surviving breast cancer patients who have completed a breast cancer clinical trial protocol at

UAMS. These women will be identified through the records of the ACRC data management office, under the direction of Ms. Jeana Naile, with Drs. Hutchins and Klimberg. Survivors from various cultural and socioeconomic backgrounds will be trained to talk with other women about their experiences as a clinical trial participant and to present the benefits and problems of that experience. These role models will serve as *Patient Advocates for Clinical Trials (PACT)* members to assist the health care team in providing a culturally sensitive, experiential focus to address and overcome some of the accrual barriers. It is anticipated that it will take three months to complete recruitment and finalize the training program. The one-day training will be scheduled at a time convenient for the trainees. If necessary, it can be repeated 2 or 3, times depending on the number of trainees and scheduling difficulties. One month will be dedicated to training session(s). This will allow approximately six weeks of methods and forms pre-testing. (See Figure 1.) The PACT members will then begin testing the patient-contact methods. Over 15 months, they will develop a systematic way to work with the health care team to meet and discuss clinical trials with all eligible breast cancer patients. Process evaluation will be included throughout the two years, and focus groups and survey evaluations will provide feasibility and some outcome measures.

Figure 1. Timeline



4.2 Sampling

An estimated 80 breast cancer patients per year are eligible to enter one of 24 SWOG or NSABP protocols at UAMS and its affiliated John L. McClellan Memorial Veterans Administration Hospital (VA). All of these patients will be included in this research. As this is a methodological feasibility study, there is no need to include experimental sampling or randomization methods. Therefore, all women who would, under current protocol standards, be approached by their surgeon or oncologist to participate in a clinical trial protocol will also be invited to speak with a PACT member.

4.3 Recruitment of PACT Members

Through the current ACRC data management system, all 97 breast cancer survivors who have participated in a clinical trial will be sent a letter from their physician (oncologist and/or surgeon) to explain this project. As a follow-up to these letters, Drs. Klimberg and Hutchins will make personal contacts with patients who meet the criteria for the PACT team.

In order to provide culturally similar PACT members with whom prospective patients can identify and trust, we will attempt to recruit women who meet the following criteria: 1) One African American and one Caucasian survivor with an income at less than or equal to 200% of poverty (\$1200/month for an individual), 2) One African American and one Caucasian survivor with a high school education and median income (\$15,000 - \$30,000), and 3) One African American and one Caucasian survivor with some college or a degree and higher income level. In addition, we will try to include a variety of ages and at least two women 65 years of age or older. This will provide the best possible cultural diversity.

Residence within the central Arkansas area is a consideration because one of the contact methods will require that PACT members be available to visit the clinic two to three days per week. It is anticipated that living over one and a half hours away from Little Rock will be too great a travel burden. Survivors from outside central Arkansas who want to participate will also be offered training; they can be called on for telephone contacts or contacts with patients who return to their area.

The investigators recognize that it may be difficult to recruit women meeting each of these criteria. At this time, some preliminary contacts by Drs. Hutchins and Klimberg and Ms Naile indicate that there are two African American patients from middle to lower income and two Caucasian patients from middle to upper income levels who may be interested in participating. These women are at least four years post-treatment.

The income criteria is expected to be more difficult to meet. If our initial recruitment efforts to fill all 6 positions fail, we will begin the project by meeting the racial criteria. We will then continue to try to recruit into the unfilled positions and modify the contact methods as necessary. We will still be able to approximate some of the most important cultural characteristics. We

would like to train at least two additional women from each race to be trained to serve as alternates in case any of the role models must end their participation.

Each PACT member will receive a stipend of \$150 for participating in the training and pre-testing phase of the project, plus mileage if she travels more than 25 miles to reach UAMS. During the 15 months of patient contact activity, she will be paid \$25 per initial direct patient contact, plus transportation, and \$15 per initial telephone contact. Follow-up contacts or visits by PACT members will not require additional payments. Telephone calling cards will be issued to PACT members for long distance calls.

The principle investigator will conduct an individual interview in person or by telephone with each survivor who agrees to participate as a PACT member, after she has been contacted by her surgeon or oncologist. During this interview, Dr. Erwin will briefly explain the project and evaluate 1) the type of experience the patient had during her clinical trial participation, 2) her interest level, enthusiasm, and ability to commit to this type of project, and 3) her communication and team-player skills. After the individual interviews, the selected candidates will be brought together for training. If a PACT member cannot complete the project, a trained alternate approximating her cultural characteristics will be recruited to complete her position.

4.4 Training of PACT Members

PACT members do not need extensive training in the protocols themselves, as they will have assistance from the data management team and protocol nurses. These women will primarily be speaking about their own experiences and decision-making processes. Training will require one group meeting of at least six hours. Additional training sessions will be held as other women are recruited, depending on attrition and initial recruitment success. As all PACT members will have spent numerous hours in the clinic over several years at ACRC, they are familiar with the staff, faculty, system, and facility.

Their communication skills and training with the encounter forms will be practiced and refined during the six weeks of pre-testing. This pre-testing time will also allow the PACT members to have creative and decision-making power about the contact and reporting methodology.

The one-day group training session will be lead by Dr. Erwin and one or more of the nurse practitioners who work with patients on clinical trials (Mack, Colvert or Foster). It will include the following topics:

1. Why are you here? The nature of clinical trials and the barriers to accrual.
Educational objective: To understand the psychosocial issues which effect participation in a clinical trial.
2. What will you do? Communication skills training, counseling skills, learning to use literature and materials, and telling their stories.
Educational objective: To be comfortable talking with women, using the literature available, and responding to patient questions about their experience.

3. What does it mean? How the project will be evaluated: their roles, the methods, and the importance of qualitative evaluation techniques.
Educational objective: To know how to use the encounter forms and participate in group sessions for evaluating the study goals.
4. How will you do it? Role-playing, practice telling their stories, and planning contact methods.
Educational objective: To be comfortable and practiced telling their stories and contacting patients by phone or in person.

ACRC has participated in the development of an adult education multi-media training program that is used to train health educators to approach an adult in a learning session. This 1-hour self-study unit will be incorporated into the PACT training sessions to give the members some background on learning styles and educational methods.

PACT members will be trained to effectively communicate their own experiences and the process and factors which helped them to choose to participate in a clinical trial. They will be instructed not to exploit their position as a survivor in unduly influencing prospective patients. They are to assist patients by providing a positive, culturally sensitive perspective about the protocol and the factors which played a role in their decision to go on a protocol. They will be trained to address myths or misconceptions that the patient may have. The investigators realize that PACT members are in a position to be influential with new patients, but the goal is not coercion or manipulation of patients. It is, rather, to enhance the communication process. This philosophy will be clearly presented to both PACT members and prospective patients. Physicians, nurses, and PACT members will be aware of this issue, and, if necessary during the contact methods testing, will consider providing patients with additional survivors who are not participants in clinical trials for a "second opinion."

The quality and consistency of each PACT member's presentation will undoubtedly vary according to a number of circumstances and factors. However, through the training process, all PACT members will be instructed to discuss the following basic topics with the prospective patient participant:

- 1) Why she chose to participate.
- 2) The benefits which she perceived from participating.
- 3) What was involved in the process for her.

This will insure a certain level of quality control among PACT members and assure that the basic information delivered to each prospective participant is comparable.

4.5 Development of Contact Methods

From the experience of the Witness Project™ and direct patient programs, like the American Cancer Society's Reach to Recovery program, it is anticipated that direct, one-on-one, personal contact may be the best method for communicating the intended messages and the experiences of

the PACT members. However, this is also the most time and labor intensive method and therefore the most costly to implement on a larger scale. We propose to test the direct, personal contact along with a personal, but more easily arranged, method of telephone contact.

Two different types of contact methods are planned: 1) direct, personal contact within the clinic (DPC); and 2) telephone contact at home following the clinic visit (TC). It is planned to test each method for a month at a time, alternating months. It is anticipated that after the first two months, PACT members and staff will refine the approach and mechanism for studying the contact methods to have a complete and systematic approach for the last 13 months of the study. Alternating the contact methods will allow the professional staff and PACT members to perform process and outcome evaluation after each method and make adjustments and changes for the next series in order to develop the most effective methodologies. As this is a feasibility study, it is important to allow opportunity for survivors and staff to refine and revise the methods throughout the study process.

During the DPC method, a schedule of all new breast cancer patients will be organized by oncology nurse specialists, Ms. Mack (medical oncology) and Ms. Colvert (surgery). With the assistance of Ms. Foster, PACT members will be matched by race and income with prospective patients and notified of the clinic visit time. All PACT members will have participated in a clinical trial, however they may not have participated in the specific trial being considered.

The ACRC Breast Clinics are from 8:30 until 4:30 on Tuesday, Wednesday and Thursday, so most new breast cancer patients will visit the clinic at these times. It is planned that by the third post-surgical visit to the ACRC, Dr. Klimberg or other surgical oncologist will briefly discuss the opportunities for adjuvant therapy and give the patient the opportunity to meet with a PACT member. If it is not possible to do this at this clinic visit, the patient will have the opportunity to speak to the PACT member during her next medical oncology consultation. During the pre-testing and first two months of testing, PACT team and physicians may decide to alter this process to best meet the needs of the patients and staff. The physician or nurse specialist will ask the patient to sign the consent form to participate in the study and visit with the PACT member. At this time, the professional staff will also tell the patient that this is part of a research project to investigate methods we use to discuss clinical trials with patients.

For the TC method, the surgical oncologist or medical oncologist will ask the patient for permission for a PACT member to contact her during the next week. The matching of survivor and patient will be the same as the DPC method. The PACT member will be notified about the patient and will call within 7 days of the clinic visit.

It is anticipated that the six PACT members will be matched with a culturally appropriate patient during the project. However, in order to evaluate the outcome in less than ideal circumstances, and to accommodate scheduling difficulties, PACT members will contact women who are not necessarily culturally similar in the last months of the study. Information from PACT members and patients about these encounters will help answer research question number 3, regarding the role of close cultural similarities. This is an important factor to consider in evaluating the feasibility of this type of program at the cooperative group level. Although it is hypothesized that

cultural similarities are important, it is necessary to understand how closely the role models need to approximate the specific cultural characteristics of patients in order to have a positive encounter and/or outcome.

Throughout the study, the nursing staff will monitor the PACT-patient encounters in order to assess the need for additional psychosocial training and support. The ACRC Behavioral Oncology program staffed by two full-time psychologists, will provide additional psychosocial training and support for PACT members as necessary.

4.6 Evaluation and Analysis

4.61 Evaluation of Training

PACT trainees will complete a qualitative evaluation form following the training session to allow them to discuss strengths and weaknesses of the process. They will be encouraged to make suggestions for improving the program in the future. To evaluate the educational objectives, PACT trainees will be asked to complete a pre- and post- training questionnaire. This will be anonymous in order to reduce the test-anxiety of the participants. It will be used in a non-judgemental way to ensure that the role models are comfortable with the concepts.

4.62 Evaluation of the Contact Methods

PACT members will complete a patient encounter form (See Appendix B) following initial discussion with the prospective patient. This will provide quantitative and qualitative evaluation of the PACT members' perspectives of the encounter. Patients will complete a similar encounter form in order to gain their opinions and to match for agreement between the two. Physicians will be encouraged to provide comments and suggestions on the contacts as well.

Four times, at approximately three-month intervals during the contact methods testing, we will organize two focus groups of 4-8 women each. One group will be patients who chose to participate in clinical trials, and one group will be patients who did not choose to participate in a clinical trial during the past three months. These focus groups will be lead by the principle investigator, Dr. Erwin. These groups are intended to include equal representation from both contact methods and all cultural backgrounds of women, dependent upon total numbers. As focus groups will be conducted four times over several months, this should allow adequate variation. It is likely that the nature of the questions discussed in the focus groups will change over time as more information is available. The goal of each group discussion will be to better understand the issues and factors which helped the women to address and overcome barriers to participation in the clinical trial, whether the women felt patient-to-patient contact provided culturally sensitive communication, and to determine which factors can be addressed by the intervention and the role models. Focus group members will not be paid for participating in the groups, but a meal will be provided and transportation will be paid for travel over 25 miles to UAMS.

PACT members will meet as a group with staff members weekly during the pre-test schedule, then monthly for the remaining months of the study. These meetings will provide qualitative process evaluation for necessary methodological revisions. Issues, problems, and positive experiences will be discussed. This will also provide team building and comraderie among the PACT members and the staff. From past experience with intervention programs using volunteers and lay personnel, the investigators recognize the importance of communication and support for the role models, and the potential for substantial qualitative data from their encounters.

4.63 Evaluation of Outcomes

The qualitative and quantitative data gathered from this study will be used to determine the feasibility and methodological componenets of improving accessibility by all women into breast cancer clinical trials and to answer the research questions. The outcomes to be measured include:

1. Responses from the PACT members and staff on training evaluation forms.
2. The attrition rate of trainees and active PACT members.
3. Responses on encounter forms from all patients contacted.
4. Responses on encounter forms from PACT members.
5. Responses from focus groups regarding the contact methods, problems and benefits.
6. Qualitative comments and ethnographic notes from staff and role models throughout the process.
7. The total number of contacts by method.
8. Comparison of the total number of women who participated in breast cancer clinical trials with totals in the past three years at UAMS.
9. Comparison of encounter form responses by contact method.
10. By contact method, the number and characteristics of women who choose to participate versus the number of women who do not choose to particpate during the study period.

These data should provide a basis for answering the study research questions and determining the feasibility of using the contact methods by role models to inform women about clinical trials. Dr. Erwin will present semiannual progress reports on the study to the SWOG CWH. Upon completion of the study, these data will provide a basis for concept development and a recommendation to the SWOG CWH regarding the applicability of this model for use within the cooperative group. Although these data will not provide adequate basis for measuring the effectiveness of the methods to increase accrual, they should provide indicators for further research on whether the recruitment and training of culturally appropriate role models to contact prospective clinical trial participants will overcome barriers to accrual and improve the accrual process.

4.64 Analysis and Data Management

It is anticipated that over the 15 months no more than 300 quantitative data forms (encounter forms from a maximum 150 breast cancer patients and PACT members following the contact) will be generated. These data can be managed on a PC-based DBase IV (or revised ACCESS) program and analyzed with SAS or SPSS. The encounter forms will be collected, stored and entered in the ACRC data management office under the direction of Ms. Naile. Analysis will be done by the Center for Outcomes Research and Effectiveness (CORE) at UAMS. Descriptive statistics will be available to characterize the patient groups. Depending on sample size and distribution, t-tests, chi-square analysis or other tests of significance will compare encounter form responses of clinical trial participants and non-participants according to the desired characteristics. Other comparisons will evaluate variations by contract method, PACT members, and other sociocultural variables.

Qualitative data from focus groups, encounter forms, and individual reports from staff and PACT member will be entered into a textbase program (Ethnograph). Process evaluation and analysis of these data will be the responsibility of Dr. Erwin with assistance from Drs. Hutchins and Klimberg. Ethnographic notes will be entered periodically and a log will be kept to document methods, revisions, attrition, and notable encounters.

Following the final evaluation and outcomes measures, a report will be compiled and presented to the SWOG CWH at the September 1997 meeting for future research and implementation recommendations.

5. HUMAN SUBJECTS

(1) The subject population includes approximately 150 women > age 18 who are referred to the Arkansas Cancer Research Center at the University of Arkansas for Medical Sciences for consultation regarding the treatment of breast cancer on a clinical trial. None will be excluded because of race or ethnic group. The primary objective of this study is to determine if intervention strategies designed to have breast cancer survivors who are former clinical trial participants consult with eligible prospective breast cancer patients will improve accessibility and accrual to clinical trials.

(2) Evaluation data will be obtained via telephone, in-person interviews, and or group discussion as described in the research proposal. The data will be used for research purposes only. Oral consent is requested before the survey begins.

(3) Recruitment of women will be accomplished under the direction of their surgeon and/or oncologist. The physician will tell them that a former clinical trial participant is available to meet with them or to telephone them and talk to them about their own experiences and the physician will ask for the patient's permission to allow the role model to talk with them. Consent for the role model to speak with the patient will be documented by a signature on the consent form. To guard against exploitation or the appearance of unnecessary pressure to

participate in clinical trials, women will also have access to a breast cancer survivor who chose not to participate in a clinical trial.

(4)/(5) The only risk to the women involved in the study concerns their confidentiality. All evaluation forms will be assigned a code number, and the forms will be maintained in the clinical research data management office along with the other IRB approved clinical trial records. Rules of the Health Care Finance Administration will be followed in obtaining any information from their patient records (regarding treatment decisions and protocol participation). All information discussed with the staff and role models will be kept confidential or encoded.

(6) No risks will occur other than those described above for the women. The benefits to the women include increased information regarding clinical trials and treatment options, and receiving the best available cancer care.

LITERATURE CITED

1. Millon-Underwood, S., Sanders, E., & Davis, M. (1993). Determinants of participation in state-of-the-art cancer prevention, early detection/screening, and treatment trials among African Americans. *Cancer Nursing*, 16(1), 25-33.
2. Modiano, M., Vilar-Werstler, P., Lash, S., et al. (1992). Increasing enrollment of minorities into clinical trials through community involvement. *Proc Annu Meet Am Soc Clin Oncol*, 11, A409.
3. Hutchins, L. (1993, October). *Groupwise analysis of gender ratios in Southwest Oncology Group studies in non-gender related tumors*. Paper presented at the SWOG Meeting plenary session, Chicago, IL.
4. Chase, E.M., Modiano, M., Brooks, R., et al. (1991, September). *Minorities participation in cancer cooperative clinical trials: Preliminary Arizona Cancer Center (ACC) experience*. Paper presented at the North American Conference on Cancer in Hispanics, Tucson, AZ.
5. Freeman, H.P. (1993). The impact of clinical trial protocols on patient care systems in a large city hospital. *Cancer* 72 (4 Suppl), 2834-8.
6. Valdivieso, M., Kraut, M., Wozniak, A., and Hussein, M. (1993). Disease and socioeconomic factors, not bias, influence participation of lung cancer patients in clinical trials. *Proc Annu Meet Am Soc Clin Oncol*, 34, A1232.
7. Rai, K., Kalra, J., Grunwald, H. (1990). Role of culture and language: Experiences at Queens Hospital Center. *Proc Annu Meet Am Soc Clin Oncol*, 9, A240.
8. Kennedy, P., Presant, C.A., Wiseman, C., et al. (1990). Recruitment of minority (MIN) patients (PTS) for cancer clinical trials (CCT). *Proc Annu Meet Am Soc Clin Oncol*, 9, A248.
9. Brawley, O.W., Hunter, C.P., Johnson, K.A., et al. (1993). The recruitment of minority patients (pts) to cancer clinical trials. *Proc Annu Meet Am Soc Clin Oncol*, 12, A363.
10. Westerman, M., Sarpal, S., Schlichting, E., et al. (1990). Protocol accrual in two low socioeconomic groups of cancer patients with different proportions of minority patients. *Proc Annu Meet Am Soc Clin Oncol*, 9, A230.
11. National Institute of Health/National Cancer Institute. (1992). *What are clinical trials all about?: A booklet for patients with cancer*. (NIH/NCI Publication No. PUB 92-2706).

12. Skinner, C.S., Strecher, V.J., & Hospers, H. (1994). Physicians' recommendations for mammography: Do tailored messages make a difference?. *Am J Public Health*, 84, 43-49.
13. Zapka, J.G., Stoddard, A.M., Costanza, M.E., & Greene, H.L. (1989). Breast cancer screening by mammography: Utilization and associated factors. *Am J Public Health*, 79, 1499-1502.
14. Jepson, C., Kessler, L.G., Portnoy, B., et al. (1991). Black-white differences in cancer prevention knowledge and behavior. *Am J Public Health*, 81, 501-504.
15. Freimuth, V.S. (1993). Narrowing the cancer knowledge gap between whites and African Americans. *Monogr Natl Cancer Inst*, 14, 81-91.
16. Coyne, C.A. & Mettger, W. (1993). The National Workgroup on Cancer and Literacy: A collaborative approach to reaching undeserved audiences. *J Cancer Education*, 8(1), 22.
17. Meade, C.D., Diekman, J., Thornhill, D. (1992). Readability of American Cancer Society patient education literature. *Oncol Nurs Forum*, 19, 51-55.
18. House, J.S., Landis, K.L., & Umberson, D. (1988). Social relationships and health. *Science*, 241, 540-545.
19. Bandura, A. (1977). *Social Learning Theory*. (Englewood Cliffs), New Jersey: Prentice Hall.
20. Bailey, E.J. (1987). Sociocultural factors and health care-seeking behavior among black Americans. *J Natl Med Assoc*, 79, 388-392.
21. Dignan, M.B., Michielutte, R., Sharp, P., et al. (1991). Use of process evaluation to guide health education in Forsyth County's project to prevent cervical cancer. *Public Health Rep*, 106, 73-77.
22. Hargreaves, M.K., Ahmed, O.L., Kofi, A. et al. (1989). Nutrition and cancer risk: Assessment and preventive program strategies for black Americans. In Jones LA (Eds.), *Minorities and cancer* (pp. 77-94). New York: Springer-Verlag.
23. Warnecke, R. (1981). Intervention in black populations. In C. Mettlin & G.P. Murphy (Eds.), *Cancer among black populations* (pp. 167-183). New York: Alan R. Liss, Inc.
24. Erwin, D.O., Spatz, T.S., & Turturro, C.L. (1992). Development of an African American role model intervention to increase breast self-examination and mammography. *J Ca Ed*, 7(4), 311-19.

25. Spatz, T.S., Erwin, D.O. et al. (in review). Witness Model Effective in Increasing BSE and Mammography. Manuscript submitted for publication.
26. Carbo, M. (1984). Research in learning style and reading: Implications for instruction. *Theory Into Practice*, 23, 72-76.
27. McCarthy, B., & Morris, S. (1992). *The 4MAT system*. Chicago: Excel, Inc.
28. Friedman, P., & Alley, R. (1984). Learning/teaching styles: Applying the principles. *Theory Into Practice*, 23, 77-81.
29. Segalowitz, S.J. (1987). *Two sides of the brain*. New York: Prentice Hall.
30. Becker, M.H., Haefner, D.P., & Kasl, S.V. (1977). Selected psychosocial models and correlates of individual health-related behaviors. *Medical Care*, 15, 27-46.
31. Wallston, B.S. & Wallston, K.A. (1978). Locus of control and health: A review of the literature. *Health Ed Monographs*, 6, 107-117.
32. Lacey, L.P., Phillips, C.W., Ansell, D., et al. (1989). An urban community-based cancer prevention screening and health education intervention in Chicago. *Public Health Rep*, 104, 536-541.
33. Prochaska, J.O., DiClemente C.C. & Norcross, J.C. (1992). In search of how people change; Applications to addictive behaviors. *American Psychologist*, 47, 1102-1114.
34. Airhihenbuwa, C.O. (1992). Health promotion and disease prevention strategies for African Americans: A conceptual model. In Braithwaite, R.L. & Taylor, S.E. (Eds.), *Health issues in the black community* (pp. 267-280). San Francisco: Jossey-Bass Publishers.
35. Green, L.W., Krueter, M.W., Deeds, S.G. & Partridge, K.B. (1980). *Health Education Planning: A Diagnostic Approach*. Palo Alto, CA: Mayfield Pub. Co.
36. Prochaska, J.O., DiClemente, C.C. (1983). Stages and processes of self-change of smoking: Toward an integrative model of change. *J Consulting and Clin Psych*, 51, 390-395.



Erwin, Deborah O.

University of
Arkansas
for Medical
Sciences

DATE: June 7, 1995

TITLE: "Using Role Models to Inform Women About
Clinical Trials" (NIH) (3750)

4301 W. Markham
Little Rock, Arkansas
72205-7199

PRINCIPAL INVESTIGATOR: Erwin, Deborah O., Ph.D.
Slot: 623-1

UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES ASSURANCE #
M-1451, IDENTIFICATION #01.

This application includes activities involving human subjects. I have reviewed and approved it by expedited review on June 1, 1995 in accordance with our assurance approved by the Public Health Service. This project will be subject to continuing review.

Robert S. Abernathy M.D.
Robert S. Abernathy, M.D., Ph.D.
Chairman
Human Research Advisory Committee

RSA/ap

Erwin, Deborah O.

Appendix B

Encounter questions for Evaluation (to be pre-tested and revised)

Method of Contact: In-Person Telephone

1. How would you describe the patient's reaction to your comments about participating in clinical trials?

Very positive 1 Positive 2 Neutral 3 Negative 4 Very negative 5

2. Do you think this patient will participate in a clinical trial?

Definitely will 1 Might 2 Unknown 3 Might Not 4 Definitely will not 5

3. How would you describe the patient's reaction to having you talk with her? Was she receptive?

Very comfortable 1 Comfortable 2 Neutral 3 Uncomfortable 4 Very uncomfortable 5

4. How would you describe the patient's behavior while you talked with her?

Very relaxed 1 Relaxed 2 Can't tell 3 Anxious 4 Very anxious 5

5. How would you describe your own feelings about your discussion with the patient?

I felt great about it 1 Good about it 2 Neutral 3 Not very good 4 I felt bad about it 5

6. Did you finish your encounter discussion? Were you able to give the patient all the information?

Yes, all 1 Most 2 Half-way 3 Only a little 4 No, none 5

7. Did the patient say she would like to talk with you again about this topic?

Yes 1 No 2

8. Do you think that you are culturally similar to the patient?

Very similar 1 Similar 2 Unknown 3 Some different 4 Not at all alike 5

9. Is your cultural background (similar or different) an important part of how you related or did not relate to the patient?

Very important 1 Important 2 Maybe 3 Not important 4 Not at all important 5

Please describe:

10. Other comments about ...

11. How could this encounter have been better or improved?

LETTER OF SUPPORT



LOYOLA
UNIVERSITY
CHICAGO

Kathy S. Albain, M.D.
Associate Professor of Medicine

2160 South First Avenue
Maywood, Illinois 60153

Telephone: (708) 327-3100
Fax: (708) 327-3231

LOYOLA UNIVERSITY MEDICAL CENTER
Cancer Center
Division of Hematology/Oncology

May 30, 1995

Deborah O. Erwin, Ph.D., CTR
Arkansas Cancer Research Center
University of Arkansas Medical Sciences
4301 West Markham Slot 623-1
Little Rock, Arkansas 72205

Dear Dr. Erwin:

Thank you for your recent presentation at the Southwest Oncology Group Committee on Women's Health Advisory Board meeting. Both Group members and our Lay Advocates are enthusiastic about the progress made on this concept and are committed to further collaboration with your group as the project matures.

Thus, this letter is to officially confirm that the Southwest Oncology Group Committee on Women's Health eagerly awaits the completion and results of the first phase of your project, the single institution pilot study: "Using Role Models to Inform Women about Clinical Trials". Once a successful and efficient survivor model is developed via your pilot study, the Southwest Oncology Group intends to provide the venue for you to conduct the second phase of the project. This second trial would test the survivor model prospectively in a cooperative group setting across targeted institutions with deficiencies in accrual of underserved women, as well as measure the contribution of the model to the positive enhancement of an individual patient's accrual experience and the consent process.

Therefore, I encourage you to submit the initial Arkansas pilot phase for funding under the National Action Plan on Breast Cancer Innovative Small Grant Program. Clearly, your project addresses several of the targeted concerns under the "Clinical Trials Accessibility" high priority area, as well as directly taps another of the six high priority areas, "Consumer Involvement". Specifically, your pilot study employs breast cancer survivors in a model which should circumvent several of the important patient barriers to participation in clinical trials. Your model indeed should remove the barriers of understanding through directed information given in a socio-culturally "matched" manner, survivor to survivor. Also, this project should overcome one of the major "physician barriers" faced by those of us who are breast cancer clinical trialists: frustration that we do not, in actual practice, have sufficient time to tailor the trial information to the patient's level or to provide adequate post-interview support after the initial presentation of the trial.

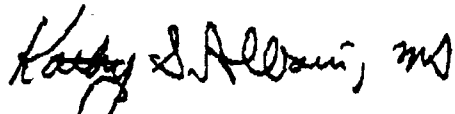
Overall, our Committee supports your project because it goes beyond the intent to simply

(Continued)

Dr. Deborah O. Erwin
Page Two

enhance accrual numbers and enters the arena of personal experience between two survivors in order to address realistic fears and concerns. Please keep me up-to-date on your progress.

Sincerely yours,



Kathy S. Albain, M.D.
Chair, Committee on Women's Health
Southwest Oncology Group

cc: Charles A. Coltman, Jr., M.D.
John J. Crowley, Ph.D.
Dana Sparks, M.A.T.
Marjorie Godfrey

APPENDIX J

Body of Southwest Oncology Group Cancer Control Research Proposal
"Enhancing Well-Being During Breast Cancer Recurrence"

Study Coordinators: Carolyn Gotay, Ph.D., Michelle M. Melin, Carol Moinpour, Ph.D., Stephanie Green, Ph.D., Kathy S. Albain, M.D., Silvana Martino, D.O., J. Wendall Goodwin, M.D., Laura Hutchins, M.D., Brian Issell, M.D. and the SWOG Lay Advocates Steering Committee.

Funded as a "Gold Standard Proposal" of the USAMRMC Breast Cancer Research Proposal.

The following grant proposal is proprietary information



DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
FORT DETRICK, FREDERICK, MARYLAND 21702-5024

11 December 1995

Breast Cancer Research Program

Charles A. Coltman
14980 Omicron Drive
San Antonio, TX 78245-3217

Dear Doctor Coltman:

It is my pleasure to inform you that your research proposal entitled, Enhancing Well-Being During Breast Cancer Recurrence, was judged to be among the top 5% of all proposals received by the 1995 DoD Breast Cancer Research Program (BCRP), earning it the distinction of "Gold Standard" proposal. Following nearly three months of evaluation and rigorous scientific peer review, the research you proposed was judged to be extremely promising and highly relevant to breast cancer.

In order for the committee to complete their evaluation of your grant, we must have documentation on Human and/or Animal Use, as appropriate, as well as your Safety Plan no later than 10 January 1996. Specific guidelines concerning these requirements can be found in the Broad Agency Announcement (BAA) For Breast Cancer Research (1 June 1995) on pages 37-38 as well as Appendices 2, 3, 4 and 5. The BAA specifically states that Appendices for Human Use & Anatomical Substances, Animal Use, and Safety must be immediately available upon USAMRMC request on or about 1 Feb 1996 (pg 38). Your Appendices are due earlier so that we can fund you as quickly as possible.

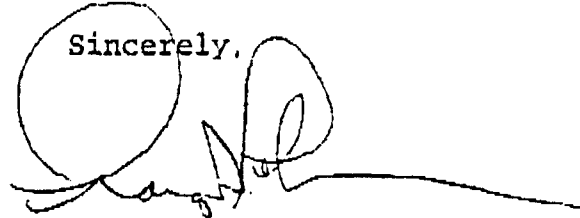
Please send five copies of these appendices to Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-PLF, Building 1076 (Breast Cancer Research Program), Fort Detrick, Frederick, MD, 21702

-2-

(ATTN: Ms. Robin King). Failure to submit the Human Use & Anatomical Substances, Animal Use and Safety documentation by 10 January 1996 may result in the removal of your proposal from the funding list. Send the attached fax cover sheet to Dr. Isabelle Crawford immediately, to acknowledge receipt of this letter and understanding of its terms.

If you have already received funding elsewhere and no longer wish to be considered by the Breast Cancer Research Program, let us know as soon as possible so that we may consider others for award. Please notify us by Fax (301-619-7796) or certified/overnight mail to the address above. Again, congratulations on a very promising proposal. Once we receive your supplemental documentation we will complete your evaluation as quickly as possible.

Sincerely,

A handwritten signature in black ink, appearing to read 'Craig D. Lebo', with a long horizontal flourish extending to the right.

Craig D. Lebo
Deputy for Acquisition Division

Attachment

Proposal Title

ENHANCING WELL-BEING DURING BREAST CANCER RECURRENCE

Please provide six (6) key words to be considered when assigning your proposal to a peer review panel.

RECURRENCE

PEER SUPPORT

QUALITY OF LIFE

DEPRESSION

PSYCHOSOCIAL

INTERVENTION

Type within outline; approximately 200 words.

WHILE MANY BREAST CANCER PATIENTS CAN REALISTICALLY EXPECT TO BE CURED OF THEIR DISEASE, SIGNIFICANT NUMBERS OF PATIENTS WILL EXPERIENCE A RECURRENCE OF THEIR BREAST CANCER AT SOME POINT. THE LIMITED RESEARCH THAT HAS FOCUSED ON THE PSYCHOSOCIAL IMPACT OF BREAST CANCER RECURRENCE HAS DEMONSTRATED THAT THIS IS A TIME OF ENORMOUS CRISIS, WITH HIGH LEVELS OF DISTRESS AND DEPRESSION, SIGNIFICANT SYMPTOMATOLOGY, AND AN ABSENCE OF EFFECTIVE COPING STRATEGIES. FEW, IF ANY, SUPPORT SERVICES ARE CURRENTLY DIRECTED AT THESE WOMEN.

THIS STUDY TESTS THE HYPOTHESIS THAT PATIENTS WILL EXPERIENCE GREATER LEVELS OF WELL-BEING AS A FUNCTION OF PARTICIPATING IN AN INTERVENTION DESIGNED FOR BREAST CANCER PATIENTS EXPERIENCING A FIRST RECURRENCE. THREE HUNDRED BREAST CANCER PATIENTS ACCRUED FROM PARTICIPATING SOUTHWEST ONCOLOGY GROUP INSTITUTIONS WILL BE ENTERED ONTO THE STUDY FOLLOWING RECURRENCE. THE WOMEN WILL BE RANDOMLY ASSIGNED TO AN INTERVENTION OR CONTROL GROUP. THE INTERVENTION WILL BE CARRIED OUT BY Y-ME, A NATIONAL BREAST CANCER SUPPORT AND ADVOCACY ORGANIZATION. THE INTERVENTION CONSISTS OF FOUR STRUCTURED SESSIONS DESIGNED TO PROVIDE INFORMATION AND PEER SUPPORT DELIVERED BY BREAST CANCER SURVIVORS VIA TELEPHONE. ENDPOINTS WILL BE ASSESSED AT BASELINE AND 3 AND 6 MONTHS LATER THROUGH VALIDATED QUESTIONNAIRES MEASURING QUALITY OF LIFE AND DEPRESSION.

THIS STUDY WILL PROVIDE INFORMATION ABOUT HOW TO IMPROVE WELL-BEING DURING A PORTION OF THE BREAST CANCER TRAJECTORY WHERE LITTLE ATTENTION HAS FOCUSED. THE INTERVENTION WILL BE DELIVERED BY INDIVIDUALS WHO ARE ESPECIALLY WELL-QUALIFIED TO PROVIDE SUPPORT: WOMEN WHO THEMSELVES HAVE EXPERIENCED BREAST CANCER RECURRENCE. THE PROJECT UTILIZES A COST-EFFECTIVE APPROACH TO INTERVENTION WITH THE POTENTIAL FOR WIDESCALE DISSEMINATION.

NOTHING ON THIS PAGE IS PROPRIETARY INFORMATION.



PLEASE DO NOT WRITE IN THIS AREA

215

23308

Enhancing Well-Being During Breast Cancer Recurrence

PROPOSAL TABLE OF CONTENTS

	<u>Page</u>
<u>Part One: Main Section</u>	
A. Research Proposal Cover Sheet Booklet	1-16
PI and Organizational Administrative Information	1-3
Requested Funding, Start Date & Duration	3
Administrative Representative	4
Authorized Representative	4
Proposal Title Page, Keywords & Abstract	5
Cost Estimate Summary	6-9
Human and Animal Use Checklists	9
PI and Institutional Official Signatures	9
Proposal Table of Contents	10
Submission Category	11
Research Area & Focus Information	11-13
Further Comments	14-15
Blank Page	16
B. Proposal Relevance	17
C. Body of Proposal	
1. Background	18
2. Hypothesis/Purpose	19
3. Technical Objectives	19
4. Methods	19
5. Investigator's Qualifications	32
D. Statement of Work	35
<u>Part Two: Detailed Cost Estimate</u>	
Summary	36
A. Direct Labor Costs	
B. Fringe Benefits and Indirect Costs	
C. Major Equipment	
D. Materials, Supplies and Consumables	
E. Subcontracts or Subgrants	
F. Travel Costs	
G. Publication and Report Costs	
H. Consultant Costs	
I. Other Direct Costs	
J. Fee	

Part 3: Addenda

A.	Acronym/Symbol Definition: Not Applicable	
B.	Illustrations: Not Applicable	
C.	Bibliography	59
D.	Personnel Bibliographic Sketches	62
E.	Existing/Pending Support	72
F.	Collaboration and Joint Sponsorship: Letters of Support	77
G.	Facilities/Equipment Description	80
H.	Additional Requirement for Fellowship Applications: Not Applicable	

Part 4: Appendices

- A. Military/Civilian Collaborations Sheet
- B. Certificate of Environmental Compliance
- C. Management Plan: Not Applicable

Appendices for Submission in February 1996 (Not Included in this Proposal)

- D. Research involving Human Use and Anatomical Substances
- E. Research involving Animals (not applicable)
- F. Safety Plan (Appendix V of BAA)

B. PROPOSAL RELEVANCE

Despite significant increases in five-year breast cancer survival rates, mortality curves for these patients have remained largely unchanged for many years. While many breast cancer patients, especially women diagnosed with Stage I disease, can realistically expect to be cured of their disease, significant numbers of patients will experience a recurrence of their breast cancer at some point following diagnosis, treatment or a disease-free period. Although this statistic is not generally emphasized, when all stages of breast cancer are considered, as many as 50% of patients will experience recurrence.

Very few studies have focused on the psychological impact of a breast cancer recurrence. The limited research in this population has demonstrated that this is a time of enormous crisis, with patients reporting high levels of distress and depression, significant symptomatology, and an absence of effective coping strategies. In fact, patients going through a recurrence appear to have access to few specialized resources; although support programs frequently offer assistance to newly diagnosed patients, hospice patients, and (increasingly) survivors, patients with a recurrence of breast cancer seem to "fall between the cracks" of available support mechanisms.

This study will test the hypothesis that patients will experience greater levels of well-being as a function of participating in an intervention designed for breast cancer patients experiencing a first recurrence. Three hundred breast cancer patients will be entered onto the study within six weeks following the diagnosis of recurrence. The patients will be accessed from four institutions affiliated with the Southwest Oncology Group, and will be randomly assigned to an intervention or control group. The intervention will be carried out by Y-ME, a national breast cancer support and advocacy organization, and consists of four structured sessions. These sessions are designed to provide information and peer support delivered by breast cancer survivors via telephone. Endpoints will be assessed at baseline, and 3 months and 6 months later through validated questionnaires assessing quality of life and depression.

This study will provide information about how to improve well-being during a portion of the breast cancer trajectory where little attention has been focused. The project utilizes a cost-effective intervention with demonstrated usefulness in cancer patients. The intervention will be delivered by individuals who are especially well-qualified to provide support: women who themselves have experienced breast recurrence. This project represents one of the first formal research collaborations between a clinical cooperative research group and a lay breast cancer organization. The project reflects the overriding motivation of both groups: to provide the best possible care and support to these cancer patients.

C. BODY OF PROPOSAL

1. BACKGROUND

A. The Psychosocial Impact of Breast Cancer Recurrence.

Despite significant increases in five-year breast cancer survival rates, mortality curves for these patients have remained largely unchanged for many years. While many breast cancer patients, especially women diagnosed with Stage I disease, can realistically expect to be cured of their disease, significant numbers of patients will experience a recurrence of their breast cancer at some point following diagnosis, treatment, or a disease-free period. Although this statistic is not generally emphasized, when all stages of breast cancer are considered, as many as 50% of patients will experience recurrence.

Recurrence marks a significant change in the breast cancer care continuum, since it brings home the limits of current knowledge in oncology. The cancer care team must acknowledge that the treatment did not work: that all of the optimism, faith in medicine, and careful compliance with treatment were not enough to forestall disease progression. The patient and family may question whether all of the suffering that they have gone through was really worth it, and they may have a sense of failure: not only about treatment, but about themselves. They must deal with a new reality: that the patient is experiencing pain and other symptoms of her recurrence, that chances for cure have been reduced, and that once again, treatment decisions need to be made.

What is a woman's experience when the worst happens -- that is, when breast cancer returns? Surprisingly, very little attention has been given to this issue in the literature: only nine studies have been reported about recurrence of any cancer during the past 15 years (1). We do know that the patients identify the threat of recurrence as one of the most feared possible outcomes of cancer. The fear of recurrence repeatedly emerges as an important psychosocial theme in breast cancer patients who are newly-diagnosed (2,3), attending follow-up visits (4), and among long-term survivors (5).

The largest study based on data from patients actually experiencing a recurrence is Worden's cross-sectional study of 102 individuals with recurrences of various cancers (6,7). Worden found that distress levels of the patients with recurrence were high and equivalent to levels in newly-diagnosed patients. Compared to newly-diagnosed patients, the individuals in this study were less willing to participate in interventions focused solely on psychosocial counseling and more concerned about their medical problems and existential concerns. Among the factors that predicted higher distress were more symptoms, lack of social support, less hope, and being younger. Cella, Mahon, and colleagues (8,9) also assessed adjustment in 40 patients within one month of recurrence; the patients represented a variety of cancer sites, and 27 were experiencing a first recurrence. Patients in this study experienced high levels of distress: they "almost universally agree that recurrence is more upsetting than initial diagnosis" (8, p. 20). There was a suggestion that having anticipated the possibility of recurrence aided adjustment: patients who reported that they were "completely surprised" by the recurrence fared the worst.

Several studies have focused on breast cancer recurrence. Silberfarb et al. (10) compared psychosocial status in groups of breast cancer patients during initial diagnosis (N=50), first recurrence (N=52), and metastatic disease (N=44). The findings indicated that "the stage of first

recurrence clearly was the most emotionally stressful time in our sample" (p. 454). Significantly, only one woman out of the 52 could identify a single coping strategy she had found helpful, in marked contrast to the other two groups. In addition, the findings of this study illustrate how recurrence is often marked by physical impairment as well: 81% of the women in the recurrence group reported pain, the highest percentage of any group. Jenkins et al. (11) evaluated 22 women with newly-diagnosed breast cancer recurrence, and found that 45% experienced depression and anxiety at the level of psychiatric diagnosis; previous psychiatric illness was a significant predictor of recurrence distress. A recent study by Lewis and Deal (1) further described problems in 15 married couples in which the wife was diagnosed with a recurrence of breast cancer. A number of problems in marital adjustment were reported, as well as depression experienced by 40% of the women; the recurrence had been diagnosed a median of 10 months previously, indicating the long-lasting psychosocial impact of breast cancer recurrence and the potential that intervention could provide a real benefit for these patients.

B. Interventions to Reduce Psychosocial Distress

No intervention directed at the needs of patients experiencing a recurrence of breast cancer (or any other cancer) has been reported. However, several reviews (12-14), including a recent meta-analysis (15), have concluded that psychosocial interventions have a positive impact on the well-being of patients across the spectrum of disease stages and sites. To date, research has not established whether one kind of intervention is more effective than another, or more appropriate for certain patients. A variety of intervention types (e.g., informational, psychological, behavioral, social support) and formats (e.g., group, individual, telephone) have demonstrated beneficial effects. Effects have been demonstrated for quality of life, symptom management, and psychological functioning. The optimal point to evaluate the impact of psychosocial interventions has not been firmly established; most studies assess outcomes at one or more intervals during the first year post-intervention (12-14), although impacts may be long-lasting, even extending to ultimate survival (e.g., 16).

In this study, we will draw on an approach which has been found effective by a number of investigators: a brief, time-limited intervention combining information and support delivered by telephone. The telephone is frequently used in providing information regarding cancer treatment and counseling (17-22). In particular, the telephone may make services available to individuals for whom traveling would pose difficulties because of geography, health, or access to transportation. The telephone-directed intervention approach is especially well-suited to the Southwest Oncology Group (SWOG) setting, given the potential of providing standardized assessment across participating institutions at a relatively low cost. Other cooperative groups, including the Eastern Cooperative Oncology Group (ECOG) and the Cancer and Leukemia Group B (CALGB), are currently conducting research protocols utilizing telephone-delivered interventions, although no other group has focused on patients with recurrence. In fact, patients with recurrence appear to have recourse to few specialized resources; although resource and support programs frequently offer assistance to newly diagnosed patients, hospice patients, and (increasingly) to survivors, patients going through a recurrence seem to "fall between the cracks."

C. The Use of Lay Organizations in Providing Support to Breast Cancer Patients

The intervention will be provided by women who are particularly well-qualified to provide support and information: breast cancer survivors who have themselves experienced recurrence. A distinctive feature of this study is its delivery of the intervention through an established national breast cancer advocacy and support organization, Y-ME. Although Y-ME

has provided telephone hotline services (using a toll-free 800 number) since 1987, the impact of the service has not been systematically assessed. This is also true for other lay programs for breast cancer patients, such as the American Cancer Society's Reach-to-Recovery program (23). This study will utilize breast cancer survivors within the context of a structured protocol, as well as standardized and validated outcome measures. If the program proves effective, it can become part of Y-ME's program and be delivered on a standard basis. The use of a voluntary organization staffed with non-health professionals represents a cost-effective approach to providing support. Y-ME has participated in a Southwest Oncology Group Lay Advisors/Advocates Steering Committee for the past two years. The lay advisors (who include representatives of national organizations and volunteers selected through a nationwide search) are special members of the Group, serve as members of Disease and other Committees (including the Committee on Women's Health and the Breast Cancer Committee), and attend semi-annual Group meetings. The lay advisors contributed to the development and design of this proposal over the past year.

D. Summary: Distinct Contributions of This Study

The primary objective of this study is to investigate the efficacy of a telephone-delivered peer counseling intervention on the well-being of women experiencing breast cancer recurrence. This study will provide information about how to improve well-being during a portion of the breast cancer trajectory where little attention has been focused. The project utilizes a cost-effective approach to intervention with demonstrated usefulness in cancer patients. The intervention will be delivered by individuals who are especially well-qualified to provide support: women who themselves have experienced breast cancer recurrence. This project represents one of the first formal research collaborations between a clinical cooperative research group and a lay breast cancer organization. The project reflects the overriding motivation of both groups: to provide the best possible care and support to cancer patients.

2. HYPOTHESIS/PURPOSE

The hypothesis of this study is that patients will experience greater levels of well-being as a function of participating in an intervention designed for breast cancer patients experiencing a first recurrence.

3. TECHNICAL OBJECTIVES

The primary research objective is to evaluate the impact of a telephone intervention delivered by breast cancer survivors on well-being in patients experiencing a first recurrence of breast cancer.

Secondary research objectives are:

1. To examine the impact of sociodemographic, clinical, and psychosocial predictors of well-being in patients experiencing a first recurrence of breast cancer.
2. To examine changes in well-being over time since recurrence.

4. METHODS

A. Initial Activities/Pilot Study

To finalize the intervention protocol, a Pilot Study will be conducted during the first eight months of this project. The Pilot Study will involve 30 patients from four Group institutions

(the University of Hawaii Minority-Based CCOP, Loyola University {Chicago}, Ozarks Regional CCOP, and the University of Arkansas Cancer Center). The investigators who will provide patients for the Pilot Study are included as part of the research team for this study; they represent a balance between university-affiliated and CCOP organizations, and between urban and rural catchment areas. Their estimates of the number of patients available at their institutions indicated that enrolling 30 patients over a six-month period would be quite feasible. Any breast cancer patient at the institution experiencing a first recurrence will be eligible for referral to the Pilot Study within the first six weeks, following documented evidence of breast cancer recurrence. In the Pilot Study, all women will be asked to participate in the intervention as described below. Only a subset of women accrued early in the Pilot Study will complete the three-month assessments, due to the short length of the pilot. Otherwise, all procedures are the same as for the main study. The specific objectives of the Pilot Study are:

1. To refine intervention protocol materials.
2. To develop operating procedures to ensure coordination and communication between the Principal Investigator (Dr. Charles A. Coltman, Jr.), the Southwest Oncology Group Operations Office, the Co-Principal Investigator (Carolyn C. Gotay, Ph.D.), the Southwest Oncology Group Statistical Center (Carol Moinpour, Ph.D. and Stephanie Green, Ph.D.), Y-ME (Ms. Michelle E. Melin), and the institutions accruing patients.
3. To develop a training program for the breast cancer survivors who will provide the intervention.
4. To finalize assessment questionnaires and examine length and ease of administration by telephone, especially with respect to burden for institution staff.
5. To examine participation and attrition.

1. Refining the intervention protocol materials. The consultants for this project - Carol L. Alter, M.D., Patricia A. Ganz, M.D. and Alfred C. Marcus, Ph.D. - all have considerable experience in developing and delivering telephone-based counseling interventions to cancer patients. All of the consultants have already developed materials that can be adapted for this project: Dr. Ganz has conducted information and support programs for newly-diagnosed patients and for breast cancer survivors (24-26), Dr. Alter has designed and pilot-tested a telephone counseling intervention for breast cancer patients (17), and Dr. Marcus, a telephone counseling protocol for breast cancer survivors (27). The specific intervention modules will build on the consultants' previous work and their knowledge of "what works," and tailored for use in this patient population by the research team. In addition, the lay members of the Group (who include three breast cancer survivors) are investigators for this project, and they will also provide feedback on the intervention. Based on pilot experience, the intervention will be modified as needed. Initial project activities will focus on developing a manual for the intervention, including presentation of information, scripts to provide appropriate, standardized responses and probes, and written materials to be mailed to the patients following each intervention session.

2. Developing operating procedures for conducting the study. As one of the research bases for the CCOP program, the Southwest Oncology Group has had considerable experience in developing, implementing, and successfully completing cancer control research protocols, including a number of intervention studies. Policies and procedures are already in place to facilitate the conduct of this study. An innovation in this project is the involvement of Y-ME in the research process. A system to integrate the Y-ME investigators within the system needs to be developed to ensure close communication between the breast cancer patient's institution

and the Y-ME-delivered intervention. Dr. Moinpour will develop a system to track any problems in coordination as well as the level of effort required to conduct this study.

3. Developing a training program. The training program for the individuals delivering the intervention will be based on Y-ME's current training model, which covers counseling skills (understanding peer support, skills to handle calls, understanding the callers' reactions, the patient and her family, coping mechanisms, medical questions), Y-ME Hotline volunteer regulations (including a description of Y-ME and policies for making referrals), and related medical information (glossary of medical terms, supplemental readings such as the PDQ for breast cancer) and a take-home exam. The Y-ME quality assurance program includes a test scenario (where the peer counselor conducts a sample interview in the presence of the supervisor) and an evaluation of actual performance (through a simulated breast cancer patient telephone call made by a supervisor). These procedures will be maintained, with the quality assurance testing occurring annually. In addition, the training program for this study will incorporate NCI materials for patients and potential study participants regarding recurrence and clinical trials. The trainees will be required to pass an exam before they can provide the intervention. The training curriculum will be developed by the research staff (Dr. Gotay, Dr. Moinpour, Ms. Melin, consultants, input from other Investigators). Ms. Melin will provide the training, which will include tape-recorded practice interviews that she will review with the trainees. Continuing education will also be required; part of Y-ME's policies require 6 hours of continuing education per year. The other members of the research team will work with Ms. Melin to ensure that the peer counselors for this project have access to appropriate educational opportunities. This will include members of the research team offering inservices at Y-ME when they are in the Chicago area.

The women recruited to be peer counselors will be identified through Y-ME's current screening, interview, and assessment procedures. The only additional criterion for this project is that the woman will have experienced one or more breast cancer recurrences. Ideally, one of the counselors already trained and working at Y-ME will be selected for this project. Ms. Melin provides full-time supervision and oversight for the Y-ME counselors.

Training for Clinical Research Associates (CRAs) as to the proper collection of patient-provided data (such as quality of life questionnaires) is provided at the twice-yearly Group meetings. This training program has been offered for a number of years. Dr. Moinpour helped to develop the curriculum, which includes a video and discussion of data management issues in ongoing and upcoming new studies. This study will be included in these updates.

4. Finalizing questionnaires. Any forms developed for this study will be modified based on problems encountered in the pilot study. The primary outcome measures in the study are standard scales which have been used in numerous other large-scale cancer patient samples. If we encounter any problems with these forms, the standard scales will not be modified, but other scales could be substituted for the main study.

5. Examining attrition. The pilot study will provide information about the extent to which attrition from the intervention is apt to be a problem. Responses of both patients who drop out of the intervention and those who do not will be useful in identifying aspects of the intervention which may require modification, as well as aspects of the program that are effective in engendering adherence. A form will be developed to capture reasons for failure to participate in all four sessions and/or complete all questionnaires at the scheduled assessment points.

B: The Main Study

1. **Overview.** The study utilizes a 2-arm randomized design with repeated measures at three time points. Three hundred breast cancer patients will commence participation following a first recurrence of breast cancer. At that time, the participants will complete a battery of instruments, including baseline measures of well-being. Participants will be stratified by age (<50 years vs. ≥50 years), time since diagnosis (<2 years vs. ≥2 years), and recurrence site (soft tissue/bone vs. visceral) and randomly assigned to intervention group: either intervention or control. Participants in the intervention group will complete a four-session intervention delivered at weekly intervals, with assessments of well-being approximately three months post-baseline, and again 6 months post-baseline. The primary outcome is well-being, including quality of life (as measured by the Cancer Rehabilitation Evaluation System-Short Form (CARES-SF) [28]) and depression (as measured by the Center for Epidemiologic Studies-Depression scale (CES-D) [29-30]).

2. **Participants.** All patients diagnosed with Stage I or Stage II breast cancer who experience a first breast cancer recurrence and are not enrolled on a Group protocol are eligible for participation in this study.

Eligibility criteria for study participation include: (1) previous treatment for Stage I or II breast cancer and diagnosed with a first recurrence of breast cancer within the past six weeks; (2) ability to read or understand English; (3) ability to provide informed consent; (4) age equal to or greater than 18 years; and (5) no current psychiatric diagnosis; and, (6) no previous enrollment or plans to enroll on a Group treatment protocol. (This eligibility criterion is included so that there is no chance that this study could interfere with ongoing protocols.) There will be no restrictions on type of prior or concurrent treatment or performance status at baseline.

It is a standing policy of the Southwest Oncology Group to include eligible patients of both sexes and all races and ethnicities in all Group clinical trials, except as restricted by specific disease site (e.g., prostate, gynecological). For example, accrual of the Southwest Oncology Group Breast Cancer Committee in 1994 totaled 1,412 patients, of which all patients were female, consistent with the incidence of the disease. This accrual included 74% (1046/1412) Caucasian patients and 9% (128/1412) African-Americans, 4% (53/1412) Hispanics and 13% (185/1412) other minority patients. Institutions chosen to participate in the pilot study represent diverse populations (rural and urban), as well as access to high proportions of minority groups (particularly Asian and Pacific Islanders, and African-Americans).

3. **Procedures.** Patients will be eligible for referral to the study within the first six weeks following breast cancer recurrence. Participants will be entered onto study by their oncologists and CRAs at the institutions where they have been treated.

Patients will be informed of the investigational nature of this study, and must sign and give written informed consent in accordance with institutional and federal guidelines. A "prestudy" form will be completed to obtain sociodemographic and clinical information. This will include: date of diagnosis, a brief summary of previous treatment(s) received (e.g., type of surgery, radiation, chemotherapy, hormonal therapy, high dose chemotherapy with stem cell transplantation), date of treatment completion, date and sites of recurrence, and current or planned treatments. The patient's past history of psychological or psychiatric dysfunction will also be included, since this factor has been shown to be an important predictor of current and future distress in previous research (12). In addition, the woman will be asked to provide home and work telephone numbers (if applicable), as well as telephone numbers for a friend

of family contact. These will assist in locating women if their telephone numbers change and minimizing the chances they will be lost to follow-up. The CRA will also make a rating of the woman's performance status. The woman will also be asked to complete the baseline questionnaires (described below).

Based on information in the "prestudy" form and completion of the baseline questionnaires, the CRA will complete an eligibility checklist to document that the woman has met the criteria for taking part in the study. The CRA will telephone the Southwest Oncology Group Statistical Center during pre-announced hours to obtain the woman's random assignment, which will be reported to the woman by the CRA. If the woman is in the intervention group, the CRA will then fax the woman's name and telephone number to Y-ME, so that the Y-ME peer counselor can initiate the intervention. However, the Y-ME peer counselor will not have access to the questionnaire data. If the woman is in the control group, she will be informed that she will be called in about three months.

After this, all women will be provided with a basic information packet including a copy of the NCI booklet "When Cancer Recurs: Meeting the Challenge Again" and a list of agencies which provide cancer-related information. Prior to the activation of the study, each participating institution will be required to compile materials about resources available in their catchment area. Project staff will compile information on national organizations such as Y-ME, the Cancer Information Service (1-800-4-CANCER), and the American Cancer Society. Although providing this minimal information to all women has the potential to weaken the effect of the intervention, we feel ethically obligated to provide some support to women who agree to take part in this study. Optimally, materials such as the ones we will distribute should be routinely offered to individuals experiencing a cancer recurrence, but we are aware that at the present time, this happens inconsistently and often not at all.

4. Stratified Randomization. Participants will be randomly assigned to one of two arms: (a) intervention; or, (b) control. This randomization will be dynamically balanced with respect to the following stratification factors, using the method of Pocock and Simon (31): age (<50 vs. \geq 50); time since diagnosis (<2 years vs. \geq 2 years); and recurrence site (soft tissue/bone vs. visceral).

5. Study Groups.

Control group. The women will receive no additional interventions. They will be asked to complete the self-administered assessment questionnaires in 3 months and 6 months. Women in the control group will be offered the same mailed materials provided to the women in the intervention (but not the telephone counseling) group at the conclusion of the study after the sixth month assessment.

Intervention group. At the time of the baseline assessment, the women will be asked to designate preferred times for telephone contact to provide the intervention. The woman will be informed that she will be called by a Y-ME peer counselor in the next few days to begin the intervention. The women will be provided with an intervention consisting of four counseling/information sessions delivered by telephone at weekly intervals. A four-session intervention represents a compromise between interventions that have been reported, which range from single sessions to six-session and longer programs (12-14). They will be contacted again in 2 months (3 months after the baseline assessment) and 5 months (6 months post-baseline) by the CRA at the institution to complete the self-administered assessment questionnaires.

A standardized intervention protocol will be used, and sessions should require no longer than 45 minutes to complete. Each session will focus on different problem areas from the group listed below. The modules reflect psychosocial, physical, and existential concerns, as reported in the literature on patients with recurrence. Each woman will be given a choice about the order in which the sessions are presented. Priority concerns are likely to vary from one woman to another, and allowing the individual to select the most important area for her first session will help to individualize the intervention.

- Session 1** Physical problems: symptom control, treatment decision-making.
- Session 2** Social support: understanding reactions of other people, how to build a social support network.
- Session 3** Existential concerns: spiritual concerns, activities that may be helpful (e.g., recording one's own oral history), the importance of hope.
- Session 4** Stress management: approaches that may be helpful, including relaxation, visualization, exercise (with physician supervision), healthy eating.

Each session will provide basic information as well as an opportunity for the woman to discuss her individual concerns. The general format for the intervention sessions will be to provide information in specified areas, active listening when the woman discusses her concerns, assistance in problem-solving (particularly to help the woman to define and prioritize her own solutions to problems), and information about resources that may be helpful (books and other written or audiovisual materials, local resources). Emphasis will be placed on providing the woman with a referral to a local community or health care agency addressing the area of concern. (As mentioned above, local information will have been assembled by all participating institutions.) Following each session, the woman will be sent a standardized packet of written or audiovisual materials to reinforce what was discussed during the session and provide additional information. (We will explore free materials available from organizations such as pharmaceutical companies; for example, one company provides complimentary relaxation tapes.) We recognize that no "solutions" or answers may exist for some questions or problems. However, our aim is to provide a safe and supportive atmosphere in which a woman will be able to discuss concerns she may have with a peer who has undergone similar experiences. Given the discomfort that health professionals, family, and friends feel at the time of recurrence, we believe that having a supportive telephone contact will provide a unique and needed resource for many women.

The intervention is not designed to provide psychotherapy. Instead, the Y-ME peer counselors will provide information, peer support, and referrals to community organizations. Procedures currently in place at Y-ME will be used if serious psychological disturbance is detected during a telephone session. In such cases, patients will be asked if the Y-ME peer counselor can contact her physician; since all study participants will have been enrolled in the project with the consent of their physicians, we will have a physician contact in all cases.

6. Study Endpoints.

General considerations. Two primary measures will be used to assess the outcome of well-being: quality of life and depression. The measures were selected according to specific criteria: coverage of the specific areas thought to be affected by the intervention; appropriateness to the study population; adequacy of the psychometric characteristics in similar populations; the availability of a self-administered questionnaire; and, documented clinical interpretability of findings (i.e., the ability of the scale scores to distinguish between clinically meaningful patient groups).

The 3-month assessment point will serve as the primary study endpoint. This endpoint was selected because the initial period following the recurrence diagnosis is likely to be the most acute time of crisis when the intervention should have the most impact, and data are most likely to be complete at this time. Because we are also interested in the longer term effects of the intervention, however, we will also collect outcome information at six months (see Table 1). The results may indicate the most appropriate time point for future studies. (We did not include an assessment point closer in time to the intervention, such as 1 month post-baseline, because we believe that intervention effects should persist three months or longer in order to justify promulgation of such an approach in this population.)

Table 1: Schedule of Assessments

Items	Assessment Times			
	Baseline	Intervention Sessions	3 Months	6 Months
Prestudy Form	x			
Psychosocial Predictors Form	x			
<i>Social Support, LOT</i>				
<i>Surprisingness</i>				
<i>SOC</i>				
Clinical Update Form			x	x
CARES-SF	x		x	x
CES-D	x		x	x
Intervention Evaluation			x	x

We anticipate that completion of the study instruments will require approximately one-half hour, based on the times reported for instrument completion in the literature. The baseline assessment will be slightly longer to accommodate the additional measures that will be asked only once. The women will complete the self-administered questionnaires in the presence of the CRA at the time of informed consent and random assignment at baseline, and at 3 and 6 months during clinic visits or by mail (if clinic visits are not scheduled at appropriate intervals). Dr. Ganz has found that obtaining CARES data in the presence of a test administrator or by mail yields comparable results (Ganz, personal communication, August 1995.)

Quality of life. A primary endpoint in this study is quality of life, which will be measured by the research format of the Cancer Rehabilitation Evaluation System-Short Form (CARES-SF) (28). The CARES-SF was derived from the more extensive CARES, which has been carefully developed based on the specific problem areas identified by cancer patients (32-33); the CARES-SF has been shown to correlate very well with its parent scale (28). The CARES-SF contains a minimum of 38 and a maximum of 57 items; the exact number varies because of skip patterns related to patient-specific experiences. Respondents rate how much of a problem they find in specified areas on five-point scales. The CARES-SF yields both an overall score and five

subscales: physical aspects, psychosocial concerns, medical interaction, marital problems, and sexual issues.

In a number of studies, this questionnaire has been shown to be valid and reliable; it differs from other quality of life instruments by providing more concrete information about patient experiences. Normative information is available, including a recent study in breast cancer survivors one, two, and three years post-diagnosis (26), which demonstrated the CARES-SF's responsiveness to change. A CARES-SF Psychosocial score of .615 or greater has been found to correctly classify breast cancer patients "at risk" for psychosocial distress, as identified in a comprehensive clinical interview by a social worker; the estimated probability of classifying women in the high risk group was .81 in a recursive partitioning model (34). In this study, the CARES-SF will provide two endpoints: 1) the overall CARES-SF score, which will provide an assessment of quality of life across multiple domains; and, 2) the scores on the CARES-SF Psychosocial scale: specifically, whether a patient scores below (low risk) or at or above (at risk) the CARES-SF Psychosocial score cutoff.

Depression. Depression will be measured by the Center for Epidemiological Studies - Depression (CES-D) (29-30). The CES-D has been extensively used in both community and patient populations, including cancer patients (1,35-38). It includes 20 symptom-related items; respondents rate the frequency of having experienced these symptoms during the past week on four point scales.

In many studies, the scale has been shown to distinguish reliably among in-patient populations and to be sensitive to changes over time. The interpretation of scores is also facilitated by a score "cutoff" of 16 (which reflects that 6 of 20 symptoms are at least moderately persistent); persons scoring above this cutoff are likely to be classified as clinically depressed when they receive a full clinical evaluation. In this study, the CES-D will be used to designate patients who score above (at risk of depression) or at or below the cutoff score (not at risk of depression).

Psychosocial Predictors. This study will also assess possible predictors of well-being. A Psychosocial Predictors Form will assess several psychosocial variables at baseline which have been found in other studies to predict well-being, or tap important concerns during recurrence. Social support will be measured by Reynolds et al.'s four-item scale, found to predict breast cancer survival (39). Optimism-pessimism will be measured using the Life Orientation Test (LOT). This 8-item scale has been demonstrated to have high levels of internal consistency and test-retest validity in breast cancer patients (40). In a recent study, Carver et al. found scores on this scale predicted breast cancer survival (41). A single question about how surprising the recurrence was will be included. Cella et al. (8) found this question correlated with recurrence distress. Antonovsky's Sense of Coherence Scale (SOC) (42) will be used to assess the meaning of recurrence to the patients; this is one of the few available scales to focus on existential concerns. We will use the short form of this scale (13 items), which has demonstrated high internal consistency and construct validity (43, 44).

Clinical Update form. At the 3 and 6 month assessments, the women will be asked about cancer treatment they are currently receiving, since treatment recommendations may change over the time of this study. This information may help to identify subgroups of interest (e.g., women who receive high dose chemotherapy with stem cell support).

Evaluation of Intervention. At 3 and 6 months, an Intervention Evaluation form will be used to obtain information about the women's overall appraisal of the intervention, primarily to provide concrete information about what the participants found helpful, and what areas could be improved to aid in future interventions. At the 3 and 6 month follow-up assessment points, all women will also be asked a series of questions about their use of community services and other forms of assistance (e.g., support groups, church groups, counseling) during the previous six months. This information will be important in evaluating whether the intervention stimulated use of resources, as well as in assessing the extent to which women in the control group sought assistance. The women will be asked specifically whether they have used Y-ME resources; since Y-ME has a national hotline, it is possible that women in either group could call Y-ME for (additional) assistance. Women in the intervention group will not be able to access their peer counselor delivering the intervention except during the scheduled sessions.

C. Analysis

1. Sample Size and Assessment Times. Three hundred patients will be randomly assigned to either the intervention or control group. Well-being data will be obtained by the registering institutions on three occasions: at study registration and at 3 and 6 months. It is assumed that 3 month questionnaire completion rates will be 85% (255 assessments) and that 6 month completion rates will be 80% (240 assessments). Although attrition could be higher, we believe it will be low for two reasons. First, since the women in this study were diagnosed originally with early stage and not metastatic disease, they are likely to be alive in 6 months; median survival for women with a first recurrence of breast cancer is approximately two years (Personal communication, S. Green, August, 1995). Second, the Southwest Oncology Group has conducted studies which include repeated quality of life questionnaires with a completion rate in excess of 85% (45). Under Dr. Moinpour's leadership, quality control procedures have been developed which have resulted in low levels of missing follow-up data. We will employ these procedures (e.g., clear specification in the protocol regarding times of administration, dedicated data monitoring time at the Group's Statistical Center that includes study endpoints in the Group's missing data report to institutions, sending queries for missing data) in the proposed study. Therefore, we believe that 85% reflects a reasonable estimate of attrition.

2. Study Duration. The expected accrual rate is 10 patients per month. Therefore, we expect accrual for this study to be completed within a 30-month period of accrual. Five hundred and two new recurrences were reported during a three-year period for three current Group breast cancer treatment protocols. Given that the target population for this study is non-protocol patients, we expect that the pool of patients experiencing a first recurrence will be considerably larger than the one based on protocol estimates. This assumption is based on Hunter et al.'s findings that only one-third of patients clinically eligible for a protocol are actually registered to a protocol (46). In addition, eligibility criteria for this study are considerably less restrictive than those employed in most treatment trials, further enhancing the numbers of women available.

3. Power Calculations.

Primary Analyses. Power calculations indicate that a sample size of 255 at three months is sufficient to test intervention versus control group differences for the three primary endpoints: 3-month CARES-SF mean total score, 3-month CARES-SF Psychosocial Summary cut-off score, and 3-month CES-D cut-off score. All estimates use one-tailed tests. An alpha level of .016 (.05 divided by 3) will be used to adjust for the three planned comparisons.

A) CARES-SF Mean Score. Patients receiving the telephone intervention are expected to show more improvement in overall quality of life than patients not receiving the intervention. A standard deviation of .24 was reported for the global (total) CARES-SF score by Ganz (47). With 80% power, $\alpha=.016$, a one-tailed test, and a sample size of 255, we can detect a .09 point mean difference in CARES-SF overall score at 3 months.

B) CARES-SF Psychosocial Summary Cut-off Score. Patients with a 3 month CARES-SF Psychosocial Summary score greater than or equal to .615 will be considered at risk for psychosocial distress, whereas patients with a psychosocial score less than .615 will be considered not at risk. Fifty percent of patients on the control arm are expected to have subscale scores above .615, whereas a smaller proportion of intervention arm patients should score above .615 on this subscale. Table 2 shows the power the study has to detect group differences based on varying percentages of patients at risk.

C) CES-D Score. Patients with a 3 month CES-D score greater than 16 will be considered at risk for depression, whereas patients with a CES-D score less than or equal to 16 will be considered not at risk. A recent study by Lewis and Deal (1) found that 40% of 15 women with a breast cancer recurrence had CES-D scores above 16. The patients in this study were a median of 10 months post-recurrence diagnosis. Given that the women in this study will be newly diagnosed with recurrence, we expect that at least 40% of the control group to score "at risk," with the proportion at risk more likely to be 50 or 60%. We expect patients in the intervention arm to be significantly more likely to have scores below the cutoff. Table 2 (see below) demonstrates the power to detect group differences.

Table 2

Power to Detect Group Differences Based on Varying Percentages of Patients

Percentage of Patients: Intervention Group*	Percentage of Patients: Control Group*	Power
.19	.40	.90
.28	.50	.90
.38	.60	.90
.43	.65	.90

*Percentages represent patients who score above the cutoff (.615 for the CARES-SF Psychosocial Summary score; 16 for the CES-D)

Secondary Analyses. Descriptive statistics for patients' sociodemographic and clinical information and psychosocial predictors will be reported along with the 3 and 6 month descriptive results for the primary endpoints.

The three well-being scales will be used as dependent variables in regression analyses to explore the effect of sociodemographic, clinical, and baseline psychosocial predictors on the efficacy of the intervention. Logistic regression will be used to examine the predictors for scoring above or below the cutoffs on the CARES-SF Psychosocial Summary score and the CES-D scores. Least-squares regression will be used to examine the predictors for the CARES-SF total score. Independent predictors considered will include sociodemographics (age, education, marital status, ethnicity), clinical variables (stage of disease, time since diagnosis, site of recurrence, treatments received, history of psychiatric dysfunction) and psychosocial predictors (social support, optimism-pessimism, how surprising the recurrence was, sense of coherence).

Both univariate analyses and stepwise regression will be used to investigate the relationships among the predictors and the endpoints in order to identify a more parsimonious group of predictors. Associations between predictors of efficacy would increase our understanding of the benefits and limitations of this intervention. In addition, statistical methods for the exploration of longitudinal data (48-50) will be applied to model within-patient changes in scores over time.

Missing Data. The best of quality control procedures cannot protect against all forms of missing data. In particular, missing data may be associated with the endpoint of interest. In this study, patients may fail to complete all assessments because they die, are too ill, or lose interest in the study. As discussed above, we do not expect a great deal of such nonrandom missing data in this study. However, we will examine this potential problem by comparing baseline well-being scores for patients who complete the 3 month questionnaires and those who do not to determine if the patients who did not complete the later questionnaires had lower quality of life or were more depressed at baseline (51).

D. Project Management

The efforts of a number of investigators - including the PI, the Co-PI, Subcontract Investigators and staffs, other Group Investigators, the consultants, and Group members (investigators who will enroll patients, and CRAs in particular) - will need to be coordinated to accomplish the goals of the project. The Southwest Oncology Group structure includes twice-yearly meetings, as well as regular communications via mail, e-mail, and faxes between meetings. All of the investigators on this project are Group members, with the exception of Dr. Marcus. As such, there is a strong history based on previous working relationships of the investigators which will facilitate this process. Special management activities for this project include:

Weekly meetings. Dr. Gotay will assume day-to-day responsibility for managing the project. She will convene weekly meetings with her staff.

Monthly conference calls among the Co-PI and Subcontract Investigators: Throughout the course of the project, monthly conference calls will be held between Dr. Gotay and the Subcontract Investigators (Dr. Moinpour and Ms. Melin) and others by invitation. In addition, Dr. Gotay and/or her staff will travel to meet with Dr. Moinpour and Ms. Melin: a trip is scheduled to the Y-ME headquarters in Years 1, 2 and 3 of the project to participate in training and continuing education for the women providing the intervention, and to the Southwest Oncology Group Statistical Center in Years 2, 3, and 4 to participate in data monitoring and analysis.

Twice-yearly face-to-face meetings. Over the course of the project, twice-yearly project meetings will be held just prior to the regular twice-yearly Group meetings. These project meetings will include Dr. Coltman, Dr. Gotay, Dr. Moinpour, and Ms. Melin, and (during Year 1) the consultants. (In years 2, 3, and 4, the consultants will not need to participate at as high a level, and they will be asked to attend only one Group project meeting per year.) During these meetings, problems with the study will be discussed, progress toward meeting accrual goals will be monitored, and questions which should be addressed to the larger group of Group investigators will be identified. During the formal Group meeting, a meeting with the other Group Investigators will be scheduled. Minutes from project meetings will be prepared and distributed to research team members. In general, the Group meetings provide an excellent opportunity to problem-solve with investigators across the country, to attend committee meetings and make announcements, and to distribute materials. The involvement of Group

leadership in this project (in the persons of Southwest Oncology Group Chair, Dr. Coltman, Committee Chairs, Drs. Albain and Martino, and Subcommittee Chair, Dr. Ganz) ensure that this study will be accorded significant attention within the group. Many research team members already have funds allocated to attend these meetings; hence, these opportunities for work on this research can occur at little extra cost to the project.

Meetings with the consultants. The consultants provide expertise in specified areas, particularly in the development of the intervention protocol and materials, and in the modification of procedures based on the pilot study. These activities occur in Year 1 of the grant, which will mean that the consultants' level of effort is greatest during this year. During Year 1, the consultants are scheduled to meet at the twice-yearly Group meetings, and an additional meeting has been scheduled at Dr. Gotay's institution for the consultants and the Subcontract Investigators early in Year 1. The consultants will also need to spend another day's effort in reviewing materials mailed to them during Year 1. In addition, the consultants will also make important contributions to data analysis and interpretation. A meeting for Dr. Gotay, Ms. Melin, and the consultants has been scheduled at the Statistical Center during Year 4. Dr. Gotay will be responsible for ensuring the participation of the consultants.

E. Strengths And Limitations of the Proposed Approach

This study has the potential to make a significant contribution to knowledge about the problems experienced during breast cancer recurrence, as well as to test the efficacy of a specific intervention. It utilizes an experimental design which includes a prospective, longitudinal component. The instruments to be used are well-validated and widely-used. The sample size is heterogeneous, draws from a nationwide network, and is large enough to detect effects of interest. The Southwest Oncology Group has a great deal of experience in this area, and demonstrated its ability to collect high quality questionnaire data. The breast cancer survivors who will administer the intervention are a unique group with a strong history of providing high quality, telephone-based care for breast cancer patients. However, several limitations should also be considered.

This study will not have sufficient statistical power to detect differences due to many potentially important factors influencing the well-being of study participants. However, exploratory analyses may generate hypotheses that can be followed up in subsequent research. The study follows patients only 6 months post-recurrence diagnosis, due to the length of time needed to accrue sufficient numbers of participants within the study time frame. This period should be a critical time when the women need support and should demonstrate benefits of the intervention. However, the effects of the intervention may extend or emerge after this time. We are considering seeking support to continue to follow these women.

One additional weakness should be mentioned. We, like large numbers of researchers across the country, have a great deal of curiosity about the potential contribution of psychosocial support to survival, especially considering the intriguing results that have been reported in this area. However, this study does not have sufficient power to examine survival effects. Assuming a median survival of two years in the control arm, either a large increase in sample size (to 1,235 patients), or a much longer follow-up period, would be required to detect a meaningful survival difference in the intervention arm. Additionally, the resources required to follow women until death exceed those in this proposal. Patient well-being is a meaningful endpoint in itself, whether or not it translates into survival differences.

5. INVESTIGATORS' QUALIFICATIONS

Principal Investigator, Dr. C. Coltman. Charles A. Coltman, Jr., M.D. (Chair, Southwest Oncology Group (SWOG)) has successfully coordinated the activities of the Group since 1981. Dr. Coltman is also Medical Director of the Cancer Therapy and Research Center, and a Professor of Medicine and the Director of Clinical Medical Oncology at the University of Texas Health Science Center at San Antonio. Under his direction, the Southwest Oncology Group has successfully applied for numerous NCI-funded cooperative agreements and R01 research grants, including Core grants for the Group, Community Clinical Oncology Program (CCOP) grant, and a supplemental grant to coordinate the large chemoprevention study for prostate cancer, the Prostate Cancer Prevention Trial (PCPT). The PCPT is a double-blinded, placebo-controlled study involving the randomization of 18,000 men to study the efficacy of finasteride in reducing the prevalence rate of prostate cancer after seven years.

Co-Principal Investigator, Dr. C. Gotay. Carolyn Cook Gotay, Ph.D. has had 16 years of research experience, 13 specific to cancer prevention, control, and treatment, which attest to her ability to lead the proposed project. Dr. Gotay's past activities include serving as PI (for the EMMES Corporation) for a contract in NCI's Cancer Therapy Evaluation Program, where she provided consultation on psychosocial aspects of treatment protocols, and four years as Health Scientist Administrator at the NCI, where she developed, monitored, and evaluated research initiatives and programs in continuing care and rehabilitation. She is currently an Associate Researcher at the University of Hawaii Cancer Research Center, where she is PI for an NCI-supported research project to develop and validate quality of life assessment instruments appropriate to Hawaii's multicultural cancer patients. Dr. Gotay serves as Co-Investigator for an NCI-supported project to investigate differences in patterns of care and outcomes (including quality of life) for breast cancer patients in a community setting where the patients reflect a wide variety of ethnic backgrounds and patterns of concurrent and intercurrent disease; and for the NCI-supported Hawaii Community Clinical Oncology Program (CCOP). Dr. Gotay has been an active member of the Group and its committees on cancer prevention and control, and women's health. Her University of Hawaii staff includes Dorothy Coleman, Clinical Trials Unit Coordinator, and Elyse Luke, CRA. Ms. Coleman is an oncology nurse and long-time Group member who has served as nurse-coordinator on Group protocols. She is thoroughly familiar with protocol design and regulations. Ms. Luke is a CRA for cancer clinical trials, and she has also had experience developing curricula for educational cancer control interventions, including completing the CIS information specialist training.

Statistical Center Co-Investigator, Dr. C. Moinpour, and Statistician, Dr. S. Green. Carol Moinpour, Ph.D. is an Assistant Member in the Public Health Sciences Division of the Fred Hutchinson Cancer Research Center, and an Affiliate Assistant Professor in the Health Services Department, School of Public Health and Community Medicine, University of Washington. She coordinates quality of life assessment on Group trials and has helped to activate five Phase III and four Phase II trials with quality of life studies. She is the Statistical Center liaison to the Behavioral and Health Outcomes Subcommittee of the Cancer Control Research Committee. Dr. Moinpour is also Chair of the Quality of Life Advisory Committee for the Prostate Cancer Prevention Trial (PCPT) and serves on the Breast Cancer Prevention Trial's Quality of Life Committee. In addition, Dr. Moinpour serves on the PCPT's Recruitment and Adherence Committee and coordinates recruitment and adherence activities for that trial. Dr. Moinpour is the PI for a three-year NCI/NCNR funded grant to validate a Spanish translation of the Southwest Oncology Group Quality of Life Questionnaire. She is also working with the World Health Organization Quality of Life (WHOQOL) assessment

project to develop a module for cancer patients. Stephanie Green, Ph.D. has been the Deputy Director of the Statistical Center since 1992. She has been the Primary Statistician for the Southwest Oncology Group Breast Cancer Committee since 1984. Dr. Green is a Member of the Program in Biostatistics, Public Health Sciences Division of the Fred Hutchinson Cancer Research Center, and an Affiliate Professor in the Department of Biostatistics, University of Washington. Dr. Green has had 16 years experience in cancer clinical trials, and is a co-author on over 30 breast cancer papers.

Y-ME Co-Investigator, Ms. M. Melin. Y-ME is a not-for-profit organization founded in 1978. It provides information, hot-line counseling, educational programs, and self-help meetings for breast cancer patients, their families, and friends. The Y-ME national office is located in Chicago, and there are 19 Y-ME centers in 13 states. Y-ME has operated a national toll-free hotline telephone counseling service since 1987; currently, there is also a Spanish language hotline and a 24-hour service. In 1994, the hotline received 17,000 calls, which were handled by eight paid counselors and 120 volunteers. Ms. Michelle E. Melin is Y-ME's Director of Patient Services. She manages the hotlines, including developing a curriculum for and conducting volunteer training, continuing education, and quality assurance. She, along with Y-ME Executive Director Sharon Green, has served as Y-ME's representative to the Group, where she sits on the Committee on Women's Health, and has made a number of presentations about Y-ME and breast cancer patient issues related to clinical trials. Ms. Melin received a MA and Certificate in Health Administration from the University of Chicago.

Consultants, Drs. C. Alter, P. Ganz, and A. Marcus. The consultants are all highly experienced in research on psychosocial aspects of breast cancer with experience in developing, implementing and coordinating clinical trial interventions across multiple institutions. The consultants provide a multidisciplinary blend of psychiatry (Dr. Alter), medical oncology (Dr. Ganz) and psychology (Dr. Marcus). Carol L. Alter, M.D., Director of Psychosocial Services at Temple University Comprehensive Cancer Center, has developed and pretested a protocol to provide telephone counseling for patients receiving chemotherapy; the materials from this study, which include a complete handbook of intervention materials, will provide a foundation for the current intervention. Patricia A. Ganz, M.D., Director of Cancer Prevention & Control Research at Jonsson Comprehensive Cancer Center (UCLA) has extensive breast cancer research experience, including a current NCI-supported R01 to test an intervention for breast cancer survivors and directing the quality of life component of the national Breast Cancer Prevention Trial. She and her colleagues developed and validated the CARES-SF, one of the primary study outcomes. Alfred C. Marcus, Ph.D., is the Director of Behavioral Science and Research at Denver's AMC Cancer Research Center. He has extensive experience in telephone-directed interventions, including serving as PI for a current NCI-funded R01 study of telephone counseling for breast cancer survivors being conducted through the Eastern Cooperative Oncology Group and directing the national Cancer Information Service Research Consortium, which is developing ways to utilize the CIS telephone service network to conduct research.

Additional SWOG Investigators, Drs. K. Albain, S. Martino, W. Goodwin, L. Hutchins, B. Issell, Ms's. A. Langer, E. Stovall, P. McCarthy, T. Beard, E. Sondak and P. Michelson. All of these Investigators are active Group members with distinguished credentials in breast cancer research and/or advocacy. Kathy S. Albain, M.D. is Chair of the Committee on Women's Health, and Silvana Martino, D.O., Chair of the Breast Cancer Committee. Dr. Albain was awarded a one-year Special Sabbatical from the first breast cancer solicitation of the USAMRRA for the calendar year 1995, to allow the definition and implementation of the

Committee on Women's Health breast cancer research agenda. One facet of this sabbatical was to organize, design and facilitate novel cross-discipline breast cancer research initiatives for the cooperative group. This proposal, a multi-committee collaboration of the Breast Cancer, Women's Health, Cancer Control Research and Advocates Steering Committees, as well as the Statistical Center, is a direct result of Dr. Albain's USAMRAA Special Sabbatical efforts, and will commence after completion of the sabbatical year.

Patients will be accrued for the pilot study from the institutions of Drs. Albain (Loyola University), J. Wendall Goodwin, M.D. (Ozarks Regional CCOP), Laura F. Hutchins, M.D. (University of Arkansas), and Brian F. Issell, M.D. (University of Hawaii MBCCOP). Institutions chosen to participate in the pilot study represent diverse populations (rural and urban), as well as access to high proportions of minority groups (particularly Asian and Pacific Islanders, and African-Americans). Ms.'s Langer, Stovall, McCarthy, Beard, Sondak and Michelson are members of the Group's Lay Advisors/Advocates Steering Committee. All of these women reflect the cancer-related interests and concerns of the lay community through their own advocacy activities and/or personal experience with cancer, including their affiliations with the following national organizations: National Alliance of Breast Cancer Organizations (Ms. Langer), National Coalition for Cancer Survivorship (Ms. Stovall) and Y-ME (represented by Ms. Melin and/or Ms. S. Green).

D. STATEMENT OF WORK

Task 1, Start-up Activities, Months 1-2

- a. Recruitment and training of staff.
- b. Finalizing the intervention curriculum.

Task 2, Pilot Study, Months 3-8

- a. Conducting the pilot study at the University of Hawaii, Loyola University (Chicago) and University of Arkansas.
- b. Revising and modifying procedures and intervention materials as needed.

Task 3, Accrual of women experiencing breast cancer recurrence to trial, Months 8-38

- a. 300 women experiencing breast cancer recurrence will be entered onto study. Accrual process will involve examination of off study forms and obtaining physician permission to contact the patients.

Task 4, Implementation of the Intervention, Months 8-39

- a. Random assignment of patient to intervention or control group; four-session intervention conducted by telephone by Y-ME staff.
- b. Monitoring of peer counselor performance, yearly continuing education.

Task 5, Data Collection, Months 8-45

- a. Data are collected at three time-points: baseline, 3 and 6 months post-randomization.

Task 6, Data Analysis, Months 6-48

- a. Data will be coded and entered onto the database on a continuing basis from the beginning of the study.
- b. Intensive outcome assessment analysis will take place from months 45 to 48.
- c. Preliminary reports of the data, such as baseline data, will be available midway through the project.
- d. Preparation of final reports and publications will occur during months 45 to 48.

Cost Estimate Summary

Title of Grant: Enhancing Well-Being During Breast Cancer Recurrence
 Principal Investigator Charles A. Coltman, Jr., M.D.

	Year 1	Year 2	Year 3	Year 4	Total 4 years
Direct Labor Costs	929	971	1,015	1,061	3,976
Fringe Benefits	212	221	231	241	905
Major Equipment					0
Material, Supplies and Consumables	500	523	547	572	2,142
Travel Costs	23,860	11,360	11,360	21,570	68,150
Publication and Report Costs	500	500	500	1,500	3,000
Consultant Costs	4,800	2,400	2,400	3,600	13,200
Other Direct Costs	1,025	1,072	1,120	1,171	4,388
Fixed Fee					0
Total Direct Costs	31,826	17,047	17,173	29,715	95,761
Total Indirect Costs (Rate 38%)	12,094	6,478	6,526	11,292	36,389
Subcontract, Subgrants	215,397	144,910	149,677	189,681	699,665
Total All Costs	259,317	168,435	173,376	230,688	831,815

APPENDIX K

Southwest Oncology Group Protocol S9626: "A Phase III Trial of Placebo versus Megestrol Acetate 20 mg/day versus Megestrol Acetate 40 mg/day as Treatment for Symptoms of Ovarian Failure in Women Treated for Breast Cancer."

Study Coordinators: J. Wendall Goodwin, M.D., Kathy S. Albain, M.D., Silvana Martino, D.O., Janet O'Sullivan, M.A., Polly Feigl, Ph.D.

Funded by supplemental grant from the Division of Cancer Prevention and Control, National Cancer Institute.

The following draft protocol proprietary information and is a privileged communication for investigational use only

SOUTHWEST ONCOLOGY GROUP

**A PHASE III TRIAL OF PLACEBO VERSUS MEGESTROL ACETATE 20 MG/DAY VERSUS
MEGESTROL ACETATE 40 MG/DAY AS TREATMENT FOR SYMPTOMS OF OVARIAN
FAILURE IN WOMEN TREATED FOR BREAST CANCER**

	<u>Page</u>
SCHEMA	2
1.0 OBJECTIVES.....	3
2.0 BACKGROUND.....	3
3.0 DRUG INFORMATION.....	7
4.0 STAGING CRITERIA.....	8
5.0 ELIGIBILITY CRITERIA.....	8
6.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME.....	10
7.0 TREATMENT PLAN.....	10
8.0 DOSAGE MODIFICATIONS AND TOXICITIES TO BE MONITORED.....	12
9.0 STUDY CALENDAR.....	13
10.0 MEASUREMENTS OF EFFICACY AND ENDPOINT DEFINITIONS.....	14
11.0 STATISTICAL CONSIDERATIONS.....	14
12.0 DISCIPLINE REVIEW.....	15
13.0 REGISTRATION GUIDELINES.....	15
14.0 DATA SUBMISSION SCHEDULE.....	15
15.0 SPECIAL INSTRUCTIONS.....	16
16.0 ETHICAL AND REGULATORY CONSIDERATIONS.....	18
17.0 BIBLIOGRAPHY.....	21
18.0 MASTER FORMS SET.....	23
19.0 APPENDIX.....	35
PARTICIPANTS: ALL SOUTHWEST ONCOLOGY GROUP, CCOP AND CGOP MEDICAL ONCOLOGISTS	

STUDY COORDINATOR:

J. Wendall Goodwin, M.D. (Medical Oncology)
Ozarks Regional CCOP
3231 S. National
Springfield, MO 65807-7304
Phone: 417/883-7422

AGENTS:

Megestrol Acetate (NSC-71423)

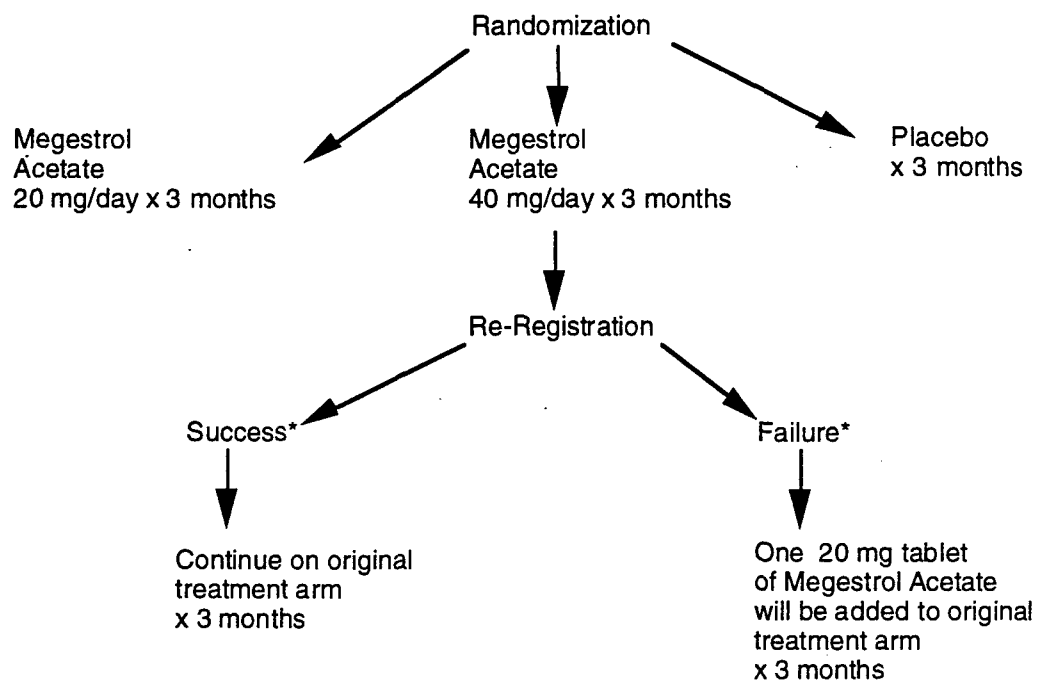
Kathy S. Albain, M.D. (Medical Oncology - Committee on Women's Health)
Loyola University Medical Center
Cancer Center, Room 109
2160 South 1st Ave
Maywood, IL 60153-5589
Phone: 708/327-3102

Janet O'Sullivan, M.A. (Biostatistics)
Polly Feigl, Ph.D.
Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street, MP-557
Seattle, WA 98104-2092
Phone: 206/667-4623

Silvana Martino, D.O. (Medical Oncology - Breast Cancer Committee)
Westlake Comprehensive Breast
Cancer Center
971 S. Westlake Blvd., Suite B
Westlake Village, CA 91361
Phone: 805/446-4950

M249/mb

SCHEMA



*As defined in Section 10.1.

1.0 OBJECTIVES

- 1.1 To compare the effectiveness and duration of benefit of placebo and two dose levels of megestrol acetate in the reduction of severe and/or frequent flushing episodes in patients with a history of adequate local and regional treatment of invasive breast cancer.
- 1.2 To document the effects, if any, of various dose levels of megestrol acetate on atrophic vaginitis and dyspareunia.
- 1.3 To evaluate the toxicity of two dose levels of megestrol acetate relative to placebo.
- 1.4 To evaluate the feasibility of accrual of patients to a placebo-controlled study evaluating megestrol acetate in patients with a history of invasive breast cancer which has undergone adequate local and regional treatment.

2.0 BACKGROUND

It is estimated that there will be approximately 180,000 cases of breast cancer in 1995 and this yearly incidence will continue through the decade. (1) For those patients with node-positive or high-risk node-negative breast cancer, postoperative adjuvant therapy is recommended. For premenopausal females the standard therapy has been systemic cytotoxic chemotherapy or more recently there has been a renewal of studies evaluating either surgical or medical ovarian ablation in addition to chemotherapy. For postmenopausal females, standard therapy has been the antiestrogen tamoxifen, and more recently studies are comparing the addition of systemic cytotoxic chemotherapy to tamoxifen. In both groups, ovarian failure caused by systemic chemotherapy or ovarian ablation in premenopausal patients and its natural occurrence in postmenopausal patients causes distressing symptoms which interfere with the quality of life and may be a threat to marital stability. The treatment of ovarian failure occurring either premenopausally, secondary to surgery, or naturally in postmenopausal females has been replacement estrogens providing there is no history of breast cancer. Estrogen therapy, however, in women with a history of treated local or local and regional breast cancer is felt to be contraindicated because of the fear of activation of latent cancer cells or causing contralateral breast cancer. In fact, the package insert of estrogen preparations states that a history of breast cancer is a contraindication to the use of estrogen-replacement therapy. (2)

There is controversy, however, as to whether estrogen and/or progestin replacement therapy does alter the natural history of treated breast cancer. DiSaia has reviewed the effects of pregnancy concurrent with breast cancer or subsequent to breast cancer and has suggested this produced no additional adverse effect. (3) Also, breast cancers which developed during estrogen replacement therapy did not have an adverse outcome, but may, indeed, have a more favorable outcome. (4) There is, however, evidence to support the contention that estrogens may have an adverse affect on the natural history of breast cancer. Obesity at the time of diagnosis of breast cancer has been an adverse prognostic factor with respect to survival which may be related to the peripheral conversion of androstenedione to estrone. (5) Additionally, some but not all adjuvant chemotherapy studies demonstrate that chemotherapy-induced amenorrhea decreases relapse rate. (6) Finally, the recently published meta-analysis demonstrated a significant reduction in the annual risk of both recurrence and death when ovarian ablation was performed below the age of 50. (7) However, there are other data which clearly do not confirm an adverse impact from the use of estrogen or progestins in breast cancer patients.

Because there is a possibility that estrogen replacement in patients with a past history of treated breast cancer may have an adverse outcome, alternative methods to treat the symptoms of ovarian failure need to be evaluated. Flushing (hot flashes) is one of the most distressing of the symptoms of ovarian steroid withdrawal. It occurs in approximately 75 percent of the women undergoing natural menopause and it may be as high as 94 to 100 percent in women who become castrate. (8) Ovarian steroid withdrawal appears to decrease the inhibitory action of hypothalamic opioidergic activity on noradrenergic neurons producing increased activity in the

thermoregulatory and GnRH centers resulting in peripheral vasodilation and pulsatile LH releases. (8) Studies have demonstrated that progestins will reduce the number of hot flashes and intensity of hot flashes. These studies have utilized the structurally similar C-21 progestins medroxyprogesterone acetate and megestrol acetate. (9 - 15) In a recent study by Loprinzi, megestrol acetate was given for four weeks in a double-blind randomized study with a cross-over at a dose of 20 mg b.i.d. in the non-placebo group. (15) In this study the frequency of hot flashes as a percent of baseline daily average was 26% for those receiving megestrol acetate and 73% in the placebo group. The hot flash score which was a measure of severity of hot flashes, also decreased significantly compared to the placebo. There was an unexplained transient increase in flushing at the institution of megestrol acetate in women taking tamoxifen. Eighty percent of the women in the study were on tamoxifen and there is no comparison of the efficacy between those receiving tamoxifen and not receiving tamoxifen. At the end of the two four-week study periods, participants could continue on megestrol acetate in an open label fashion. No long-term data is available on these patients (Loprinzi, Personal Communications), nor does the Loprinzi study address durability of benefit. The current study, which will have a six-month duration, will determine if a lower dose than studied by Loprinzi et al. is also effective, as well as address the unanswered question of durability of benefit. It will also attempt to answer some of the possible long-term side effects of megestrol acetate with respect to weight gain, edema, vaginal bleeding episodes, thrombotic events, depressive symptoms and effect on vaginal atrophy. Other concerns, such as the effects of progestins on tamoxifen-induced endometrial changes, cardiovascular mortality and the possible influence of C-21 progestogen acetate on hormonally hyper-sensitive tumors (breast and endometrial cancer) are either being evaluated in other studies or will require larger trials of longer durations. For example, in another Southwest Oncology Group study, medroxyprogesterone acetate (10 mg per day for 14 days every three months) will be prospectively tested as a potential preventive agent against tamoxifen-induced endometrial changes. Data regarding the frequency and severity of hot flashes in the medroxyprogesterone acetate versus placebo arms of this trial would be intriguing to collect to determine if very low dose, infrequent progestin therapy could also ameliorate hot flashes. However, funding is currently not available to add this aspect to the trial. Furthermore, the present study is designed to use longer-term and continuous treatment with the more potent progestin megestrol acetate in order to ameliorate severe symptoms at the time of the study entry.

Cardiovascular disease in women rapidly increases after menopause and becomes the largest cause of morbidity and mortality in women. Premature surgical menopause also appears to be an increased risk factor for cardiovascular disease. (16) Estrogen replacement in postmenopausal women appears to reduce coronary events possibly by its beneficial effect of lowering cholesterol and particularly low-density lipoprotein cholesterol while increasing high-density lipoprotein cholesterol. (17 - 19) Osteoporosis is also a significant problem in postmenopausal women and estrogen replacement plus calcium appears to produce an increase in spinal trabecular mineral content compared to those given calcium alone or no therapy. (20) There are no data regarding any impact on future cardiovascular events from the use of replacement progestins.

Tamoxifen appears to have both estrogen antagonist and agonist effects, the direction of which is organ-specific. The estrogen agonist effects of tamoxifen have been shown in studies by Love to improve lipoprotein profiles and to show a slight improvement in mineral bone density. (21, 22) Other studies yield contradictory results with respect to tamoxifen's effect on lipids and bone mineral preservation. Tamoxifen, however, does not appear to improve the undesirable ovarian effects, in particular flushing, and is associated with an increase in endometrial carcinoma. (23) The effect of megestrol acetate on blood lipids appears varied. When given as a single agent at very low doses (0.5 mg) over one year, it appears to have either no effect on or slightly lowers serum cholesterol. (24 - 26) However, at very high doses (800 mg a day) it lowered total cholesterol, but also had a lowering effect on high-density lipoprotein cholesterol. (27) The C-21 progestins decrease calcium excretion and also when added to an estrogen, appear to decrease mortality from osteoporotic hip fractures, suggesting that megestrol acetate may have a beneficial effect on retarding of the rate of osteoporosis. (28, 29)

The effects of long-term progestational agents on the induction of breast cancer remains to be completely defined. There is a further increase in the mitotic rate and thymidine labeling index

during the luteal phase of the menstrual cycle and there are epidemiologic studies that suggest that the number of luteal cycles and therefore the relative time spent in the luteal phase may be a risk factor for the induction of carcinoma of the breast. (30, 31) Some studies have suggested an increased risk of breast cancer with depo-medroxyprogesterone acetate with prolonged use, particularly in the subgroup below 25 years of age or before the first first-term pregnancy. (32) A review of progestins and breast cancer has not found any conclusive evidence for a relationship between progestins and induction of breast cancer. (33) However, this review stated further study was needed in high-risk groups which included extended hormone exposure before the age of 25 or for the first full-term pregnancy, or exposure in the postmenopausal period. Nevertheless, there is data that in the breast, progestins may shift the estrone/estradiol equation to the inactive estrone, such that there would be less concern about stimulation of breast carcinoma development or progression. And, it is possible that progestins may have benefit in retarding recurrence (extrapolating from their benefit in the treatment of metastatic disease). Finally, in the present study the treatment is only for 6 months rather than the prolonged use discussed above.

The long-term effects of continuous progestational agents on the endometrium are still being evaluated. In a study of 41 women receiving conjugated estrogens plus varying doses of norethindrone for a median of 8 years, found that after a transient period of irregular bleeding, all achieved amenorrhea. Six of the 41 then experienced episodes of breakthrough bleeding. Those who did not have any breakthrough bleeding had an inactive atrophic endometrium while two of those who did develop bleeding also had an atrophic endometrium. Two had polyps and two had adenocarcinoma. (34) Administered progestins raise the level of endometrial 17 beta hydroxy steroid dehydrogenase levels which converts estradiol to less-active estrone and, also decrease nuclear estradiol receptors and DNA synthesis. A 20 mg dose of megestrol acetate for six weeks can reduce morphologic changes of adenomatous or atypical hyperplasia to the normal state. (35) Short-term medroxyprogesterone acetate leads to a rapid induction of 17 beta hydroxy steroid dehydrogenase, though with continued administration this level is decreased. Tamoxifen alone did not stimulate this enzyme and when tamoxifen and medroxyprogesterone acetate were given in combination, there was similar induction of the 17 beta hydroxy steroid dehydrogenase. (36) The effects of lower short-term cyclical doses of the less potent medroxyprogesterone acetate on endometrial estrogen and progesterone receptors, oncogenes, 17 beta hydroxy steroid dehydrogenase activity and pathology on biopsy while on tamoxifen are objectives of another Southwest Oncology Group study. It is beyond the scope, intent and feasibility of the present study to monitor the endometrium in a heterogeneous group of patients who will have been on tamoxifen for a variable amount of time if at all.

Vaginal bleeding upon initiation of megestrol acetate treatment of metastatic breast cancer is not uncommon, is usually self-limited and may not require an endometrial biopsy. In a setting similar to this study, vaginal bleeding was reported by 31% of the women in Loprinzi's study at the completion of their initial four weeks with 80% of it occurring within the first two weeks of discontinuing the megestrol acetate. (15) On the present study, the incidence of bleeding will be variable on each arm, and it will be unknown which patients are receiving Megace[®] such that short period of observation is not recommended. Gynecologic oncologic consultants recommend, therefore, that all subjects who develop bleeding will have an immediate endometrial biopsy and continue study unless suspicious pathology is found. However, patients who had received an endometrial biopsy (see Section 5.6) at the time of study or at time of tamoxifen initiation may forego this biopsy unless bleeding persists beyond two weeks or recurs. Furthermore, bleeding would be expected at the end of the study due to hormone withdrawal, so it is recommended that all participants be referred for gynecological evaluation if the bleeding is out of proportion to a normal period or it happens greater than two weeks after discontinuation of the study drug.

The present study will be conducted as a double-blinded study with a placebo and two levels of Megace[®]. The total duration of treatment will be six months. However, at three months those participants not achieving the prescribed reduction in frequency of hot flashes will have 20 mg of megestrol acetate added to their study drugs in an open label form. The study will otherwise remain blinded and continue for an additional three months. In this way, we will simultaneously

study the effect of dose escalation in patients still symptomatic after 3 months as well as answer the durability of benefit question. Patients will go off study after 6 months and the investigator will be informed of the assigned dose of Megace[®]. Subsequent treatment open label will be left to the discretion of the physician. Toxicity data will be obtained, particularly with respect to edema, weight gain or depression. In summary, the following six treatment groups are possible.

Megestrol Acetate Dose * months 1 - 3	Efficacy Evaluation at 3 months	Megestrol Acetate Dose **, months 4 - 6
0 (placebo)	Success	0 (placebo)
0 (placebo)	Failure	20 mg /day
20 mg/day	Success	20 mg /day
20 mg/day	Failure	40 mg /day
40 mg/day	Success	40 mg /day
40 mg/day	Failure	60 mg /day

*Initial dose randomly assigned (at first registration).

**Actual dose is still blind in months 4 - 6 (patients reregistered at end of month 3).

Three months from the completion of the study, a follow-up questionnaire will be obtained relating whether the patient's symptoms relapsed after discontinuing the Megace[®] or whether patients were continued on open label Megace[®] at the investigators discretion. Also, the incidence in frequency and duration of vaginal bleeding during and at the end of the study will be reported during the study and follow-up. Overall, the principal endpoint of the study will be reduction in flushing episodes. It is hoped that the results of this study and others will pave the way for a prospective look at longer durations of treatment on breast cancer outcome.

Of principal interest in the study will be those patients who have been on tamoxifen for greater than six months before entering the study. It is felt that there are adequate numbers of women, who meet the entry criteria who have been on tamoxifen for six months or greater and are still symptomatic, to answer the study questions with sufficient statistical power. However, the study will not be limited to these patients alone. It is recognized that some women have severe symptoms for the first few months of tamoxifen and then experience diminishing flushing episodes after 6 - 8 months on tamoxifen. Thus, these women would not meet the criteria for entry into the study if made to wait 6 months. However, it is felt strongly that this group should also be studied and should not be allowed to experience symptoms that reduce their quality of life for an additional 4 months waiting to become eligible for this study. It would be anticipated that this other group (on tamoxifen for at least 1 month up to 6 months) would be heterogeneous: a certain number of women would without treatment have their flushing episodes decrease to a level which would not meet eligibility for study entry at 6 months, whereas the remaining number would have their symptoms "naturally" continue beyond six months. Thus by allowing entry at 1 - 6 months of tamoxifen, possible inferences could be made with respect to early treatment of flushing symptoms if there were none, or very few relapses in this group. Loprinzi, et al. did not analyze prior duration of tamoxifen, but noted carry-over effects in the groups who received the placebo after megestrol acetate. (15) The number of flushing episodes did not return to baseline. Flushing scores have been reported to be higher in women with longer duration of climacteric complaints or prior hormone replacement therapy. (37) It is also unknown whether this would predict for a higher relapse rate at the completion of the study. These data will be collected in the present trial.

Finally, women who are not on tamoxifen but who meet other study eligibility requirements will also be eligible for a test of the efficacy and potential toxicities of the megestrol acetate. Thus, this trial will also examine the potential benefit of Megace[®] in breast cancer survivors made symptomatic by chemotherapy or who are naturally experiencing refractory menopausal symptoms. Regardless of prior treatment, the women entering this trial will be homogeneous

based on the severity of hot flashes. Postmenopausal status will not be a requirement since menses may continue for a while sporadically during disabling menopausal symptoms.

In sum, the present study is one of several efforts of the Southwest Oncology Group to either better understand, ameliorate and/or prevent distressing effects of otherwise beneficial treatment in breast cancer survivors. These studies are vastly different in objective and design, yet are complementary in the sense that progestins (different type, dose, duration and schedule) are being tested in terms of a.) treatment of menopausal symptoms, and either b.) reversal or c.) potential prevention of tamoxifen-induced endometrial changes. Once the results of these studies are known, together with other trials in this area by other groups, the intergroup mechanism will be positioned to mount a large prospective trial comparing the best approaches from these pilot studies in order to look at their effects on long-term breast cancer outcome.

3.0 DRUG INFORMATION

3.1 Megestrol Acetate (NSC-71423)

- a. Chemistry: Megestrol acetate is a synthetic derivative of the naturally occurring steroid hormone, progesterone. Megestrol possesses marked progestational properties and demonstrates anti-estrogenic, anti-gonadotrophic and anti-androgenic activity.

Megestrol acetate is a white crystalline solid with a molecular weight of 384.5.

- b. Pharmacokinetics: The pharmacokinetics of megestrol, as measured by HPLC indicate peak serum levels in two and three hours after oral administration of doses from 20 to 200 mg.

The serum elimination curve appears to be biphasic with terminal $t_{1/2}$ of 15 to 20 hours. Megestrol is eliminated mostly in the urine as inactive metabolites and 8 to 30% in the feces. There is no aromatization to estrogenic substances.

- c. Mechanism of Action: The mechanism of action of megestrol is not fully known, although it has shown high binding affinities for progesterone, androgen and glucocorticoid receptors in human breast cancer.

- d. Toxicity: Megestrol is virtually free of adverse effects. Minor weight gain less than 10% lean body mass is the most prevalent side effect. Rarely, carpal tunnel syndrome, deep vein thrombophlebitis, pulmonary embolism, nausea, vomiting, edema, breakthrough bleeding, dyspnea, tumor flare (with or without hypercalcemia), hyperglycemia, alopecia, hypertension and rash have been reported while on megestrol therapy.

- e. Formulation: Megestrol acetate is supplied in 20 mg and 40 mg tablets.

- f. Supplier: Megestrol acetate is commercially available, but will be supplied for this study by Bristol Myers Squibb. Distribution procedures are being negotiated and will be included in the final version of the protocol.

3.2 Placebo

- a. Formulation: Tablets identical in appearance to megestrol acetate.

- b. Administration: 20 mg tablet p.o. b.i.d.

- c. Supplier: Placebo will be supplied by Bristol Myers Squibb. Distribution procedures are being negotiated and will be included in the final version of the protocol.

4.0 **STAGING CRITERIA**

- 4.1 AJCC/WHO pathologic stages are defined below.

Primary Tumor (T)

- T1 Tumor 2 cm or less in greatest dimension
 - T1a 0.5 cm or less in greatest dimension
 - T1b More than 0.5 cm but not more than 1 cm in greatest dimension
 - T1c More than 1 cm but not more than 2 cm in greatest dimension
- T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension
- T3 Tumor more than 5 cm in greatest dimension

Regional Lymph Nodes (N)

- N0 No regional lymph node metastasis
- N1 Metastasis to movable ipsilateral axillary lymph node(s)

Distant Metastasis (M)

- M0 No distant metastasis

5.0 **ELIGIBILITY CRITERIA**

- 5.1 Randomization - Step 1

- a. Patients must have had stage T1 - 3, N0 - 1, M0 infiltrating breast cancer treated with appropriate local and regional therapy.
- b. Patients must have completed all therapy (surgery, chemotherapy) for their breast cancer except tamoxifen and breast radiotherapy, either or both of which may be ongoing.
- c. Patients must be able and willing to fill out the Patient Log of Menopausal Symptoms. The patient must have completed the Patient Log of Menopausal Symptoms and Cover Sheet for the period of seven days immediately prior to randomization. Patients must have had ≥ 10 hot flashes during that week or 5 - 9 hot flashes with an overall severity rating of "Quite a bit" or "Extremely" for that week, for the patient to be eligible (see Section 18.0).
- d. Patients must never have participated in any National Cancer Institute sponsored breast cancer adjuvant protocols.
- e. Menopausal status must be known and both pre- and postmenopausal women are eligible.

1. Premenopausal is defined as either having regular menses or, if the last menstrual period was 4 - 12 months ago the patient must have a premenopausal FSH level.
2. Postmenopausal is defined by the following criteria:
 - i. Natural menopause: last menstrual period at least one year prior to registration.
 - ii. Surgical menopause: bilateral oophorectomy at least two months prior to the diagnosis of breast cancer.
 - iii. Patients who are 4-12 months from their last menstrual period and not on postmenopausal estrogen will be considered postmenopausal if the FSH is elevated to the postmenopausal range.
 - iv. Patients on postmenopausal estrogen therapy will be considered postmenopausal if they are 55 years of age or older. All other patients must have a postmenopausal level of FSH (it may take as long as 1-2 weeks after stopping estrogen for FSH to rise to postmenopausal level). Postmenopausal estrogen therapy must be discontinued in all patients.
- f. Endometrial biopsy is optional. However, if an endometrial biopsy was performed within one year prior to study entry or at the time of start of tamoxifen therapy, it must be normal.
- g. Patients must have a negative pregnancy test obtained within 28 days prior to registration if there is any concern that pregnancy may be the cause of amenorrhea.
- h. Patients must have no history of deep venous thrombosis.
- i. Patients must have a fasting glucose level obtained within 60 days prior to registration.
- j. Postmenopausal patients must have no history of recurrent or persistent vaginal bleeding. If the patient has had any vaginal bleeding within the past year, she must have a subsequent normal endometrial biopsy prior to study entry.
- k. Prior hormone therapy is allowed except for treatment with Megace[®]. Patients must not be on steroids or other hormones (i.e., prednisone, estrogens) except tamoxifen. Patient must be willing to discontinue prior therapy (except tamoxifen) within one week prior to registration in order to be eligible for this study.
- l. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.
- m. If Day 28 or 60 falls on a on a weekend or holiday, the limit may be extended to the next working day.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is

done on a Monday, the Monday four weeks later would be considered Day 28.

- n. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.
- o. At the time of patient registration, the date of institutional review board approval for this study must be provided to the Statistical Center.

5.2 Re-Registration - Step 2

All patients are to be re-registered at three months after registration.

- a. Patients must have completed the 3-month Patient Log of Menopausal Symptoms and must have been evaluated as per Section 10.1 for symptom improvement (success or failure).
- b. Patient must have begun treatment at least 3 months (90 days) prior to re-registration.
- c. Patient must not have been on protocol treatment for more than 3 months and 2 weeks (104 days).

6.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME

6.1 Stratification Factors

- a. Tamoxifen use: > 6 months vs. 1 - 6 months vs. none
- b. Flushing episode: < 5 per **day** vs. 5 - 9 per **day** vs. > 9 per **day**
- c. Symptomatic flushing duration: ≤ 6 months vs. > 6 months

6.2 Descriptive Factors

- a. Chemotherapy: yes vs. no
- b. Menopausal status: pre- vs. post-

7.0 TREATMENT PLAN

Patients will be treated for a total of 6 months. A re-registration will occur at the end of Month 3 and treatment will continue for another 3 months. At the completion of the 6 months, the treatment assignment will be unblinded and treatment continued at the discretion of the investigator.

7.1 Randomization - Step 1

- a. Patients will be randomly assigned to one of the following three initial treatment arms in a double-blind fashion.

<u>AGENT</u>	<u>DOSE</u>	<u>ROUTE</u>	<u>DAYS</u>
Megestrol Acetate	20 mg/d	PO	Daily x 3 months
Megestrol Acetate	40 mg/d	PO	Daily x 3 months
Placebo		PO	Daily x 3 months

S9626. A Phase III Trial of Placebo versus Megestrol Acetate 20 mg/day versus Megestrol Acetate 40 mg/day as Treatment for Symptoms of Ovarian Failure in Women Treated for Breast Cancer

9.0 STUDY CALENDAR

REQUIRED STUDIES	PRE STUDY	MO 1	MO 2	MO 3	MO 4	MO 5	MO 6	MO 9
PHYSICAL								
History and Physical Exam	X			X			X	X
Weight and Performance Status	X			X			X	
Toxicity Notation		X√		X			X	
LABORATORY								
FSH †	X							
Fasting Glucose	X			X			X	
Pregnancy Test *	X							
ASSESSMENTS								
Pt. Log of Menopausal Symptoms and Cover Sheet	X			X∞			X◇	
Offstudy Physician Questionnaire								X
Re-registration				X§				
TREATMENT								
Megestrol Acetate/Placebo		X	X	X§	X	X	X°	

**NOTE: All forms to be used in this study are found in Section 18.0.
Forms Submission Guidelines can be found in Section 14.0.**

- √ This assessment can be done by telephone interview with the patient in order to record any symptoms to the study drug (Megace® or placebo) on the flow sheet.
- † If postmenopausal status is questionable (i.e. monthly menses ceased, no bilateral oophorectomy, LMP < 6 months), then an FSH level must be obtained.
- * Patients must have a negative pregnancy test if there is any concern that pregnancy may be the cause of amenorrhea.
- ∞ First post-registration assessment at end of 3rd full month of treatment.
- ◇ Second post-registration assessment at end of 6th full month of treatment.
- § Patients will be evaluated for success or failure and re-registered. If the patient is a success, she will continue on the original assigned treatment arm. If the patient is considered a failure, she will have one 20 mg tablet of megestrol acetate added to her original treatment arm. (See Section 7.2.)
- ° After completion of 6 full months of treatment, the treatment assignment will be unblinded and treatment will be continued at the discretion of the investigator.

- b. Patients will complete the Patient Log of Menopausal Symptoms prior to randomization and at Months three and six. Patients must complete the forms regardless of whether they remain on treatment at the scheduled assessments. See Study Calendar (Section 9.0).
- c. Treatment with assigned arm will continue for three months, with the second three months determined according to Section 7.2.

7.2 Re-Registration - Step 2

- a. All patients will be re-registered after completing 3 months of treatment. Patients must also have completed their 3-month Patient Log of Menopausal Symptoms questionnaire. At three months, patients will be evaluated for success or failure as per Section 10.1. If success, continue on assigned treatment for 3 more months. If failure, one 20 mg megestrol acetate tablet will be added to the patient's blinded daily dose.

<u>3 month evaluation</u>	<u>Dose of Megestrol Acetate</u>
Success	to be continued as for the first 3 months
Failure	add 20 mg megestrol acetate to the patient's blinded daily dose

- b. Study treatment will continue for a total duration of six months. The patient will complete the Patient Log of Menopausal Symptoms at the end of six months. At the end of six months, the treatment assignment will be unblinded. Continued treatment with megestrol acetate will be at the discretion of the physician.

7.3 Three months from completion of the protocol treatment (9 months from start) investigators will complete a post-study form which will include whether symptoms continued, improved, recurred, progressed or remained unchanged; how the recurrent or progressive symptoms were treated; whether the study drug has been continued and, if so, at what dose. Also, the form will document information on post-treatment vaginal bleeding.

7.4 **Criteria for Removal from Protocol Treatment:**

- a. Recurrence of disease at investigator's discretion.
- b. Progression of symptoms.
- c. Unacceptable toxicity.
- d. Completion of protocol treatment at Month 6.
- e. Severe vaginal bleeding beyond 2 weeks which does not abate after gynecologic evaluation and treatment (see Section 8.1), or pathologic abnormality following endometrial biopsy for vaginal bleeding.
- f. Unblinding of treatment.
- g. The patient may withdraw from the study at any time for any reason.

7.5 All reasons for discontinuation of treatment must be documented in the Flow Sheets.

7.6 All patients will be followed for nine months after beginning protocol treatment.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

- 8.1 Vaginal bleeding during the treatment period (6 months): If vaginal bleeding occurs during the treatment period and the patient has had a normal endometrial biopsy within 60 days prior to study entry, she is to be referred for endometrial biopsy only if the bleeding persists beyond 2 weeks. If she did not have a prestudy biopsy, one should be done regardless of the duration of bleeding. In either case, patients will continue on protocol treatment if no endometrial abnormality is found upon pathologic examination, unless in the opinion of the investigator, the bleeding is too severe.
- 8.2 Vaginal bleeding after completing treatment: Vaginal bleeding that persists for greater than two weeks after completion of the study will be referred for gynecologic evaluation.
- 8.3 Weight gain is often observed with Megace[®]. If weight gain is unacceptable to the patient, and it cannot be controlled by exercise and diet, the patient may elect to discontinue study treatment.
- 8.4 Hyperglycemia is very rarely observed with Megace[®] treatment. If it occurs at too severe a degree, the patient's physician may elect to add drug (oral or insulin) treatment or alternatively remove the patient from the study.
- 8.4 For treatment or dose modification related questions, please contact Dr. Goodwin at 417/883-7422 or Dr. Albain at 708/327-3102.
- 8.5 Unexpected or fatal toxicities (including suspected reactions) must be reported to the Operations Office, to the Study Coordinator, to the IRB and the NCI. The procedure for reporting adverse reactions is outlined in Section 16.0.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 The primary endpoint is symptom improvement (Y/N) defined as:

A 75% reduction in the number of hot flashes for 3 month assessment compared to baseline. All other patients will be considered to have a treatment failure, including dropouts.

To calculate 75% reduction: divide the total number of hot flashes at month 3 by the total number of hot flashes at baseline. This number must be .25 (25%) or less. (i.e., if a patient has 88 hot flashes at baseline and 28 at the 3 month assessment, then $28/88 = .318$ - this patient did not have subjective improvement.)

10.2 The secondary endpoint is symptoms status at 6 months. This will provide information on the results of the dose escalation and on durability of responses seen at the 3 month evaluation. Calculate both percentage change in hot flashes from number at month three and number at baseline.

10.3 Physician reported data will also be collected on choice of treatment after going off study, symptom status (better, worse, unchanged), vaginal bleeding and endometrial biopsies (3 months after completing protocol treatment).

11.0 STATISTICAL CONSIDERATIONS

The main objective of this study is to compare the effectiveness of placebo and two levels of megestrol acetate in the reduction of severe and/or frequent flushing episodes.

A secondary endpoint is to document the effects of various doses of megestrol acetate on atrophic vaginitis and dyspareunia.

The data used to predict the anticipated success rate of megestrol acetate was taken from the studies of Bullock, et al., Morrison, et al., Loprinzi, et al., Schiff, et al., and Albrecht, et al. They reported a mean reduction in flushing episodes of 25% with a range of 20% to 27% in the placebo arm, and a median of 75% reduction in the treatment arm with a range of 73% to 90%. All of the studies used medroxyprogesterone acetate except Loprinzi, which used megestrol acetate. In his study, 24% of patients on the placebo arm and 71% of patients on the treatment arm experienced a > 50% reduction in the number of hot flashes.

11.1 A total sample size of approximately 279 eligible patients (93 patients per arm) would allow detection of the differences below for three comparisons; placebo vs. low dose, placebo vs. high dose and low dose vs. high dose. (Three .017 one sided tests with 90% power, i.e., .05 p value jointly.)

<u>Treatment</u>	<u>Assumed success rate, i.e., Percent of patients with \geq 75% reduction in flushing episodes at 3 months.</u>
Placebo	25%
Low Dose	50%
High Dose	75%

- 11.2 Anticipated accrual: The target enrollment is 90 patients per year. If the actual accrual at months 6 - 18 is close to 75% of this figure, the study will be extended. Otherwise, closure will be proposed.
- 11.3 Time for study completion: 4 years (3 years for accrual, 1 year for follow-up).
- 11.4 Any toxicity occurring with at least a 2% probability is likely to be seen at least once (98% chance).

12.0 DISCIPLINE REVIEW

There is no Discipline Review in conjunction with this study.

13.0 REGISTRATION GUIDELINES

- 13.1 There will be two registrations for this study (see Section 5.0 and 7.0).
- 13.2 All patients must be registered with the Southwest Oncology Group Statistical Center by telephoning 206/667-4623, 6:30 a.m. to 5:00 p.m. Pacific time, Monday through Friday, excluding holidays. Patients must be registered for Step 1 prior to initiation of treatment (no more than one working day prior to the planned start of treatment).

Patients must be registered for Step 2 at least 90 days and no longer than 104 days after registration to Step 1.
- 13.3 The caller must be prepared to answer every question on the eligibility checklist.
- 13.4 The caller must also be prepared to provide the date of institutional review board approval for this study. Patients will not be registered if the IRB approval date is not provided or is > 1 year prior to the date of registration.
- 13.5 Exceptions to the current registration policies will not be permitted. Therefore, late registrations (after initiation of treatment), exceptions to eligibility requirements, participation by an institution/member not identified as eligible **AND/OR** cancellations will not be allowed.

14.0 DATA SUBMISSION SCHEDULE

- 14.1 Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.
- 14.2 Master forms are included in Section 18.0 and (with the exception of the sample consent form) must be photocopied for data submission to the Statistical Center.
- 14.3 Group members and CCOPs must submit two copies of all data forms directly to the Statistical Center in Seattle. CGOPs must submit (number of copies to be determined by the Group member) copies of all forms to their Group member institution for forwarding to the Statistical Center.

14.4 WITHIN 14 DAYS OF RANDOMIZATION - STEP 1:

Submit copies of the following:

- a. Eligibility Checklist - Step 1
- b. Patient Log of Menopausal Symptoms and Cover Sheet
- c. Study Specific Breast Cancer Prestudy
- d. Study Specific Flow Sheet documenting history and physical, prestudy tests/exam results, the first seven days of protocol treatment and toxicity notations.

14.5 WITHIN 14 DAYS AFTER RE-REGISTRATION - STEP 2:

Submit copies of the following:

- a. Eligibility Checklist - Step 2
- b. Patient Log of Menopausal Symptoms and Cover Sheet
- c. Study Specific Flow Sheet

14.6 AT MONTH 6:

- a. Patient Log of Menopausal Symptoms and Cover Sheet
- b. Study Specific Flow Sheet

14.7 AT MONTH 9:

Submit copies of the following:

- a. Post Treatment Questionnaire
- b. Study Specific Flow Sheet

14.8 WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit copies of the Off Treatment Notice and final on treatment Flow Sheets documenting required parameters as specified in Section 9.0.

15.0 SPECIAL INSTRUCTIONS

- 15.1 All patients will complete the Patient Log of Menopausal Symptoms at the required intervals: pre-randomization (**pre-registration** assessment); months 3 (**1st post-registration** assessment) and 6 (**2nd post-registration** assessment).
- 15.2 The Patient Log of Menopausal Symptoms will be completed by the patient prior to randomization for one week to determine eligibility for the study. An instructions page is attached to the Log.
 - a. Patients complete the **Daily Log** of hot flashes for seven days, noting the number of flushes experienced each day and, if any occur, the severity of flushes for each day. At the end of seven days, the patient records the total number of

hot flashes for the week and provides an overall severity rating of flushing for the entire week. Patients are eligible if they have 10 or more hot flashes during the pre-randomization week or if they have 5 - 9 flushes and the overall severity rating for the week is "Quite a bit" or "Extremely". The patient will also complete the Log of hot flashes daily for seven days two more times: at months 3 and 6 post-randomization.

- b. The Patient Log of Menopausal Symptoms has another set of questions, **Ratings with a One-Month Time Frame**, that is completed **only on day seven** each time the Log is scheduled. The time frame for these questions is one month versus the daily time frame of the hot flash log. Within the Ratings with a One-Month Time Frame section, note that instructions differ for different sets of items.
- 15.3 The first time the patient completes the Patient Log of Menopausal Symptoms: Please read the instructions to the patient and make certain that the patient understands how to complete the different parts of the Patient Log of Menopausal Symptoms. Explain the specific administration times for this protocol. It should take less than a minute each day to do the Daily Log. On day seven when all parts of the questionnaire are completed, it should take the patient about ten minutes. Patients should be directed to report all symptoms or problems even if they cannot attribute the cause to menopause-related symptoms or their treatment. When a patient completes the Patient Log of Menopausal Symptoms on subsequent occasions, please remind her that different sections of the questionnaire have different instructions and that she read the instructions carefully before answering the questions.
 - 15.4 It is permissible to assist patients with completing the questionnaires being careful to influence the patient's response. Note on the cover sheet what assistance was required and indicate the reason (e.g., elderly, too sick, etc.). Discourage family members from 1) being present while the patient completes the questionnaire and/or 2) influencing patients responses to the question.
 - 15.5 It is very important to review the questionnaire after the patient has completed it to be sure all of the questions have been answered and that only one answer has been marked.
 - a. If the patient has marked more than one answer per question, ask the patient which answer reflects how she is feeling.
 - b. If the patient has skipped a question, tell the patient that a question was not answered and ask if she would like to answer the question. Always give the patient the option to refuse. Indicate on the form by the question that the patient did not want to answer this question.
 - 15.6 If a patient refuses or cannot complete the questionnaire for some reason, then this must be documented on the cover sheet and mailed to the Statistical Center on the same day that this occurs. The patient should be then asked to complete the Patient Log of Menopausal Symptoms at the next scheduled time.
 - 15.7 Since a patient is completing the Patient Log of Menopausal Symptoms at home, she needs to be reminded prior to each assessment and be provided with a copy of the complete questionnaire. A one-week window is allowed on either side of the assessment date.
 - a. When a patient is registered on S9626, a calendar will be provided to the institution with dates of upcoming assessments noted. A copy of this calendar can be given to the patient with the reminder that the Patient Log of Menopausal Symptoms is to be completed at home. You may wish to make a copy of the

Study Calendar and include it with the specific calendar for the patient's name in the patient's file.

- b. If treatment is delayed, the assessment schedule should be defined from the beginning of treatment, not from randomization.

15.8 For each scheduled time, complete a cover sheet and attach it to the Patient Log of Menopausal Symptoms. If the patient did not complete the questionnaire, you must submit a cover sheet documenting the reason. See Section 14.0 for data submission guidelines.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

For each drug supplied for a study, an accountability ledger containing current and accurate inventory records covering receipt, dispensing, and the return of study drug supplies must be maintained. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the accountability ledger; the identification code of the subject to whom drug is dispensed, the date(s) and quantity of drug dispensed to the subject, and the date(s) and quantity of drug returned by the subject; subjects should return empty containers to the investigator, with the return noted on the ledger. These Accountability Forms must be readily available for inspection and are open to FDA inspection at any time.

Adverse Experiences

Any adverse experience, if deemed drug related, must be reported to the Operations Office Adverse Drug Reaction (ADR) representative (210/677-8808), who will obtain information on the ADR. Depending on the nature of the reaction and whether it was caused by an investigational or commercial agent, the ADR representative will advise whether the report to the NCI should be phoned in, written in, or both. See guidelines below. On Phase II and III studies, all deaths considered drug-related must be reported immediately to the ADR representative. On double-blinded studies, if the investigator must know what treatment the subject received to make therapeutic decisions, the code for that particular subject can be broken by telephoning the Statistical Center.

All adverse experiences must also be reported to the Institutional Review Board within 10 days and documentation of this report sent to the Operations Office.

All adverse experiences must also be recorded in the appropriate section of the case report form. The report should include, whenever possible, the investigator's written medical judgment as to relationship of the adverse experience to study medication(s) (i.e., "probable", "possible" or "unrelated").

GUIDELINES FOR REPORTING OF ADVERSE DRUG REACTIONS (ADRS)
OCCURRING WITH **COMMERCIAL AGENTS**

The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) **should be reported by telephone to the Operations Office (210/677-8808), within 24 hours of occurrence, your Institutional Review Board (IRB) and by written notification to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:**

- (a) Any ADR which is **BOTH serious** (life threatening [Grade 4] or fatal [Grade 5]) and unexpected.^{1,2,3} Occurrences of secondary AML or MDS must also be reported* (see below).
- (b) Any increased incidence of a known ADR which has been reported in the package insert or the literature.
- (c) Any death on study if **CLEARLY** related to the commercial agent(s) below:

The ADR report should be documented on Form FDA-3500 and mailed to the address below:

(*For reporting cases of secondary AML or MDS, please use the "NCI/CTEP Secondary AML/MDS Report Form" in lieu of the Form FDA-3500.)

Investigational Drug Branch
P. O. Box 30012
Bethesda, MD 20824

Send a copy of the Form FDA-3500 or the "NCI/CTEP Secondary AML/MDS Report Form" (for reporting cases of secondary AML or MDS only), all data records and a copy of documentation of notification of your IRB to the Operations Office within 10 working days.

ATTN: ADR Program
Southwest Oncology Group
14980 Omicron Drive
San Antonio, TX 78245-3217

Copies of the "NCI/CTEP Secondary AML/MDS Report Form" will be forwarded from the Operations Office to the Statistical Center within one working day.

- 1. See Section 19.0, Southwest Oncology Group Toxicity Criteria.
- 2. A list of all known toxicities can be found in either the Background section, Drug Information or Informed Consent Form of the protocol.
- 3. Reactions judged definitely not to be treatment related should not be reported. However, a report shall be submitted if there is only a reasonable suspicion of drug effect.

17.0 **BIBLIOGRAPHY**

1. Wingo PR, Tona T, Boulder S. Cancer Statistics Ca A Cancer Journal for Clinicians 45 #1, Jan/Feb 8-30, 1995.
2. Physicians Desk Reference Medical Economics Date 46th edition, 1992.
3. DiSaia PJ. Hormone replacement therapy in patients with breast cancer. *Cancer* 71(4):1490-1500, 1993.
4. Bergkvist, Adamiho, Persson, Bergstrom, Krusemo. Prognosis after breast cancer diagnosis in women exposed to estrogens and estrogen progestogen replacement therapy. *Am J Epidemiol* 130(2):221-228, 1989.
5. Senie RT, Rosen PO, Roads P, Lesser ML, Kinnie DW. Obesity at diagnosis of breast carcinoma influences duration of disease-free interval. *Ann Int Med* 116:26-32, 1992.
6. Richard MA, O'Reilly SM, Howell A, et al. Adjuvant cyclophosphamide, methotrexate and 5-fluorouracil in patients with axillary node-positive breast cancer: update of the Guy's/Manchester trial. *J Clin Oncol* 8(12):2032-2039, 1990.
7. Early breast trialist collaborative group. Systematic treatment of early breast cancer by hormonal, cytotoxic or immunotherapy. *Lancet* 33:9, 1992.
8. Casper RF, Yen SSC. Neuroendocrinology of menopausal flashes and hypothesis of flush mechanism. *Clinical Endocrinology* 22:293-312, 1985.
9. Miller KL. Alternatives to estrogen for menopausal symptoms. *Clin Obstet Gyn* 35(4):884-893, 1992.
10. Bullock JL, Massey FM, Gambrell RD. Use of medroxyprogesterone acetate to prevent menopausal symptoms. *Obstet Gyn* 46(2):165-168, 1975.
11. Walsh B, Schiff I. Vasomotor flushes. *Progress Clin Bio Res* 320:71-87, 1988.
12. Morrison JC, Martin DC, Blair RA, et al. The use of medroxyprogesterone acetate for relief of climacteric symptoms. *Am J Obstet Gyn* 138:99, 1980.
13. Schiff I, Tulchinsky D, Cramer D, Ryan KJ. Oral medroxyprogesterone in the treatment of menopausal symptoms. *JAMA* 244:1443-1445, 1980.
14. Albrecht BH, Schiff I, Tulchinsky D, Ryan K. Objective evidence that placebo and oral medroxyprogesterone acetate therapy diminish menopausal vasomotor flushes. *Am J Obstet Gyn* 139:631, 1981.
15. Loprinzi CL, Michalak JC, Quella SK, et al. Megestrol acetate for the prevention of hot flashes. *NEJM* 331:347-352, 1994.
16. Stampfer MJ, Colditz GA, Willett WC, et al. Post menopausal estrogen therapy and cardiovascular disease: ten year follow-up from the nurses' health study. *NEJM* 323(11):756-762, 1991.
17. Sullivan JM, Aag CW, Lemp GF, et al. Post menopausal estrogen use in coronary atherosclerosis. *Ann Int Med* 108358-108363, 1988.
18. Barrett-Conner E, Busch TL. Estrogen and coronary heart disease in women. *JAMA* 265(14):1861-1867, 1991.

19. Judd JL, Meldrum DR, Deftos LJ, Henderson BE. Estrogen replacement therapy: indications and complications. UCLA Conference. *Ann Int Med* 98:195-205, 1983.
20. Ettinger B, Genant HK, Cann CE. Post menopausal bone loss prevented by treatment with low-dose estrogen and calcium. *Ann Int Med* 106:40-45, 1987.
21. Love RR, Weibe DA, Newcomb PA, et al. Effects of tamoxifen on cardiovascular risk factors in post-menopausal women with breast cancer. *Ann Int Med* 115:860-864, 1991.
22. Love RR, Mozes RD, Barden HS, et al. Effects of tamoxifen on bone mineral density in post menopausal women with breast cancer. *NEJM* 326(13):842-856, 1992.
23. Mayfield SG, Carp JE, Ford LG, Door FA, Kramer BS. Potential role of tamoxifen in prevent of breast cancer. *JNCI* 83(20):1450-1459, 1991.
24. Donde UM, Virkar K. The effect of combination and low dose progestogen contraceptives on serum lipids. *Fertility Sterility* 26(1):62-67, 1975.
25. Spellacy WN, Newton RE, Buhi WC, Birk SA. Lipid and carbohydrate metabolic studies after one year of megestrol acetate treatment. *Fertility Sterility* 27(2):157-161, 1976.
26. Donde UM, Virkar K. Effect of contraceptive steroids on serum lipids. *Am J Obstet Gyn* 12(21):736-742, 1975.
27. Loprinzi CL, Schaid DJ, Dose AM, Burnham NL, Jensen MD. Body-composition changes in patients who gain weight while receiving megestrol acetate. *J Clin Oncol* 11:152-154, 1993.
28. Erlik Y, Meldrum DR, LaGasse LD, Judd HL. Effect of megestrol acetate on flushing and bone metabolism in post-menopausal women. *Maturitas* 3(14):211-224, 1992.
29. Henderson BE, Ross RK, Lobo RA, Pike MC, Mack TM. Re-evaluating the role of progestogen therapy after the menopause. *Fertility Sterility* 49:9S-11S, 1988.
30. Spicer DV, Pike MC. Sex steroids and breast cancer prevention. *JNCI Monograph* 16:139-147, 1994.
31. Henderson BE, Ross RK, Judd HL, Krailo MD, Pike MC. Do regular ovulatory cycles increase breast cancer risk? *Cancer* 56:1206-1208, 1985.
32. Stanford JL, Thomas DB. Exogenous progestins and breast cancer. *Epidemiologic Rev* 15(1):98-107, 1993.
33. Staffa JA, Newschaffer CJ, Jones JK, Miller V. Progestins and breast cancer: An epidemiologic review. *Fertility Sterility* 57(3):473-491, 1992.
34. Leather AT, Savvas M, Studd JWW. Endometrial histology and bleeding patterns after eight years of continuous combined estrogen and progestogen therapy in postmenopausal women. *Obstet Gyn* 78(6):1008-1010, 1991.
35. Creasy GW, Kafrissen ME, Upmalis D. Review of endometrial estrogens and progestins. *Obstet Gyn Survey Supp* 47(9):654-678, 1992.
36. Neumannova M, Kauppila A, Kivinen S, Vihko R. Short-term effects of tamoxifen, medroxyprogesterone acetate, and their combination on receptor kinetics and 17B-hydroxysteroid dehydrogenase in human endometrium. *Obstet Gyn* 66(5):695-700, 1985.
37. Wiklund I, Holst J, Karlberg J, et al. A new methodological approach to the evaluation of quality of life in postmenopausal women. *Maturitas* 14:211-244, 1992.

18.0 MASTER FORMS SET

- 18.1 The Model Informed Consent form is included in this section. It must be reviewed and approved by the Institutional Review Board prior to registration.
- 18.2 Patient Log of Menopausal Symptoms
- 18.3 Quality of Life Cover Sheet
- 18.4 Breast Cancer Prestudy for Studies SXXXX, SYYYY
- 18.5 Study Specific Flow Sheet
- 18.6 Post-Treatment Questionnaire
- 18.7 Off Treatment Notice

**CONSENT FORM
AND
INFORMATION ABOUT**

S9626, A Phase III Trial of Placebo Versus Megestrol Acetate 20 mg/Day Versus Megestrol Acetate 40 mg/Day as Treatment for Symptoms of Ovarian Failure in Women Treated for Breast Cancer

TO BE CONDUCTED AT

- I. You have been asked to participate in a research study to determine the effectiveness and dosage of the drug megestrol acetate (Megace[®]) in reducing menopausal symptoms (change of life symptoms) that develop as a result of ineffective production of estrogen (female hormone) from the ovaries.

You are invited to participate in this research study because you have a history of treated breast cancer and are experiencing either 10 or more flushing episodes (hot flashes) per week or 5 - 9 hot flashes per week that you consider to be severe. These hot flashes occur when the level of the female hormone, estrogen, in the bloodstream drops to a low level. This drop in the female hormone level may be caused from surgical removal of the ovaries, the natural event called menopause (change of life), or the effects of chemotherapy used to prevent your breast cancer from returning.

We want to find out the lowest dose of megestrol acetate (Megace[®]) that will lower the number of weekly hot flashes by at least 75%.

We also want to monitor any side effects or toxicities of the treatment and determine its effect on your sense of well being (quality of life), particularly in respect to marital relations.

We cannot and do not guarantee you will benefit if you take part in this study. The therapy you receive may even be harmful, but the intent of the therapy is to be helpful. In any case, your care will be monitored closely and all necessary precautions taken.

- II. If you decide to take part in this study, you will be given a questionnaire to determine the number of flushing episodes (hot flashes) you have during the seven day period. If you have 10 or more flushing episodes (hot flashes) during this seven day period, you will be eligible for registration into the study. You may not be taking any hormones or steroids, i.e., prednisone, etc., other than the antiestrogen (estrogen hormone blocking) drug tamoxifen (Nolvadex[®]). You must have completed all of your chemotherapy if you have been receiving chemotherapy.

If you are eligible to take the study drug, you will be required to have an initial physical examination, periodic examinations, and a blood glucose determination within the past three months. If there is a question as to your menopausal (change of life) status, a blood test may be required to help determine this.

You will be randomly assigned (assignment by chance) to receive a placebo (a pill with no active substance) or 20 mg of megestrol acetate (Megace[®]) or 40 mg of megestrol acetate (Megace[®])

daily for three months. If this schedule is not beneficial in reducing the number of flushing episodes (hot flashes) by at least 75% after three months, you will be given an additional 20 mg of megestrol acetate (Megace®) daily for three more months.

There are circumstances under which your doctor might be required to discontinue your treatment with this drug whether you agree or not. These circumstances include: should your tumor return; the side effects of the treatment are too dangerous for you; new information about the drug becomes available and this information suggests the drug will be ineffective or unsafe for you.

Administration of the drug will be (provided free of charge/charged in the usual way). The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be (charged in the usual way/provided at a reduced rate). The Southwest Oncology Group will provide you with the agent(s) megestrol acetate and/or placebo free of charge for this study.

You will have routine laboratory tests on a regular basis while you are on this study so your doctor can see how your body is responding to treatment.

Significant new findings that relate to your treatment will be discussed with you.

- III. Some of the side effects some people have had from megestrol acetate (Megace®) and/or the placebo are outlined below.

Megestrol Acetate (Megace®)

Megestrol acetate is an approved drug in metastatic (spread to other organs such as bone or liver) breast cancer. Its ability to prevent the occurrence of breast cancer has not been determined. To date, it has not been proven to play a role in the development of breast cancer, but information on this drug in respect to causing breast cancer is still limited.

The side effects of megestrol acetate, while bothersome, are rarely life threatening. The most frequent side effect is weight gain which is not necessarily associated with fluid retention but is a result of increased appetite. Thromboembolic phenomena including thrombophlebitis (clots in the veins of the lungs) have been rarely reported. Other rare possible side effects include: nausea and vomiting, edema, breakthrough bleeding, dyspnea (shortness of breath), hyperglycemia (increase in blood sugar), alopecia (hair loss), hypertension (increased blood pressure), rash, and carpal tunnel syndrome (weakness of the hands with tingling in the fingers). Vaginal bleeding is sometimes seen when megestrol acetate is discontinued and will generally stop on its own.

Placebo

These tablets do not contain any medication. These tablets will look just like the tablets containing megestrol acetate, however, there should not be any side effects.

- IV. The standard effective treatment in reducing flushing episodes (hot flashes) and other menopausal symptoms is replacement estrogen. The safety in giving estrogen to a woman with a history of breast cancer has yet to be determined. Other alternative treatments include either the drug clonidine or the drug bellaral. Your doctors feel that your treatment on this study will give you at least as good a chance as you might expect from other therapies.
- V. If you are pregnant, you cannot take part in this study. You may take a urine test to see if you are pregnant before you start treatment if there is any concern that pregnancy may be the reason you are not having your period.

- VI. If you experience illness as a result of treatment on this study, you will (will not) receive free emergency medical treatment. We cannot give you free continuing medical care and/or hospitalization, nor can we pay you to take part in this study.
- VII. We will keep any information we learn from this study confidential and disclose it only with your permission. By signing this form, however, you allow us to make your records available to the National Cancer Institute, the Food and Drug Administration, a qualified representative of the drug manufacturer and the Southwest Oncology Group. If we publish the information we learn from this study in a medical journal, you will not be identified by name.
- VIII. Whether or not you take part in this study will not affect your future relations with your doctors (there will be no loss of benefit or change in attitude) or _____ (hospital name). If significant new findings are developed during the course of this study which may relate to your willingness to continue, this information will be provided to you. In addition, you understand that you may refuse to continue on this study at any time after the start of therapy, without fear of prejudice to additional treatment that may be needed.
- IX. The doctor(s) involved with your care can answer any questions you may have about the drug program. In case of a problem or emergency, you can call the doctors listed below day or night.

Office

Home

Dr.

Dr.

Dr.

You can also call the Institutional Review Board (# _____) if you have any questions, comments or concerns about the study or your rights as a research subject.

- X. We will give you a copy of this form to keep.
- XI. You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer after reading and understanding all the information on this form.

Date

Signature of Subject

Signature of Witness

Signature of Investigator

Time

Patient Log of Menopausal Symptoms

SWOG
Study No.

S

Protocol Step **Patient Instructions for Daily Log:**

1. You will be completing the Daily Log once a day for seven days prior to beginning treatment. If you stay on the study, you will complete the Daily Log for a week two additional times: Month 3 and Month 6. The Log consists of a daily count of hot flushes and, if any occur, an overall rating of their severity for that day.
2. First check the **week** the count/rating takes place (PreRegistration, Month 3, Month 6).
3. Please record the date (month/day/year) in the space just below each day (Day 1, Day 2, etc.).
4. On each day please note the **Number** of hot flushes or flashes you experienced. If you had no hot flushes, write a "0" for the day. Record the total number of hot flushes for the week in the Total No. column (last column on the right).
5. Then, for each day, rate the **Severity** of the hot flushes (that is, how much the hot flushes bothered you). The rating scale goes from "Not at all" to "Extremely". If you had no hot flushes, do not answer the Severity question.
6. Finally, think back over the entire week and rate the overall severity of hot flushes for that week in the last column on the right.

Definitions:

Hot Flashes/Flashes: A hot flash is usually experienced as a sudden feeling of warmth, followed by sweating, and a change in skin color that appears reddish, like a blush. Some women also experience a rapid heart beat, a feeling of head fullness, or a feeling of fullness in the chest.

Patient Instructions for Ratings With a One-Month Time Frame:

1. In addition to the Daily Log, there are several questions to be answered on day seven each time you do daily logs for a week. You should consider the **past four weeks or month** as a time frame when you give your answers. There will always be three months between times that you complete the questionnaire. We recognize that these questions deal with personal matters, but your cooperation in answering them is very important in our evaluation of the treatment.

Definitions:

Vaginal Dryness: Some women experience a sense of dryness, irritation, or itchiness in their vagina; this is somewhat like the uncomfortable, itchy feeling of dry skin. Other women notice dryness of the vagina during sexual activity. This is usually described as "poor lubrication". Some women experience dryness both ways.

2. Page three of this Log contains a list of symptoms you may be experiencing. Check **No** if you did not have the symptom. If you did have this symptom or problem, check **Yes** and select the word that best describes how much the problem bothered you.

Thank you for participating in this study.

Patient Log of Menopausal Symptoms

SWOG Study No. **S**

Protocol Step

SWOG Patient No.

Patient's Initials _____ (First, Middle, Last)

Institution / Member _____ Physician _____

- SCHEDULE:**
- 0- Pre-registration (Randomization)
 - 1- 1st Post-registration Assessment (3 Months)
 - 2- 2nd Post-registration Assessment (6 Months)

Instructions: Please refer to page one for instructions for Daily Log and instructions for Monthly Ratings.

DAILY LOG

Date (M/D/Y)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Total No. of Flashes	
	/ /	/ /	/ /	/ /	/ /	/ /	/ /		
Number of Hot Flashes/Flashes Today								<input type="text"/>	
Severity of Hot Flashes/Flashes Today - How much they bothered you. <i>(Check one rating if any hot flushes)</i>	<input type="checkbox"/> Not at all <input type="checkbox"/> Slightly <input type="checkbox"/> Moderately <input type="checkbox"/> Quite a bit <input type="checkbox"/> Extremely	<input type="checkbox"/> Not at all <input type="checkbox"/> Slightly <input type="checkbox"/> Moderately <input type="checkbox"/> Quite a bit <input type="checkbox"/> Extremely	<input type="checkbox"/> Not at all <input type="checkbox"/> Slightly <input type="checkbox"/> Moderately <input type="checkbox"/> Quite a bit <input type="checkbox"/> Extremely	<input type="checkbox"/> Not at all <input type="checkbox"/> Slightly <input type="checkbox"/> Moderately <input type="checkbox"/> Quite a bit <input type="checkbox"/> Extremely	<input type="checkbox"/> Not at all <input type="checkbox"/> Slightly <input type="checkbox"/> Moderately <input type="checkbox"/> Quite a bit <input type="checkbox"/> Extremely	<input type="checkbox"/> Not at all <input type="checkbox"/> Slightly <input type="checkbox"/> Moderately <input type="checkbox"/> Quite a bit <input type="checkbox"/> Extremely	<input type="checkbox"/> Not at all <input type="checkbox"/> Slightly <input type="checkbox"/> Moderately <input type="checkbox"/> Quite a bit <input type="checkbox"/> Extremely	<input type="checkbox"/> Not at all <input type="checkbox"/> Slightly <input type="checkbox"/> Moderately <input type="checkbox"/> Quite a bit <input type="checkbox"/> Extremely	Overall Severity <input type="checkbox"/> Not at all <input type="checkbox"/> Slightly <input type="checkbox"/> Moderately <input type="checkbox"/> Quite a bit <input type="checkbox"/> Extremely

RATINGS WITH A ONE-MONTH TIME FRAME

Answer at the end of the week, on the last day you complete the daily logs.

Since there is a great deal of variation in how often couples have sexual intercourse, think back over the past 4 weeks. Did you have sexual intercourse? No Yes

If No, Please check any of the following reasons that might be involved:

- 1- My partner is physically incapable of intercourse
- 2- My partner does not accept my body image
- 3- I have a loss of body image
- 4- I do not have the desire
- 5- Intercourse has become painful
- 6- I do not have a partner

If Yes, Please answer the following questions:

Were you aware of vaginal dryness? Never Almost Never Some-times Almost Always Always

If you had vaginal dryness over the past 4 weeks, how much did it bother you? Not at all Slightly Moderately Quite a bit Extremely

Did you have Pain with intercourse? Never Almost Never Some-times Almost Always Always

If you had pain over the past 4 weeks, how much did it bother you? Not at all Slightly Moderately Quite a bit Extremely

DRAFT
SWOG Study No. S [] [] [] [] [] []

Post-Treatment Questionnaire

Protocol Step

SWOG Patient No. [] [] [] [] [] [] Patient's Name _____ (L.F.M)

Institution / Member _____ S.S. No. [] [] [] - [] [] - [] [] [] []

Physician _____ Hospital No. _____

Groups other than SWOG: Group Name/Study No./Pt No. _____ / _____ / _____

Amended data: Yes, mark amended items in red.

Instructions: To be completed by the physician 9 months after registration.

In the past 3 months did the patient feel that the number of flushing episodes: increased
 decreased
 remained the same

Did vaginal bleeding that lasted more than two weeks occur in the past 3 months? No Yes

Is the patient taking megestrol acetate? No Yes

If Yes: Dose of megestrol acetate: _____

If No and patient not assigned to placebo:

Date megestrol acetate was discontinued [] [] - [] [] - [] [] (MDY)

Was further treatment prescribed? No Yes

If Yes:
What treatment was prescribed and what dose?
New treatment: _____
Dose: _____

Notes:

By: _____ Date: _____

FLOW SHEET		S9626				PT. #	REG DATE
DATE 19	Mo./Day					UNIT #	PAGE
DAY ON STUDY						PATIENT	
						INVESTIG.	
TREATMENT						INSTITUTION	
Blinded Drug						STUDY #	S9626 RX. #
LABS / TESTS						DISEASE CATEGORY: Cancer Control-Breast	
FSH (see Section 9.0)						PROGRESS NOTES (DATE EACH)	
Fasting Glucose						Note any meds used to control side effects	
Pregnancy Test (see Section 9.0)							
Endometrial Biopsy §							
PHYSICAL							
TEMPERATURE							
WEIGHT (kg) (lb)							
HEMORRHAGE							
INFECTION							
Blood Pressure / Pulse							
Performance Status							
ASSESSMENTS							
Patient Log of Menopausal Symptoms and Cover Sheet							
Post-Treatment Questionnaire							
TOXICITY							
Alopecia							
Dyspnea							
Edema							
Hyperglycemia							
Hypertension							
Nausea/Vomiting		/	/	/	/	/	
Other-specify							
Pulmonary Embolism							
Rash							
Thrombophlebitis							
Tumor Flare							
Vaginal bleeding							
Weight gain							

* Please list institutional lower limits of normal for platelets and upper limits of normal for laboratory tests as indicated.
§ If done, list results on Flow Sheet.

QUALITY OF LIFE Cover Sheet

SWOG Study No.

Protocol Step

SWOG Patient No. Patient's Name _____ (L) _____ (F) _____ (M)

Institution / Member _____ Physician _____

Groups other than SWOG: Group Name/Study No./Pt No. _____ / _____ / _____

Amended data: Yes, mark amended items in red.

Instructions: Submit two copies of this cover sheet to the SWOG Statistical Center each time the patient is scheduled to complete the QUALITY OF LIFE Questionnaire(s), whether the Questionnaire(s) is(are) actually completed or not. Other cooperative groups: see protocol for mailing instructions.

Scheduled time to obtain QUALITY OF LIFE Questionnaire(s) and Cover Sheet (check one):

(Patients are followed even if off treatment)

Pre-registration

Post-registration Assessment Number

QUALITY OF LIFE Questionnaire(s) completed?

No Yes, Date Questionnaire(s) completed: - - (M,D,Y)

If Completed, Did patient require assistance? No Yes

Describe: _____

If Completed, Questionnaire(s) administered:

0- in the clinic

1- by telephone

8- Other (Please specify) _____

If Not completed, Please give reason (check one):

1- Patient kept appointment for examination, but could not complete Questionnaire(s) due to illness.

2- Patient kept appointment for examination, but refused to complete Questionnaire(s) for reason other than illness.
Specify reason: _____

3- Patient refused to complete Questionnaire(s) by telephone interview.
Specify reason: _____

4- Patient could not be contacted.

5- Questionnaire not administered due to institution error.

6- Patient off treatment, but **cannot be contacted for follow-up.**

7- Patient died.

8- Other reason, specify: _____

I have reviewed the Cover Sheet and Questionnaire(s). All forms are complete or an explanation is given for any missing data.

Data Manager/Nurse Oncologist _____ Phone # _____ Date _____

Notes:

Patient Log of Menopausal Symptoms

SWOG Study No. **S**

Protocol Step

SWOG Patient No.

Patient's Initials _____ (First, Middle, Last)

RATINGS WITH A ONE-MONTH TIME FRAME (Continued)

Instructions: A list of potential problems or symptoms is provided below. If you did not have the problem, check **No**. If you did have the problem, check **Yes** and select the word that best describes how much the problem bothered you during the **past month**.

Did You Experience These Symptoms During The Past Month?

Date Completed: - -
(Month Day Year)

No Yes

If Yes, How Much Did the Symptom Bother You? (Check One)

Nausea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Not at all	<input type="checkbox"/> Slightly	<input type="checkbox"/> Moderately	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Extremely
Vomiting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Not at all	<input type="checkbox"/> Slightly	<input type="checkbox"/> Moderately	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Extremely
Swelling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Not at all	<input type="checkbox"/> Slightly	<input type="checkbox"/> Moderately	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Extremely
Inflammation of leg veins	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Not at all	<input type="checkbox"/> Slightly	<input type="checkbox"/> Moderately	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Extremely
Weight gain If Yes, record how much: _____ lbs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Not at all	<input type="checkbox"/> Slightly	<input type="checkbox"/> Moderately	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Extremely
Vaginal bleeding	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Not at all	<input type="checkbox"/> Slightly	<input type="checkbox"/> Moderately	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Extremely
Breast tenderness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Not at all	<input type="checkbox"/> Slightly	<input type="checkbox"/> Moderately	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Extremely
Feeling tired	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Not at all	<input type="checkbox"/> Slightly	<input type="checkbox"/> Moderately	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Extremely
Headache	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Not at all	<input type="checkbox"/> Slightly	<input type="checkbox"/> Moderately	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Extremely
Feeling downhearted and blue	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Not at all	<input type="checkbox"/> Slightly	<input type="checkbox"/> Moderately	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Extremely
Loss of appetite	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Not at all	<input type="checkbox"/> Slightly	<input type="checkbox"/> Moderately	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Extremely
Night sweats	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Not at all	<input type="checkbox"/> Slightly	<input type="checkbox"/> Moderately	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Extremely
Difficulty concentrating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Not at all	<input type="checkbox"/> Slightly	<input type="checkbox"/> Moderately	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Extremely
Other Problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Not at all	<input type="checkbox"/> Slightly	<input type="checkbox"/> Moderately	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Extremely

Specify Symptom: _____

I have reviewed this form for completeness.

Data Manager/Nurse Oncologist _____ Phone # _____ Date _____

OFF TREATMENT NOTICE

Amended data: Yes, mark amended items in red

Disease Committee _____ SWOG Study No. Protocol Step

SWOG Pt. No. Patient Name _____ (L,F,M)

Institution/Member _____ Physician _____

Groups other than SWOG: Group Name/Study No./Pt. No. _____ / _____ / _____

INSTRUCTIONS: For each protocol step, submit this form within 2 weeks after completion (or discontinuation) of treatment. List protocol-directed treatments that the patient received.

Chemotherapy: List regimens, start and stop dates. For multidrug regimens, do not list individual drugs separately; stop date would be the date all drugs in the regimen were discontinued.

Surgery: List type of surgery and in the "stop" column the date of surgery.

Radiation: List sites, start and stop dates (inclusive of boosts and implants).

Indicate an unknown part of a date with a horizontal line drawn across the appropriate boxes.

Start Date (M,D,Y)	Stop Date (M,D,Y)	REGIMEN or PROCEDURE or SITE(S)
<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>	
<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>	
<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>	
<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>	
<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>	

(If more room is required please continue on a separate page.)

REASON OFF TREATMENT (Check one)

- 1 Treatment completed per protocol
- 2 Toxicity, medically required, specify _____
- 3 Patient refused, due to toxicity, specify _____
- 4 Patient refused, other than toxicity, specify _____
- 5 Progression or relapse. Sites: _____
- 6 Death (attach NOTICE OF DEATH form)
- 7 Other, specify _____

DATE OFF TREATMENT

Date of completion, progression, death or decision to discontinue therapy -- (M,D,Y)

Will patient receive FURTHER TREATMENT?

No Yes, specify: _____ Unknown

Date of LAST CONTACT (or death): -- (M,D,Y)

VITAL STATUS: Alive Dead (attach NOTICE OF DEATH form)

Notes:

272

19.2 UNBLINDING GUIDELINES

a. **General Considerations**

In this breast cancer chemoprevention study, **S9626**, patients AND study staff are blinded to the individual assignment of Coded Drug (double blind conditions). During the course of **S9626** it may become necessary to identify the patient's treatment, i.e., unblind the treatment assignment. The conditions for unblinding a **S9626** patient are detailed in this appendix.

In general, patients SHOULD NOT be unblinded to either the Run-in Drug or the Coded Drug unless a condition exists where the knowledge of the patient's treatment assignment would directly influence or affect his/her immediate care, or if an emergency situation arises. Unblinding is NOT appropriate when drug is discontinued for reasons outlined in the section below.

Unblinding of all **S9626** treatment assignments will be done by the Washington Poison Center (WPC) with medical advise from a panel of three resource physicians appointed for this study. Calls for information about Run-in or Coded Drug, or the study in general, should be directed to the Southwest Oncology Group Statistical Center.

b. **Guidelines for Discontinuation of Coded Drug**

The following events MAY require PERMANENT discontinuation of Coded Drug:

- Diagnosis of 2nd primary or progressive disease;
- intercurrent illness which would affect assessments of clinical status to a significant degree and/or whose treatment would require discontinuation of Coded Drug;
- unacceptable side effects as determined by the physician and/or patient;
- patient's request.

Permanent discontinuation of the Coded Drug for any reason must be document on the *flow sheet* and the *Off Treatment Notice*.

The following events MAY require TEMPORARY discontinuation of Coded Drug:

- Treatment of and/or hospitalization for a medical problem;
- assessment of symptoms or side effects potentially related to Coded Drug.

Temporary discontinuation of the Coded Drug for any reason must be document on the *flow sheet*.

Refer to Treatment Plan and Toxicity/Dose Modification sections of this protocol for details on discontinuation of drug.

c. Guidelines for Unblinding of Coded Drug

The following events MAY require unblinding of Coded Drug:

- A compelling medical need as determined by a physician, e.g., occurrence of a severe or life-threatening reaction, inclusive of an adverse drug reaction, which may have been attributable to Coded Drug, or existence of a condition where the knowledge of the patient's treatment assignment would directly influence or affect his immediate care;
- ingestion of the Coded Drug by persons other than the patient or in excessive quantity;
- exposure of a pregnant woman to the Coded Drug;
- exposure of a child to the Coded Drug;
- progressive disease.

Note: Adverse drug reactions should be reported as required per Section 16.0 of this protocol.

d. Procedure for Unblinding

The procedure for unblinding the treatment assignment for a patient is as follows:

- All unblinding must be done by the registering physician or designee.
- Call the WPC collect at 206/526-2121 or at 800/732-6985 if calling from within Washington State. The WPC is accessible 24 hours per day, 365 days per year for unblinding calls. Informational calls should be directed to the Statistical Center during standard business hours.
- Provide the WPC with the following information:

Study number: **S9626**
Southwest Oncology Group patient number
Patient name
Coded Drug ID number and bottle number
Name and telephone number of the caller
Reason unblinding is required

This information will be recorded by the WPC on a special form, *Report of Unblinding*. This form will be faxed to the Statistical Center by the WPC and added to the patient's record.

- Unblinding for ingestion of the Coded drug by a pregnant woman will not require the authorization of a resource physician.
- Unblinding for ingestion of the Coded Drug by a child will not require the authorization of a resource physician.
- Unblinding for ingestion of the drug either in excessive amounts or by a person other than the patient will be done **ONLY** when a compelling medical need exists and/or unblinding has been authorized by a resource physician.

- Unblinding for a "compelling medical need" must be authorized by a physician designated as a resource physician for this protocol.

The treating physician (or designee) would provide the WPC with the information needed to determine if unblinding is required for the patient. The WPC would contact the resource physician, provide the required information, and obtain the authorization to unblind, if necessary. Based on the decision of the resource physician, the WPC would call the treating physician with either the unblinded treatment assignment or a treatment recommendation from the resource physician.

If a resource physician cannot be reached by the WPC, treatment of the patient should proceed as if the drug ingested were an active agent.

- Unblinding of Coded Drug for any reason must be documented on the *flow sheet* and the *Off Treatment Notice*.

All unblinded patients are taken off treatment and followed per the requirements of the Southwest Oncology Group protocol.

Any questions regarding unblinding may be directed to one of the following resource physicians:

J. Wendall Goodwin, M.D.
Ozarks Regional CCOP
3231 S. National
Springfield, MO 65807-7304
Phone: 417/883-7422
Fax: 417/883-0208

Mace L. Rothenberg, M.D.
Executive Officer
Southwest Oncology Group Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3217
Phone: 210/677-8808
Fax: 210/677-0006

Kathy S. Albain, M.D.
Loyola University Medical Center
Cancer Center, Room 109
2160 South 1st Ave
Maywood, IL 60153-5589
Phone: 708/327-3102
Fax: 708/327-3231

APPENDIX L

Southwest Oncology Group Protocol S9342: "A Study of the Late Cardiac Effects of Two Different Adjuvant Chemotherapy Regimens in Women with Node Negative Breast Cancer Treated on S8897."

Study Coordinators: Patricia Ganz, M.D., Kathy S. Albain, M.D., Laura Hutchins, M.D., Stephanie J. Green, Ph.D.

Funded by supplemental awards from the National Cancer Institute.

The following draft protocol is proprietary information and is a privileged communication for investigational use only

SOUTHWEST ONCOLOGY GROUP

**A STUDY OF THE LATE CARDIAC EFFECTS OF TWO DIFFERENT ADJUVANT CHEMOTHERAPY
REGIMENS IN WOMEN WITH NODE NEGATIVE BREAST CANCER TREATED ON SWOG-8897**

ANCILLARY

	<u>Page</u>
1.0 OBJECTIVES.....	2
2.0 BACKGROUND.....	2
3.0 DRUG INFORMATION.....	5
4.0 STAGING CRITERIA.....	5
5.0 ELIGIBILITY CRITERIA	6
6.0 DESCRIPTIVE FACTORS.....	6
7.0 TREATMENT PLAN.....	6
8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS.....	7
9.0 STUDY CALENDAR.....	8
10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS.....	9
11.0 STATISTICAL CONSIDERATIONS	9
12.0 DISCIPLINE REVIEW.....	9
13.0 REGISTRATION GUIDELINES.....	9
14.0 DATA SUBMISSION SCHEDULE	10
15.0 SPECIAL INSTRUCTIONS	10
16.0 ETHICAL AND REGULATORY CONSIDERATIONS	10
17.0 BIBLIOGRAPHY	11
18.0 MASTER FORMS SET.....	13

PARTICIPANTS: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, CGOP AND HIGH
PRIORITY MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS,
SURGEONS AND PATHOLOGISTS

SWOG STUDY COORDINATORS:

Patricia Ganz, M.D. (Medical Oncology)
UCLA Division of Cancer Prevention and
Control Research
Jonsson Comprehensive Cancer Center
1100 Glendon Avenue, Suite 711
Los Angeles, CA 90024
Phone: 310/206-1404

Stephanie J. Green, Ph.D. (Biostatistics)
Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street, MP-557
Seattle, WA 98104-2092
Phone: 206/667-4623

Kathy S. Albain, M.D. (Committee on Women's Health)
Loyola University Medical Center
Cancer Center, Room 109
2160 South 1st Ave
Maywood, IL 60153-5589
Phone: 708/327-3102

CARDIAC CONSULTANTS:

Janine Krivokapich, M.D. (Cardiology)
UCLA

Kathleen Ward, M.D. (Cardiology)
Loyola University

Laura Hutchins, M.D. (SWOG-8897 Study Coordinator)
Hematology/Oncology, Slot 508
University of Arkansas for Medical Science
4301 W. Markham Street
Little Rock, AR 72205-7101
Phone: 501/686-5222

M330/mb

1.0 OBJECTIVES

- 1.1 To compare the frequency of sub-clinical congestive heart failure in women treated with CMF or CAF chemotherapy in SWOG-8897 as measured by resting MUGA scan at 5 and 10 years after randomization.
- 1.2 To estimate the frequency of late cardiac effects (congestive heart failure, cardiac ischemic events, clinical symptoms) in women treated with CMF or CAF chemotherapy in SWOG-8897.
- 1.3 To prospectively monitor annual cardiac events between the 5th and 10th year after randomization.

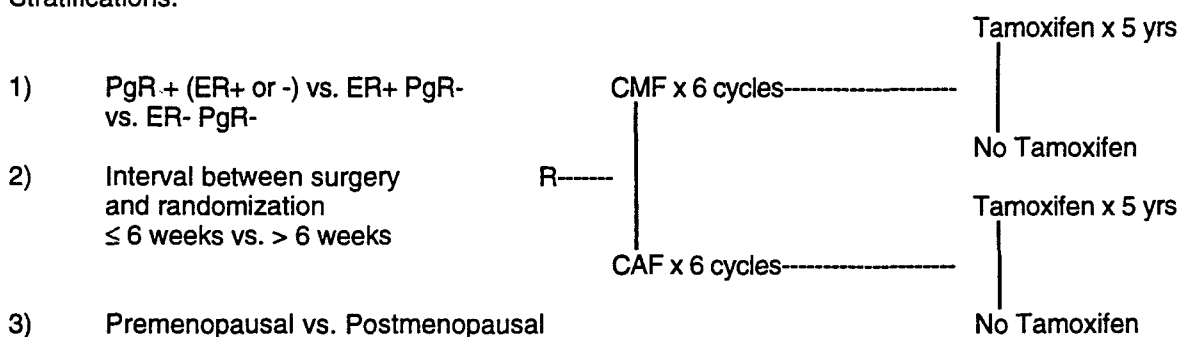
2.0 BACKGROUND

Adjuvant Therapy in Node Negative Women

Women with node negative breast cancer are expected to have long-term disease-free survival in excess of 70% without adjuvant therapy. (1, 2) Adjuvant chemotherapy is being utilized in these women to enhance long-term survival and potential for cure in those who are at risk of recurrence. Because of the inadequacy of current prognostic factors, a significant number of node negative women are exposed to the risks of adjuvant therapy without clear-cut benefit. The optimum adjuvant treatment regimen for node negative women is uncertain, and many clinical trials are in progress to answer this important question. The clinical trial SWOG-8897 ("Phase III Comparison of Adjuvant Chemotherapy with or without Endocrine Therapy in High-Risk, Node Negative Breast Cancer Patients, and a Natural History Follow-up Study in Low-Risk, Node Negative Patients") was designed to answer the question of whether a doxorubicin-containing regimen was superior to a standard adjuvant regimen without doxorubicin (see Schema below). Although the designers of this trial were cognizant of the potential for detrimental late cardiac effects in women treated with doxorubicin, resources were not available to prospectively evaluate cardiac function in the trial participants. A baseline evaluation of cardiac function with MUGA scan was performed at the discretion of the investigator if clinically indicated; those patients with an abnormal study were subsequently excluded from randomization. The data collection and endpoint monitoring for SWOG-8897 does not include sufficiently detailed documentation of cardiac events or history; however, an exercise multigated equilibrium radionuclide cineangiography (MUGA scan) is requested for the five year assessment. In this proposal, we intend to address the original concerns regarding the late cardiac effects of doxorubicin by performing a two group comparison of breast cancer survivors who were treated with either CMF or CAF (secondary randomization to tamoxifen or nil) at their fifth year and tenth year clinical evaluation.

SWOG-8897 SCHEMA

Stratifications:



Cardiac Toxicity of Doxorubicin

Doxorubicin-induced heart failure was recognized over 20 years ago and was shown to be related to the total dose administered. (4) Subsequent to this report and others, the total dose of 550 mg/m² was identified as the cut-off point above which congestive heart failure was likely to occur. For patients receiving mediastinal radiation, a total dose of 450 mg/m² has been suggested as a maximum. However, early on in the use of doxorubicin, it was noted that some patients developed detectable cardiac abnormalities before the development of clinical heart failure, and at lower doses than were associated with overt congestive heart failure. (5) Myocardial biopsy and right-sided cardiac catheterization were used to document evidence of myocardial damage at doses significantly less than 550 mg/m². (6) In addition, patient sensitivity to myocardial damage varied significantly, such that some patients had little damage despite high total doses of doxorubicin.

Myocardial biopsy and cardiac catheterization are invasive and expensive procedures, and are not ideal for studying large numbers of patients. Therefore, non-invasive cardiac assessment techniques have been used to detect early evidence of myocardial damage. The most widely used non-invasive technique has been multigated equilibrium radionuclide cineangiography (MUGA scanning or RNA) with determination of left ventricular ejection fraction (LVEF). Initially, criteria were developed to guide continued chemotherapy with cardiotoxic drugs using resting LVEF. (7) These criteria were developed for patients with normal resting baseline ejection fractions ($\geq 50\%$). Mild cardiotoxicity is defined as an absolute decrease in LVEF of $\geq 10\%$ and an absolute LVEF of $> 45\%$. Moderate cardiotoxicity is defined as an absolute decrease of LVEF of $\geq 15\%$ and absolute LVEF of $\leq 45\%$. Severe cardiotoxicity is an LVEF of $\leq 30\%$. If the LVEF is $> 45\%$ and has not fallen by more than 15% from baseline value, then therapy can be continued with careful follow-up.

Schwartz et al. used the results of resting RNA and clinical outcome in 1,487 patients monitored over a 7 year period to identify a subset at high risk for developing clinical heart failure due to doxorubicin. (8) This subset had one or two of the following three criteria: 1) a decrease of resting LVEF of $\geq 10\%$ to an absolute value $\leq 50\%$; 2) a cumulative dose of > 450 mg/m², and, 3) an abnormal baseline LVEF of $\leq 50\%$. The incidence of clinical heart failure in the entire group of 1,487 patients was 16% during treatment, with an additional 1.3% during the follow-up period. However, in these patients, doxorubicin treatment was continued only if one of the above criteria was not met. The incidence of heart failure was 2.9% versus a 20.8% incidence in those in whom therapy was continued despite having met one of the above criteria.

Long-term studies are now available that reveal that doxorubicin cardiotoxicity may not be manifested during the initial treatment period, but may present as "subacute" toxicity (during the 4 years after therapy cessation), or at > 5 years after therapy as "chronic" cardiotoxicity. (9) Lipschultz reported abnormalities of left ventricular afterload and/or contractility determined by echocardiography in 57% of 115 children with acute lymphoblastic leukemia who received doxorubicin 1 - 15 years earlier. (10) In another large study of patients receiving doxorubicin (studied with echocardiography), Steinherz et al. found a 23% incidence of abnormal contraction, which increased to 38% in those patients followed for 10 years or longer. (11) Clinical correlates for these laboratory investigations include case reports of cancer survivors who have been asymptomatic, but develop overt congestive heart failure during pregnancy or with the adoption of a vigorous exercise program.

Cardiac Effects of Tamoxifen

The physiologic effects of tamoxifen have recently been reviewed by Nayfield et al., and, in a number of studies reviewed, tamoxifen was shown to lower serum cholesterol by 10 - 15% in postmenopausal women receiving this agent. (12) Until recently, the survival implications of these biologic differences have not been known. However, the 10 year update of the international overview of adjuvant tamoxifen studies suggested a 12% decrease in deaths due to causes other than breast cancer among the patients who received tamoxifen, with a suggestion

that these were related to a reduction in vascular disease. (13) Recently, Rutqvist and colleagues were able to link the hospitalization and mortality data in Sweden on 2,365 postmenopausal patients who had participated in a randomized trial comparing tamoxifen (40 mg daily for 2 or 5 years) versus no adjuvant endocrine therapy. (14) They found that tamoxifen resulted in a significantly reduced incidence of hospital admissions for cardiac disease and that the findings favored 5 versus 2 years of tamoxifen. There was little difference between the tamoxifen and control groups for admissions due to thromboembolism. (14) In our proposed study, we will be exploring the association of cardiac events with assignment to tamoxifen.

Non-Invasive Evaluation of Cardiac Function (15 - 17)

Both two-dimensional echocardiography and multigated equilibrium radionuclide cineangiography (MUGA scanning or RNA) have been used to evaluate left ventricular ejection fraction, chamber sizes, and wall motion. Echocardiography has the advantages that the size of each chamber can easily be accurately measured and that all walls are imaged. It also allows easy detection of pericardial effusions. Echocardiography is routinely combined with Doppler evaluation which allows detection of valvular regurgitation and analysis of diastolic function. A disadvantage of Doppler echocardiography is that in up to 5% of patients, adequate images are not obtainable to quantitate ejection fraction, evaluate the wall motion for all walls, detect all regurgitations, and/or measure diastolic function. RNA can be performed adequately in virtually all patients, but precise chamber dimensions are not available, all walls are not easily imaged, valvular regurgitation is not imaged, and pericardial disease is not readily detected. Both tests can be performed with exercise stress to uncover abnormalities of both ejection fraction and wall motion that may not be evident on a resting study. Echocardiography is superior in detecting wall motion abnormalities because all walls are visualized, and thickening can be directly assessed in addition to wall motion on a beat to beat basis, both at rest and with stress. RNA only looks at wall motion indirectly as it affects the internal dimensions of the left and right ventricular cavities. With exercise, only one view can be visualized; also, since RNA requires the addition of several hundred successive cycles to create an image with adequate counts, the patient must maintain peak exercise for 2 minutes in order to have adequate count acquisition. Despite the advantages of echocardiography over RNA, the latter technique has been applied on a more routine basis nationally for assessing cardiac function in patients at risk for cardiotoxicity. This is likely due to the fact that most of the original studies using echocardiography utilized only one dimensional M-mode data and did not take advantage of the two-dimensional capabilities which have been described above. In addition, we performed a survey of the 10 Group clinical centers with the highest recruitment to **SWOG-8897**, polling them as to the availability, quality and cost of the two procedures. We found that the MUGA scan was most widely available and was felt to be most reliable at their sites.

Multigated equilibrium radionuclide cineangiography (MUGA) involves intravenous injection of 99m-technetium labeled red blood cells, which label the blood pool, and imaging of radioactivity over the heart using a standard Anger scintillation camera. Rest images are obtained in 3 standard views: 45 degree LAO, anterior, and 70 degree LAO. Each rest image requires approximately 5 minutes of count acquisition. Data acquisition is synchronized with the electrocardiogram and data are summed for several hundred cycles. In this study only a resting MUGA will be performed to ensure standardization across multiple clinical centers.

Significance

Adjuvant chemotherapy has been recommended for women with axillary node negative breast cancer since the May 1988 NCI "Clinical Alert", and the subsequent publication of several key clinical trials in the New England Journal of Medicine in February 1989. (1, 2) Although the prognosis for individual women with node negative disease varies according to several prognostic factors, as many as 60 - 70% of these women will be cured by primary surgical treatment, and may have little if any benefit from the addition of systemic chemotherapy. (3) It is essential, therefore, to carefully evaluate the role of prognostic factors in node negative breast cancer, and test alternative chemotherapy regimens in this group of patients. **SWOG-8897** was designed to

answer these important questions. Risk status was determined by tumor size and hormone receptor status. For small tumors (≤ 2 cm), flow cytometry data were used as an additional criterion. High-risk patients were randomly assigned to receive either cyclophosphamide, methotrexate and 5-fluorouracil (CMF) or cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) for 6 cycles, and to receive tamoxifen or nothing for five years. The main questions addressed by this study were 1) whether six months of CAF is better than six months of CMF in terms of overall survival; and, 2) whether tamoxifen adds to chemotherapy, particularly within the subset of ER-patients.

SWOG-8897 began accruing patients in July 1989, with closure of the trial in March 1993. Because of the low event rate in this population, it will be some time until the survival and disease-free survival differences between the two treatments will be known. However, it is expected that the differences between these two chemotherapy regimens will be modest, and could potentially be offset by the late cardiac effects of doxorubicin. The participants in this clinical trial are now reaching their five year clinical assessment. This clinical evaluation represents an extremely important opportunity to perform a formal cardiac evaluation on these women to assess the late effects of adjuvant chemotherapy, with particular emphasis on the comparison of CMF and CAF, through this proposed trial. Further, we will be able to perform exploratory analyses on the effects of tamoxifen adjuvant therapy on cardiac events. The cost-effectiveness of this proposal to obtain critical cardiac function data in these patients is enhanced by utilization of the resources of the Southwest Oncology Group, as patients eligible for this study are already identified and are in regular follow-up, and Group investigators are highly committed to studying these important questions.

Patients enrolled in **SWOG-9342** will establish a prospective cohort of breast cancer survivors whose cardiac status will be monitored for the next 5 years. This more detailed assessment of cardiac status will provide long-term information about adjuvant therapy for breast cancer. This will also be the beginning of a research program to study preventive strategies for CHF using ACE inhibitors or other cardioprotective agents. Although we will attempt to enroll all eligible patients from **SWOG-8897**, there may be higher motivation to participate among CAF-treated patients which may lead to some unmeasured bias in the results.

In this multicenter study, we have chosen to use the resting LVEF as the primary endpoint because of its high reproducibility without external review and quality assurance measures. An LVEF below 50% determined by MUGA scan will be considered abnormal, and representative of subclinical congestive heart failure in this population. Our sample size and recruitment goals are designed to detect a 25% difference in the number of women with an LVEF $< 50\%$ between the CAF and CMF treated groups. We will over-sample subjects at the 5-year assessment so as to have an adequate sample of subjects for the 10-year comparisons. The difference of 25% was chosen primarily because of its clinical significance. Differences that are less than this amount would not represent an important outcome for patients or physicians.

Inclusion of Women and Minorities:

This study involves only patients previously registered to **SWOG-8897**. No new patients will be registered.

3.0 DRUG INFORMATION

Chemotherapy is not part of this study.

4.0 STAGING CRITERIA

The staging criteria for **SWOG-8897** will be used.

5.0 ELIGIBILITY CRITERIA

- 5.1 Patients must be registered to Arms I - IV of SWOG-8897 and have completed at least one course of chemotherapy as assigned (i.e., CMF or CAF). Completion of tamoxifen is not a requirement for this study. Registration to SWOG-9342 must occur 5 years 3 months from the time of randomization to 6 years post-randomization.
- 5.2 Pregnant or nursing women must agree not to have a nuclear medicine study (but may otherwise participate). Women of reproductive potential may not participate unless they have agreed to use an effective contraceptive method during and for one month after the MUGA scan.
- 5.3 Patients must be disease-free, without a past recurrence, and have an anticipated survival of at least 5 years.
- 5.4 All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.
- 5.5 At the time of patient registration, the date of institutional review board approval for this study must be provided to the Statistical Center.

6.0 DESCRIPTIVE FACTORS

Patients will be described by:

- 6.1 Assigned SWOG-8897 treatment group:
 - Arm I - CMF X 6 cycles
 - Arm II - CAF X 6 cycles
 - Arm III - CMF X 6 cycles followed by tamoxifen for five years
 - Arm IV - CAF X 6 cycles followed by tamoxifen for five years

7.0 STUDY PLAN

- 7.1 Pregnant or nursing women may not to have a nuclear medicine study, but may otherwise participate.
- 7.2 Baseline and yearly cardiovascular and routine history and physical examination questionnaires will be completed by the clinician (see Section 18.0 for forms).
- 7.3 Laboratory Evaluation of Cardiac Status

Resting MUGA scans will be performed at Years 5 and 10 after registration on SWOG-8897.
- 7.4 Criteria For Removal From Protocol:

The patient may withdraw from the study at any time for any reason. The reason must be documented in the Cardiac History and Clinical Examination Form.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

Toxicities are monitored by physician report in **SWOG-8897**. Dosage modifications are not applicable in this companion study. Physicians will follow the dosage modifications given in **SWOG-8897**.

9.0 STUDY CALENDAR

Note: All forms to be used in this study are listed in Section 18.0. Forms submission guidelines are found in Section 14.0.

All subjects will have an annual cardiac history and clinical examination (performed annually between the 5th and 10th years of follow-up, within one month of anniversary of registration to **SWOG-9342**):

Cardiac History and Clinical Examination:

Past Medical History

Current Cardiac Symptoms

Physical Examination

At the five and ten year annual assessments, all subjects will also undergo the following assessments:

Laboratory Evaluation of Cardiac Status:

Pregnancy Test (if indicated) - prior to performance of MUGA scan

Resting MUGA scan

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Endpoints

- a. The number of women with a resting MUGA LVEF < 50% at 5 years and 10 years after randomization on SWOG-8897.
- b. Secondary endpoints - other cardiac events and clinical symptoms will be summarized in order to characterize the types of problems these patients are having after five and ten years on study.

11.0 STATISTICAL CONSIDERATIONS

Assuming the patients enrolled on this study are representative of the patients randomized to SWOG-8897, a difference of .25 in the probability of LVEF < 50 between the CAF and CMF groups would be clinically important to detect. Seventy patients per group will be required for a .05 level test to have power .9 to detect a difference of .25. We anticipate approximately 2/3 of registered patients will still be participating at Year 10. One hundred-five patients per arm will be registered in order to have 70 per group at the end of the study.

After accrual is complete, consideration will be given to continuing the study with the cardiac questionnaires only (without the MUGA requirement) in order to collect additional information on clinical events.

In addition, other cardiac events and clinical symptoms will be summarized in order to characterize the types of problems node negative breast cancer patients on adjuvant clinical trials are having after 5 years on study. The secondary endpoints will also be explored with respect to their associations with doxorubicin use, tamoxifen use, radiotherapy use and baseline (at registration) patient characteristics.

12.0 DISCIPLINE REVIEW

Discipline review is not part of this study.

13.0 REGISTRATION GUIDELINES

- 13.1 Registration. Southwest Oncology Group Investigators: All patients must have been registered to SWOG-8897 and must have completed at least one course of assigned chemotherapy. Telephone the Southwest Oncology Group Statistical Center, 206/667-4623, 6:30 a.m. to 5:00 p.m. Pacific time, Monday through Friday, excluding holidays.
- 13.2 At the time of registration, the caller must be prepared to answer every question on the eligibility checklist for SWOG-9342 and provide descriptive factors.
- 13.3 The caller must also be prepared to provide the date of institutional review board approval for SWOG-9342. Patients will not be registered if the IRB approval date is not provided or is > 1 year prior to the date of registration. The caller must also supply the date the informed consent was signed.
- 13.4 Exceptions to the current registration policies will not be permitted. Therefore, exceptions to eligibility requirements, participation by an institution/member not identified as eligible **AND/OR** cancellations will not be allowed.

14.0 DATA SUBMISSION SCHEDULE

- 14.1 Data must be submitted according to the protocol requirements for **ALL** patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.
- 14.2 Master forms are included in Section 18.0 and (with the exception of the sample consent form) must be photocopied for data submission to the Statistical Center.
- 14.3 Group members and CCOPs must submit two copies of all data forms directly to the Statistical Center in Seattle. CGOPs will submit (number of copies to be determined by the Group Member) copies to their Group Member institution for forwarding to the Statistical Center.
- 14.4 WITHIN 14 DAYS OF REGISTRATION:
Submit the following:
Eligibility Checklist for **SWOG-9342**
- 14.5 AFTER THE FIVE YEAR ASSESSMENT AND ANNUALLY THROUGH YEAR TEN:
Cardiac History and Clinical Examination Form (or an explanation why this form will not be submitted)
- 14.6 AFTER THE FIVE YEAR AND TEN YEAR ASSESSMENTS:
MUGA Scan Result Form (or an explanation why this form will not be submitted)

15.0 SPECIAL INSTRUCTIONS

There are no special instructions for this study.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

17.0 BIBLIOGRAPHY

1. Fisher B, Constantino J, Redmond C, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. *N Engl J Med* 320:479-484, 1989.
2. Fisher B, Redmond C, Dimitrov NV, et al. A randomized clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node-negative breast cancer who have receptor-negative tumors. *N Engl J Med* 320:473-478, 1989.
3. McGuire WL, Tandon D, Allred C, et al. How to use prognostic factors in axillary node-negative breast cancer patients. *J National Cancer Institute* 82:1006-1015, 1990.
4. Lefrak Ea, Pitha J, Rosenheim S, Gottlieb J. A clinicopathologic analysis of adriamycin cardiotoxicity. *Cancer* 32:302-314, 1973.
5. Rinehart JJ, Lewis RP, Balcerzak SSP. Adriamycin cardiotoxicity in man. *Ann Intern Med* 81:475-478, 1974.
6. Bristow MR, Mason JW, Billingham ME, Daniels JR. Doxorubicin cardiomyopathy: Evaluation by phonocardiography, endomyocardial biopsy, and cardiac catheterization. *Ann Intern Med* 88:168-175, 1978.
7. Alexander J, Dainiak N, Berger HJ, Goldman L, Johnstone D, Reduto L, Duffy T, Schwartz P, Gottschalk A, Zaret BL. Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiology. *N Engl J Med* 300:278-283, 1979.
8. Schwartz RG, McKenzie WB, Alexander J, Sager P, D'Souza A, Manatunga A, Schwartz PE, Berger HJ, Setaro J, Surkin L. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiology. *Am J Med* 82:1109-1118, 1987.
9. Steinherz LJ, Steinherz PG. Delayed anthracycline cardiac toxicity. *In* Principles and Practice of Oncology, JB Lippincott, Philadelphia, PPO Updates, 1-15, 1991.
10. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med* 324:808-815, 1991.
11. Steinherz L, Steinherz P, Tan C, et al. Cardiac toxicity 4 - 20 years after completing anthracycline therapy. *Proc Am Soc Clin Onc* 8:296, 1989.
12. Nayfield SG, Karp JE, Ford LG, et al. Potential role of tamoxifen in prevention of breast cancer. *J National Cancer Institute* 83:1450-1459, 1991.
13. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy, 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 339:1-15, 71-85, 1992.
14. Rutzvist LE, Mattson A (Stockholm Breast Cancer Study Group). Cardiac and thromboembolic morbidity among postmenopausal women with early stage breast cancer in a randomized trial of adjuvant tamoxifen. *J Natl Cancer Inst* 85:1398-1406, 1993.
15. Maddahi J, Berman DS, Silverberg R, et al. Validation of a two-minute technique for multiple gated scintigraphic assessment of left ventricular ejection fraction and regional wall motion. *J Nucl Med* 19:669, 1978.

16. Maddahi J, Berman DS, Matsuoka DT, et al. A new technique for assessing right ventricular ejection fraction using rapid multiple-gated equilibrium cardiac blood pool scintigraphy. Description validation and finding, in chronic coronary artery disease. *Circulation* 60:581, 1979.
17. Rodriques EA, Lahiti A, Hinge DA, et al. Left ventricular diastolic function in patients with chronic stable angina: Comparison with normal subjects. *Am J Non-Invas Cardiol* 2:244, 1988.

18.0 MASTER FORMS SET

This section includes copies of all data forms which must be completed for this study. These include:

- 18.1 Sample Consent Form
- 18.2 Cardiac History and Clinical Examination Form
- 18.3 MUGA Scan Result Form

**CONSENT FORM
AND
INFORMATION ABOUT**

SWOG-9342, A Study Of The Late Cardiac Effects Of Two Different Adjuvant Chemotherapy Regimens In Women With Node Negative Breast Cancer Treated On **SWOG-8897**

Type B: Companion Protocol

TO BE CONDUCTED AT

- I. You are invited to take part in this research study because you have had a breast cancer that has been removed by surgery and have been registered to receive chemotherapy in a specific research study, **SWOG-8897**.

We want to find out whether there are any long-term effects on the heart from the treatment you received.

We cannot and do not guarantee you will benefit if you take part in this study.

- II. If you decide to take part in this study, you will have several tests done to evaluate how well your heart is working. These tests will be done after you have been on the research study **SWOG-8897** for five years and again after ten years. The tests will include a complete medical history and physical examination, blood pressure, a cardiopulmonary examination and a resting MUGA scan. A MUGA scan is a test which requires injection of a radioisotope (radioactive material) into a vein followed by a scanned picture of the heart. A computer then can calculate how well the heart pumps. You may experience some pain or discomfort from the injection. You will also have a medical history and physical examination for this study annually between the fifth and tenth year.

The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be (charged in the usual way/provided at a reduced rate).

- III. There may be other ways to evaluate your heart function such as examination by your general physician. It is not known if the evaluation you receive will offer any increased benefit than that currently available outside of participation in this research, although it may have some influence on the way patients with breast cancer are treated in the future.
- IV. In order to participate fully in this study, you should have avoided becoming pregnant from the first day of your most recent menses (menstrual period). You should avoid becoming pregnant for at least one month after the MUGA scans. Pregnancy within one month after the MUGA scans may create a potential risk to the unborn baby. Pregnant women may participate in other aspects of the study (avoiding the MUGA scan). You may take a urine test to see if you are pregnant before you start treatment. If you are sexually active, we strongly recommend you take precautions to avoid the possibility of becoming pregnant because the MUGA scan could be harmful to an unborn child.

- V. If you experience illness as a result of treatment on this study, you will (will not) receive free emergency medical treatment. We cannot give you free continuing medical care and/or hospitalization, nor can we pay you to take part in this study.
- VI. We will keep any information we learn from this study confidential and disclose it only with your permission. By signing this form, however, you allow us to make your records available to the National Cancer Institute, the Food and Drug Administration and the Southwest Oncology Group. If we publish the information we learn from this study in a medical journal, you will not be identified by name.
- VII. Whether or not you take part in this study will not affect your future relations with your doctors (there will be no loss of benefit or change in attitude) or _____ (hospital name). If significant new findings are developed during the course of this study which may relate to your willingness to continue, this information will be provided to you. In addition, you understand that you may refuse to continue on this study, at any time after the start of therapy, without fear of prejudice to additional treatment that may be needed.
- VIII. The doctor(s) involved with your care can answer any questions you may have about the drug program. In case of a problem or emergency, you can call the doctors listed below day or night.

Office

Home

Dr.

Dr.

Dr.

You can also call the Institutional Review Board (# _____) if you have any questions, comments or concerns about the study or your rights as a research subject.

- IX. We will give you a copy of this form to keep.
- X. You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer after reading and understanding all the information on this form.

Date

Signature of Subject

Signature of Witness

Signature of Investigator

Time

Southwest Oncology Group

DRAFT

Page 1 of 2

SWOG 9342 - Cardiac History and Clinical Examination Form

SWOG Study No. **S 9 3 4 2** Protocol Step

SWOG Patient No. Patient's Name _____ (L.F.M)

Institution / Member _____ S.S. No. - -

Physician _____ Hospital No. _____

Groups other than SWOG: Name/Study No./Pt No. _____ / _____ / _____

Amended data: Yes, mark amended items in red.

Instructions: **To be completed by physician ANNUALLY.**

Date of Clinical Exam - - (MDY) Annual F/U (Check one) 5 6 7
 8 9 10

*For the rest of page 1: If Annual F/U is 5, indicate ANY prior experience.
 If Annual F/U is 6-10, indicate experience in PAST YEAR ONLY.*

Past Medical History:

	No	Yes	Unknown
Cigarette smoking (≥ 20 packs)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hypertension	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Elevated fasting lipid profile	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diabetes			
Type I	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Type II	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Heart murmur	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Arrhythmia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Congestive heart failure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cardiomyopathy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Coronary artery disease			
Angina	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Myocardial infarction	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Cardiac Evaluation/Tests:

	No	Yes*	Unknown	*If Yes, state result:
Stress test without imaging (e.g., exercise, dobutamine)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
Stress test with imaging (e.g., thallium, echo)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
MUGA at rest	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
with exercise	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
Holter monitor or event recorder	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
Echocardiogram	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
Cardiac catheterization	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____

Invasive Cardiac Procedures:

	No	Yes	Unknown
Coronary artery bypass surgery	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Angioplasty	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Electrophysiologic studies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Cardiac Hospitalizations:

	No	Yes	Unknown
Arrhythmia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pulmonary edema/CHF	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Angina	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Myocardial infarction	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SWOG 9342 - Cardiac History and Clinical Examination Form

SWOG Study No. **S 9 3 4 2** Protocol Step

SWOG Patient No.

Patient's Name _____ (L.F.M)

Current Medications:	No	Yes	Unknown
Diuretic	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Beta blocker	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ACE inhibitor	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Calcium channel blocker			
Amlodipine	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nitrates	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lipid lowering drugs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Current cardiac symptoms and signs:	No	Yes	Unknown
Shortness of breath with moderate exercise (e.g., 2 flights of stairs)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shortness of breath with mild exercise (e.g., 1 block level ground)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shortness of breath at rest	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Paroxysmal nocturnal dyspnea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Orthopnea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pedal edema (2+ or greater)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lightheadedness or dizziness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Loss of consciousness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Palpitations or abnormal heart rhythm	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fatigue impairing daily activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Anginal chest pain with exertion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Anginal chest pain at rest	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Results of annual follow-up exam for this study:

BP sitting: _____ / _____ HR: _____

Jugular venous pulsation: normal elevated

Lungs: clear rales rhonchi effusion

Heart: size normal enlarged

 murmur:

 systolic no yes

 diastolic no yes

 S₃ no yes

 S₄ no yes

 rhythm normal abnormal

Abdomen: liver span normal increased

Extremities: no edema 1+ 2+ 3+ 4+

Current Cardiac Diagnoses (check all that apply):

- None
- Congestive heart failure
- Angina pectoris
- Hypertension
- Atrial arrhythmia
- Ventricular arrhythmia
- Cardiomyopathy

Examiner's signature _____

Southwest Oncology Group

DRAFT

Page 1 of 1

SWOG 9342 - MUGA SCAN Results Form

SWOG Study No.

S 9 3 4 2

Protocol Step

SWOG Patient No. Patient's Name _____ G.P.M.

Institution / Member _____ S.S. No. -

Physician _____ Hospital No. _____

Groups other than SWOG: Name/Study No./Pt No. _____ / _____ / _____

Amended data: Yes, mark amended items in red.

Date of MUGA - - (MDY)

Visit F/U (Check one): 5 yr 10 yr

Was the patient's MUGA scan reimbursed through insurance? No Yes

Resting LV ejection fraction: _____ %

Institutional Lower Limit of Normal _____ %

LV wall motion: normal abnormal other

By: _____ Date: _____ *

SWOG 03-26-96 SW346

APPENDIX M

Southwest Oncology Group Protocol S9630: "A Randomized Comparison of Medroxyprogesterone Acetate and Observation for Prevention of Endometrial Pathology in Postmenopausal Breast Cancer Patients Treated with Tamoxifen. Phase III."

Study Coordinators: Ronald K. Potkul, M.D., Kathy S. Albain, M.D., Caryl Saloman, M.D., Sharon Wilczynski, M.D., Ph.D., Polly Feigl, Ph.D., Janet O'Sullivan, M.A.

Funded by supplemental award from the National Cancer Institute.

The following draft protocol proprietary information and is a privileged communication for investigational use only

SOUTHWEST ONCOLOGY GROUP

**A RANDOMIZED COMPARISON OF MEDROXYPROGESTERONE ACETATE (MA) AND OBSERVATION
FOR PREVENTION OF ENDOMETRIAL PATHOLOGY IN POSTMENOPAUSAL BREAST
CANCER PATIENTS TREATED WITH TAMOXIFEN**

PHASE III

	<u>Page</u>
SCHEMA	2
1.0 OBJECTIVES.....	3
2.0 BACKGROUND.....	4
3.0 DRUG INFORMATION.....	7
4.0 STAGING CRITERIA.....	10
5.0 ELIGIBILITY CRITERIA	10
6.0 STRATIFICATION FACTORS/RANDOMIZATION SCHEME.....	12
7.0 TREATMENT PLAN.....	12
8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS.....	16
9.0 STUDY CALENDAR.....	17
10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS.....	18
11.0 STATISTICAL CONSIDERATIONS	18
12.0 DISCIPLINE REVIEW.....	21
13.0 REGISTRATION GUIDELINES.....	22
14.0 DATA SUBMISSION SCHEDULE.....	22
15.0 SPECIAL INSTRUCTIONS	23
16.0 ETHICAL AND REGULATORY CONSIDERATIONS	24
17.0 BIBLIOGRAPHY	26
18.0 MASTER FORMS SET.....	29
19.0 APPENDIX.....	34

PARTICIPANTS: ALL SOUTHWEST ONCOLOGY GROUP, CCOP AND CGOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

STUDY COORDINATORS:

Ronald K. Potkul, M.D. (Gynecologic Oncology)
Loyola University Medical Center
Department of Obstetrics & Gynecology
2160 S. First Avenue
Maywood, IL 60153
Phone: 708/327-3311

Kathy S. Albain, M.D. (Medical Oncology)
Committee on Women's Health)
Loyola University Medical Center
Cancer Center, Room 109
2160 South 1st Avenue
Maywood, IL 60153-5589
Phone: 708/327-3102

Caryl Saloman, M.D. (Radiology Consultant)
Loyola University Medical Center
Department of Radiology
2160 S. First Avenue
Maywood, IL 60153
Phone: 708/216-6720

AGENTS:

Medroxyprogesterone Acetate
Tamoxifen (Nolvadex) (NSC-180973)

Sharon Wilczynski, M.D., Ph.D. (Pathology)
Dept of Anatomical Pathology
City of Hope
1500 E Duarte Rd
Duarte, CA 91010
Phone: (818) 359-8111 ext = 3318

Polly Feigl, Ph.D. (Biostatistics)
Janet O'Sullivan, M.A.
Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street
Seattle, WA 98104-2092
Phone: 206/667-4623

M426/mb

SCHEMA

NEWLY DIAGNOSED EARLY BREAST CANCER; NOT ENROLLED ON OR ELIGIBLE FOR OTHER SOUTHWEST ONCOLOGY GROUP ADJUVANT PROTOCOLS

BASELINE ENDOMETRIAL BIOPSY (EMB)
BASELINE ENDOVAGINAL SONOGRAM (EVS)

ABSENCE OF PROLIFERATIVE CHANGES, HYPERPLASIA, ATYPIA, CARCINOMA
BEGIN TAMOXIFEN (OR PRIOR TAMOXIFEN UP TO 28 DAYS)

RANDOMIZATION

OBSERVATION ALONE

Medroxyprogesterone acetate (MA)
10 mg/Day x 14 days
EVERY 3 MONTHS

EVS + EMB* AT YEAR ONE

MAJOR
PATHOLOGIC
ABNORMALITY+

NO TISSUE, PROLIFERATIVE CHANGES,
POLYP OR OTHER BENIGN DIAGNOSIS

ENDOMETRIAL CARCINOMA

CONTINUE YEARLY EVS + EMB**

OFF STUDY

HYPERPLASIA WITH OR WITHOUT ATYPIA
Continue tamoxifen and begin
medroxyprogesterone acetate total dose
20 mg/Day x 6 weeks

RE-BIOPSY

NO TISSUE, PROLIFERATIVE
CHANGES, POLYP OR OTHER
BENIGN DIAGNOSIS

ENDOMETRIAL CARCINOMA

Continue tamoxifen, and begin
medroxyprogesterone
acetate total dose 20 mg/Day for an
ADDITIONAL 6 weeks

RESUME YEARLY EVS + EMB**

OFF STUDY

RE-BIOPSY

NO TISSUE, PROLIFERATIVE
CHANGES, POLYP OR OTHER
BENIGN DIAGNOSIS

PERSISTENT HYPERPLASIA WITH OR WITHOUT ATYPIA

See Section 7.2a

*If vaginal bleeding occurs at any point between the protocol-specified yearly EMB and EVS, refer to Section 7.3 to determine whether immediate EMB + EVS is indicated.

**Re-enter Schema at EVS + EMB at Year 1 box; patients continue observation or MA as randomized.

+Major pathologic abnormality = carcinoma or hyperplasia with or without atypia.

1.0 **OBJECTIVES**

Primary Objectives

- 1.1 Endometrial abnormality rates
 - a. To compare endometrial pathologic diagnoses (in particular, proliferative changes, hyperplasia, hyperplasia with atypia and carcinoma) for postmenopausal, tamoxifen-treated breast carcinoma patients WITHOUT prior chemotherapy, randomly assigned to observation or cyclical medroxyprogesterone acetate.
 - b. To compare endometrial pathologic diagnoses (in particular, proliferative changes, hyperplasia, hyperplasia with atypia and carcinoma) for postmenopausal, tamoxifen-treated breast carcinoma patients WITH prior chemotherapy, randomly assigned to observation or cyclical medroxyprogesterone acetate.
- 1.2 Endometrial pathologic diagnoses resulting in tamoxifen discontinuation and intermittent bleeding
 - a. To compare endometrial pathologic diagnoses resulting in tamoxifen discontinuation (persistent endometrial hyperplasia, atypia or carcinoma) and intermittent bleeding in breast cancer patients WITHOUT prior chemotherapy receiving tamoxifen and randomized to observation or cyclical medroxyprogesterone acetate.
 - b. To compare endometrial pathologic diagnoses resulting in tamoxifen discontinuation (persistent endometrial hyperplasia, atypia or carcinoma) and intermittent bleeding in breast cancer patients WITH prior chemotherapy receiving tamoxifen and randomized to observation or cyclical medroxyprogesterone acetate.

Secondary objectives

- 1.3 To compare endovaginal ultrasound with endometrial biopsy in the detection of these abnormalities.
- 1.4 Oncogene Expression
 - a. To compare changes over time in endometrial oncogene expression (e.g., c-fos, c-jun, IGF1) and receptor status for postmenopausal tamoxifen-treated breast carcinoma patients WITHOUT prior chemotherapy randomly assigned to medroxyprogesterone acetate vs. observation.
 - b. To compare changes over time in endometrial oncogene expression (e.g., c-fos, c-jun, IGF1) and receptor status for postmenopausal tamoxifen-treated breast carcinoma patients WITH prior chemotherapy randomly assigned to medroxyprogesterone acetate vs. observation.
- 1.5 To describe associations among change in gene expression, receptor status, endometrial abnormality, length of tamoxifen exposure, and prior chemotherapy for the patients described in Sections 1.6 and 1.7 above.
- 1.6 To determine the feasibility of collecting centrally frozen tissue hysterectomy specimens from tamoxifen-treated breast carcinoma patients for the purpose of analyzing the regulation of 17 Beta-hydroxysteroid dehydrogenase activity in endometrial tissue.

- 1.7 To establish a national repository of paraffin blocks and frozen endometrial tissue from tamoxifen-treated breast cancer patients.

2.0 **BACKGROUND**

Tamoxifen, a non-steroidal antiestrogen is commonly used for the treatment of hormone dependent breast cancer. (1, 2) This agent is felt to act by inhibiting the growth of breast cancer cells by competitive binding with estrogen through the estrogen receptor, thereby producing an anti-proliferative effect. (1) Since the initial report by Killackey, et al. in 1985 suggesting a possible link between tamoxifen use and the development of endometrial cancer, approximately 115 cases of tamoxifen-associated cancer of the uterus had been reported. (3-14) The majority of these studies were limited by their anecdotal and case control nature.

More recently, the results of the National Surgical Breast and Bowel Project (NSABP) B-14 trial were published. (15) This randomized trial of tamoxifen vs placebo in women with estrogen receptor (ER) - positive breast cancer with negative axillary nodes revealed a 7.5-fold increase in the risk in developing endometrial cancer in the tamoxifen-treated group. Two of the 1424 patients assigned to receive placebo developed endometrial cancer; however both had subsequently received tamoxifen for treatment of breast cancer recurrence. Fifteen patients of the 1419 patients randomized to tamoxifen treatment developed endometrial cancer. Eight additional cases of uterine cancer occurred in the 1,220 tamoxifen-treated patients registered in NSABP B-14 subsequent to randomization. The mean duration of tamoxifen therapy was 35 months, with 36% of the endometrial cancers developing within two years of beginning tamoxifen. The average annual hazard rates for endometrial cancer were 0.2/1,000 in the placebo group and 1.6/1,000 in the randomized tamoxifen-treated group.

It is well-established that unopposed estrogen administration is associated with an increased risk of developing endometrial carcinoma. These cancers tend to be predominantly early stage, low grade, and have a favorable prognosis. If the effect of tamoxifen on the endometrium is that of a weak estrogen agonist, one would expect associated endometrial cancers to have clinical and pathologic characteristics comparable to those associated with estrogen. There have been conflicting reports on whether this in fact is the case. A report from the Yale Tumor Registry suggested that uterine cancers occurring in breast cancer patients on tamoxifen behaved more aggressively, as 67% of the uterine cancers were high-grade lesions. (10) Other recent studies failed to confirm these findings and strongly suggested that tamoxifen acted as a weak estrogen agonist on the endometrium. (13-15) This concept was supported by recent publications demonstrating an increased rate of estrogen-like changes in the endometrium, i.e., proliferative endometrium, adenomatous hyperplasia with and without atypia, in tamoxifen-treated women compared to non-users. (17,18) These studies were small, containing only approximately 100 patients. Postmenopausal patients should not have tissue on biopsy if the endometrium is not being stimulated and is otherwise normal. A recently published study evaluated 61 postmenopausal women on tamoxifen by obtaining endometrial tissue on biopsy. (17) The results suggested evidence of estrogen-like stimulation in 40% of the group. Proliferative or hyperplastic endometrium, atypical hyperplasia, and benign polyps were found in 13%, 16%, and 8% respectively of the 61 women. A better understanding of the actions of tamoxifen on the endometrium in a larger cohort of postmenopausal patients should aid in clarification of this issue. The present study will provide longitudinal prospective data in large homogenous sample of postmenopausal patients who have normal baseline endometrial studies.

The published data support an association between tamoxifen acting as the estrogen agonist and the development of both benign and malignant endometrial neoplasia. In the case of estrogen, it has been shown that the addition of a progestin significantly decreases abnormal changes in the endometrium as compared with patients receiving unopposed estrogen. (19) This is accepted to the point that patients receiving postmenopausal estrogen replacement therapy plus a progestin are not routinely screened for endometrial pathology unless they have abnormal bleeding. The question arises whether a cyclic progestin in women receiving tamoxifen can decrease the rate of both benign and malignant endometrial neoplasia to a point where screening also would be

deemed unnecessary. There is evidence in the literature that the use of quarterly progestin in the form of medroxyprogesterone 10 mg per day for 14 days is equivalent to monthly progesterone in reducing the rate of endometrial hyperplasia in patients receiving premarin. (20) There is absolutely no evidence to support that this very low dose in short duration has any adverse effect on breast cancer outcome.

Recommendations regarding screening are not well-established. Periodic sampling of the endometrium, using an endometrial suction biopsy device (Pipelle, Unimar, Wilmington, Connecticut) is being evaluated. (21) Transvaginal sonography may provide a non-invasive means of screening for endometrial pathology in tamoxifen-treated breast cancer patients. Unfortunately, the definition of an abnormal endometrial stripe remains to be determined. One report in the literature using 5 mm as the cut off of an abnormal endometrial echo found that approximately 50% of patients undergoing endometrial sampling on that basis had no abnormal pathology. (11) A second study reported a predictive value of 100% (16 of 16) for atypical hyperplasia or polyps when the endometrial stripe was 8 mm or greater. (17) These reports are all on limited numbers of patients. This proposed study prospectively evaluates potential screening techniques (sonogram and biopsy) for endometrial pathology in women with breast cancer treated with tamoxifen over a period of five years.

RATIONALE FOR MOLECULAR CORRELATES

The effects of estrogen and progesterone on the physiology of normal endometrium are well known. The mechanisms by which estradiol regulates proliferation of human estrogen-responsive cells involve a series of events beginning with binding of estradiol to its receptor followed by activation of the receptor, interaction of the activated receptor with hormone response elements of specific genes and modification of their transcription rates. (22) Estradiol also enhances expression of proto-oncogenes (eg., c-myc, c-fos, c-jun, c-ras, IGF1) involved in the regulation of gene expression and DNA synthesis. (23) Progesterone and other progestins counteract the action of estrogens in the endometrium by 1) reducing estrogen receptor levels, 2) increasing the rate of metabolism of estradiol to the inactive estrogen, estrone (E2 to E1) and sulfated metabolites, and 3) interfering with estrogen-induced transcriptional actions through still undetermined mechanisms.

In addition to the known antiestrogenic effects of tamoxifen, in some situations, the drug exhibits estrogenic effects or a mixed agonist/antagonist action. (24) Several recent clinical studies have suggested a possible link between tamoxifen use and the development of endometrial carcinoma, presumably due to the estrogen-like stimulation of the endometrium by the antiestrogen. (6, 15)

Unopposed estrogen is an important risk factor for endometrial cancer. (25) Estradiol is the most active biologic estrogen and the intensity of exposure to this hormone is critical in the process of carcinogenesis of the endometrium. Extensive in vitro studies on the human endometrium have demonstrated that estradiol levels in the tissue can be regulated by hormone-dependent target tissue metabolism. (26) These findings led to the conclusion that the blood level of estradiol is only one of the parameters to be considered in the evaluation of the hormonal influence on the endometrium. The intensity of the cellular exposure to estradiol is determined by the circulating estradiol concentration, the endometrial estrogen receptor levels, and the activity of the endometrial 17-Beta hydroxysteroid dehydrogenase (17-HSD). This enzyme catalyzes the reversible conversion of estrone (E1) into the more potent estrogen, estradiol (E2). (27) Progesterone and, in turn, the progesterone receptors appear to drive this reaction in the reverse direction towards the less active estrone. (28)

Compared with normal breast tissue, breast tumors have an increased ability to convert estrone to the biologically more active 17-Beta-estradiol. (27) This reversible interconversion in the breast is also mediated by the enzyme 17-HSD. Intracellular estradiol has been demonstrated to stimulate reductive 17-HSD (E1 to E2) in the MCF-7 human breast cancer cell. Progesterone and tamoxifen appear to stimulate the reverse oxidative direction (E2 to E1) thus reducing the intracellular estradiol level. (29, 30) These observations suggest that in the breast, tamoxifen, in addition to

blocking estradiol at the receptor, may act also by reducing the intracellular levels of E2. The effects of tamoxifen on this enzyme in the postmenopausal estradiol-free endometrium and in the premenopausal endometrium are unknown.

It is well documented that exogenous estrogens in postmenopausal women will lead to an increase in the endometrial estrogen and progesterone receptor levels equal to or greater than those found in the proliferative phase of premenopausal women. (31) The action of progesterone leads to a reduction of these receptors. The variable levels of these receptors and their potential predictive use in the study of the development of endometrial changes and frank cancer in women with breast cancer on tamoxifen needs to be clarified.

Finally, many laboratories have investigated the actions of tamoxifen in animal models such as the rat uterus. (32) The majority of early studies used uterine growth and/or histological changes as an endpoint. More recently several cellular oncogenes such as c-fos appear to be over-expressed in estrogen- and tamoxifen treated animals, indicating that tamoxifen may be acting as a full agonist in the rat uterus (33). The effects of tamoxifen plus or minus progesterone on these growth related proto-oncogenes is unknown in human endometrium and may play a role in the early development of hyperplasias and endometrial cancer.

In summary, the effect of estrogen on the endometrium has been extensively studied on a molecular and biologic cellular level. The effect of the tamoxifen on breast cancer cells has also extensively been studied at the cellular level in animal models. In these settings it appears to function as an antiestrogen. Clinical and animal data suggest that tamoxifen may be acting as an estrogen agonist on the endometrium. The aims of these molecular correlates analyses are to better understand the effects of tamoxifen on the endometrium and to specifically determine whether the effects of tamoxifen differs from what is known of estrogen, as well as correlate changes at the molecular level with the pathologic findings in patients with endometrial abnormalities of proliferative changes, hyperplasia, hyperplasia with atypia and carcinoma. In addition, the effect of cyclical low dose medroxyprogesterone acetate on these molecular findings will be studied.

STUDY DESIGN

The study is a prospective study of patients at the start of five years of adjuvant tamoxifen randomized to cyclic low dose medroxyprogesterone acetate or not. All of the patients will have a normal prestudy endometrial biopsy to eliminate the possibility of any pre-existing condition. A prestudy endovaginal sonogram will establish baseline data. The prospective study contains four groups of postmenopausal women on tamoxifen: plus or minus prior chemotherapy and plus or minus cyclic medroxyprogesterone acetate. Yearly endovaginal sonogram and endometrial biopsy will be performed. As outlined below, patients with hyperplasia or atypia will receive a higher dose of protracted medroxyprogesterone acetate in attempt to reverse the abnormality while continuing adjuvant tamoxifen.

All sonograms and biopsies will be subject to a central review. The paraffin blocks from all endometrial biopsies in which tissue is obtained will be stored at Loyola University Cancer Center in a repository. Selected blocks will be evaluated according to the Statistical Considerations (Section 11.0), and along with the remaining blocks will constitute a bank for future studies. The estrogen and progesterone receptor content will be measured using immunohistochemical technique on these blocks. In addition, expression of the c-fos, c-jun and IGF1 oncogenes will be evaluated by using *in situ* hybridization. These techniques will allow us to separate the endometrial cells from the stromal cells in making these determinations. (See Appendix Section 19.2 for detailed methods.)

Patients in this study will have yearly biopsies which will allow us to serially study the pathologic abnormality rates, receptor contents and oncogene expression in the patients who have a positive biopsy (excluding benign polyps). The paraffin blocks of endometrial biopsies from Years 1 - 5 will be placed in the repository. All biopsies from Year 2 will be evaluated for receptor content and oncogene expression. Those patients with abnormalities at Year 2 will have the Year 1 biopsy

examined for possible early changes in receptor content and oncogene expression. Every attempt will be made to study Year 3, 4 and 5 specimens in patients with Year 2 abnormalities, but it is conceivable that biopsy material may not be available if abnormalities are reversed by medroxyprogesterone acetate treatment, and conversely, new abnormalities may surface beyond Year 2 (even though normal at Year 2). We estimate that material will be available in approximately 50 patients Years 3 - 5, although the analyses required will be better defined after Year 2.

We will also request for patients who undergo a hysterectomy for endometrial cancer or hyperplasia that a portion of the endometrium be snap-frozen and sent to us for evaluation. The 17-HSD enzyme activity will be evaluated in these frozen specimens that are available, since this cannot be determined on paraffin blocks. The enzyme activity will be determined using standard methods employing tritiated precursors. (29) This part of the study will be exploratory.

This study will not be adequately powered to determine any impact of very low dose cyclical medroxyprogesterone acetate on breast cancer outcome. Should this treatment be successful in lowering endometrial abnormality rates, a larger prospective trial in a homogenous tamoxifen-treated cohort will be designed.

3.0 DRUG INFORMATION

3.1 Tamoxifen (Nolvadex) (NSC-180973)

a. DESCRIPTION

The physical form of tamoxifen is a fine white essentially odorless crystalline powder. The anti-estrogenic effects appear to be competitive binding of estrogen receptor sites on cells. In cytosols, derived from human breast adenocarcinoma, tamoxifen competes with estradiol for ER protein.

b. TOXICOLOGY

Human Toxicology: Toxicity attributable to tamoxifen is minimal and consists mainly of hot flashes (20%) and irregular menses; transient nausea (10%); and vaginal discharge or dryness (9%). Vaginal bleeding, hypercalcemia, depression, dizziness, alopecia, headache, skin rash and edema occur rarely (3%). Up to 20% of the patients will develop a mild leukopenia or thrombocytopenia, usually during the second week of therapy, which resolves spontaneously within a week and does not require discontinuation of the drug. Eight percent of the patients in the combined series of Tormey and Morgan developed a characteristic flare reaction within one month of starting the drug. These flare reactions usually consisted of an increase in osseous pain or an increase in erythema and the size of cutaneous lesions. Development of flare reactions was not predictive of failure in breast cancer, as 3/7 flare reactions went on to exhibit improvement or response. Approximately 1% of patients develop hypercalcemia. Abnormal liver function tests including rare cases of more severe liver abnormalities such as fatty liver, cholestasis (back-up of bile), hepatitis, and hepatic necrosis (destruction of liver cells) have been observed. A few of these serious cases resulted in death but whether tamoxifen was the cause of these problems still remains uncertain. Ocular changes, including cataracts, have been reported in a few patients treated for prolonged periods of time with doses that are several times the highest recommended daily dose of 40 mg. These changes consisted of retinopathy, corneal changes, cataracts and a decrease in visual acuity.

Data from one large United States study have not shown an increase in other (non-uterine) cancers in women taking tamoxifen. However, other unpublished data suggests a possible increase in second cancers of the gastrointestinal tract among women receiving the drug. There have been a few reports of liver cancer

that have occurred in women taking tamoxifen. Although tamoxifen can cause liver cancer in rats, it is not known to be a cause of liver cancer in humans. Whether an increased risk for other (non-uterine) cancers is associated with tamoxifen is still uncertain and continues to be evaluated.

An increased risk of uterine cancer has been observed in patients taking tamoxifen. Death from uterine cancer is therefore a possibility. Physicians should promptly evaluate any pelvic complaints in patients taking tamoxifen. Endometrial changes may include polyps, hyperplasia and endometriosis. Other adverse reactions reported infrequently include: distaste for food, depression, dizziness and light-headedness. Infrequent reports of thromboembolic events, ovarian cysts, hyperlipidemia, abnormal PAP smears, and anticoagulant effect may occur when used in combination with coumarin type anticoagulant, and T₄ elevations were reported for a few postmenopausal patients. Patients with a history of thromboembolic problems should discuss the indication for tamoxifen treatment carefully with their physician.

For women of childbearing potential: Women should not become pregnant while taking tamoxifen, and should use barrier or non-hormonal contraceptive measures if sexually active and otherwise at risk of pregnancy. Although no clinical evidence is available to prove that tamoxifen may cause fetal harm when administered to a pregnant woman, effects on reproductive function are expected from the antiestrogenic properties of tamoxifen, and studies conducted on mice has demonstrated some fetal deformities, including miscarriage, birth defects, and long-term effects on sexual development (which could be similar to the long-term effects caused by DES, a hormone medication that was given to pregnant women in the past). Women whose mothers took DES (diethylstilbestrol) during pregnancy have an increased risk of developing cancer or other changes of the vagina or cervix, and may have trouble bearing children. The relevance of these findings from animal studies to women who may accidentally take tamoxifen during pregnancy while taking protocol therapy is uncertain. To date, exposure of unborn infants to tamoxifen has not been shown to cause cancer later in the lives of these children. Nonetheless it is essential that patients use effective non-hormonal contraceptive methods to avoid pregnancy while taking tamoxifen, and for at least two months after completing or discontinuing tamoxifen.

c. PHARMACOLOGY

Animal Studies: In the rat, mouse, beagle dog and rhesus monkey, maximum blood levels of tamoxifen are seen one to six hours and 24 - 44 hours after an oral dose. The drug is hydroxylated in the liver to a number of different compounds and excreted in the bile. After a conjugation, an extensive enterohepatic circulation exists, and the conjugated metabolites are hydrolyzed to the unconjugated metabolite, reabsorbed and reconstituted. Eventually the drug is excreted in the feces in the metabolized form. Very little drug is excreted in the urine. Biphasic half lives of five to 12 hours and 62 - 170 hours were seen in the animal experiments. The antiestrogenic properties of the metabolite are unknown; however, the monohydroxyl metabolite is thought to have activity.

Human Studies: Utilizing a method incorporating ion pair extraction, photochemical activation and chromatographic analysis, maximum blood levels of tamoxifen and metabolite are found to occur within three to twelve hours after a single dose of tamoxifen of 10 mg/M². Preliminary data indicate an initial half-life of 7 - 14 hours with secondary peak four or more days later. Metabolism in humans is similar to animals, with extensive enterohepatic circulation. Half-life after prolonged 10 mg/M² BID dosage is variable, but appears to be between four and 14 days. Drug is excreted mainly as conjugates. It is slowly excreted in feces,

with only small amounts appearing in the urine. Studies now suggest that the bioavailability of 10 mg bid and 20 mg once daily are equivalent (Buzdar Frye and Ho, et al. Proc ASCO, 1993).

Formulation: Tamoxifen is supplied in tablets containing the equivalent of 10 mg of tamoxifen.

Storage and Stability: Slightly soluble in water, soluble in ethanol, methanol and acetone. The drug substance is stable for at least five years under normal storage conditions and should be protected from light and moisture. Minimum shelf-life appears to be two years.

Administration: Oral.

Supplier: This drug is commercially available for purchase by the third party. This drug will not be supplied by the NCI.

3.2 Medroxyprogesterone acetate (oral)

a. DESCRIPTION

Chemistry: Medroxyprogesterone acetate is a derivative of progesterone. It is a white to off-white, odorless crystalline powder, stable in air, melting between 200 and 210°C.

Chemical Name:

Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6a)-

b. TOXICOLOGY

Animal Studies: Beagle dogs treated with medroxyprogesterone acetate developed mammary nodules some of which were malignant. Although nodules occasionally appeared in control animals, they were intermittent in nature. Their significance with respect to humans has not been established.

Human Toxicity: Breast tenderness or galactorrhea has been reported rarely.

The following adverse reactions have been observed in women taking progestins including medroxyprogesterone acetate: breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, edema (because of this, conditions such as epilepsy, migraine, asthma, cardiac or renal dysfunction require careful observation), change in weight, cervical erosion, cholestatic jaundice, anaphylactoid reactions and anaphylaxis, rash (allergic) with and without pruritus, urticaria, acne, alopecia, hirsutism, mental depression, pyrexia, insomnia, nausea and somnolence. Thromboembolic phenomena including thrombophlebitis, cerebral thrombosis, pulmonary embolism have been reported. Aminoglutethimide administered concomitantly with this drug may significantly depress the bioavailability of medroxyprogesterone acetate.

There is increased risk of minor birth defects in children whose mothers take this drug during the first 4 months of pregnancy

c. PHARMACOLOGY

Medroxyprogesterone acetate, administered orally or parenterally in the recommended doses to women with adequate endogenous estrogen, transforms proliferative into secretory endometrium. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant

estrogenic activity. Progesterone and progesterone-like drugs have been used to prevent miscarriage in the first few months of pregnancy. No adequate evidence is available to show that they are effective for this purpose. Parenteral medroxyprogesterone acetate has been used as a contraceptive agent.

Formulation: Each medroxyprogesterone acetate tablet contains medroxyprogesterone acetate along with inactive ingredients: calcium stearate, corn starch, lactose, mineral oil, sorbic acid, sucrose and talc. Medroxyprogesterone acetate tablets are available in many different strengths and package sizes.

Solubility: It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water.

Storage and Stability: Store at controlled room temperature 15 - 30°C.

Administration: In this study, medroxyprogesterone acetate will be given orally at a dose of 20 mg/day.

Supplier: Medroxyprogesterone acetate is commercially available and should be obtained through a third party. This drug will not be supplied by the NCI.

4.0 STAGING CRITERIA

4.1 AJCC/WHO pathologic stages are defined below.

Primary Tumor (T)

- T1 Tumor 2 cm or less in greatest dimension
- T1a 0.5 cm or less in greatest dimension
- T1b More than 0.5 cm but not more than 1 cm in greatest dimension
- T1c More than 1 cm but not more than 2 cm in greatest dimension
- T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension
- T3 Tumor more than 5 cm in greatest dimension

Regional Lymph Nodes (N)

- N0 No regional lymph node metastasis
- N1 Metastasis to movable ipsilateral axillary lymph node(s)

Distant Metastasis (M)

- M0 No distant metastasis

5.0 ELIGIBILITY CRITERIA

5.1 Patients must have been diagnosed with primary invasive adenocarcinoma of the breast. Patients must not have sarcoma, lymphoma, or apocrine, adenocystic or squamous cell cancer of the breast. Patients must not have recurrent invasive breast cancer.

- 5.2 Patients must have had definitive local treatment of the primary lesion (mastectomy or breast-sparing procedure with breast radiotherapy) and have undergone an axillary node sampling. Patients whose most extensive breast surgery was a breast-sparing procedure must have received radiation therapy or must be planning to receive radiation therapy at the start of tamoxifen treatment.
- 5.3 Tumor must be ER or PgR positive, or ER AND PgR unknown. Positive is defined as ≥ 10 fmol/mg cytosol protein if measured in these units; otherwise positive is defined according to institutional standards.
- 5.4 Tumor must be staged as T1 - 3, N0 - 1 and M0.
- 5.5 Patient must be currently free of breast cancer (no evidence of disease). This is left to investigator judgement, but generally should include no evidence of distant disease on chest x-ray or mammogram of the opposite breast prior to registration, within 12 weeks prior to surgery; and no gross or microscopically positive surgical margins noted in the final surgery or pathology reports. One exception to the latter is focal positive microscopic margins following lumpectomy as long as definitive radiation is given.
- 5.6 All patients must be female and postmenopausal as defined by the following criteria:
 - a. Natural menopause: last menstrual period at least one year prior to registration.
 - b. Surgical menopause: bilateral oophorectomy at least two months prior to the diagnosis of breast cancer.
 - c. Patients who are 4-12 months from their last menstrual period will be considered postmenopausal if the FSH is elevated to the postmenopausal range.
 - d. Patients on postmenopausal estrogen therapy will be considered postmenopausal if they are 55 years of age or older. All other patients must have a postmenopausal level of FSH (it may take as long as 1-2 weeks after stopping estrogen for FSH to rise to postmenopausal level). Postmenopausal estrogen therapy must be discontinued in all patients.
- 5.7 Patients who have undergone a hysterectomy are ineligible.
- 5.8 Patients must have completed any adjuvant chemotherapy (but are not required to have received it). Patients who are currently eligible for or who were treated on any adjuvant Intergroup trial are not eligible for this study. Patients must not be planning to receive concurrent chemotherapy.
- 5.9 Patients must be planning to start five years of adjuvant tamoxifen or must have started tamoxifen ≤ 28 days prior to registration and be planning to receive adjuvant tamoxifen for five years.
- 5.10 If patients had bone scans done which showed hot spots, these must be confirmed benign by x-ray or biopsy within 42 days prior to registration.
- 5.11 Patients must have received a pelvic examination, an endovaginal sonogram (EVS) and endometrial biopsy (EMB) within 42 days prior to registration. The results of the biopsy must show either no tissue obtained or a benign finding such as a polyp. Patients with endometrial hyperplasia, proliferative changes, atypical hyperplasia or carcinoma are ineligible.
- 5.12 Institutions must be willing to submit adequate materials (as listed in Section 12.0) from all endometrial biopsies and the endovaginal sonograms, including H&E slides (if available)

tissue blocks (if available), biopsy report, ultrasound film, ultrasound report and the gynecologist's operative and pathology report of the biopsy procedure.

- 5.13 All patients must be informed of the investigational nature of this study and give written informed consent in accordance with institution and federal guidelines.
- 5.14 At the time of registration, the date of institutional review board approval for this study must be provided to the Statistical Center.

6.0 STRATIFICATION FACTORS/RANDOMIZATION SCHEME

- 6.1 Patients will be stratified for prior adjuvant chemotherapy: yes vs. no.
- 6.2 Patients will be stratified by number of positive nodes: 0 -3 vs. ≥ 4 .
- 6.3 Randomization will be dynamically balanced with respect to the stratification factors using the method of Pocock and Simon. (50)

7.0 TREATMENT PLAN

- 7.1 Patients will receive standard adjuvant tamoxifen for five years. Patients will be randomized to observation or medroxyprogesterone acetate (MA) 10 mg/day for 14 days every three months for five years.

Arm I - Tamoxifen alone (observation)

Agent	Dose	Schedule	Duration
Tamoxifen	20 mg/day	daily	five years

Arm II - Tamoxifen and MA

Agent	Dose	Schedule	Duration
Tamoxifen	20 mg/day	daily	five years
MA	10 mg/day	14 consecutive days q 12 weeks (beginning 12 weeks after the start of tamoxifen)	five years

- 7.2 All patients will undergo an annual endovaginal sonogram and endometrial biopsy. See Section 12.0 for instructions related to centralized pathology review and centralized sonogram review.
 - a. If hyperplasia (with or without atypia) is found, the patient will continue tamoxifen and begin a course of medroxyprogesterone acetate, total dose 20 mg/day for six weeks (regardless of study arm) and then be rebiopsied.
 - 1. Upon rebiopsy, if no hyperplasia is found the patient will continue tamoxifen, resume annual EVS and EMB and continue treatment according to assigned arm.

2. Upon rebiopsy, if hyperplasia (with or without atypia) is found the patient will again continue tamoxifen and receive a second course of medroxyprogesterone acetate, total dose 20 mg/day for six weeks and then be rebiopsied.
 - i. If no hyperplasia is found the patient will continue tamoxifen, resume annual EVS and EMB and continue treatment according to assigned arm.
 - ii. If simple hyperplasia only persists, at this point there are several options which the medical oncologist, gynecologist and patient should consider together: continue tamoxifen with 3 - 6 month follow-up; continue tamoxifen and treat with MA 20 mg/day for six weeks and rebiopsy; discontinue tamoxifen and start alternate adjuvant treatment; or continue tamoxifen and perform a hysterectomy. If tamoxifen is discontinued or a hysterectomy is performed, the patient is removed from study.
 - iii. Upon rebiopsy, if hyperplasia with atypia persists, tamoxifen should continue and a hysterectomy should be performed. The patient will be removed from study.
 - b. If endometrial cancer is found, the patient should be removed from study.
 - c. If no hyperplasia or cancer is found the patient will continue tamoxifen, annual EVS and EMB and treatment according to assigned arm.
- 7.3 Vaginal bleeding may occur within 72 hours of any biopsy. It may also occur as self-limited withdrawal bleeding following the cycles of medroxyprogesterone acetate. Any other bleeding at any other time is to be evaluated with EVS and EMB.
- 7.4 Endovaginal Sonography (EVS) Procedure - gray scale imaging (35 - 49)
- a. Record transducer manufacturer, frequency.
 - b. Examine uterus and adnexa in sagittal and transverse planes.
 - c. Measure and record uterine dimensions (AP, CC in sagittal plane; TR in transverse plane) using electronic calipers.
 - d. Measure and record maximal AP endometrial thickness (stripe) in sagittal plane using electronic calipers.
 1. If fluid is not seen in the endometrial canal, measure the maximal AP endometrial thickness by placing the anterior caliper at the junction of the anterior endometrial echo and the subendometrial hypoechoic zone (halo) and the posterior caliper at the junction of the posterior endometrial echo and the subendometrial hypoechoic zone (halo). Record this measurement as the AP endometrial thickness.
 2. If fluid is seen in the endometrial canal, measure the AP endometrial thickness as in Section 7.4d.1 above; record.

Also measure the AP dimension of the fluid collection on the same image and record.
 - e. Obtain representative images of the uterus adequate to completely characterize the endometrium with respect to: echogenicity; uniformity of echotexture; location and appearance of focal thickening, if present; cystic spaces, if present;

integrity or lack thereof of the subendometrial lucent "halo"; and fluid or sonolucent material within the endometrial cavity, if present.

- f. If cystic spaces are identified, use pulsed-wave Doppler and/or color Doppler imaging to demonstrate if there is internal flow indicating identity as vascular structures. Record representative image and pulsed-wave Doppler flow tracing.
- g. If endometrial echo is not visible, note reason, e.g., distorted by myomas, retroversion, technical factors, etc.
- h. Note and record incidental pathology, e.g., leiomyomas, ovarian masses.

7.5 Color Doppler Imaging (CDI) - optional, perform if available, in addition to EVS (Section 7.4). This information will be used for exploratory comparison with EVS and with biopsy.

- a. Record CDI frequency and parameters used in 1 - 3 below:
 - 1. Use lowest velocity flow setting, 1 - 2 cm/sec, or lower, if available.
 - 2. If possible use pulse repetition frequency in the range of 2 - 42 KHz.
 - 3. Set wall filter at minimum, 50 - 100 Hz.
 - 4. Use 1.5 - 2 mm Doppler sample volume.
 - 5. Set gain just below threshold for background noise.
 - 6. If possible, determine SPTA from transducer information provided by manufacturer and record this value.
- b. Assess endometrium for flow with CDI.
 - 1. Obtain and record 3 independent pulsed Doppler arterial waveforms and representative images from any focal areas of increased vascularity; otherwise, obtain and record pulsed Doppler arterial waveforms and representative images from three separate sites within the endometrium.
 - 2. For each waveform tracing, manipulate the transducer angle to maximize the Doppler signal. Measure and record maximum systolic and diastolic velocities for each tracing.

If available, use machine software package to calculate and record resistive index (RI), pulsatility index (PI) and S:D ratio.
- c. Repeat procedure in (b) to assess the myometrium for flow.
- d. Repeat procedure in (b) to assess paracervical uterine artery waveforms. If possible obtain at least one measurement from each side.
- e. If flow cannot be detected in any of these regions, please indicate this observation.

7.6 Endometrial Biopsy Procedure (to be performed after EVS)

- a. Standard outpatient gynecologic endometrial biopsy (EMB) will be performed using the Pipelle® (Unimar). The Pipelle® is a single use, sterile, disposable curette for obtaining a histological biopsy of the uterine mucosal lining. The device consists of a clear, flexible, polypropylene sheath that is 23.5 cm in length

with an outside diameter of 3.1 mm. Rapid movement of the piston within the sheath from its fully inserted position to its maximum retracted position creates a negative pressure (suction) within the lumen of the sheath. This negative pressure draws the mucosal tissue through the curette opening and into the lumen of the sheath as the curette scrapes against the endometrial wall.

- i. With the piston fully advance within the sheath, insert Pipelle® through cervical canal into the uterine cavity until resistance is felt (prior determination of the uterine depth with a uterine sound is recommended).
 - ii. While holding sheath, pull piston back completely thus creating maximum negative pressure with the sheath. Leave piston fully retracted.
 - iii. Simultaneously twirl sheath between fingers while moving sheath laterally and in and out between fundus and internal os three or four times to obtain sample.
 - iv. Remove Pipelle® from uterus and cut off distal tip just proximal to curette opening.
 - v. Advance piston rod to expel sample into transport medium.
 - vi. Use of a tenaculum may or may not be necessary to accomplish insertion of the Pipelle®. Clinical judgement should be used to determine its need.
- b. If cervical stenosis exists, a paracervical block with local anesthetic can be employed to allow gentle dilation with a small cervical dilator to allow EMB.
- c. If EMB unsuccessful then
- i. If endometrial echo is greater than 5 mm (abnormal), obtaining endometrial tissue is required by dilation and curettage.
 - ii. If endometrial echo is less than or equal to 5 mm (normal), no tissue required for study.

7.7 Criteria for Removal from Study.

- a. Development of endometrial cancer.
- b. Hysterectomy performed.
- c. The patient is removed from treatment with tamoxifen for persistent hyperplasia.
- d. Completion of five years of tamoxifen treatment.
- e. Recurrence of breast cancer.
- f. Unacceptable toxicity from tamoxifen or from MA. The toxicity must be documented in the submitted Flow Sheet.
- g. Development of intercurrent non-cancer related illnesses that prevent either continuation of tamoxifen or MA or regular follow-up.
- h. The patient may withdraw from the study at any time for any reason.

- 7.8 All reasons for discontinuation of tamoxifen or MA must be documented in the Flow Sheets.
- 7.9 All patients will be followed until death.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 Tamoxifen Related Toxicity

- a. Fluid retention should be managed with diuretics and a low-salt diet.
- b. Skin Rash: Therapy should be continued at the discretion of the investigator unless the dermatologic problems cannot be controlled with topical steroids and antihistamines.
- c. Menopausal Symptoms: No therapy modification is indicated for hot flashes. Toxicity will be recorded. Non-hormonal anti-flushing agents may be employed.
- d. Vaginal discharge: Patients should be told to report any vaginal discharge, so that infection may be ruled out. In the absence of pathogens, no treatment is indicated and the problem is usually self-limiting.

8.2 Medroxyprogesterone Acetate Related Toxicity: Contact the Study Coordinator (see Section 8.4, below) for non self-limited vaginal bleeding (i.e., persists beyond 10 days) or any Grade 3 or 4 toxicity.

8.3 Management of biopsy complications: The patient will have signed an institution-specific, standard IRB approved pre-surgical biopsy consent form separate from the consent form for this study. Self-limited vaginal spotting or bleeding as well as cramping or pain are common events. Routine gynecologic management of rare, unexpected post-biopsy events such as severe hemorrhage or perforation will be used. If symptoms of bleeding or cramping persist beyond one week, or any other Grade 3 or 4 event occurs, contact the Study Coordinator (see Section 8.4, below).

8.4 For treatment or dose modification related questions, please contact Dr. R.K. Potkul at 708/327-3314 or Dr. Kathy Albain at 708/327-3102. Specific radiologic questions should be addressed to Dr. Caryl Saloman at 708/216-6720.

8.5 Any adverse reactions, as well as any deaths on study which might be attributed to drug, must be reported to the Cooperative Group, the NCI, the IRB, and the Study Coordinator (see Section 16.0).

9.0 STUDY CALENDAR

¥ Σ

REQUIRED STUDIES	PRE	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
PHYSICAL ¥																			
History and Physical	X													X					
Pelvic Examination	X																		
Weight & Performance Status	X													X					
Toxicity Notation														X					
Endometrial Biopsy Σ ¶	X																		
LABORATORY																			
ER/PgR Assay	X																		
Pathology submission ¶	X																		
X-RAYS AND SCANS																			
Opp. Breast Mammogram Ω	X																		
Chest X-ray ©	X																		
Bone Scan	X ^f																		
Liver scan/CT of liver/brain	X [#]																		
Endovaginal sonogram Σ	X																		
Sonogram film submission ¶																			
TREATMENT (see Section 7.0)																			
Arm I																			
Observation																			
Tamoxifen †		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Radiotherapy √																			
Arm II																			
Medroxyprogesterone acetate £														X	X				
Tamoxifen †		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Radiotherapy √																			

NOTE: Forms are found in Section 18.0. Forms submission guidelines may be found in Section 14.0.

¥ Repeat physician visit every three months for three years. After three years, physician visits may decrease to every six months indefinitely; however, patients on Arm II must receive MA prescriptions every 12 weeks until the end of their full five years of tamoxifen. A pelvic examination is required annually.

Σ Patients will have an endovaginal sonogram and endometrial biopsy at the end of the first, second, third, fourth and fifth years of tamoxifen. If the patient has hyperplasia with or without atypia at any of these annual exams, she will continue tamoxifen with medroxyprogesterone acetate 20 mg/day X 6 weeks (regardless of study arm) and then will be re-biopsied. Further treatment decisions will be based on the treatment plan outlined in Section 7.0.

¶ Must be submitted within 30 days after any EVS and EMB (including prestudy - see Section 12.0). The Endometrial Pathology (EMB) Submission Form must be submitted even if no tissue is obtained.

Ω Repeat annually. If the patient had breast-conserving surgery, the affected breast should be followed every six months for two years, then annually.

© Repeat annually for 5 years, then as indicated.

^f Optional. If obtained, hot spots must be confirmed as benign by x-ray or biopsy. Repeat as clinically indicated.

[#] Only if symptoms or signs of disease are present. Repeat as clinically indicated.

[†] Tamoxifen is given for a full five years from its start date.

[£] MA is given every 12 weeks FROM THE TIME OF START OF TAMOXIFEN for five years.

[√] Patients whose most extensive surgery was a breast sparing procedure must have received RT or must be planning to receive RT at the start of tamoxifen treatment.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

- 10.1 The primary clinical endpoint for this study is endometrial pathologic diagnosis (normal or abnormal) two years after randomization.
- a. "Normal" for postmenopausal patients is no tissue (from attempted biopsy) or other benign finding such as polyps.
 - b. "Abnormal" for postmenopausal patients is proliferative change, hyperplasia, hyperplasia with atypia, carcinoma, (i.e. proliferative change or a "major pathologic abnormality").
- 10.2 Secondary endpoints include:
- a. Occurrence of endometrial pathologies that result in discontinuation of tamoxifen before conclusion of the 5 year treatment period. For example, these pathologies may include persistent hyperplasia with or without atypia despite continuous medroxyprogesterone acetate, and carcinoma.
 - b. Occurrence of intermittent bleeding, defined as:
 1. incidence of withdrawal bleeding after cyclic medroxyprogesterone acetate is completed

OR

 2. bleeding at all other times (except bleeding that starts within 72 hours after biopsy)
 - c. EVS endpoints:
 1. EVS major endpoint is endometrial stripe thickness in mm
 2. Minor endpoints are whether the stripe was well defined and if cystic spaces were present or not.
 - d. patient discontinuation of treatment due to toxicity
 - e. Molecular endpoints:
 1. description of oncogene expression at Year 2 compared to baseline and over-time when feasible. Also compare between two arms for effect of cyclical MA.
 2. receptor status at Year 2 compared to baseline and over-time when feasible. Also, compare between two arms for effect of cyclical MA.
 3. 17 B hydroxydehydrogenase enzyme levels in hysterectomy specimens

11.0 STATISTICAL CONSIDERATIONS

The primary clinical goal of this prospective study is to compare rates of endometrial pathologic diagnosis in two groups of patients: those randomly assigned to observation only vs medroxyprogesterone acetate. INDEPENDENT ANALYSES WILL BE CONDUCTED FOR TWO SUBSETS of patients, i.e. those with and without chemotherapy prior to tamoxifen. Early analyses will focus on results at the end of two years of tamoxifen treatment but the definitive analyses will incorporate the longitudinal results over the five years of tamoxifen treatment.

11.1 Sample size and power

This study is designed to accrue 208 patients in each of two subsets: SUBSET I, patients WITHOUT prior chemotherapy; SUBSET II, patient WITH prior chemotherapy. In each subset half the patients will be randomly assigned to MA and half to observation.

	Target Sample Sizes		
	MA	Treatment Arm Patient Subset Observation	
I: no prior chemo	104	104	208
II: prior chemo	104	104	208
	208	208	416

We assume a 15% drop out rate by the end of year 2 (due to lost to follow up, refusal of biopsy etc) which results in 88 attempted biopsies per arm within each subset. This sample size assures detection of a 75% reduction in endometrial pathologic diagnosis rate at two years (from the expected 30% in the observation arm to 7.5% in the MA arm) with probability 96% independently in each of the two subsets, using a 5% two sided test. In this sample size calculation, "endometrial pathologic diagnosis" is defined as in Section 10.1b.

From the Lancet article by Kedar et al (ref Lancet 343 May 28, 1994) we estimate that 40% of the attempted biopsies will yield material and that 60% will be unsuccessful (which is normal for a post-menopausal woman). The expected 30% endometrial pathologic diagnosis rate for the observation arm assumes that three quarters of the successful biopsies will be classified as pathologically abnormal. This is approximately the rate given in the Lancet report, where 79% (19/24) of the successful biopsies were pathologically abnormal: (8 proliferation or hyperplasia, 10 atypical hyperplasia, 1 mitotic cells) which corresponds to 31% (19/61) of all biopsies attempted. Twenty-one percent (5/24) of the successful biopsies reported in the Lancet article were polyps, i.e., were normal by the definition in Section 10.1a.

Power is still adequate if the pathologic diagnosis rate falls below the expected rate of 30%. With 104 patients accrued per arm, power is 90% (80%) to detect a 75% reduction from 25%(20%) endometrial pathologic diagnosis rate to 6.3% (5%). As above the drop out rate is assumed to be 15% at end of year two.

11.2 Major EVS endpoint of thickness of stripe and minor endpoints of cystic spaces (yes or no) and well-defined stripe (yes or no) will be correlated with endometrial pathologic diagnosis.

11.3 Precision of Oncogene Expression Frequencies

Tissue samples for the analysis of molecular correlates will be collected during the course of this clinical trial. At two years, we anticipate approximately 35 biopsy samples per treatment arm in each subset of patients, after accounting for dropouts and unsuccessful biopsy attempts, $(.85 \times .40 \times 104 = 35)$. The table below shows the 95% confidence interval for three selected values for the percent of cases expressing a particular gene.

no. of patients	no. of patients expressing gene	percent of patients with gene expressed	Exact 95% C.I.
35	18	51	34 - 69
35	9	26	12 - 43
35	4	11	3 - 27

Similar tables are given below for denominators one half and twice as large. The table with 18 patients would apply if half the patients on a particular arm were pathologically abnormal and one were interested in estimating the percent of such patients expressing a specified oncogene. The table for 70 patients is relevant to estimating percent of patients with oncogene expression if one ignores treatment, subset (prior chemotherapy yes/no) or pathologic abnormality (assuming a 50% pathologic abnormality rate.)

no. of patients	no. of patients expressing gene	percent of patients with gene expressed	Exact 95% C.I.
18	9	50	26 - 74
18	5	28	10 - 53
18	2	11	1 - 35
no. of patients	no. of patients expressing gene	percent of patients with gene expressed	Exact 95% C.I.
70	35	50	38 - 62
70	18	26	16 - 38
70	7	10	4 - 20

The 95% confidence intervals when all 140 biopsy specimens are used to estimate the frequency of gene expression are half as long as those for the table with 35 patients. That is, the estimates are twice as precise. However one would not automatically combine all these patient groups since there is interest in investigating the effect of MA treatment, prior chemotherapy, and pathologic abnormality on gene expression.

The above figures also apply to percent of biopsy samples with uterine estrogen and progesterone receptor positivity.

With respect to studying changes in gene expression over time, it is clear that only very strong trends will be detectable since the available sample sizes will inevitably decrease from those described above at two years.

- 11.4 Duration of study: An accrual period of 1.5 years is planned. Analysis of two year biopsy samples should be complete 2.5 years after accrual ends, i.e., 4.0 years after the study begins. Five year longitudinal results will take at least three years longer.

12.0 DISCIPLINE REVIEW

12.1 Pathology Review

- a. All endometrial tissue obtained at biopsy on this study will undergo review. Materials must be submitted within 30 days of every endometrial biopsy (including prestudy biopsy) to:

Southwest Oncology Group Pathology Office
Fred Hutchinson Cancer Research Center MP-557
1124 Columbia Street
Seattle, WA 98104-2092
Phone: 206/667-4623

- b. Patients must have sufficient information and pathological material to verify findings on pathology report.
- c. The following materials are to be submitted within 30 days of any endometrial biopsy:
1. Paraffin block and representative H&E stained slides. If the institutional pathologist is unable to release the entire paraffin block, 10 unstained paraffin sections already cut onto slides may be submitted.
 2. Corresponding Pathology and Operative Reports. The absence of the Operative Report should not delay or prevent the forwarding of the pathology materials to the Seattle Office.
 3. Endometrial Pathology (EMB) Submission Form.
- d. Pathology gross reports and microscopic material should be reviewed for adequacy (by the Southwest Oncology Group institutional pathologist) prior to forwarding to the Seattle office.

12.2 Sonogram Review

- a. All sonogram films and reports on this study will undergo review. Materials will be submitted within 30 days of every endovaginal sonogram (including prestudy) to:

Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street, MP-557
Seattle, WA 98104-2092
Phone: 206/667-4623

- b. The following materials are to be submitted within 30 days of any endovaginal sonogram:
1. Sonogram films
 2. Corresponding sonogram report
 3. EVS Submission Form
- c. Reports and films should be reviewed for adequacy prior to forwarding to the Seattle office.

13.0 REGISTRATION GUIDELINES

- 13.1 All patients must be registered with the Southwest Oncology Group Statistical Center by telephoning 206/667-4623, 6:30 a.m. to 5:00 p.m. Pacific time, Monday through Friday, excluding holidays. Patients must be registered prior to initiation of protocol treatment no more than one working day prior to the planned start of treatment. See Section 5.9 for exception.
- 13.2 At the time of registration, the caller must be prepared to answer every question on the eligibility checklist and provide descriptive factors.
- 13.3 The caller must also be prepared to provide the date of institutional review board approval for this study. Patients will not be registered if the IRB approval date is not provided or is > 1 year prior to the date of registration. The caller must also supply the date the informed consent was signed.
- 13.4 Exceptions to the current registration policies will not be permitted. Therefore, late registrations (after initiation of treatment), exceptions to eligibility requirements, participation by an institution/member not identified as eligible **AND/OR** cancellations will not be allowed.

14.0 DATA SUBMISSION SCHEDULE

- 14.1 Data must be submitted according to protocol requirements for ALL patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible.
- 14.2 Master forms are included in Section 18.0 and, with the exception of the sample consent form, must be photocopied for data submission.
- Members and CCOPs must submit two copies of all data forms directly to the Statistical Center in Seattle. CGOPs will submit (number of copies to be determined by the Group Member) copies to their Group Member institution for forwarding to the Statistical Center.
- 14.3 WITHIN TWO WEEKS OF REGISTRATION ON STUDY:
- a. Eligibility Checklist.
 - b. Prestudy Form.
 - c. Study Specific Flow Sheet.
 - d. Pathology report from breast cancer diagnosis.
- 14.4 WITHIN THIRTY DAYS OF ANY EVS AND BIOPSY:
- Submit materials and forms as outlined in Section 12.0.
- 14.5 EVERY THREE MONTHS WHILE ON STUDY:
- Submit the Study Specific Flow Sheet.
- 14.6 WITHIN 14 DAYS OF DIAGNOSIS OF ENDOMETRIAL CANCER OR OTHER SECOND PRIMARY:
- Submit the Notice of Second Primary Malignancy Form.

14.7 WITHIN 14 DAYS OF HYSTERECTOMY (if performed):

Submit materials outlined in Section 15.1.

14.8 WITHIN 14 DAYS OF SHIPPING TISSUE FROM HYSTERECTOMY TO DR. POTKUL PER SECTION 15.0:

Submit a copy of the Specimen Submission Form to the Statistical Center.

14.9 WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit copies of a Study Specific Flow Sheet documenting date, site and method for determining progression/relapse of breast cancer.

14.10 WITHIN 14 DAYS OF COMPLETION OF TAMOXIFEN TREATMENT:

Document date off tamoxifen on the Flow Sheet.

14.11 WITHIN 14 DAYS OF OFF STUDY:

Submit copies of the Off Treatment Notice and final On Treatment Flow Sheets.

14.12 WITHIN FOUR WEEKS AFTER LEARNING OF PATIENTS DEATH:

Submit a Notice of Death Form documenting death information and a final Flow Sheet.

15.0 SPECIAL INSTRUCTIONS

15.1 If a hysterectomy is performed it is requested that a portion of the endometrium be snap frozen in liquid nitrogen and shipped with a copy of the Specimen Submission Form on dry ice to Loyola University Cancer at the address below. The frozen tissue will be cataloged and stored in a -70 degree freezer:

Ronald K. Potkul, MD
Loyola University Medical Center
Department of Obstetrics & Gynecology
2160 S. First Avenue
Maywood, IL 60153
Phone: 708/327-3314

15.2 The Federal guidelines for shipment are as follows:

- a. The specimen must be wrapped in an absorbable material;
- b. The specimen must then be placed in an AIRTIGHT container (like a resealable bag);
- c. Pack the resealable bag and specimen in a styrofoam shipping container;
- d. Pack the styrofoam shipping container in a cardboard box.
- e. The cardboard box must be marked as "BIOHAZARD".

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

For each drug supplied for a study, an accountability ledger containing current and accurate inventory records covering receipt, dispensing, and the return of study drug supplies must be maintained. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the accountability ledger; the identification code of the subject to whom drug is dispensed, the date(s) and quantity of drug dispensed to the subject, and the date(s) and quantity of drug returned by the subject; subjects should return empty containers to the investigator, with the return noted on the ledger. These Accountability Forms must be readily available for inspection and are open to FDA inspection at any time.

Adverse Experiences

Any adverse experience, if deemed drug related, must be reported to the Operations Office Adverse Drug Reaction (ADR) representative (210/677-8808), who will obtain information on the ADR. Depending on the nature of the reaction and whether it was caused by an investigational or commercial agent, the ADR representative will advise whether the report to the NCI should be phoned in, written in, or both. See guidelines below. On Phase II and III studies, all deaths considered drug-related must be reported immediately to the ADR representative. On double-blinded studies, if the investigator must know what treatment the subject received to make therapeutic decisions, the code for that particular subject can be broken by telephoning the Statistical Center.

All adverse experiences must also be reported to the Institutional Review Board within 10 days and documentation of this report sent to the Operations Office.

All adverse experiences must also be recorded in the appropriate section of the case report form. The report should include, whenever possible, the investigator's written medical judgment as to relationship of the adverse experience to study medication(s) (i.e., "probable", "possible" or "unrelated").

GUIDELINES FOR REPORTING OF ADVERSE DRUG REACTIONS (ADRS)
OCCURRING WITH COMMERCIAL AGENTS

The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) **should be reported by telephone to the Operations Office (210/677-8808), within 24 hours of occurrence, your Institutional Review Board (IRB) and by written notification to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:**

- (a) Any ADR which is **BOTH** serious (life threatening [Grade 4] or fatal [Grade 5])and unexpected.^{1,2,3} Occurrences of secondary AML or MDS must also be reported* (see below).
- (b) Any increased incidence of a known ADR which has been reported in the package insert or the literature.
- (c) Any death on study if **CLEARLY** related to the commercial agent(s)

The ADR report should be documented on Form FDA-3500 and mailed to the address below:

(*For reporting cases of secondary AML or MDS, please use the "NCI/CTEP Secondary AML/MDS Report Form" in lieu of the Form FDA-3500.)

Investigational Drug Branch
P. O. Box 30012
Bethesda, MD 20824

Send a copy of the Form FDA-3500 or the "NCI/CTEP Secondary AML/MDS Report Form" (for reporting cases of secondary AML or MDS only), all data records and a copy of documentation of notification of your IRB to the Operations Office within 10 working days.

ATTN: ADR Program
Southwest Oncology Group
14980 Omicron Drive
San Antonio, TX 78245-3217

Copies of the "NCI/CTEP Secondary AML/MDS Report Form" will be forwarded from the Operations Office to the Statistical Center within one working day.

1. See Section 19.0, Southwest Oncology Group Toxicity Criteria.
2. A list of all known toxicities can be found in either the Background section, Drug Information or Informed Consent Form of the protocol.
3. Reactions judged definitely not to be treatment related should not be reported. However, a report shall be submitted if there is only a reasonable suspicion of drug effect.

17.0 BIBLIOGRAPHY

1. Bardon S, Vignon F, Derocq D, Rochefort H. The antiproliferative effects of tamoxifen in breast cancer cell: Mediation by the estrogen receptor. *Molec Cell Endocr* 35:89-96, 1984.
2. Furr BJ, Jordan VC. The pharmacology and clinical uses of tamoxifen. *Pharmac Ther* 25:127-206, 1984.
3. Killackey MA, Hakes TB, Pierce VK. Endometrial adenocarcinoma in breast cancer patients receiving antiestrogens. *Cancer Treat Rep* 69:237-238, 1985.
4. Hardell L. Tamoxifen as risk factor for carcinoma of corpus uteri (letter). *Lancet* 3:563, 1988.
5. Neven P, Muylder X, Van Belle Y, et al. Tamoxifen and the uterus and endometrium (letter). *Lancet* 1:375, 1989.
6. Fornander TB, Cedermark A, Mattsson L, Skoog T, et al. Adjunction tamoxifen in early breast cancer: Occurrence of new primary cancers. *Lancet* 21:117-120, 1989.
7. Atlante G, Pozzi M, Vincenzoni C, et al. Four case reports presenting new acquisitions on the association of breast and endometrial cancer. *Gynecol Oncol* 37:378-380, 1990.
8. Matthew A, Chabon AB, Kabakow B, et al. Endometrial carcinoma in five patients with breast cancer on tamoxifen therapy. *NY State J Med* 90:207-208, 1990.
9. Malfetano JH. Tamoxifen-associated endometrial carcinoma in postmenopausal breast cancer patients. *Gynecol Oncol* 39:82-84, 1990.
10. Magriples U, Naftolin F, Schwartz PE, et al. High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. *J Clin Oncol* 11:485-490, 1993.
11. Lahti E, Blanco G, Kauppila A, et al. Endometrial changes in postmenopausal breast cancer patients receiving tamoxifen. *Obstet Gynecol* 81:660-664, 1993.
12. Seoud M A-F, Johnson J, Weed JC. Gynecologic tumors in tamoxifen-treated women with breast cancer. *Obstet Gynecol* 82:165-169, 1993.
13. VanLeeuwen FE, Benraadt J, Coebergh JWW, et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet* 343:448-452, 1994.
14. Barakat RR, Wong G, Curtin JP, et al. Tamoxifen use in breast cancer patients who subsequently develop corpus cancer is not associated with a higher incidence of adverse histologic features. *Gynecol Oncol* 55:164-168, 1994.
15. Fisher B, Costantino JP, Redmond CK, et al. Endometrial cancer in tamoxifen-treated breast cancer patients: Findings from NSABP B-14. *JNCI* 86:527-537, 1994.
16. Fornander T, Hellstrom A-C, Moberger B. Descriptive clinicopathologic study of 17 patients with endometrial cancer during or after adjuvant tamoxifen in early breast cancer. *JNCI* 85:1850-1855, 1993.
17. Kedar RP, Bourne TH, Powles TJ, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomized breast cancer prevention trial. *Lancet* 343:1318-1321, 1994.
18. Cohen I, Rosen DJD, Shapier J, et al. Endometrial changes with tamoxifen: comparison between tamoxifen-treated and non-treated asymptomatic postmenopausal breast care patients. *Gyn Onc* 52, 185-190, 1994.

19. Gambrel RD. Prevention of endometrial cancer with progestins. *Maturitas* 8:159-168, 1986.
20. Ettinger B, Selby J, Citron JT, Vangessel A, et al. Cyclic hormone replacement therapy using quarterly progestin. *Obstet Gynecol* 86:693-700, 1994.
21. Barakat RR. The effect of tamoxifen on the endometrium. *Oncology*, 9:129-139,1995.
22. Dichson RB, Lippman ME. Estrogenic regulation of growth and polypeptide growth factor secretion in human breast carcinoma. *Endocr. Rev* 8:20, 1989.
23. Odom LD, Barrett JM, Pantzis CG, Stoddard LD, McDonough PG. Immunocytochemical study of fas and myc proto-oncogene polypeptide expression in the human menstrual cycle. *Am J Obstet Gynecol*. 161:1663, 1989.
24. Kumar V, Chambon P. The estrogen receptor binds tightly to its estrogen responsive elements as a ligand-induced homodimer. *Cell* 55:145-156, 1988.
25. Knapp RC, Berkowitz RS. Gynecologic Oncology. New York: McMillan, 1986.
26. Tseng L, Mazella J. Cyclic changes of estradiol metabolic enzymes in human endometrium during the menstrual cycle. In Kimball FA (ed). The Endometrium. New York: SP Medical and Scientific Books, 211-226, 1980.
27. Bonney RC, Reed MJ, Beranek PA, Ghilchik MW, James BH. Metabolism of estradiol in vitro by normal breast and tumor tissue in postmenopausal women. *J Steroid Biochem* 24:361-364, 1986.
28. Maentausta O, Peltoketo H, Isomaa V, Jouppila P, Vihko R. Immunological measurement of human 17 beta-hydroxy steroid dehydrogenase. *J Steroid Biochem* 36:673-680, 1990.
29. Gompel A, Malet C, Spritzer P, Laladrerie JP, et al. Progestin effect on cell proliferation and 17 beta-hydroxy steroid dehydrogenase activity in normal human breast cells in culture. *Clin Endocrin and Metab* 63:1174-1180, 1986.
30. Speirs V, Adams EF, White MC. The antiestrogen tamoxifen blocks the stimulatory effects of interleukin 6 on 17 beta hydroxy-steroid dehydrogenase activity in MCS-7 cells. *J Steroid Biochem Molec Biol* 46:605-611, 1993.
31. Whitehead MI, Townsend PT, Pryse-Davies J, Ryder TA, King RJ. Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium. *NEJM* 305:1599-1605, 1981.
32. Clark JH, Peck EJ, Hardin JW, Eriksson H. Biology and pharmacology of estrogen receptor binding: Relationship to uterine growth. In O'Malley and Birnbaumer (eds). Receptors and Hormone Action. New York: Academic Press, 1-31, 1987.
33. Kirkland, Murthy L, Stancel G. Tamoxifen stimulates expression of the cfos proto-oncogene in eroded uterus. *Molec Pharmacology* 43:709-714, 1993.
34. Higgins GD, Uzelin DM, Phillips GE, Burrell CJ. Presence and distribution of human papillomavirus sense and antisense RNA transcripts in genital cancer. *J General Virology* 72:885-895, 1991.
35. Kurjak A, Shalan H, Sosic A, Benic S, Zudenigo D, Kupasic S, Predanic M. Endometrial carcinoma in postmenopausal women: Evaluation by transvaginal color Doppler ultrasonography. *Am J Obstet Gynecol* 169(6):1597-1603, 1993.
36. Kupesic-Urek S, Shalan M, Kurjak A. Early detection of endometrial cancer by transvaginal color Doppler. *Eur J of Obstet and Gyn and Repr Bio* 49:46-49, 1993.

37. Campbell S, Bourne T, Crayford T, Pittrof R. The early detection and assessment of endometrial cancer by transvaginal colour Doppler ultrasonography. *Eur J Obstet Gynecol and Reprod Biol* 49:44-45, 1993.
38. Hulka CA, Hall DA, McCarthy K, Simeone JF. Endometrial polyps, hyperplasia and carcinoma in postmenopausal women: Differentiation with endovaginal sonography. *Radiol* 191(3):755-758, 1994.
39. Nasri MN, Shepherd JH, Setchell EM, Lowe DG, Chard T. The role of vaginal scan in measurement of endometrial thickness in postmenopausal women. *Br J Obstet Gynecol* 98:470-475, 1991.
40. Carter RJ, Lau M, Saltzman AK, Hartenbach EM, Chen D, Johnson PF, Fowler JM, Carlson JW, Carson LF, Twiggs LB. Gray scale and color flow Doppler characterization of uterine tumors. *J Ultrasound Med* 13(11):835-840, 1994.
41. Chan FY, Chau MT, Pun TC, Lam C, Ngan HYS, Leong L, Wong RLC. Limitations of transvaginal sonography and color Doppler imaging in the differentiation of endometrial carcinoma from benign lesions. *J Ultrasound Med* 13:623-628, 1994.
42. Lin MO, Gosink BB, Wolf SI, Feldesman MR, Stuenkel CA, Braly PS, Pretorius DH. Endometrial thickness after menopause: effect of hormone replacement. *Radiol* 180:427-432, 1991.
43. Tapper R, Cohen I, Altaras M, Shapira J, Cordoba M, Dror Y, Beyth Y. Doppler flow evaluation of pathologic endometrial conditions in postmenopausal breast cancer patients treated with tamoxifen. *J Ultrasound Med* 13:635-640, 1994.
44. Kurjac A, Kupesic-Urak S, Schulman M, Zalud I. Transvaginal color flow Doppler in the assessment of ovarian and uterine blood flow in infertile women. *Fertil Steril* 56:870-873, 1991.
45. Pellerito JS, Taylor KJW, Quedene-Case C, Hammers LW, Scoutt LM, Ramos IM, Meyer WR. Ectopic pregnancy: Evaluation with endovaginal color flow imaging. *Radiology* 183:407-411, 1992.
46. Emerson DS, Cartier MS, Altieri LA, Felker RE, Smith WC, Stovall TG, Gray LA. Diagnostic efficacy of endovaginal color dopper flow imaging in an ectopic pregnancy screening program. *Radiology* 183:413-420, 1992.
47. Fleischer AC, Rodgers WH, Bhaskara KR, Kepple DM, Worrell JA, Williams L, Jones III HW. Assessment of ovarian tumor vascularity with transvaginal color Doppler sonography. *J Ultrasound in Medicine* 10:563-568, 1991.
48. Bourne TH, Campbell S, Whitehead MI, Royston P, Steer CV, Collins WP. Detection of endometrial cancer in postmenopausal women by transvaginal ultrasonography and colour flow imaging. *Br Med J* 301:369, 1990.
49. Cohen I, Rosen DJD, Topper R, Crodobe M, Shapira Y, Altaras MM, Dror Y, Yigael D, Beyth Y. Ultrasonographic evaluation of the endometrium and correlation with endometrial sampling in postmenopausal patients treated with tamoxifen. *J Ultrasound med* 5:275-280, 1993.
50. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 31:103-115, 1975.

18.0 MASTER FORMS SET

- 18.1 Sample Consent Form
- 18.2 Intergroup Adjuvant Breast Cancer Prestudy Form
- 18.3 EVS Submission Form
- 18.4 Study Specific Flow Sheet
- 18.5 Endometrial Pathology (EMB) Submission Form
- 18.6 Specimen Submission Form
- 18.7 Notice of Second Primary Malignancy
- 18.8 Off Treatment Notice
- 18.9 Notice of Death

CONSENT FORM AND INFORMATION ABOUT

A Randomized Comparison of Medroxyprogesterone Acetate (MA) and Observation for Prevention of Endometrial Pathology in Postmenopausal Breast Cancer Patients Treated With Tamoxifen

Phase III

TO BE CONDUCTED AT

- I. You are invited to take part in this research study because you have had a breast cancer that has been removed by surgery and you are about to begin receiving tamoxifen. We want to find out the effects of tamoxifen treatment on your uterus and whether the addition of medroxyprogesterone acetate makes any difference in these effects.

As you know, tamoxifen has been reported, in rare cases, to cause uterine cancer. We want to learn more about all uterine changes caused by tamoxifen.

As part of the ongoing scientific and biotechnological activities of the Southwest Oncology Group and its agents, tissue samples from your uterus will be preserved and used for research and development purposes. As a result of these biotechnological activities, an economic benefit may be derived directly or indirectly by the Southwest Oncology Group, individual researchers, and others engaged in these activities. By signing this consent form, you authorize the preservation and use of tissue specimens taken from you.

We cannot and do not guarantee you will benefit if you take part in this study. The treatment you receive may even be harmful. If you take part in this study, the treatment may help increase the time you remain free of disease, and/or abnormal endometrial tissue may be found earlier than it may have been found otherwise.

- II. You currently have begun or will begin tamoxifen treatment for your breast cancer. This study is trying to answer the question whether taking medroxyprogesterone acetate (MA) (a female hormone) will decrease the rate of uterine abnormalities. You will either receive the medroxyprogesterone acetate (MA) or not. This will be decided by a system called "randomization" which is similar to flipping a coin. Either way, you will be followed closely by ultrasound and biopsy to determine if you are developing any of these abnormalities which will be treated appropriately. You will be taking tamoxifen daily. If you are randomized to receive the medroxyprogesterone acetate (MA), you will receive by mouth for fourteen days in a row beginning about twelve weeks after you start receiving the tamoxifen. The fourteen days of MA will be repeated every three months. If you are randomized to tamoxifen alone, you will not receive MA. Regardless of your treatment you will be examined at the end of each year on study by endovaginal sonogram and endometrial biopsy. An endovaginal sonogram involves inserting a probe into your vagina and taking "pictures" of the walls of your uterus. An endometrial biopsy involves inserting a small instrument into your vagina to remove a small piece of tissue from your uterus. If this tissue shows changes in the cells, you will receive MA daily by mouth for six weeks (regardless of which treatment you were previously receiving), then you will have another biopsy. If the second biopsy still shows changes in the cells, you will receive another six weeks of daily MA, then you will have another biopsy. If this tissue still shows changes in the cells, you will be treated as recommended by your doctor. These options, might include: discontinuing tamoxifen, surgery to remove your uterus (hysterectomy), continuing treatment with tamoxifen and MA, beginning treatment with another drug or drugs, and continuing tamoxifen with more frequent pelvic examinations.

As long as your biopsy tissue shows normal cells, you will continue treatment and annual examinations on this study as long as you are receiving tamoxifen (up to five years).

There are circumstances under which your doctor might be required to discontinue your treatment with these drug whether you agree or not. These circumstances include: your tumor returns despite the treatment; you develop endometrial cancer; you have a hysterectomy; the side effects of the treatment are too dangerous for you; new information about the drug becomes available and this information suggests the drug will be ineffective or unsafe for you.

Administration of the drugs will be charged in the usual way. The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be (charged in the usual way/provided at a reduced rate).

Tamoxifen and medroxyprogesterone acetate are commercially available.

- iii. Side effects some people have had after receiving tamoxifen and medroxyprogesterone acetate are listed as follows according to how often these side effects have been reported:

Tamoxifen

Adverse effects include hot flashes, nausea (vomiting is rare), vaginal bleeding, vaginal discharge and dryness, menstrual irregularities, and skin rash. Other side effects, rarely seen, are an increase in calcium in the body; swelling in the arms, legs, hands and feet; loss of appetite, distaste for food, pruritus vulvae (genital itching), depression, dizziness, headache, leg cramps, lightheadedness, hair thinning or partial hair loss, confusion, and fatigue. The drug may transiently decrease the blood cells produced in the bone marrow. A mild decrease in the white cells (necessary for fighting infection) and platelets (important for blood clotting) can occur shortly after the drug is started, but they will return to normal, even if the drug is continued. An increased risk of cataracts was noted in rats. An increased incidence of cataracts has not been reported in humans, although vision or eye effects, such as cataracts, corneal scarring or retinal changes, have been reported in a few patients. Tamoxifen should not be taken during pregnancy due to potential hazard to the fetus. Tamoxifen may cause changes in the lining of the uterus (endometrium) including polyps, hyperplasia and endometriosis (endometrial cells outside the uterus). An early sign of these changes may be abnormal vaginal bleeding or pelvic pain. Patients should report such symptoms to their physician immediately and seek evaluation in a timely fashion. The level of increased risk of uterine cancer associated with tamoxifen is still uncertain. After an average of 8 years of follow-up, the annual risk observed in a large-scale trial of breast cancer patients taking 20 mg of tamoxifen daily is about 2 per 1,000 women. This means that on the average two cases of endometrial cancer were diagnosed among every 1,000 women receiving tamoxifen during each year of study participation and follow-up. This level of risk is approximately three times greater than that of a similar group of women in the general population. Uterine cancer is a potentially life-threatening illness. Some breast cancer patients who developed uterine cancer while taking tamoxifen in the above study have subsequently died from uterine cancer. However, most of the uterine cancers that have occurred have been diagnosed at an early stage when treatment is highly effective. The treatment for early-stage uterine cancer usually involves a hysterectomy (surgical removal of the uterus) as well as removal of the fallopian tubes and ovaries, and may include radiation therapy. In view of this risk, it is currently recommended that all patients receiving tamoxifen have a gynecologic examination before starting treatment and at least yearly thereafter. Of course, if you have had a total hysterectomy, there is no risk of getting uterine cancer. Data from one large United States study have not shown an increase in other (non-uterine) cancers in women taking tamoxifen. However, other unpublished data suggests a possible increase in second cancers of the gastrointestinal tract among women receiving the drug. There have been a few reports of liver cancer that have occurred in women taking tamoxifen. Although tamoxifen can cause liver cancer in rats, it is not known to be a cause of liver cancer in humans. Whether an increased risk for other (non-uterine) cancers is associated with tamoxifen is still uncertain and continues to be evaluated. Ovarian cysts have been noted in premenopausal women. Abnormal liver function tests including rare cases of

more severe liver abnormalities such as fatty liver, cholestasis (back-up of bile), hepatitis, and hepatic necrosis (destruction of liver cells) have been seen. A few of these serious cases resulted in death but whether tamoxifen was the cause of these problems still remains uncertain. Women on tamoxifen have an increased risk for developing phlebitis and blood clots. In one study, 4 of 1,414 women receiving placebo (0.3%) versus 21 of 1,403 women receiving tamoxifen (1.5%) developed deep vein thrombosis or embolism. Rarely, death has occurred from such events. Patients with a pre-existing history of such problems should discuss the indication for tamoxifen treatment carefully with their physician.

For women of childbearing potential: Women should not become pregnant while taking tamoxifen and should use barrier or non-hormonal contraceptive measures if sexually active and otherwise at risk of pregnancy. Although no clinical evidence is available to prove that tamoxifen may cause fetal harm when administered to a pregnant woman, effects on reproductive function are expected from the antiestrogenic properties of tamoxifen, and studies conducted on mice have demonstrated some fetal deformities, including miscarriage, birth defects, and long-term effects on sexual development (which could be similar to the long-term effects caused by DES, a hormone medication that was given to pregnant women in the past). Women whose mothers took DES (diethylstilbestrol) during pregnancy have an increased risk of developing cancer or other changes of the vagina or cervix, and may have trouble bearing children. The relevance of these findings from animal studies to women who may accidentally take tamoxifen during pregnancy is uncertain. To date, exposure of unborn infants to tamoxifen has not been shown to cause cancer later in the lives of these children. Nonetheless, it is essential that patients use effective non-hormonal methods to avoid pregnancy while taking tamoxifen, and for at least two months after completing or discontinuing tamoxifen therapy.

Tamoxifen has been shown to decrease the risk of breast cancer recurrence after appropriate surgery. For this reason, it is approved by the Food and Drug Administration for treatment of postmenopausal women with axillary node-positive disease and for women with axillary node-negative breast cancer. It is also approved for treatment of metastatic breast cancer in women and men. Studies have also shown that tamoxifen can reduce the occurrence of secondary breast cancers in women who are taking the drug to prevent recurrence of their original tumor. In addition, it has been shown to lower the level of cholesterol and other fats in the blood, and this may reduce the risk of heart disease. Loss of bone minerals is also slowed by tamoxifen which may result in fewer bone fractures as women age.

Medroxyprogesterone Acetate

Breast tenderness and milk production have been reported. Allergic reactions including itching, swelling, hives and skin rash have also been seen occasionally. Acne, hair loss and hair growth have occurred in a few cases. The formation of blood clots and resulting blockage of a blood vessel are also possible. This could lead to inflammation of vein, possible blockage of a vein or artery in the brain, lungs or heart.

The following side-effects have been observed in women taking this type of drug (progestin): breakthrough bleeding, spotting, change in menstrual flow, lack of a menstrual period, swelling, weight changes, changes in vaginal discharge, depression, difficulty sleeping, nausea, sleepiness, allergic reactions (including severe reactions) fever and jaundice.

Endometrial Biopsy

Complications of endometrial biopsy include pain, cramping similar to menstrual cramps, bleeding (usually spotting for 48 hours) and rarely perforation of the uterus resulting in major bleeding, abdominal pain and fever.

Endovaginal Sonogram

Complications of endovaginal sonogram are minor discomfort similar to a pelvic examination.

- IV. If you decided not to participate in this study, your doctor would regularly check you for these uterine changes probably using ultrasound and/or biopsy, and treat you accordingly. (There is no "standard" treatment.) It is not known if the treatment you receive will offer any increased benefit than that currently available outside of participation in this research.
- V. If you experience illness as a result of treatment on this study, you will be offered emergency medical treatment and continuing medical care including hospitalization if necessary. This treatment will not be free but must be paid in the same way as your regular medical care is paid. We cannot pay you to take part in this study.
- VI. We will keep any information we learn from this study confidential and disclose it only with your permission. By signing this form, however, you allow us to make your records available to the National Cancer Institute, the Food and Drug Administration and the Southwest Oncology Group. If we publish the information we learn from this study in a medical journal, you will not be identified by name.
- VII. Whether or not you take part in this study will not affect your future relations with your doctors (there will be no loss of benefits or change in attitude) or _____ (hospital name). If you decide to take part, you are free to stop whenever you want to.
- VIII. The doctor(s) involved with your care can answer any questions you may have about the drug program. In case of a problem or emergency, you can call the doctors listed below day or night.

Office

Home

Dr.

Dr.

Dr.

You can also call the Institutional Review Board (# _____) if you have any questions, comments or concerns about the study or your rights as a research subject.

- IX. We will give you a copy of this form to keep.
- X. You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer after reading and understanding all the information on this form.

Date

Signature of Subject

Signature of Witness

Signature of Investigator

Time

**Breast Cancer Prestudy
for Studies SXXXX, SYYYY**

SWOG Study No.

Protocol Step

SWOG Patient No. Patient's Name _____ (L.F.M)

Institution / Member _____ S.S. No. - -

Physician _____ Hospital No. _____

Groups other than SWOG: Group Name/Study No./Pt No. _____ / _____ / _____

Amended data: Yes, mark amended items in red.

Instructions: All dates are MONTH, DAY, YEAR. Indicate an unknown part of a date with a horizontal line drawn across the appropriate boxes.

PATIENT CHARACTERISTICS

Date of birth - -

Menopausal status

- 1- Pre (regular menses or <4 months since LMP and premenopausal FSH **not** on estrogen replacement)
- 2- Post (prior bilateral ovariectomy OR >12 mo since LMP with **no** prior hysterectomy)
- 3- Other (pre/post will be defined by age or by FHS at the Statistical Center)

DISEASE DESCRIPTION

Most extensive surgery

- 1- Breast sparing procedure plus axillary dissection
- 2- Mastectomy

Date of mastectomy or date of axillary dissection, if breast sparing procedure - -

Receptor status (>10 is positive if measured in fmols/mg cytosol protein; otherwise use institutional standards)

- | | | | |
|----|--------------------------------------|-----|--------------------------------------|
| ER | 1- <input type="checkbox"/> Positive | PgR | 1- <input type="checkbox"/> Positive |
| | 2- <input type="checkbox"/> Negative | | 2- <input type="checkbox"/> Negative |
| | 3- <input type="checkbox"/> Unknown | | 3- <input type="checkbox"/> Unknown |

Pathologic tumor size (maximum diameter of entire lesion including both invasive and intraductal components; use longest lesion with an invasive component) . cm

Number of positive nodes

Prior non-Tamoxifen hormonal treatment No Yes

TREATMENT

Tamoxifen Start Date - -

Tamoxifen Stop Date - -

Did the patient receive adjuvant chemotherapy? No Yes

If Yes,

- Chemotherapy Regimen
- 1- CAF
 - 2- CMF
 - 3- Other, specify: _____

Chemotherapy Start Date - - Chemotherapy Stop Date - -

Was an endometrial biopsy performed? No Yes

If Yes, Check result:

- 1- No tissue obtained
- 2- Proliferative changes
- 3- Hyperplasia
- 4- Hyperplasia with atypia
- 5- Carcinoma
- 6- Polyp
- 7- Other, specify: _____

By: _____

Date: _____

SWOG 02-20-96 SW340

Southwest Oncology Group

DRAFT
SWOG Study No. _____

Page 1 of 1

EVS SUBMISSION FORM

Protocol Step

SWOG Patient No. Patient's Name _____ L.F.M.

Institution / Member _____ S.S. No. - -

Physician _____ Hospital No. _____

Groups other than SWOG: Name/Study No./Pt No. _____ / _____ / _____

Amended data: Yes, mark amended items in red.

Instructions: All dates are MONTH, DAY, YEAR.

Indicate an unknown part of a date with a horizontal line drawn across the appropriate boxes.

Exam date - -

Exam sequence #

Transducer manufacturer _____

Frequency (MHZ) _____

Maximum AP endometrial stripe thickness (mm): Anterior SWT _____

Posterior SWT _____

DWT _____

Fluid seen in endometrial canal No Yes

Cystic space present No Yes

Endometrial margins well defined No Yes

Please check the one that applies:

- 1- Grey scale only
- 2- Color doppler only
- 3- Grey scale and color doppler

If color doppler:

Velocity setting _____

Pulse repetition frequency _____

Wall filter _____

Doppler sample volume _____

SPTA _____

Review Acceptability

- 1- Yes
 - 2- No
 - 3- Insufficient
- (List what is needed in Notes section)

Notes:

By: _____

Date: _____

SWOG 04-23-96 SW337

FLOW SHEET

S _____

PT. # _____

REG DATE _____

DATE 19 Mo./Day						UNIT # _____	PAGE _____
DAY ON STUDY						PATIENT _____	
TREATMENT						INVESTIGATOR: _____	
Medroxyprogesterone acetate						INSTITUTION _____	
Tamoxifen						STUDY # _____	RX. # _____
Radiotherapy						DISEASE CAT: _____	BREAST
PHYSICAL						PROGRESS NOTES (DATE EACH)	
BSA							
TEMP							
WEIGHT (kg)							
HEIGHT (cm)							
Performance Status							
Endometrial Biopsy							
X-RAYS AND SCANS							
Mammogram							
Liver scan/CT of liver/brain							
Chest x-ray							
Bone scan							
Endovaginal sonogram							
TOXICITY							
Erythema							
Other pain - specify site							
Allergy							
Skin rash/Urticaria							
Pruritus							
Edema							
Dermatologic - other (specify)							
Alopecia							
Phlebitis/Thrombosis/Embolism							
Incontinence							
1. Vaginal bleeding (post-biopsy)							
2. Vaginal bleeding							
Somnolence							
Insomnia							
Anxiety/Depression	/	/	/	/	/		
Nausea/Vomiting	/	/	/	/	/		
Liver-clinical							
Hot flashes							
Anorexia							
Dizziness/Headache	/	/	/	/	/		
Myalgia/Fatigue	/	/	/	/	/		
Confusion							
Vaginitis							
Conjunctivitis/Keratitis	/	/	/	/	/		
Eye-other (specify)							
Fatigue							
Endometrial - other (specify)							
other (specify)							

- 1. Vaginal bleeding beginning within 72 hours after biopsy
- 2. Vaginal bleeding - other

OFF TREATMENT NOTICE		Amended data: <input type="checkbox"/> Yes, mark amended items in red.
Disease Committee: _____		SWOG Study No. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Protocol Step <input type="text"/>
SWOG Pt. No. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Patient's Name _____ (L,F,M)	
Institution / Member _____		Physician _____
Groups other than SWOG: Group Name/Study No./Pt No. _____ / _____ / _____		
INSTRUCTIONS: For each protocol step, submit this form within 2 weeks after completion (or discontinuation) of treatment. List protocol-directed treatments that the patient received. Chemotherapy: List regimens, start and stop dates. For multidrug regimens, do not list individual drugs separately; stop date would be the date all drugs in the regimen were discontinued. Surgery: List type of surgery and in the "stop" column the date of surgery. Radiation: List sites, start and stop dates (inclusive of boosts and implants). Indicate an unknown part of a date with a horizontal line drawn across the appropriate boxes.		
Start Date (M,D,Y)	Stop Date (M,D,Y)	REGIMEN or PROCEDURE or SITE(S)
<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>	
<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>	
<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>	
<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>	
<input type="text"/> - <input type="text"/> - <input type="text"/>	<input type="text"/> - <input type="text"/> - <input type="text"/>	
(If more room is needed please continue on a separate page)		
Reason OFF TREATMENT (Check one) 1- <input type="checkbox"/> Treatment completed per protocol 2- <input type="checkbox"/> Toxicity, medically required, specify: _____ 3- <input type="checkbox"/> Patient refused, due to toxicity, specify: _____ 4- <input type="checkbox"/> Patient refused, other than toxicity, specify: _____ 5- <input type="checkbox"/> Progression or relapse. Sites: _____ 6- <input type="checkbox"/> Death (attach Notice of Death form) 7- <input type="checkbox"/> Other, specify: _____		
Date OFF TREATMENT Date of completion, progression, death or decision to discontinue therapy <input type="text"/> - <input type="text"/> - <input type="text"/> (M,D,Y)		
Will patient receive Further Treatment? <input type="checkbox"/> No <input type="checkbox"/> Yes, specify: _____ <input type="checkbox"/> Unknown		
Date of Last Contact (or death): <input type="text"/> - <input type="text"/> - <input type="text"/> (M,D,Y)		
VITAL STATUS: <input type="checkbox"/> Alive <input type="checkbox"/> Dead (attach Notice of Death form)		
Notes:		

By: _____ Date: _____ SWOG 02-28-89 SW060

NOTICE OF DEATH

Amended data: Yes, mark amended items in red.

Disease Committee _____ Most Recent SWOG Study No.

SWOG Patient No. Patient Name _____
(L) (F) (M)

Institution / Member _____ Physician _____

Groups other than SWOG: Group Name/Study No./Pt. No. _____ / _____ / _____

INSTRUCTIONS: Submit within 4 weeks of knowledge of death.

Date of death - - (M,D,Y)

Causes of Death

Any cancer (check one)

- 1- No 2- Primary cause 3- Contributory 4- Possible 5- Unknown

If patient has had multiple tumor types, specify those which were causes of death:

Toxicity from disease related treatment (check one)

- 1- No 2- Primary cause 3- Contributory 4- Possible 5- Unknown

If 2, 3, or 4, specify treatment and toxicity

Non-cancer and non-treatment related causes (check one)

- 1- No 2- Primary cause 3- Contributory 4- Possible 5- Unknown

If 2, 3, or 4, specify

Autopsy done? No Yes Unknown

Death information obtained from (check all that apply):

- Autopsy report
- Medical record / death certificate
- Physician
- Relative or friend
- Other, specify _____

Notes:

BY: _____ DATE: _____ SWOG 02-28-89 SW059

19.2 Research Methods for Molecular Studies of Endometrial Tissue

Estrogen and Progesterone Receptor Determination:

An immunohistochemical localization of estrogen and progesterone receptors will be performed using commercial reagent kits (Abbott Laboratories, Diagnostic Division, North Chicago, IL) according to the instructions of the manufacturer. The results will be evaluated as specific staining, color absent (negative): weak (+): moderate (+ +): and strong (+ + +).

In-situ hybridization (ISH) for proto-oncogene expression:

The ISH procedures have been described previously in detail. (34) Briefly, 5 μ m sections of formalin-fixed, paraffin-embedded tissues were placed on 3aminopropyltrieth-oxysilane-coated slides, dewaxed, rehydrated and refixed in 4% paraformaldehyde. Sections were then treated with proteinase K (25 μ g/ml), refixed in paraformaldehyde, acetylated, then dehydrated through graded ethanols and air-dried. An aliquot (2.5 μ l) of ³²P-labelled probe mix containing 50,000 to 100,000 d.p.m. of 125I (0.05 to 0.1 ng of RNA) per μ l was placed on the section, covered with a 13 mm round siliconized coverslip, placed under liquid paraffin and hybridized for 16 h at 50°C. Slides were then washed RNase A-treated, washed, dried and dipped in Ilford K2 emulsion and exposed in light-tight boxes at 4°C for 1 to 2 weeks. Slides were developed with Kodak D19 developer and Rapid fixer, stained with Gill's hematoxylin and eosin and mounted in Depex.

Scoring of biopsies was performed by visual assessment of grains, using probes of the opposite sense and stromal cells as negative controls. Intensity of the signal was estimated using a + to + + + scale where + was at least two times background levels and up to approximately 20 grains/cell, + + 21 to 50, + + + 51 to 100 and + + + + > 100 grains per cell. To confirm that signals detected with each probe were due to RNA-RNA hybrids and not RNA-DNA hybrid formation, each probe was compared to a section hybridized with a probe from the identical construct but transcribed in the opposite (mRNA sense) direction .

17-Hydroxysteroid dehydrogenase enzyme activity assay

Oxidative and reductive 17-HSD activity will be determined in tissue homogenates from hysterectomy specimens. The 17-HSD activity will be assessed by determining the ability of the endometrial homogenate to convert either [3H] E1 to [3H] E2 or vise-versa by methods described in the literature. (28) The endometrial homogenate is incubated with [3H] E1 or [3H] E2 in serum-free media for four hours at 37°C, then the steroids will be extracted from the media with twice the volume of diethyl ether, the samples will be dried down and separated by thin layer chromatography on silica gel plates with a 4:1 mixture of dichloromethane-ethyl acetate as the mobile phase. Spots corresponding to either E1 or E2 will be visualized under UV light by incorporation of an excess of cold carrier into each sample, cut out, eluted with methanol and counted in a scintillation counter.

APPENDIX N

Southwest Oncology Group Protocol S9631: "A Cross-Sectional Study to Estimate the Incidence of Endometrial Pathology in Women Receiving Tamoxifen on S8814 and S8897."

Study Coordinators: Ronald K. Potkul, M.D., Kathy S. Albain, M.D., Caryl Saloman, M.F., Sharon Wilczynski, M.D., Ph.D., Laura F. Hutchins, M.D., Stephanie J. Green, Ph.D., Janet O'Sullivan, M.A.

Funded by supplemental award from the National Cancer Institute.

The following draft protocol is proprietary information and is a privileged communication for investigational use only

SOUTHWEST ONCOLOGY GROUP

A CROSS-SECTIONAL STUDY TO ESTIMATE THE INCIDENCE OF ENDOMETRIAL PATHOLOGY IN
WOMEN RECEIVING TAMOXIFEN ON **SWOG-8814** (INT-0100) AND **SWOG-8897** (INT-0102)

	<u>Page</u>
SCHEMA	3
1.0 OBJECTIVES.....	4
2.0 BACKGROUND.....	4
3.0 DRUG INFORMATION.....	7
4.0 STAGING CRITERIA.....	7
5.0 ELIGIBILITY CRITERIA.....	7
6.0 DESCRIPTIVE FACTORS.....	8
7.0 TREATMENT PLAN.....	8
8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS.....	12
9.0 STUDY CALENDAR.....	13
10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS.....	13
11.0 STATISTICAL CONSIDERATIONS	13
12.0 DISCIPLINE REVIEW.....	14
13.0 REGISTRATION GUIDELINES.....	13
14.0 DATA SUBMISSION SCHEDULE.....	16
15.0 SPECIAL INSTRUCTIONS.....	17
16.0 ETHICAL AND REGULATORY CONSIDERATIONS.....	17
17.0 BIBLIOGRAPHY.....	21
18.0 MASTER FORMS SET.....	24
19.0 APPENDICES.....	27

PARTICIPANTS: ALL SOUTHWEST ONCOLOGY GROUP, CCOP AND CGOP MEDICAL
ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; NCCTG,
CALGB AND ECOG

**STUDY COORDINATORS
(SOUTHWEST ONCOLOGY GROUP):**

Ronald K. Potkul, M.D. (Gynecologic Oncology)
Loyola University Medical Center
Department of Obstetrics & Gynecology
2160 S. First Avenue
Maywood, IL 60153
Phone: 708/327-3314

Sharon Wilczynski, M.D., Ph.D. (Pathology)
Dept of Anatomical Pathology
City of Hope
1500 E Duarte Rd
Duarte, CA 91010
Phone: (818) 359-8111 ext = 3318

Kathy S. Albain, M.D. (Medical Oncology-CWH)
Loyola University Medical Center
Cancer Center, Room 109
2160 South 1st Avenue
Maywood, IL 60153-5589
Phone: 708/327-3102

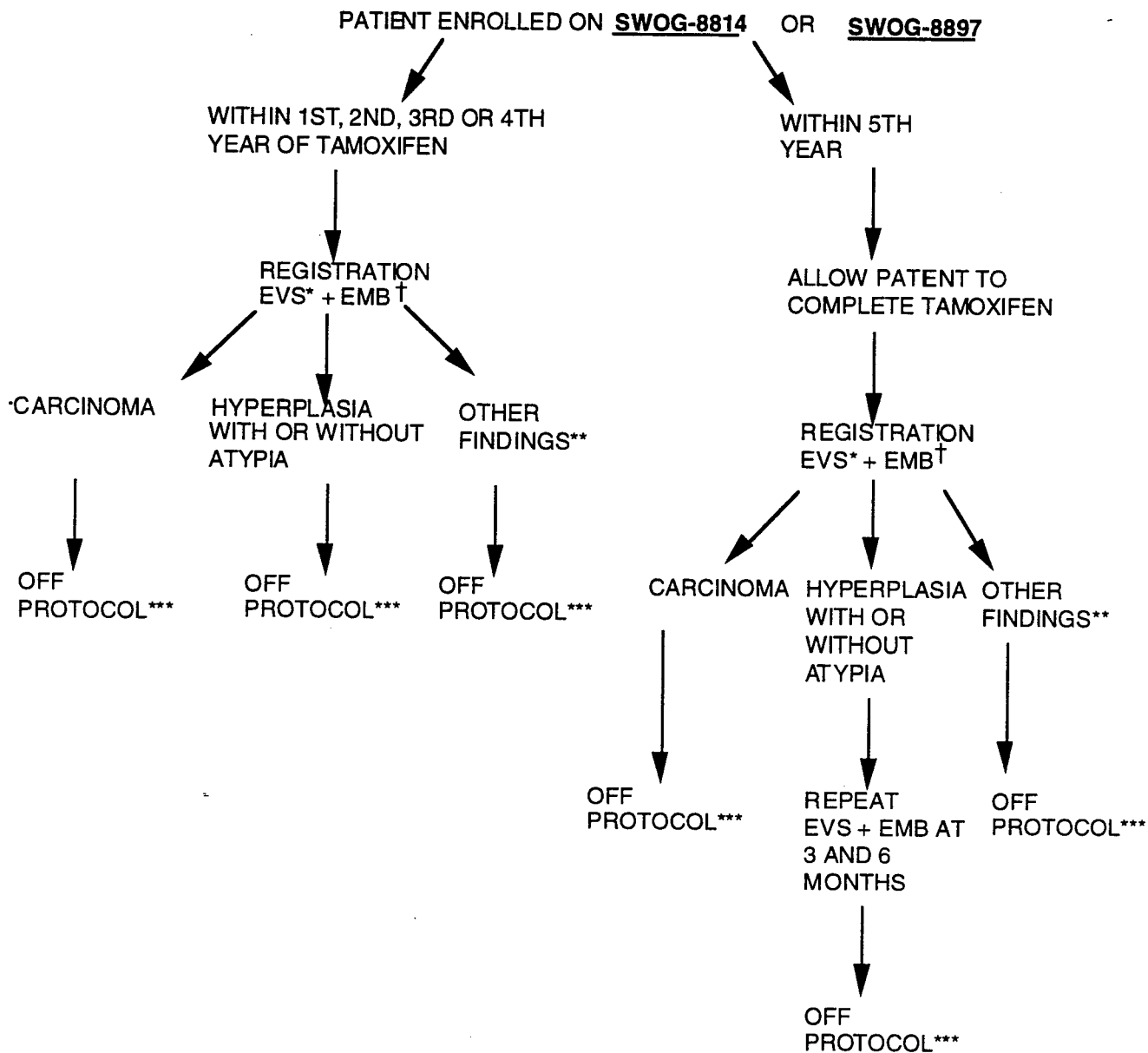
Laura F. Hutchins, M.D. (Medical Oncology)
Hematology/Oncology, Slot 508
University of Arkansas for Medical Science
4301 W. Markham Street
Little Rock, AR 72205-7101
Phone: 501/686-8530

Caryl Saloman, M.D. (Radiology Consultant)
Loyola University Medical Center
Department of Radiology
2160 S. First Avenue
Maywood, IL 60153
Phone: 708/216-6720

Stephanie J. Green, Ph.D. (Biostatistics)
Janet O'Sullivan, M.A.
Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street, MP-557
Seattle, WA 98104-2092
Phone: 206/667-4623

M423/mb

SCHEMA



*Endovaginal Sonogram

†Endometrial biopsy

**No tissue, benign polyps, normal premenopausal, postmenopausal proliferative changes (continue follow-up according to treatment protocol SWOG-8814 or SWOG-8897)

***See Section 7.0 for recommendations on management, then continue follow-up according to treatment protocol (SWOG-8814 or SWOG-8897)

1.0 OBJECTIVES

Primary Objective

- 1.1 To estimate the incidence of endometrial abnormalities (in particular hyperplasia, hyperplasia with atypia, carcinoma, postmenopausal proliferative changes and benign polyps) in breast cancer patients receiving tamoxifen on SWOG-8814 and SWOG-8897.

Secondary Objectives

- 1.2 To compare endovaginal ultrasound with endometrial biopsy in the detection of these abnormalities.
- 1.3 To describe the distributions of gene expression (e.g., c-fos, c-jun, IGF1) and receptor status in endometrial biopsy specimens obtained from tamoxifen-treated breast carcinoma patients, in relation to
 - a. length of tamoxifen exposure
 - b. menopausal status
 - c. prior chemotherapy
 - d. endometrial abnormalities
- 1.4 To determine the feasibility of collecting centrally frozen tissue hysterectomy specimens from tamoxifen-treated breast carcinoma patients for the purpose of analyzing the regulation of 17 Beta-hydroxy steroid dehydrogenase activity in endometrial tissue.
- 1.5 To establish a repository of paraffin blocks and frozen endometrial tissue from tamoxifen-treated breast cancer patients.

2.0 BACKGROUND

Tamoxifen, a non-steroidal antiestrogen is commonly used for the treatment of hormone dependent breast cancer (1, 2). This agent acts by inhibiting the growth of breast cancer cells by competitive binding with estrogen through the estrogen receptor, thereby producing an anti-proliferative effect (1). Since the initial report by Killackey, et al in 1985 suggesting a possible link between tamoxifen use and the development of endometrial cancer, approximately 115 cases of tamoxifen-associated cancer of the uterus had been reported (3-14). The majority of these studies were limited by their anecdotal and case control nature.

More recently, the results of the National Surgical Breast and Bowel Project (NSABP) B-14 trial were published (15). This randomized trial of tamoxifen vs placebo in women with estrogen receptor (ER) - positive breast cancer with negative axillary nodes revealed a 7.5-fold increase in the risk in developing endometrial cancer in the tamoxifen-treated group. Two of the 1424 patients assigned to receive placebo developed endometrial cancer; however, both had subsequently received tamoxifen for treatment of breast cancer recurrence. Fifteen patients of the 1419 patients randomized to tamoxifen treatment developed endometrial cancer. Eight additional cases of uterine cancer occurred in the 1220 tamoxifen-treated patients registered in NSABP B-14 subsequent to randomization. The mean duration of tamoxifen therapy was 35 months, with 36% of the endometrial cancers developing within two years of beginning tamoxifen. The average annual hazard rates for endometrial cancer were 0.2/1000 in the placebo group and 1.6/1000 in the randomized tamoxifen-treated group.

It is well-established that unopposed estrogen administration is associated with an increased risk of developing endometrial carcinoma. These cancers tend to be predominantly early stage, low grade, and have a favorable prognosis. If the effect of tamoxifen on the endometrium is that of a weak estrogen agonist, one would expect associated endometrial cancers to have clinical and pathologic characteristics comparable to those associated with estrogen. There have been conflicting reports on whether this in fact is the case. A report from the Yale Tumor Registry suggested that uterine cancers occurring in breast cancer patients on tamoxifen behaved more aggressively, as 67% of the uterine cancers were high-grade lesions (10). Other recent studies failed to confirm these findings and strongly suggest that tamoxifen acted as a weak estrogen agonist on the endometrium (13-15). This concept was supported by recent publications demonstrating an increased rate of estrogen-like changes in the endometrium, i.e., proliferative endometrium, adenomatous hyperplasia with and without atypia, in tamoxifen-treated women compared to non-users (17,18). These studies were small, containing only approximately 100 patients. Postmenopausal patients should not have tissue on biopsy if the endometrium is not being stimulated and is otherwise normal. A recent study evaluated 61 postmenopausal women on tamoxifen by obtaining endometrial tissue by biopsy (17). The results suggested evidence of estrogen-like stimulation in 40% of the group. Proliferative or hyperplastic endometrium, atypical hyperplasia, and benign polyps were found in 13%, 16%, and 8% respectively of the 61 women. A better understanding of the actions of tamoxifen on the endometrium in a larger cohort of postmenopausal patients should aid in clarification of this issue. Furthermore, very little is known regarding the effects of tamoxifen on the premenopausal endometrium. Tissue is normally expected on endometrial biopsy during the secretory phase of the menstrual cycle; however, hyperplastic or proliferative changes should not be found during this phase.

The current study will take advantage of the large number of available patients in **SWOG-8814** and **SWOG-8897** to better characterize the tamoxifen-associated endometrial changes at varying points in time during the 5-year course prescribed in the treatment protocols. The study population will consist of postmenopausal and premenopausal patients with an intact uterus who are enrolled on tamoxifen arms of Southwest Oncology Group protocols **SWOG-8814** and **SWOG-8897**. Endometrial assessment of both endovaginal sonogram (EVS) and endometrial biopsy (EMB) will be obtained once within years 1, 2, 3, 4 or at the end of five years of protocol-specified tamoxifen treatment. In order not to mis-classify normal premenopausal proliferative endometrium as hyperplasia, premenopausal women will be biopsied during the secretory phase (Day 22 - 27) of the cycle. Premenopausal status will be confirmed by FSH level. An estradiol level will be required to determine possible up-regulation by the tamoxifen.

The published data support an association between tamoxifen and the development of both benign and malignant endometrial neoplasia. Recommendations regarding prospective screening are not well-established. Periodic sampling of the endometrium, using an endometrial suction biopsy device (Pipelle, Unimar, Wilmington, Connecticut) is being evaluated (19). Transvaginal sonography may provide a non-invasive means of screening for endometrial pathology in tamoxifen-treated breast cancer patients. Unfortunately, the definition of an abnormal endometrial stripe remains to be determined. One report in the literature using 5 mm as the cut off of an abnormal endometrial echo found that approximately 50% of patients undergoing endometrial sampling on that basis had no abnormal pathology (11). A second study reported a predictive value of 100% (16 of 16) for atypical hyperplasia or polyps when the endometrial stripe was 8 mm or greater (17). These reports are all on limited numbers of patients. This study will be the largest study to evaluate and compare radiologic and pathologic techniques for diagnosis of endometrial abnormalities in women of all ages with breast cancer treated with variable durations of tamoxifen for use in future prospective studies and in screening.

RATIONALE FOR MOLECULAR CORRELATES

The effects of estrogen on the physiology of normal endometrium are well known. The mechanisms by which estradiol regulates proliferation of human estrogen-responsive cells involve a series of events beginning with binding of estradiol to its receptor followed by activation of the receptor, interaction of the activated receptor with hormone response elements of specific genes

and modification of their transcription rates (20). Estradiol also enhances expression of proto-oncogenes (e.g, c-myc, c-fos, c-jun, c-ras, IGF1) involved in the regulation of gene expression and DNA synthesis (21).

In addition to the known antiestrogenic effects of tamoxifen, in some situations the drug exhibits estrogenic effects or a mixed agonist/antagonist action. (22) The clinical studies which suggested a link between tamoxifen use and the development of endometrial carcinoma proposed as a mechanism the estrogen-like stimulation of the endometrium by the antiestrogen. (6, 15)

Unopposed estrogen is an important risk factor for endometrial cancer (23). Estradiol is the most active biologic estrogen and the intensity of exposure to this hormone is critical in the process of carcinogenesis of the endometrium. Extensive in vitro studies on the human endometrium have demonstrated that estradiol levels in the tissue can be regulated by hormone-dependent target tissue metabolism (24). These findings led to the conclusion that the blood level of estradiol is only one of the parameters to be considered in the evaluation of the hormonal influence on the endometrium. The intensity of the cellular exposure to estradiol is determined by the circulating estradiol concentration, the endometrial estrogen receptor levels, and the activity of the endometrial 17-Beta hydroxysteroid dehydrogenase (17-HSD). This enzyme catalyzes the reversible conversion of estrone (E1) into the more potent estrogen, estradiol (E2) (25).

Compared with normal breast tissue, breast tumors have an increased ability to convert estrone to the biologically more active 17-Beta-estradiol (25). This reversible interconversion in the breast is also mediated by the enzyme 17-HSD. Intracellular estradiol has been demonstrated to stimulate reductive 17-HSD ($E1 \rightarrow E2$) in the MCF-7 human breast cancer cell. Tamoxifen appear to stimulate the reverse oxidative direction ($E2 \rightarrow E1$) thus reducing the intracellular estradiol level. (27, 28) These observations suggest that in the breast, tamoxifen, in addition to blocking estradiol at the receptor, may act also by reducing the intracellular levels of E2. The effects of tamoxifen on this enzyme in the postmenopausal estradiol-free endometrium and in the premenopausal endometrium are unknown.

It is well documented that exogenous estrogens in postmenopausal women will lead to an increase in the endometrial estrogen and progesterone receptor levels equal to or greater than those found in the proliferative phase of premenopausal women (29). The variable levels of these receptors and their potential predictive use in the study of the development of endometrial changes and frank cancer in women with breast cancer on tamoxifen needs to be clarified.

Finally, many laboratories have investigated the actions of tamoxifen in animal models such as the rat uterus. (30) The majority of early studies used uterine growth and/or histological changes as an endpoint. More recently several cellular oncogenes such as c-fos appear to be over-expressed in estrogen- and tamoxifen treated animals, indicating that tamoxifen may be acting as a full agonist in the rat uterus. (31) The effects of tamoxifen on these growth related proto-oncogenes is unknown in human endometrium and may play a role in the early development of hyperplasias and endometrial cancer.

In summary, the effect of estrogen on the endometrium has been extensively studied on a molecular and biologic cellular level. The effect of the tamoxifen on breast cancer cells has also extensively been studied at the cellular level in animal models. In these settings it appears to function as an antiestrogen. Clinical and animal data suggest that tamoxifen may be acting as an estrogen agonist on the endometrium. The aims of the molecular correlates analyses are to better understand the effects of tamoxifen on the endometrium, as well as to correlate changes at the molecular level with the pathologic findings in patients with endometrial abnormalities of proliferative changes, hyperplasia, hyperplasia with atypia and carcinoma.

RESEARCH DESIGN FOR MOLECULAR CORRELATES STUDY

The paraffin blocks from all endometrial biopsies in which tissue is obtained will be stored at Loyola University Cancer Center. Selected blocks from the postmenopausal cohort and all blocks from the premenopausal cohort will be evaluated according to the Statistical Considerations (Section 11.0), and along with the remaining blocks will constitute a national bank for future studies. The estrogen and progesterone receptor content will be measured using immunohistochemical technique on these blocks. In addition, expression of the c-fos, c-jun and IGF1 oncogenes will be evaluated by using *in-situ* hybridization. Both of these techniques will allow separation of the endometrial cells from the stromal cells in making these determinations. (See Appendix Section 18.2 for detailed methods.)

We will also request for patients who undergo a hysterectomy for endometrial cancer or atypical hyperplasia that a portion of the endometrium be snap-frozen and sent to us for evaluation. The 17-HSD enzyme activity will be evaluated in these frozen specimens that are available, since this cannot be determined on paraffin blocks. The enzyme activity will be determined using standard methods employing tritiated precursors. (27) This part of the study will be exploratory.

RECOMMENDATIONS IF ENDOMETRIAL ABNORMALITIES DETECTED

This study will assess those women who are enrolled at the time of completion of one to five years of tamoxifen. In this way, information will be obtained on the natural history of endometrial abnormalities. For women enrolled after 1, 2, 3 or 4 years of tamoxifen, if atypical hyperplasia is detected, the tamoxifen may be continued but a 6-week course of medroxyprogesterone acetate is recommended to attempt to reverse this lesion, which has a high rate of progression to carcinoma. It is not recommended that medroxyprogesterone acetate be added for simple hyperplastic or proliferative changes. The pathologic findings will be compared to the sonogram results regarding thickness of the endometrial stripe.

3.0 DRUG INFORMATION

Drug information is not applicable for this study.

4.0 STAGING CRITERIA

Staging criteria are not applicable for this study.

5.0 ELIGIBILITY CRITERIA

- 5.1 Patients must have been registered to either SWOG-8814 or SWOG-8897.
- 5.2 Patients must be either currently receiving tamoxifen as part of assigned treatment on SWOG-8814 or SWOG-8897 for ≤ 4 years, or within two weeks after discontinuation of tamoxifen (in their fifth year of receiving tamoxifen).
- 5.3 Patients who have undergone a hysterectomy are not eligible.
- 5.4 If the patient was premenopausal at the time of registration to SWOG-8897, FSH and estradiol must have been performed within 42 days prior to registration to this study. Additionally, the date of the patients last menstrual period must be available.
- 5.5 Institutions must be willing to submit materials (as listed in Section 12.0) from the endometrial biopsy and the endovaginal sonogram, including H&E slides (if available), tissue blocks (if available) or 10 unstained slides, biopsy report, ultrasound film,

ultrasound report and the gynecologist's operative and pathology report of the biopsy procedure.

- 5.6 Pregnant women may not participate. Women of child-bearing potential must be planning to use effective contraception.
- 5.7 All patients must be informed of the investigational nature of this study and give written informed consent in accordance with institution and federal guidelines.
- 5.8 At the time of registration, the date of institutional review board approval for this study must be provided to the Statistical Center.

6.0 DESCRIPTIVE FACTORS

- 6.1 Treatment protocol number and treatment arm: SWOG-8814 - Arm 1, SWOG-8814 - Arm 2, SWOG-8814 - Arm 3, SWOG-8897 - Arm 3, SWOG-8897 - Arm 4.
- 6.2 Current menopausal status: premenopausal vs. postmenopausal as defined by the following criteria:
 - a. Natural menopause: last menstrual period at least one year prior to registration.
 - b. Surgical menopause: bilateral oophorectomy at least two months prior to the diagnosis of breast cancer.
 - c. Patients who are 4-12 months from their last menstrual period will be considered postmenopausal if the FSH is elevated to the postmenopausal range.
 - d. Patients on postmenopausal estrogen therapy will be considered postmenopausal if they are 55 years of age or older. All other patients must have a postmenopausal level of FSH (it may take as long as 1-2 weeks after stopping estrogen for FSH to rise to postmenopausal level). Postmenopausal estrogen therapy must be discontinued in all patients.
- 6.3 Time from start of tamoxifen: $\leq 1, > 1 - 2, > 2 - 3, > 3 - 4, = 5$

7.0 MANAGEMENT PLAN

- 7.1 Follow-up guidelines on this study will be based on whether patients are either still receiving tamoxifen or have completed tamoxifen at the end of five years, and will be determined by the results of an endometrial biopsy.
- 7.2 All patients currently at the end of their first to fourth year of receiving tamoxifen will undergo an endovaginal sonogram and endometrial biopsy within four weeks after registering to this study. See Section 12.0 for instructions related to centralized pathology review and centralized sonogram review. The patient is then removed from the protocol.

The following recommendations are made to guide off-study treatment:

- a. **If hyperplasia with or without atypia is found, the patient will continue tamoxifen as planned on SWOG-8814 or SWOG-8897, and it is recommended that the patient additionally receive medroxyprogesterone acetate 20 mg/day for six weeks and then be rebiopsied.**

Upon rebiopsy following treatment with medroxyprogesterone acetate, if treatment reverses the abnormality, i.e., no hyperplasia with or without atypia or carcinoma is found, the patient should continue tamoxifen and follow-up as planned on SWOG-8814 or SWOG-8897, and be followed as per their gynecologist's recommendation.

Upon rebiopsy following treatment with medroxyprogesterone acetate, if hyperplasia with or without atypia persists, a hysterectomy is recommended. In the special circumstance of persistent simple hyperplasia without prior atypia, the gynecologist may elect to follow the patient closely with repeat biopsies and continue tamoxifen. Patients receiving a hysterectomy should continue tamoxifen and follow-up as planned on SWOG-8814 or SWOG-8897. Please see Section 15.0.

If there is progression to carcinoma, follow Section 7.2b.

- b. If carcinoma is found a hysterectomy is recommended. Patients receiving a hysterectomy should continue tamoxifen and follow-up as planned on SWOG-8814 or SWOG-8897. Please see Section 15.0.
- c. If none of the abnormalities in Section 7.2a or b are found, the patient should continue on tamoxifen and follow-up per SWOG-8814 or SWOG-8897.

7.3 Patients within their fifth year of receiving tamoxifen will delay registration to this study until they are within two weeks after completing the full five years of tamoxifen and then will undergo an endovaginal sonogram and endometrial biopsy within four weeks after registering to this study. See Section 12.0 for instructions related to centralized pathology review and centralized sonogram review.

- a. If hyperplasia with or without atypia is found the patient should remain on this study and be followed with a repeat sonogram and biopsy at three months. If 3-month biopsy is normal or without hyperplasia or carcinoma, document result, and remove the patient from the protocol. If hyperplasia with or without atypia persists, repeat sonogram and biopsy at six months (three months after the 3-month biopsy). Document result and remove the patient from the protocol.

The following recommendations are made to guide off-study treatment:

- 1. If hyperplasia with or without atypia persists at six months, it is recommended that the patient receive medroxyprogesterone acetate 20 mg/day for six weeks and then repeat the biopsy.

Upon rebiopsy following treatment with medroxyprogesterone acetate, if treatment reverses the abnormality, i.e., no hyperplasia with or without atypia or carcinoma is found, the patient should continue follow-up as planned on SWOG-8814 or SWOG-8897, and be followed as per their gynecologist's recommendation.

Upon rebiopsy following treatment with medroxyprogesterone acetate, if hyperplasia with or without atypia persists, a hysterectomy is recommended. In the special circumstance of persistent simple hyperplasia without prior atypia, the gynecologist may elect to follow the patient closely with repeat biopsies. Patients receiving a hysterectomy should continue follow-up as planned on SWOG-8814 or SWOG-8897. Please see Section 15.0.

If there is progression to carcinoma, follow Section 7.2b.

2. **If pathologic abnormality does not persist at six months, the patient should continue follow-up on SWOG-8814 or SWOG-8897 and should be followed as per their gynecologist's recommendation.**
- b. If carcinoma is found, the patient is removed from the protocol and a hysterectomy is recommended. Please see Section 15.0. Patients should continue follow-up as planned on SWOG-8814 or SWOG-8897.
- c. If no hyperplasia or carcinoma is found, the patient will be removed from the protocol and followed as per their gynecologist's recommendation. Patients should continue follow-up as planned on SWOG-8824 or SWOG-8897.

7.4 Endovaginal Sonography (EVS) Procedure - gray scale imaging (33 - 47)

- a. Record transducer manufacturer, frequency.
- b. Examine uterus and adnexa in sagittal and transverse planes.
- c. Measure and record uterine dimensions (AP, CC in sagittal plane; TR in transverse plane) using electronic calipers.
- d. Measure and record maximal AP endometrial thickness (stripe) in sagittal plane using electronic calipers.
 1. If fluid is not seen in the endometrial canal, measure the maximal AP endometrial thickness by placing the anterior caliper at the junction of the anterior endometrial echo and the subendometrial hypoechoic zone (halo) and the posterior caliper at the junction of the posterior endometrial echo and the subendometrial hypoechoic zone (halo). Record this measurement as the AP endometrial thickness.
 2. If fluid is seen in the endometrial canal, measure the AP endometrial thickness as in Section 7.4d.1 above; record.

Also measure the AP dimension of the fluid collection on the same image and record.
- e. Obtain representative images of the uterus adequate to completely characterize the endometrium with respect to: echogenicity; uniformity of echotexture; location and appearance of focal thickening, if present, cystic spaces, if present; integrity or lack thereof of the subendometrial lucent "halo"; and fluid or sonolucent material within the endometrial cavity, if present.

- f. If cystic spaces are identified, use pulsed-wave Doppler and/or color Doppler imaging to demonstrate if there is internal flow indicating identity as vascular structures. Record representative image and pulsed-wave Doppler flow tracing.
 - g. If endometrial echo is not visible, note reason, e.g., distorted by myomas, retroversion, technical factors, etc.
 - h. Note and record incidental pathology, e.g., leiomyomas, ovarian masses.
- 7.5 Color Doppler Imaging (CDI) - perform if available, in addition to EVS (Section 7.4). This information will be used for exploratory comparison with EVS and with biopsy.
- a. Record CDI frequency and parameters used in 1 - 3 below:
 - 1. Use lowest velocity flow setting, 1 - 2 cm/sec, or lower, if available.
 - 2. If possible use pulse repetition frequency in the range of 2 - 42 KHz.
 - 3. Set wall filter at minimum, 50 - 100 Hz.
 - 4. Use 1.5 - 2 mm Doppler sample volume.
 - 5. Set gain just below threshold for background noise.
 - 6. If possible, determine SPTA from transducer information provided by manufacturer and record this value.
 - b. Assess endometrium for flow with CDI.
 - 1. Obtain and record 3 independent pulsed Doppler arterial waveforms and representative images from any focal areas of increased vascularity; otherwise, obtain and record pulsed Doppler arterial waveforms and representative images from three separate sites within the endometrium.
 - 2. For each waveform tracing, manipulate the transducer angle to maximize the Doppler signal. Measure and record maximum systolic and diastolic velocities for each tracing.

If available, use machine software package to calculate and record resistive index (RI), pulsatility index (PI) and S:D ratio.
 - c. Repeat procedure in (b) to assess the myometrium for flow.
 - d. Repeat procedure in (b) to assess paracervical uterine artery waveforms. If possible obtain at least one measurement from each side.
 - e. If flow cannot be detected in any of these regions, please indicate this observation.
- 7.6 Endometrial Biopsy Procedure (to be performed after EVS)
- a. Standard outpatient gynecologic endometrial biopsy (EMB) will be performed using the Pipelle® (Unimar). The Pipelle® is a single use, sterile, disposable curette for obtaining a histological biopsy of the uterine mucosal lining. The device consists of a clear, flexible, polypropylene sheath that is 23.5 cm in length with an outside diameter of 3.1 mm. Rapid movement of the piston within the sheath from its fully inserted position to its maximum retracted position creates a

negative pressure (suction) within the lumen of the sheath. This negative pressure draws the mucosal tissue through the curette opening and into the lumen of the sheath as the curette scrapes against the endometrial wall. **In order not to mis-classify normal premenopausal proliferative endometrium as hyperplasia, premenopausal women will be biopsied during the secretory phase (Day 22 - 27) of the menstrual cycle.**

- i. With the piston fully advance within the sheath, insert Pipelle® through cervical canal into the uterine cavity until resistance is felt (prior determination of the uterine depth with a uterine sound is recommended).
 - ii. While holding sheath, pull piston back completely thus creating maximum negative pressure with the sheath. Leave piston fully retracted.
 - iii. Simultaneously swirl sheath between fingers while moving sheath laterally and in and out between fundus and internal os three or four times to obtain sample.
 - iv. Remove Pipelle® from uterus and cut off distal tip just proximal to curette opening.
 - v. Advance piston rod to expel sample into transport medium.
 - vi. Use of a tenaculum may or may not be necessary to accomplish insertion of the Pipelle®. Clinical judgement should be used to determine its need.
- b. If cervical stenosis exists, a paracervical block with local anesthetic can be employed to allow gentle dilation with a small cervical dilator to allow EMB.
 - c. If EMB unsuccessful then
 - i. If endometrial echo is greater than 5 mm (abnormal), obtaining endometrial tissue is required by dilation and curettage.
 - ii. If endometrial echo is less than 5 mm (normal), no tissue required for study.

7.7 Criteria for Removal from Protocol.

- a. No further biopsies or sonograms required per protocol.
- b. The patient may withdraw from the study at any time for any reason.

7.8 All reasons for discontinuation of protocol must be documented.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

- 8.1 Management of biopsy complications: Self-limited vaginal spotting or bleeding as well as cramping or pain are common events. Routine gynecologic management of rare, unexpected post-biopsy events such as severe hemorrhage or perforation will be used. If symptoms of bleeding or cramping persist beyond one week, or any other Grade 3 or 4 event occurs, contact the Study Coordinator (see Section 8.2, below).

- 8.2 For treatment or dose modification related questions related to progestin or biopsy complications, please contact Dr. R. K. Potkul at 708/327-3314 or Dr. Kathy Albain at 708/327-3102. Specific radiologic questions regarding sonograms should be addressed to Dr. Caryl Saloman at 708/216-6720.
- 8.3 Any adverse reactions, as well as any deaths on study which might be attributed to the biopsy procedure, must be reported to the Cooperative Group, the NCI, the IRB, and the Study Coordinator (see Section 16.0).

9.0 STUDY CALENDAR

There is no study calendar for this study.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

- 10.1 The primary clinical endpoint is endometrial pathologic status. The following possible results will be recorded: proliferative premenopausal endometrium, secretory premenopausal endometrium, proliferative postmenopausal endometrium, benign polyp, hyperplasia, hyperplasia with atypia and carcinoma.
- 10.2 EVS secondary endpoints are:
- Primary EVS endpoint is endometrial stripe thickness in mm
 - Secondary endpoints are whether or not the stripe was well defined and if cystic spaces were present or not.
- 10.3 Molecular endpoints: Description of gene expression and receptor status in relation to length of tamoxifen exposure, menopausal status, prior chemotherapy and endometrial results will be recorded.

11.0 STATISTICAL CONSIDERATIONS

- 11.1 Estimated sample size:

Approximately 1540 disease-free patients without prior hysterectomy on **SWOG-8897** and **SWOG-8814** are receiving tamoxifen. It is estimated that 200 patients from **SWOG-8897** will still be premenopausal at the time this study opens. It is also estimated there will be about 75% participation on this study. Thus we anticipate a sample size of 150 premenopausal and 1000 postmenopausal patients. The postmenopausal sample sizes in the various time intervals are estimated to be approximately 250 (years 3, 4 and 5), 150 (year 2) and 100 (year 1)

- 11.2 Pathologic Abnormality studies:

Since not having biopsy material available is normal for postmenopausal women, postmenopausal women with failed biopsy will be included in the denominator for estimating abnormality rates. With sample sizes of 250, 150 and 100, probabilities of abnormalities can be estimated to within $\pm .06$, $\pm .08$ and $\pm .10$ or better, respectively.

- 11.3 Association of pathologic abnormalities with thickness of stripe and presence of cystic spaces will be explored.

11.4 Molecular marker studies:

Forty percent of participating postmenopausal and 100% of premenopausal women should have biopsy material available, resulting in sample sizes of about 150 (pre), 100 (post years 3, 4, 5), 60 (post yr 2) and 40 (post yr 1) available for the gene expression study. Initially the premenopausal patients and the year 5 and 2 year postmenopausal patients will be analyzed for gene expression. The remainder will be housed in the central repository at Loyola for future study. The probability of a particular gene being expressed (given material is available) can be estimated to within $\pm .08$, $\pm .10$, and $\pm .13$ respectively in these three groups.

- 11.5 Differences among the various subsets (pre-post menopausal, year of tamoxifen, chemo-no chemo) with respect to abnormalities, gene expression and hormone receptor status will be explored. In addition, exploratory correlations in premenopausal patients of preregistration estradiol level with the above factors will be made to assess for relationship between these levels, duration of tamoxifen and development of abnormalities.

12.0 DISCIPLINE REVIEW

12.1 Pathology Review

- a. All endometrial tissue obtained at biopsy on this study will undergo review. Materials must be submitted within 30 days of every endometrial biopsy or dilation and curettage required on this protocol to:

Southwest Oncology Group Pathology Office
Fred Hutchinson Cancer Research Center MP-557
1124 Columbia Street
Seattle, WA 98104-2092
Phone: 206/667-4623

- b. Patients must have sufficient information and pathological material to verify findings on pathology report.
- c. The following materials are to be submitted within 30 days of any endometrial biopsy or dilation and curettage required on this protocol:
1. Paraffin block and representative H&E stained slides from the endometrial biopsy or dilation and curettage. If the institutional pathologist is unable to release the entire paraffin block, 10 unstained paraffin sections already cut onto slides may be submitted.
 2. Corresponding Pathology Report.
 3. Endometrial Pathology (EMB) Submission Form.
- d. Pathology gross reports and microscopic material should be reviewed for adequacy (by the Southwest Oncology Group institutional pathologist) prior to forwarding to the Seattle office.

12.2 Sonogram Review

- a. All sonogram films and reports on this study will undergo review. Materials will be submitted within 30 days of every endovaginal sonogram to:

Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street, MP-557
Seattle, WA 98104-2092
Phone: 206/667-4623

- b. The following materials are to be submitted within 30 days of any endovaginal sonogram:
1. Sonogram films
 2. Corresponding sonogram report
 3. EVS Submission Form
- c. Reports and films should be reviewed for adequacy prior to forwarding to the Seattle office.

13.0 REGISTRATION GUIDELINES

- 13.1 Registration, Southwest Oncology Group Investigators: All patients must be registered with the Southwest Oncology Group Statistical Center by telephoning 206/667-4623, 6:30 a.m. to 5:00 p.m. Pacific time, Monday through Friday, excluding holidays. Patients must be registered prior to biopsy no more than four weeks prior to the planned biopsy. **No exceptions will be permitted.**

Registration, NCCTG Investigators: All patients will be registered by calling NCCTG at 507/284-4130, 8:30 a.m. to 4:30 p.m., Central Time, Monday through Friday, excluding holidays. Patients must be registered prior to biopsy, no more than four weeks prior to the planned biopsy. **No exceptions will be permitted.** The NCCTG office will contact the Southwest Oncology Group Statistical Center to register the patient. A confirmation of registration will be forwarded to the institution through the NCCTG office.

Registration, ECOG Investigators: **A signed HHS 310 Form, a copy of the Institution's IRB-approved informed consent document, and written justification for any changes made to the informed consent for this protocol must be on file at the ECOG Operations Office before an ECOG Institutions may enter patients.** The signed HHS 310, institution informed consent, and investigators justification for changes will be submitted to the following address:

ECOG Coordinating Center
303 Boylston Street
Brookline, MA 02146-7648

Patients must not have protocol procedures performed prior to registration.

To register eligible patients on study, the investigator will telephone the Central Randomization Desk at the ECOG Statistical Center Data Management Office at 617/632-2022. ECOG members should not call the Southwest Oncology Group directly. The following information will be requested: Protocol Number; Investigator Identification

(including institution name and/or affiliate and investigator's name); Patient Identification (including patient's name or initials and chart number, patient's social security number, patient demographics [sex, birth date, race, nine-digit zip code and method of payment]); Eligibility Verification. Patients must meet all of the eligibility requirements listed in Section 5.0. The randomization specialist will verify eligibility by asking questions from the checklist. In addition, the Randomization Desk will verify IRB approval. The ECOG Randomization Desk will then contact the Southwest Oncology Group Statistical Center to enter the patient, after which the ECOG Office will contact the institution to relay confirmation for that patient. The Southwest Oncology Group Statistical Center will forward a confirmation of registration to the ECOG Randomization Desk for routing to the ECOG participating institution. Patients must be registered prior to biopsy no more than four weeks prior to the planned biopsy. **No exceptions will be permitted.**

If a patient does not receive protocol therapy, the patient MAY NOT be canceled.

Registration, CALGB Investigators: Investigators affiliated with CALGB will contact the CALGB Registrar's Office at the Data Management Center at Duke (919/286-4704), 9:30 a.m. to 4:00 p.m. Eastern Time, Monday through Friday, excluding holidays. The Data Management Center in turn will contact the Southwest Oncology Group Statistical Center for registration. The Southwest Oncology Group Statistical Center will forward a confirmation of registration to the CALGB Registrar's Office which will subsequently forward the confirmation of registration to the participating institution. Patients must be registered prior to biopsy no more than four weeks prior to the planned biopsy. **No exceptions will be permitted.**

- 13.2 At the time of registration, the caller must be prepared to answer every question on the eligibility checklist and provide descriptive factors.
- 13.3 The caller must also be prepared to provide the date of institutional review board approval for this study. Patients will not be registered if the IRB approval date is not provided or is > 1 year prior to the date of registration. The caller must also supply the date the informed consent was signed.
- 13.4 Exceptions to the current registration policies will not be permitted. Therefore, late registrations (after initiation of treatment), exceptions to eligibility requirements, participation by an institution/member not identified as eligible **AND/OR** cancellations will not be allowed.

14.0 DATA SUBMISSION SCHEDULE

- 14.1 Data must be submitted according to protocol requirements for ALL patients registered, including patients deemed to be ineligible.
- 14.2 Master forms are included in Section 18.0 and, with the exception of the sample consent form, must be photocopied for data submission.
 - a. Southwest Oncology Group members and CCOPs must submit two copies of all data forms directly to the Statistical Center in Seattle. CGOPs will submit (number of copies to be determined by the Group Member) copies to their Group Member institution for forwarding to the Statistical Center.
 - b. ECOG members - The original data forms as listed in Section 18.0 should be submitted at the required intervals to the ECOG Statistical Center Data Management Office. Include the Southwest Oncology Group and ECOG study number and patient number. The Statistical Center Data Management Office will forward 2 copies of the forms to the Southwest Oncology Group Statistical Center.

- c. CALGB members will send 2 copies of all forms to the CALGB-Data Management Center for forwarding to the Southwest Oncology Group Statistical Center. Include the Southwest Oncology Group patient number and protocol number on all forms as well as the CALGB patient number and protocol number.
- d. NCCTG members will send 2 copies of all forms to the NCCTG Operations Office for forwarding to the Southwest Oncology Group Statistical Center. Include the Southwest Oncology Group patient number and protocol number on all forms as well as the NCCTG patient number and protocol number.

14.3 WITHIN TWO WEEKS OF REGISTRATION ON STUDY:

Eligibility Checklist.

14.4 WITHIN THIRTY DAYS OF ANY EVS AND BIOPSY OR DILATION AND CURETTAGE:

Submit materials and forms as outlined in Section 12.0. If a requested procedure is not performed, please submit the required forms with a notation explaining why the procedure was not performed.

15.0 SPECIAL INSTRUCTIONS

- 15.1 If a hysterectomy is performed it is requested that a portion of the endometrium be snap frozen in liquid nitrogen and shipped with a copy of the Specimen Submission Form on dry ice to Loyola University Cancer at the address below. The frozen tissue will be cataloged and stored in a -70 degree freezer:

Ronald K. Potkul, MD
Loyola University Medical Center
Department of Obstetrics & Gynecology
2160 S. First Avenue
Maywood, IL 60153
Phone: 708/327-3314

- 15.2 The Federal guidelines for shipment are as follows:

- a. The specimen must be wrapped in an absorbable material;
- b. The specimen must then be placed in an AIRTIGHT container (like a resealable bag);
- c. Pack the resealable bag and specimen in a styrofoam shipping container;
- d. Pack the styrofoam shipping container in a cardboard box.
- e. The cardboard box must be marked as "BIOHAZARD".

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Adverse Experiences

Any adverse experience, if deemed treatment related, must be reported to the Operations Office Adverse Reaction (AR) representative (210/677-8808), who will obtain information on the AR. Adverse Reactions (ARs) for CALGB patients will be reported to the Southwest Oncology Group Operations Office (210/677-8808). Copies of all ARs for patients registered through each Cooperative Group will be forwarded to the appropriate group's central office. For ECOG and NCCTG guidelines, see next page. Depending on the nature of the reaction, the AR representative will advise whether the report to the NCI should be phoned in, written in, or both. See guidelines below. On Phase II and III studies, all deaths considered treatment-related must be reported immediately to the AR representative.

All adverse experiences must also be reported to the Institutional Review Board within 10 days and documentation of this report sent to the Operations Office.

All adverse experiences must also be recorded in the appropriate section of the case report form. The report should include, whenever possible, the investigator's written medical judgment as to relationship of the adverse experience to study treatment (i.e., "probable", "possible" or "unrelated").

GUIDELINES FOR REPORTING OF ADVERSE REACTIONS (ARS)
OCCURRING ON THIS STUDY

Southwest Oncology Group and CALGB institutions

The following guidelines for reporting adverse reactions (ARs) apply to any research protocol. The following ARs experienced by patients accrued to these protocols and attributed to the protocol treatment **should be reported by telephone to the Southwest Oncology Group Operations Office (210/677-8808), within 24 hours of occurrence, your Institutional Review Board (IRB) and written notification to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:**

- (a) Any AR which is **BOTH** serious (life threatening [Grade 4] or fatal [Grade 5]) and unexpected.^{1,2,3}
- (b) Any increased incidence of a known AR which has been reported in the package insert or the literature.
- (c) Any death on study if **CLEARLY** related to the protocol treatment.

The AR report should be documented on Form FDA-3500 and mailed to the address below:

Investigational Drug Branch
P. O. Box 30012
Bethesda, MD 20824

Send a copy of the Form FDA-3500, all data records and a copy of documentation of notification of your IRB to the Operations Office within 10 days.

ATTN: ADR Program
Southwest Oncology Group
14980 Omicron Drive
San Antonio, TX 78245-3217

1. See Section 19.0, Southwest Oncology Group Toxicity Criteria.
2. A list of all known toxicities can be found in either the Background section, Drug Information or Informed Consent Form of the protocol.
3. Reactions judged definitely not to be treatment related should not be reported. However, a report shall be submitted if there is only a reasonable suspicion of treatment effect.

NCCTG institutions

Fax, then report in writing to NCCTG Operations Office (no telephone calls necessary) within five working days:

1. Any ADR that is both serious and unexpected: life threatening (Grade 4) or fatal (Grade 5).
2. Any increased incidence of a known ADR that has been reported in the package insert or the literature.
3. Any death on study, if clearly related to the commercial agent(s).

The ADR report must be documented on the ADR form (Form FDA 3500) and the original mailed to:

North Central Cancer Treatment Group
Operations Office
200 First Street, SW
Rochester, MN 55905

The NCCTG Operations Office will immediately forward a copy of the ADR form to Southwest Oncology Group and to IDB if deemed a reportable ADR.

ECOG Institutions

ADR reporting should be based on the Southwest Oncology Group Toxicity Criteria (Appendix 19.1).

Written Adverse Drug Reaction reports are to be submitted ONLY on the Adverse Reaction (ADR) Form for Investigational Drugs (Form 391R), and the form must be signed by the treating investigator. The Southwest Oncology Group will accept this form in lieu of the 2 page NCI Adverse Drug Reaction (ADR) form and the 1 page FDA Adverse Drug Reaction (ADR) Form (3500). All ADR reports sent to ECOG are to be accompanied by copies of all available and updated study data (on-study forms, flow sheets, follow-up forms, etc.) as well as evidence of notification to the institutional IRB.

This protocol does not contain IND agents; toxicities occurring on treatment arms are to be considered commercial.

Guidelines for reporting of toxicities occurring with commercially available agents:

- Any ADR which is BOTH serious (Grade 4) or life-threatening (Grade 5) AND unexpected,
- Any Grade 5 event while on treatment if CLEARLY related to the commercial agent(s),
- Any increased incidence of a known ADR.

Submit original written ADR form to the IDB and a copy to the ECOG Data Management Office within 5 working days of the event.

The ECOG Data Management Office will call the Southwest Oncology Group Operations Office to report the telephone ADR calls. The ADR forms will be forwarded to the Southwest Oncology Group Operations Office by the ECOG Data Management Office.

NCI Telephone Number: 301/230-2300
NCI Mailing Address:
Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824

ECOG Telephone Number: 617/632-3610
ECOG Address:
ECOG Data Management Office
ATTN: ADR
303 Boylston Street
Brookline, MA 02146-7215

Non-Treatment Related Toxicities: If a toxicity is felt to be outside the definitions listed above and unrelated to the protocol treatment, this must be clearly documented on the flow sheets which are submitted to the ECOG Data Management Office according to the Data Submission Schedule. This does not in any way obviate the need for reporting the toxicities described above.

17.0 BIBLIOGRAPHY

1. Bardon S, Vignon F, Derocq D, Rochefort H. The antiproliferative effects of tamoxifen in breast cancer cell: Mediation by the estrogen receptor. *Molec Cell Endocr* 35:89-96, 1984.
2. Furr BJ, Jordan VC. The pharmacology and clinical uses of tamoxifen. *Pharmac Ther* 25:127-206, 1984.
3. Killackey MA, Hakes TB, Pierce VK. Endometrial adenocarcinoma in breast cancer patients receiving antiestrogens. *Cancer Treat Rep* 69:237-238, 1985.
4. Hardell L. Tamoxifen as risk factor for carcinoma of corpus uteri (letter). *Lancet* 3:563, 1988.
5. Neven P, Muylder X, Van Belle Y, et al. Tamoxifen and the uterus and endometrium (letter). *Lancet* 1:375, 1989.
6. Fornander TB, Cedermark A, Mattsson L, Skoog T, et al. Adjuvant tamoxifen in early breast cancer: Occurrence of new primary cancers. *Lancet* 21:117-120, 1989.
7. Atlante G, Pozzi M, Vincenzoni C, et al. Four case reports presenting new acquisitions on the association of breast and endometrial cancer. *Gynecol Oncol* 37:378-380, 1990.
8. Matthew A, Chabon AB, Kabakow B, et al. Endometrial carcinoma in five patients with breast cancer on tamoxifen therapy. *NY State J Med* 90:207-208, 1990.
9. Malfetano JH. Tamoxifen-associated endometrial carcinoma in postmenopausal breast cancer patients. *Gynecol Oncol* 39:82-84, 1990.
10. Magriples U, Naftolin F, Schwartz PE, et al. High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. *J Clin Oncol* 11:485-490, 1993.
11. Lahti E, Blanco G, Kauppila A, et al. Endometrial changes in postmenopausal breast cancer patients receiving tamoxifen. *Obstet Gynecol* 81:660-664, 1993.
12. Seoud M A-F, Johnson J, Weed JC. Gynecologic tumors in tamoxifen-treated women with breast cancer. *Obstet Gynecol* 82:165-169, 1993.
13. VanLeeuwen FE, Benraadt J, Coebergh JWW, et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet* 343:448-452, 1994.
14. Barakat RR, Wong G, Curtin JP, et al. Tamoxifen use in breast cancer patients who subsequently develop corpus cancer is not associated with a higher incidence of adverse histologic features. *Gynecol Oncol* 55:164-168, 1994.
15. Fisher B, Costantino JP, Redmond CK, et al. Endometrial cancer in tamoxifen-treated breast cancer patients: Findings from NSABP B-14. *JNCI* 86:527-537, 1994.
16. Fornander T, Hellstrom A-C, Moberger B. Descriptive clinicopathologic study of 17 patients with endometrial cancer during or after adjuvant tamoxifen in early breast cancer. *JNCI* 85:1850-1855, 1993.
17. Kedar RP, Bourne TH, Powles TJ, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomized breast cancer prevention trial. *Lancet* 343:1318-1321, 1994.

18. Cohen I, Rosen DJD, Shapier J, et al. Endometrial changes with tamoxifen: comparison between tamoxifen-treated and non-treated asymptomatic postmenopausal breast care patients. *Gyn Onc* 52, 185-190, 1994.
19. Barakat RR. The effect of tamoxifen on the endometrium. *Oncology*, 9:129-139,1995.
20. Dichson RB, Lippman ME. Estrogenic regulation of growth and polypeptide growth factor secretion in human breast carcinoma. *Endocr. Rev* 8:20, 1989.
21. Odom LD, Barrett JM, Pantzis CG, Stoddard LD, McDonough PG. Immunocytochemical study of fas and myc proto-oncogene polypeptide expression in the human menstrual cycle. *Am J Obstet Gynecol.* 161:1663, 1989.
22. Kumar V, Chambon P. The estrogen receptor binds tightly to its estrogen responsive elements as a ligand-induced homodimer. *Cell* 55:145-156, 1988.
23. Knapp RC, Berkowitz RS. Gynecologic Oncology. New York: McMillan, 1986.
24. Tseng L, Mazella J. Cyclic changes of estradiol metabolic enzymes in human endometrium during the menstrual cycle. In Kimball FA (ed). The Endometrium. New York: SP Medical and Scientific Books, 211-226, 1980.
25. Bonney RC, Reed MJ, Beranek PA, Ghilchik MW, James BH. Metabolism of estradiol in vitro by normal breast and tumor tissue in postmenopausal women . *J Steroid Biochem* 24:361-364, 1986.
26. Maentausta O, Peltoketo H, Isomaa V, Jouppila P, Vihko R. Immunological measurement of human 17 beta-hydroxy steroid dehydrogenase. *J Steroid Biochem* 36:673-680, 1990.
27. Gompel A, Malet C, Spritzer P, Laladrerie JP, et al. Progestin effect on cell proliferation and 17 beta-hydroxy steroid dehydrogenase activity in normal human breast cells in culture. *Clin Endocrin and Metab* 63:1174-1180, 1986.
28. Speirs V, Adams EF, White MC. The antiestrogen tamoxifen blocks the stimulatory effects of interleukin 6 on 17 beta hydroxy-steroid dehydrogenase activity in MCS-7 cells. *J Steroid Biochem Molec Biol* 46:605-611, 1993.
29. Whitehead MI, Townsend PT, Pryse-Davies J, Ryder TA, King RJ. Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium. *NEJM* 305:1599-1605, 1981.
30. Clark JH, Peck EJ, Hardin JW, Eriksson H. Biology and pharmacology of estrogen receptor binding: Relationship to uterine growth. In O'Malley and Birnbaumer (eds). Receptors and Hormone Action. New York: Academic Press, 1-31, 1987.
31. Kirkland, Murthy L, Stancel G. Tamoxifen stimulates expression of the cfos proto-oncogene in eroded uterus. *Molec Pharmacology* 43:709-714, 1993.
32. Higgins GD, Uzelin DM, Phillips GE, Burrell CJ. Presence and distribution of human papillomavirus sense and antisense RNA transcripts in genital cancer. *J General Virology* 72:885-895, 1991.
33. Kurjak A, Shalan H, Sobic A, Benic S, Zudenigo D, Kupasic S, Predanic M. Endometrial carcinoma in postmenopausal women: Evaluation by transvaginal color Doppler ultrasonography. *Am J Obstet Gynecol* 169(6):1597-1603, 1993.
34. Kupesic-Urek S, Shalan M, Kurjak A. Early detection of endometrial cancer by transvaginal color Doppler. *Eur J of Obstet and Gyn and Repr Bio* 49:46-49, 1993.

35. Campbell S, Bourne T, Crayford T, Pittrof R. The early detection and assessment of endometrial cancer by transvaginal colour Doppler ultrasonography. *Eur J Obstet Gynecol and Reprod Biol* 49:44-45, 1993.
36. Hulka CA, Hall DA, McCarthy K, Simeone JF. Endometrial polyps, hyperplasia and carcinoma in postmenopausal women: Differentiation with endovaginal sonography. *Radiol* 191(3):755-758, 1994.
37. Nasri MN, Shepherd JH, Setchell EM, Lowe DG, Chard T. The role of vaginal scan in measurement of endometrial thickness in postmenopausal women. *Br J Obstet Gynecol* 98:470-475, 1991.
38. Carter RJ, Lau M, Saltzman AK, Hartenbach EM, Chen D, Johnson PF, Fowler JM, Carlson JW, Carson LF, Twigg LB. Gray scale and color flow Doppler characterization of uterine tumors. *J Ultrasound Med* 13(11):835-840, 1994.
39. Chan FY, Chau MT, Pun TC, Lam C, Ngan HYS, Leong L, Wong RLC. Limitations of transvaginal sonography and color Doppler imaging in the differentiation of endometrial carcinoma from benign lesions. *J Ultrasound Med* 13:623-628, 1994.
40. Lin MO, Gosink BB, Wolf SI, Feldesman MR, Stuenkel CA, Braly PS, Pretorius DH. Endometrial thickness after menopause: effect of hormone replacement. *Radiol* 180:427-432, 1991.
41. Tapper R, Cohen I, Altaras M, Shapira J, Cordoba M, Dror Y, Beyth Y. Doppler flow evaluation of pathologic endometrial conditions in postmenopausal breast cancer patients treated with tamoxifen. *J Ultrasound Med* 13:635-640, 1994.
42. Kurjac A, Kupesic-Urak S, Schulman M, Zalud I. Transvaginal color flow Doppler in the assessment of ovarian and uterine blood flow in infertile women. *Fertil Steril* 56:870-873, 1991.
43. Pellerito JS, Taylor KJW, Quedene-Case C, Hammers LW, Scoutt LM, Ramos IM, Meyer WR. Ectopic pregnancy: Evaluation with endovaginal color flow imaging. *Radiology* 183:407-411, 1992.
44. Emerson DS, Cartier MS, Altieri LA, Felker RE, Smith WC, Stovall TG, Gray LA. Diagnostic efficacy of endovaginal color dopper flow imaging in an ectopic pregnancy screening program. *Radiology* 183:413-420, 1992.
45. Fleischer AC, Rodgers WH, Bhaskara KR, Kepple DM, Worrell JA, Williams L, Jones III HW. Assessment of ovarian tumor vascularity with transvaginal color Doppler sonography. *J Ultrasound in Medicine* 10:563-568, 1991.
46. Bourne TH, Campbell S, Whitehead MI, Royston P, Steer CV, Collins WP. Detection of endometrial cancer in postmenopausal women by transvaginal ultrasonography and colour flow imaging. *Br Med J* 301:369, 1990.
47. Cohen I, Rosen DJD, Topper R, Crodobe M, Shapira Y, Altaras MM, Dror Y, Yigael D, Beyth Y. Ultrasonographic evaluation of the endometrium and correlation with endometrial sampling in postmenopausal patients treated with tamoxifen. *J Ultrasound med* 5:275-280, 1993.

18.0 MASTER FORMS SET

- 18.1 Sample Consent Form
- 18.2 Endovaginal Sonogram (EVS) Submission Form
- 18.3 Endometrial Pathology (EMB) Submission Form
- 18.4 Specimen Submission Form

CONSENT FORM AND INFORMATION ABOUT

A Cross-Sectional Study to Estimate the Incidence of Endometrial Pathology in Women Receiving Tamoxifen on **SWOG-8814** (INT-0100) And **SWOG-8897** (INT-0102)

TO BE CONDUCTED AT

- i. You are invited to take part in this research study because you have had a breast cancer that has been removed by surgery, you are being treated on one of two research studies, and you are currently receiving tamoxifen without signs of recurrence of your breast cancer. We want to find out the effects of tamoxifen treatment on your uterus.

As you know, tamoxifen has been reported, in rare cases, to cause uterine cancer. We want to learn more about all uterine changes caused by tamoxifen.

As part of the ongoing scientific and biotechnological activities of the Southwest Oncology Group and its agents, tissue samples from your uterus will be preserved and used for research and development purposes. As a result of these biotechnological activities, an economic benefit may be derived directly or indirectly by the Southwest Oncology Group, individual researchers, and others engaged in these activities. By signing this consent form, you authorize the preservation and use of tissue specimens taken from you.

We cannot and do not guarantee you will benefit if you take part in this study. If you take part in this study, abnormal endometrial tissue may be found earlier than it may have been found otherwise.

- ii. You have already been placed on tamoxifen as part of your treatment. In this study, a small syringe will be inserted into your uterus to obtain a very small biopsy. In addition, a small probe will be inserted into your vagina and ultrasound pictures will be taken of the lining of your uterus. The results of the biopsy and ultrasound will be studied. In the event of abnormalities, you will be removed from this study and your doctor will discuss further treatment options with you (including stopping tamoxifen, beginning treatment with medroxyprogesterone acetate and hysterectomy).

The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be (charged in the usual way/provided at a reduced rate).

- iii. Side effects some people have had after receiving medroxyprogesterone acetate are listed as follows:

Endometrial Biopsy

Complications of endometrial biopsy include pain, cramping similar to menstrual cramps, bleeding (usually spotting for 48 hours) and rarely perforation of the uterus resulting in major bleeding, abdominal pain and fever.

Endovaginal Sonogram

Complications of endovaginal sonogram are minor discomfort similar to a pelvic examination.

- IV. There are many suggested screening systems and possible treatments for endometrial changes. Please talk with your doctor about these. It is not known if the screening and/or treatment you receive will offer any increased benefit than that currently available outside of participation in this research.
- V. If you are pregnant, you cannot take part in this study. You will take a urine test to see if you are pregnant before you start treatment. If you are sexually active, we strongly recommend you take precautions to avoid the possibility of becoming pregnant because we do not know how this drug could affect an unborn child.
- VI. If you experience illness as a result of treatment on this study, you will be offered emergency medical treatment and continuing medical care including hospitalization if necessary. This treatment will not be free but must be paid in the same way as your regular medical care is paid. We cannot pay you to take part in this study.
- VII. We will keep any information we learn from this study confidential and disclose it only with your permission. By signing this form, however, you allow us to make your records available to the National Cancer Institute, the Food and Drug Administration and the Southwest Oncology Group. If we publish the information we learn from this study in a medical journal, you will not be identified by name.
- VIII. Whether or not you take part in this study will not affect your future relations with your doctors (there will be no loss of benefit or change in attitude) or _____ (hospital name). If significant new findings are developed during the course of this study which may relate to your willingness to continue, this information will be provided to you. In addition, you understand that you may refuse to continue on this study, at any time after the start of therapy, without fear of prejudice to additional treatment that may be needed.
- IX. The doctor(s) involved with your care can answer any questions you may have about the drug program. In case of a problem or emergency, you can call the doctors listed below day or night.

Office

Home

Dr.

Dr.

Dr.

You can also call the Institutional Review Board (# _____) if you have any questions, comments or concerns about the study or your rights as a research subject.

- X. We will give you a copy of this form to keep.
- XI. You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer after reading and understanding all the information on this form.

Date

Signature of Subject

Signature of Witness

Signature of Investigator

Time

Southwest Oncology Group

DRAFT

Page 1 of 1

EVS SUBMISSION FORM

Protocol Step

SWOG Patient No. Patient's Name _____ LEM

Institution / Member _____ S.S. No. - -

Physician _____ Hospital No. _____

Groups other than SWOG: Name/Study No./Pt No. _____ / _____ / _____

Amended data: Yes, mark amended items in red.

Instructions: All dates are MONTH, DAY, YEAR.

Indicate an unknown part of a date with a horizontal line drawn across the appropriate boxes.

Exam date - -

Exam sequence #

Transducer manufacturer _____

Frequency (MHZ) _____

Maximum AP endometrial stripe thickness (mm): Anterior SWT _____

Posterior SWT _____

DWT _____

Fluid seen in endometrial canal No Yes

Cystic space present No Yes

Endometrial margins well defined No Yes

Please check the one that applies:

- 1- Grey scale only
- 2- Color doppler only
- 3- Grey scale and color doppler

If color doppler:

Velocity setting _____

Pulse repetition frequency _____

Wall filter _____

Doppler sample volume _____

SPTA _____

Review Acceptability

- 1- Yes
 - 2- No
 - 3- Insufficient
- (List what is needed in Notes section)

Notes:

363

By: _____

Date: _____

SWOG 04-23-96 SW337

19.2 Research Methods for Molecular Studies

Estrogen and Progesterone Receptor Determination:

An immunohistochemical localization of estrogen and progesterone receptors will be performed using commercial reagent kits (Abbott Laboratories, Diagnostic Division, North Chicago, IL) according to the instructions of the manufacturer. The results will be evaluated as specific staining, color absent (negative): weak (+): moderate (+ +): and strong (+ + +).

In-situ hybridization (ISH) for proto-oncogene expression:

The ISH procedures have been described previously in detail (32). Briefly, 5 μ m sections of formalin-fixed, paraffin-embedded tissues were placed on 3aminopropyltrieth-oxysilane-coated slides, dewaxed, rehydrated and refixed in 4% paraformaldehyde. Sections were then treated with proteinase K (25 μ g/ml), refixed in paraformaldehyde, acetylated, then dehydrated through graded ethanols and air-dried. An aliquot (2.5 μ l) of ³²P-labelled probe mix containing 50,000 to 100,000 d.p.m. of 125I (0.05 to 0.1 ng of RNA) per μ l was placed on the section, covered with a 13 mm round siliconized coverslip, placed under liquid paraffin and hybridized for 16 h at 50°C. Slides were then washed RNase A-treated, washed, dried and dipped in Ilford K2 emulsion and exposed in light-tight boxes at 4°C for 1 to 2 weeks. Slides were developed with Kodak D19 developer and Rapid fixer, stained with Gill's hematoxylin and eosin and mounted in Depex.

Scoring of biopsies was performed by visual assessment of grains, using probes of the opposite sense and stromal cells as negative controls. Intensity of the signal was estimated using a + to + + + + scale where + was at least two times background levels and up to approximately 20 grains/cell, + + 21 to 50, + + + 51 to 100 and + + + + > 100 grains per cell. To confirm that signals detected with each probe were due to RNA-RNA hybrids and not RNA-DNA hybrid formation, each probe was compared to a section hybridized with a probe from the identical construct but transcribed in the opposite (mRNA sense) direction .

17-Hydroxysteroid dehydrogenase enzyme activity assay

Oxidative and reductive 17-HSD activity will be determined in tissue homogenates from hysterectomy specimens. The 17-HSD activity will be assessed by determining the ability of the endometrial homogenate to convert either [3H] E1 to [3H] E2 or vice-versa by methods described in the literature (26). The endometrial homogenate is incubated with [3H] E1 or [3H] E2 in serum-free media for four hours at 37°C, then the steroids will be extracted from the media with twice the volume of diethyl ether, the samples will be dried down and separated by thin layer chromatography on silica gel plates with a 4:1 mixture of dichloromethane-ethyl acetate as the mobile phase. Spots corresponding to either E1 or E2 will be visualized under UV light by incorporation of an excess of cold carrier into each sample, cut out, eluted with methanol and counted in a scintillation counter.

APPENDIX O

Body of Southwest Oncology Group IDEA Grant Proposal 7/17/96 to the USAMRMC Breast Cancer Program: "Clonal Hematopoiesis as a Marker of Genetic Damage following Adjuvant Chemotherapy for Breast Cancer: Pilot Study of the Southwest Oncology Group to Evaluate Incidence"

Study Coordinators: Wendy Stock, M.D., Marilyn L. Slovak, Ph.D., Cheryl Willman, M.D.

Originating Committee: Southwest Oncology Group Committee on Women's Health (Kathy S. Albain, M.D., Chair)

Southwest Oncology Group Disease Committees: Breast Cancer Committee (Silvana Martino, D.O., Chair) and Leukemia Committee (Frederick R. Appelbaum, M.D., Chair)

Funding: Pending

The following grant proposal is proprietary information.

D. BODY OF PROPOSAL

368

BACKGROUND/RATIONALE

Therapy-related myelodysplasia (t-MDS) and/or therapy-related leukemia (t-AML) have emerged as uncommon but well-established complications of adjuvant therapy for breast cancer using dose-intensive regimens¹⁻³. t-MDS and AML evolve as a result of expansion of an abnormal clone of hematopoietic stem cells which have acquired somatic mutations conferring a growth advantage.

According to the Jacobs model for leukemogenesis⁴, the mutations resulting in clonal hematopoiesis may occur without any obvious hematological change (no dysplasia or cytopenias noted). Subsequently, the acquisition of a variety of additional genetic lesions may be essential for the development of MDS (preleukemia) or overt leukemia. Clonal chromosomal abnormalities have been reported in the majority of cases of t-MDS/AML. The most frequently reported abnormalities involve complete loss or interstitial deletions of the long arm of chromosomes 7 and/or 5. Typically, these leukemias develop following alkylating agent-induced damage at a median of 3-5 years following therapy⁵. A second group of therapy-related leukemias, described by Pederson-Bjergaard and others, are associated with rearrangements of the *MLL* gene in chromosome band 11q23⁶⁻⁹. The 11q23-associated t-AMLs often develop following treatment with drugs that target DNA-topoisomerase II (e.g., epipodophyllotoxins, anthracyclines) with a very short (12 to 18 months) latency following treatment⁸.

Over the last ten years, anthracyclines have become a major component of combination chemotherapy regimens for breast cancer. Two recent adjuvant breast cancer trials, the NSABP-B25 and NCIC^{2,3}, employing dose-intensive anthracycline-based chemotherapy, reported rates of t-MDS/AML that are two to four-fold higher than in previous adjuvant studies. These monocytic leukemias occurred following a short latency period (all within two years of adjuvant therapy), a characteristic finding of the hematologic disorders linked to the topoisomerase II inhibitors. Cytogenetic analysis revealed rearrangements of 11q23 in five of eight of these cases. Further concern about the development of t-MDS/AML following high-dose chemotherapy (with or without stem cell rescue) for breast cancer may be warranted based on the alarming data emerging on high rates of development of t-MDS and AML following autologous transplantation for lymphoma, where the incidence of therapy-related leukemias has been estimated to be as high as 18% at six years following transplantation¹⁰⁻¹⁴.

These studies raise three major concerns: 1) Does genetic damage leading to the development of clonal hematopoietic stem-cell disorders occur with unacceptable frequency in patients receiving these intensive, anthracycline-based adjuvant regimens for the treatment of breast cancer? 2) Will careful monitoring of this patient population reveal additional t-MDS/AML with long-term follow-up? and, 3) Does the administration of recombinant hematopoietic growth factors (CSFs) used to minimize morbidity and facilitate scheduled drug dosing play a potentiating role in the development of these secondary malignancies?

Genetic damage may be induced by chemotherapeutic agents used in the treatment of breast cancer. This damage may result in clonal proliferation which, according to the Jacobs model of neoplasia, is an essential early (initial?) step in leukemogenesis, occurring prior to the development of clinical abnormalities. Data demonstrating the presence of clonal proliferation following chemotherapy exist. Carter and others found evidence of clonal hematopoiesis in more than 30% of 70 clinically asymptomatic patients who had received prior cytotoxic chemotherapy for lymphoma^{4,15,16}. Busque et al. found that clonal hematopoiesis existed in eight of 12 (66%) patients with Hodgkin's or Non-Hodgkin's lymphomas studied prior to autologous transplantation (all had received prior chemotherapy), and that this value was

significant ($p < 0.0033$) when compared to normal control donors¹⁷. Gale et al. have shown that sequential X-linked clonality assays are predictive of subsequent evolution to frank MDS/AML¹⁸. These provocative studies suggest that the presence of clonal hematopoiesis following chemotherapy may be a relatively common event. Pilot studies are needed to determine the clinical relevance of these interesting findings.

The development of clonal hematopoiesis may be one of the earliest events that occurs in an evolving neoplastic process¹⁸. Thus, assays to detect clonality, such as the PCR-based HUMARA (human androgen receptor assay), may define the primary steps in the evolution to MDS or AML^{19,20}. The HUMARA is informative in more than 90% of females and is, therefore, probably the optimal clonality assay for testing female blood or marrow samples for clonal hematopoiesis at regular intervals²¹.

Genomic instability at simple repeated DNA sequences, or microsatellites, is a sensitive marker of a clonal cell population resulting from genetic damage^{22,23}. It appears that instability in these repeated sequences is a result of defective DNA replication/repair mechanisms. In two recent publications, genomic instability in microsatellite repeat sequences has been detected in patients with leukemia and myelodysplasia; these preliminary data suggest that microsatellite variants arising from genomic instability can be used as clonal markers in hematologic malignancies^{24,25}. Therefore, the microsatellite instability and the HUMARA assays are complementary PCR-based methods of detecting genetic damage, and can be done using a very small amount of DNA obtained from blood or buccal smears.

HYPOTHESIS/PURPOSE

Clonal hematopoiesis and microsatellite instability may be early markers of genetic damage, preceding the acquisition of critical, recurring genetic alterations associated with the development of therapy-related MDS and acute leukemia. Alternatively, clonal hematopoiesis and microsatellite instability may occur quite commonly, but may not necessarily be significant early markers of leukemogenesis. Determination of whether genetic damage resulting in microsatellite instability and/or clonal hematopoiesis occurs following specific high-dose chemotherapeutic regimens is a critical initial step to understanding the clinical significance of these findings, and to their possible relationship to the subsequent development of a therapy-related hematologic malignancy following adjuvant therapy for breast cancer.

This pilot study will test the hypothesis that genetic damage defined by the presence of clonal hematopoiesis can be detected in a subset of patients following dose-intensive adjuvant therapy on a current Southwest Oncology Group (SWOG) trial for breast cancer. The HUMARA will serve as a general clonality assay, while the microsatellite instability assays will assess genetic damage at specific chromosomal loci in genomic regions associated with the development of t-MDS/AML.

TECHNICAL OBJECTIVES (SPECIFIC AIMS)

1. To estimate the incidence of early genetic damage, defined by the presence of clonal hematopoiesis using a general clonality assay, the HUMARA, in pretreatment blood and bone marrow, apheresis and two sequential post-treatment specimens of female patients following dose-intensive adjuvant chemotherapy regimens for breast cancer.
2. To screen these samples for the presence of defective DNA mismatch repair mechanisms using assays to detect microsatellite instability as an alternative means of detecting a clonal population resulting from genetic damage following dose-intensive adjuvant regimens for breast cancer.

METHODS

Study design: A pilot study to estimate the incidence of clonal hematopoiesis in sequential blood and bone marrow samples from female patients following dose-intensive adjuvant chemotherapy for breast cancer. For this pilot, samples will be obtained prior to initiation of treatment, from collected stem cell specimens (in 100 patients randomized to autologous stem cell transplant), and at three and twelve months following completion of treatment. Tissue from buccal mucosal brushings will be collected at each timepoint and serve as an internal somatic control for each patient sample (as outlined in Table 1, Addenda B, "Illustrations/Diagrams"). Genetic damage will be evaluated at these timepoints by two methods, the HUMARA clonality and microsatellite instability assays. In cases with positive HUMARA and/or microsatellite assays, reverse-transcriptase (RT)-PCR analysis will be performed to detect aberrant *MLL* gene transcripts as an initial step in targeting specific genes associated with anthracycline-induced damage. Banked specimens will be available for all future molecular studies.

Study Population: The study population consists of 200 women with breast cancer who are also enrolled on a single randomized Southwest Oncology Group dose-intensive adjuvant study, (S9623, "A Comparison of Intensive Sequential Chemotherapy using Doxorubicin plus Paclitaxel plus Cyclophosphamide with High Dose Chemotherapy and Autologous Hematopoietic Progenitor Cell Support for Primary Breast Cancer in Women with 4-9 Involved Axillary Lymph Nodes, Phase III, Intergroup") for women with four to nine positive nodes. This companion correlative study will be linked to this treatment study, but will have a separate protocol and informed consent document. One hundred patients from each arm of S9623 will be enrolled on our study. Treatment on S9623 consists of randomization to two arms: Arm A) sequential cycles of dose-intensive therapy with adriamycin, paclitaxel and cyclophosphamide with hematopoietic growth factor support; or, Arm B) four cycles of adriamycin and cyclophosphamide (AC) followed by autologous stem cell collection (peripheral blood apheresis or bone marrow) and subsequent myeloablative chemotherapy requiring stem cell and hematopoietic growth factor support. (A table of the treatment schedule is included as Table 2 in Addenda B, "Illustrations/Diagrams.")

It is a standing policy of the Southwest Oncology Group to include eligible patients of both sexes and all races and ethnicities in all Group clinical trials, except as restricted by specific disease site (e.g., prostate, gynecological). For example, accrual of the Southwest Oncology Group Breast Cancer Committee in 1995 totaled 2,065 patients, of which all patients were female, consistent with the incidence of the disease. This accrual included 81% (1672/2065) Caucasian patients and 10% (197/2065) African-Americans, 5% (117/2065) Hispanics and 4% (79/2065) other minority patients.

Statistical Considerations: One hundred patients per arm from S9623 will be accrued on this study. The length of accrual is anticipated to be 2 years. Compliance with the three month blood draw should be nearly complete; at 12 months following completion of treatment, approximately 15% might be anticipated to have relapsed or refused and not have samples available. The probability of clonal hematopoiesis at a particular timepoint can be established to within +/- 0.1 with a sample size of 100 per arm, and to within +/- 0.11 with a sample size of 85. A two-sided .05 level test of the association of the treatment group with presence or absence of clonality will have adequate power to detect differences of .25 or greater (power at least .93 for the pretreatment and three month timepoint and .88 for the 12 month post-treatment timepoint, if sample size decreases to 85 per arm).

Change in status between pretreatment, stem cell collection, and the three and twelve month post-treatment samples will be explored, as will concordance of the HUMARA and microsatellite assays. Association of other pre-study patient characteristics and tumor-related

variables with presence or absence of clonality by HUMARA or microsatellite assays will also be explored.

Sample collection: Two ml of a pretreatment bone marrow aspirate from each patient (required for entry to S9623) will be collected into EDTA tubes and will serve as a very sensitive control for detection of any pre-treatment abnormality. Sixty ml of blood will be collected from registered patients prior to initiation of treatment, and at three and twelve months following completion of all chemotherapy. For the 100 women in our study who are randomized to the autologous stem cell transplant arm of S9623, 2 ml from the stem cell collection will also be obtained for analysis. Two buccal mucosa brushings using a soft cytology brush will be collected from each enrolled patient (internal somatic control tissue) at each of these timepoints (see Table 1, Addenda B, "Illustrations/Diagrams"). Cytology brushes will then be placed in sterile test tubes for storage and shipping. All samples will be sent at room temperature by overnight courier to arrive within 24 hours at the existing Southwest Oncology Group tissue repository at the University of New Mexico, directed by Cheryl L. Willman, M.D, where samples will be processed for DNA and RNA. Additional cells will be cryopreserved. Samples will be subsequently batched to send to the University of Illinois at Chicago for the microsatellite instability and RT-PCR assays (Dr. Wendy Stock) and the City of Hope laboratories for the HUMARA assay (Dr. Marilyn Slovak). The repository at the University of New Mexico will retain frozen cells and DNA on all samples for future studies.

Sample Processing: DNA is extracted from buccal mucosa swabs according to published methods²⁶. DNA for more than twenty PCR reactions can be collected from a single mucosal brushing.

High molecular weight DNA will be prepared from the blood and apheresis samples following Ficoll-gradient separation, according to standard proteinase K digestion and phenol/chloroform extraction methods²⁷. Cells from each blood sample (a minimum of 20-30 X 10⁶ cells) will be frozen for viability according to standard methods²⁸.

HUMARA assay: DNA samples from each of the 200 patients enrolled will be studied at the timepoints outlines previously. Clonality at the HUMARA locus will be assessed by PCR amplification according to Willman et al.²¹ using the primers described by Gale et al.,²⁹ and quantitated by the method of Delabesse et al.³⁰ Willman et al. have performed mixing experiments which demonstrate that the percentage of clonal cells can be estimated with an error of $\pm 10\%$, and that a clonal population of cells can be detected if they constitute more than 10 percent of the cells in a polyclonal background. Assays will be performed in duplicate or triplicate.

Microsatellite instability assay: Microsatellite instability will be assessed at five chromosomal loci: 7q31 (D7S522 marker)²⁸, 5q31 (Mfd27 marker)²⁹, 17p12 (Mfd41 marker)³⁰, 8p22 (LPL marker)³¹, and 11q23 (D11S939 marker)³². Although the microsatellite assay is a general assay for genomic instability, we have chosen highly polymorphic microsatellites from regions known to be associated with t-MDS/AML since these markers may also provide information about loss of heterozygosity in these genomic regions³³. The PCR assays will be done in duplicate according to published methods²¹⁻²³.

Detection of MLL gene rearrangements: In cases where the HUMARA or microsatellite repeat assays are positive for clonal hematopoiesis, sensitive reverse-transcriptase PCR assays, using

RNA from banked specimens, will be used to detect *MLL* fusion transcripts commonly reported in AML with 11q23 abnormalities^{34,35}.

Study Limitations/Alternative Approaches: Two potential weaknesses in this study exist. First, a clonal population of cells comprising less than 10% of the mononuclear cell population may not be detectable by the HUMARA. Selection of CD34-positive mononuclear cells (stem cell phenotype) will improve the sensitivity of our assays for detection of smaller clonal stem cell populations. As proposed, we will also be able to study an enriched stem cell population from the apheresis or bone marrow specimens which are collected from patients randomized to the transplant arm of S9623. Also, we have published on the feasibility of performing CD34-positive flow cytometric selection from banked peripheral blood cells³⁹. Using the MiniMACS (Miltenyi Biotec, Inc.) flow-sorting system, designed for excellent rare event isolations and separations⁴⁰, we plan to study CD34-positive cells in a number of post-treatment (3 and 12 month) blood samples.

The second limitation involves the possibility of excessive Lyonization (inactivation of one X-chromosome) or age-acquired skewing, because it mimics clonal dominance. To control for this possibility, age-matched controls (18-60 years) will be studied concomitantly, as described by Busque et al.⁴¹ through a separate funding mechanism (Dr. Slovak).

Finally, blood samples will be obtained from any Group patient enrolled on adjuvant breast cancer studies who has been identified (through the Group data base) as having t-MDS/AML. Presumably, clonal abnormalities will be identified by HUMARA and/or microsatellite analyses in these patients, thus providing "proof of concept" and crucial preliminary data for submission of a future grant where study of the evolution of clonal hematopoiesis to MDS/AML following adjuvant treatment for breast cancer is a goal.

Award Category Special Requirements: Detection of early genetic damage following potentially curative adjuvant chemotherapy provides a unique and novel method for obtaining crucial, preliminary data on potential risk factors (genetic susceptibility, chemotherapy regimen, hematopoietic growth factors) which may predispose up to 15% (or more) of patients who receive adjuvant therapy for breast cancer to the development of life-threatening t-MDS/AML.

Investigators' Qualifications: The Southwest Oncology Group has an excellent record for performing Group-wide, correlative studies. Dr. Charles A. Coltman, Jr., Chair of the Southwest Oncology Group since 1981, will serve as the Principal Investigator (PI) of this grant and will subcontract all funding to the following investigators. Dr. Wendy Stock will serve as the project coordinator and perform the microsatellite instability assays and PCR analysis of the *MLL* transcripts. Dr. Stock directs the leukemia program and is co-director of the molecular diagnostics laboratory at the University of Illinois at Chicago. Dr. Marilyn L. Slovak, a co-investigator, directs the cytogenetics laboratory at the City of Hope National Medical Center, and is the Chair of the Southwest Oncology Group Cytogenetics Committee. Dr. Slovak's laboratory will perform the HUMARA clonality assay. The leukemia cell repository laboratory at the University of New Mexico, directed by Dr. Cheryl L. Willman, receives and processes more than 600 patient samples each year. The samples are subsequently distributed to perform a variety of Group-wide studies as part of the NCI-funded Southwest Oncology Group grant and other subcontracts. Dr. Willman, Chair of the Southwest Oncology Group Leukemia Biology Subcommittee, will provide expertise with the HUMARA clonality assay as needed to facilitate successful completion of this proposal. Dr. Stephanie Green, deputy director of the Southwest Oncology Group Statistical Center and statistician of the Breast Cancer Committee, defined the statistical goals of this study and will be responsible for the analysis of the data generated in this pilot study.



DEPARTMENT OF THE ARMY

US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y)

2 Feb 98

MEMORANDUM FOR Administrator, Defense Technical Information
Center, ATTN: DTIC-OCP, Fort Belvoir,
VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for Grant DAMD17-94-J-4220. Request the limited distribution statement for Accession Document Number **ADB215798** be changed to "Approved for public release; distribution unlimited." This report should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Betty Nelson at DSN 343-7328 or email: betty_nelson@ftdetrck-ccmail.army.mil.

FOR THE COMMANDER:

PHYLLIS M. RINEHART
Deputy Chief of Staff for
Information Management

Comp
1/24/2000