July 31, 1998

Quality of life analyses were sent; the cover sheet indicated that the analyses were completed for a presentation at a conference May 17-20, 1998. Participant eye findings reported to MedWatch during the course of the trial were also included.

FDA Request for Information July 28, 1998

1. Supply additional documentation for participant P41078UCD.

2. Clarify the dose of tamoxifen used in the Italian chemoprevention trial. The protocol sent by Zeneca stated that 10 mg of tamoxifen daily was used, while the Lancet article reported a daily dose of 20 mg.

3. Please explain why the requested CRFs were not submitted in their entirety, and why the FDA was not asked about the excluded material.

Sponsor Reply 7/31/98

Question 2. An older version of the protocol was initially submitted to the FDA. The final protocol version indicated that 20-mg daily was the tamoxifen dose used in the study.

Question 3. The sponsor indicated that Zeneca was unaware that the individual assessments of QOL contained demographic data.

Sponsor Reply 8/4/98

Additional information was supplied for the participant in question 1.

Meeting July 30, 1998

This meeting was requested by Zeneca to discuss information from the NCI meeting July 7-8, 1998 and how to incorporate this information into the product labeling. During this meeting, agreement was reached on the following points:

- The Agency agreed that the Gail model and a diagnosis of LCIS should be used to characterize women who should be considered for tamoxifen chemoprevention therapy
- DCIS should not be included in the label as a risk factor that warrants consideration for tamoxifen therapy, as the data from NSABP B-24 has not been submitted for review and women with DCIS were excluded from participation in P-1
- Zeneca and the NSABP will create tables that describe the combinations of risk factors needed for trial entry (similar to the sample tables used in the protocol and on a pocket guide for investigators) and will estimate what percent of the study population is described by these groups
- If these guidelines are provided, Zeneca may refer to the Gail model in the label without mandating that the Gail model "risk disk" be considered as part of the label
- Zeneca should create a patient package insert for the chemoprevention indication for tamoxifen
- The Royal Marsden and Italian tamoxifen chemoprevention studies were discussed; both the sponsor and the FDA will address these trials in their ODAC presentations.

During the course of the meeting, the NSABP made a reference to their submitted manuscript. The Division noted that we had requested submission of a copy of the

manuscript as soon as possible on at least 2 occasions, as a study report was not included in the sNDA. Zeneca replied that the sponsor had intended to send it in the ODAC briefing package. The Division was given a copy by Drs. Costantino and Wolmark at the meeting.

FDA Request for Information August 5, 1998

The following information was requested:

1. Clarification of ER/PR determinations
2. Accrual to substudies
3. Clarification of reporting of compliance data
4. What was the collection rate of blood samples at the time of an event?
5. Was central review used for cancers that developed on study?
6. Please report breast cancer events by the risk strata prospectively specified in the protocol; the manuscript uses a different set of risk levels.
7. Were any participants diagnosed with inflammatory breast cancer or metastatic disease at presentation?

Sponsor reply, August 12, 1998

All of the above points were addressed; the content of the replies is addressed in the review.

FDA Request for Information August 14, 1998

The following information was requested:

1. Please comment on the section in the protocol that states that an attempt at modeling a dose-response relationship would be made in the final analysis.
2. As 8127 women over the age of 50 were enrolled, rather than the 10,000 identified as the sample size required to evaluate cardiovascular effects of tamoxifen, do you think the lack of effect of tamoxifen on reducing the incidence of MI is due to a lack of power?
3. Additional information on an endometrial cancer participant with a suspicious mammogram was requested.
4. Please provide a list of the number of cases of DCIS and invasive breast cancer diagnosed on each arm after the participant went off-study.
5. Were participants removed from study for a diagnosis of DCIS?
6. Provide the documentation for the re-assignment of spine fractures.
7. Provide the rationale for exclusion of a participant with a T2 compression fracture from the spine fracture list.
8. Provide the guidelines used to classify fractures as radial head fractures versus Colles' fractures.
9. Provide any follow-up on the one participant who became pregnant on study and who was due to deliver in June 1998.

Sponsor reply August 19, 1998

Questions 1-6, 8-9 were answered. Details of the responses are included in the relevant sections. The following points were made:

The NSABP noted that all events in all participants were reported, regardless of whether the participant was on or off study drug.

Documentation of the participants removed from the spine fracture list was provided.

Additional review of the reports of the radial head fractures was begun to ensure correct coding, based on the FDA correspondence. The FDA will be notified of any changes in coding as a result of the review.

Sponsor reply August 20, 1998

Question 7. The participant was added to the spine fracture list.

Sponsor submission August 14, 1998

The sponsor submitted an agenda for the Zeneca presentation at ODAC; forwarded to the division 8/21/98.

FDA Request for Information August 17, 1998

1. Please provide the pathology report for a participant with endometrial cancer in order to verify her staging.

Sponsor reply August 19, 1998

The requested documentation was provided.

FDA Request for Information August 24, 1998

How many women on each treatment arm completed 5 years of drug therapy?

Sponsor reply August 26, 1998

The sponsor provided the requested information.

Sponsor submission 8/28/98

This submission contained a letter signed by the NSABP with regard to the summary statements in the draft FDA review. Specifically, the NSABP objected to the reviewer's comment that "...only breast cancers that occurred on study drug were reported...". The reviewer discussed this issue directly with the NSABP on September 1, 1998; the issue was clarified for the ODAC as well.

Sponsor submission 8/31/98

The agenda for the Zeneca presentation at ODAC was amended.

FDA Request for Information 9/10/98

1. Provide individual risk assessments for all women as well as a detailed analysis describing the women who actually entered NSABP P-1 with special attention to women over age 60. Discuss why the "risk disk" calculates a 5-year risk of breast cancer less than 1.7% for women aged 60 or greater with no additional risk factors for breast cancer.

2. Provide a multivariate analysis of the treatment effect across the risk subsets. The model should include interaction terms of treatment by risk factors in addition to the main terms.

3. Outline plans for a participant and physician education program.

4. (a) Provide follow-up data since the data lock date of 1/31/98. (b) Provide the current status of all breast cancers that have occurred, including recurrences if known. (c) Analyze the total number of breast cancer cases analyzed over time, including cases

found since 1/31/98. (d) Analyze the number of ER(-) cases diagnosed over time, including cases found since 1/31/98.

5. What was the collection rate of serum samples at baseline?

6. Please comment on a list of cases where the FDA and NSABP assessments differ.

7. Supply the final assessment of Colles' and radial head fractures when the NSABP review is complete.

A list of Phase IV commitments was also attached; the sponsor was asked to commit to these requirements (re-requested 10/8/98).

Sponsor reply 9/17/98

Addressed questions 1 and 2

Sponsor reply 9/23/98

Addressed question 6.

NSABP database submission 9/24/98

Addressed question 4a but did not include information about non-breast non-endometrial cancers.

Sponsor reply 9/25/98

Addressed question 4b and question 5.

Sponsor reply 10/13/98

Incomplete response to question 4d.

Sponsor submission 9/17/98

A reviewer comment regarding a protocol violation was clarified with additional documentation.

Sponsor submission 10/7/98

The sponsor submitted a sample of planned promotional materials.

FDA Request for Information 10/7/98

1. Provide updated information on new cases of non-breast non-endometrial cancers.

2. Provide the pathology reports for the additional cases of non-invasive breast cancer diagnosed since the data lock date of 1/31/98.

3. Provide TNM and ER status of invasive breast cancers diagnosed since 1/31/98.

4. FDA corrected several case assessments.

5. Clarify the fracture review process.

Sponsor submission 10/15/98

The requested pathology reports were supplied.

NSABP database submission 10/16/98

Addressed question 1.

FDA Request for Information 10/8/98

1. Provide your plan for evaluating the etiology of thromboembolic events.

2. Provide a timeline for the submission of NSABP P-1B, P-1G, and Dr. Krag's substudy.

3. Provide a timeline for reporting the central pathology review results from NSABP P-1.

4. Provide the monitoring plans for the NSABP P-1 participants.

5. Describe your plans for a participant and physician education program.

6. Clarify the classification of Colles' fractures.

7. Define "protocol-specified bone fractures."

8. The protocol specified wrist fractures, not Colles' fractures. The database lists radial and hand fractures. Explain the ascertainment procedure for wrist fractures versus upper radial fractures.

Sponsor reply 10/13/98

Addressed questions 2-3 and 6-8.

Questions 1, 4, and 5 incompletely addressed.

FDA correspondence 10/14/98

Listed outstanding issues required in full prior to the goal date of October 30, 1998.

Sponsor reply 10/20/98

Satisfactorily addressed outstanding issues.

3.1.4 ODAC Meeting

The questions and votes from the Oncologic Drug Advisory Committee meeting on September 2, 1998 are summarized in Appendix C.

3.2 Key Volume Numbers

Labeling	Volume 1; updated in meeting package for July 30, 1998
ERSMAC report	Volume 3
Protocol	Volume 3
Protocol amendments	Submission 114.1
Table of contents for CRFs	6/24/98 submission
Case report forms:	
Deaths	111.1-111.47
Breast cancer, invasive	111.48-111.148
Non-invasive breast cancer	Approximately 111.128-111.48 + others
Endometrial cancer	111.15--111.52, random
DVT	111.5--111.251, random
PE	111.13—111.252, random
Stroke	111.10—111.254, random

4.0 Chemistry/Manufacturing Controls

Tamoxifen is a marketed drug; this information has been previously reviewed. No new information in this category was submitted.

5.0 Animal Pharmacology/Toxicology

Tamoxifen is a marketed drug; this information has been previously reviewed. No new information in this category was submitted.

6.0 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

Tamoxifen is a marketed drug; this information has been previously reviewed. No new information in this category was submitted.

7.0 Relevant Human Experience/Literature Review

The published literature on tamoxifen dates back to the early 1970s; a MedLine search yielded 7210 articles. Over 3000 articles refer to adverse events associated with tamoxifen and are readily available.

8.0 Summary of Clinical Study: NSABP P-1, "A clinical trial to determine the worth of tamoxifen for preventing breast cancer"

Trial Accrual Dates: June 1, 1992 to September 30, 1997
Data Cutoff: January 31, 1998

One pivotal trial was submitted in this sNDA, NSABP P-1, a prospective multicenter randomized double-blind trial of tamoxifen versus placebo for 5 years in women considered at high risk for breast cancer. The study was conducted by the NSABP and randomized 13,388 women at 324 sites grouped into 134 centers in the United States and Canada. The original database submission contained tables of derived data in SAS and were translated at FDA into MS Access for review. Primary data in ASCII were submitted, after multiple requests, from July 23, 1998 through August 4, 1998 and were translated at FDA into MS Access.

No supportive data was formally submitted for review; however, the published literature on tamoxifen is extensive and readily available.

8.1 Rationale and Objectives

Extensive preclinical data has shown that tamoxifen can inhibit or prevent the initiation and promotion of breast cancer in rats and mice. At least 5 trials of adjuvant tamoxifen in early stage breast cancer patients and the recently published meta-analysis (Early Breast Cancer Trialists' Collaborative Group, Lancet 351: 1451-67, 1998)

demonstrate a 50% reduction in the risk of a new breast primary with tamoxifen treatment. Tamoxifen has been used extensively in breast cancer patients, both early and late stage, since 1971 and although associated with toxicity, has been generally well-tolerated. These data formed the basis for starting a prevention trial in high-risk women.

The objectives of the trial were:

- To test whether long-term tamoxifen therapy is effective in (a) preventing the occurrence of invasive breast cancer and (b) reducing mortality attributed to breast cancer
- To evaluate whether the administration of tamoxifen reduces mortality from cardiovascular disease
- To evaluate the effect of tamoxifen on the incidence of bone fractures
- To evaluate toxicity and side effects of tamoxifen therapy in order to assess benefit versus risk resulting from the use of tamoxifen in women at increased risk of developing breast cancer

8.2 Design

8.2.1 Eligibility

In order to be eligible for the trial, participants must have been:

- Aged 60 or more at study entry, or
- Have been between the ages of 35-59 with additional breast cancer risk factors such that their minimum predicted risk of developing breast cancer within the next 5 years was at least as great as that of women aged 60 or more, or
- Have been aged 35 or greater with a diagnosis of lobular carcinoma in situ (LCIS)

The rationale for these eligibility requirements is discussed below:

The selection of age 60 and greater was based on SEER data, which shows an increased risk of breast cancer from age 30 to age 60, with a plateau at greatest risk at age 60 and older. At age 60, the average woman has a lifetime risk of approximately 10% of developing breast cancer. The risk of developing breast cancer in the next five years at age 60 has been reported to be 1.7%. At this age, the risk of cardiovascular disease, another primary endpoint of the study, also increases. The Framingham cardiovascular trial data indicate that women aged 60 or more have an 11% risk of a myocardial infarction over the next 10 years.

For women under the age of 60, the Gail model, a multivariate logistic regression model, was used to predict risk. This model was used because it is one of the few models that has reported risk estimates for combinations of risk factors, has expressed risk in terms of probability of occurrence over time, is based on the largest collection of epidemiologic data available (Breast Cancer Detection Demonstration Project [BCDDP] screening trial) with subject characteristics that are likely to be similar to those women entered on P-1, and includes both genetic (family history) and non-genetic risk factors.

The variables included in the model are:

- Number of first-degree relatives with breast cancer,
- Age at menarche,
- Age at first live birth
- Number of breast biopsies
- Histologic diagnosis of atypical hyperplasia

Eligible participants were those women who were predicted by the Gail model to have a lifetime risk of breast cancer of 10% or greater, with at least a 1.7% chance of developing breast cancer in the next 5 years.

In addition, women aged 35 or more with a diagnosis of LCIS were eligible on this basis alone, because of the significantly increased bilateral lifetime risk of breast cancer associated with this pathologic entity.

Minimum relative risks required to enter the trial were calculated for women of each age group. These relative risks indicated the degree of risk required for a woman of a specified age to have the same initial risk as that of a 60 year old woman. The age-specific relative risks were calculated from 1983-1987 SEER breast cancer incidence rates. The rate for women aged 60-64 was used as the baseline rate. Once these relative risks were calculated, they were incorporated into a lifetime risk function with an adjustment for age-specific competing risk of death from all causes except breast cancer, using 1988 U.S. mortality rates. This function resulted in a lifetime probability of developing breast cancer. However, the SEER-derived age-specific relative risks are based on 60 year old women who are at increased risk of breast cancer because of age and other risk factors. Based on BCDDP data, it was estimated that this group of 60 year old women has a relative risk of breast cancer of 1.73 relative to a group with no risk factors. The risk estimates were therefore multiplied by 1.73 to obtain rates relative to women with no breast cancer risk factors (see the following table). The Gail model was then used to estimate the composite relative risk of breast cancer of a potential participant. The relative risk derived from the Gail model was compared to the minimum age-specific relative risk calculated from SEER data. Potential participants must have had a relative risk greater than or equal to the listed age-specific relative risk:

Table 1. Minimum relative risk required to enter trial (NSABP P-1 protocol, Table 7, section 2.16)

Age (yrs)	Relative to average woman of the same age*	Relative to a woman of the same age with no risks#
35	5.07	8.75
40	2.65	4.57
45	1.80	3.10
50	1.52	2.62
55	1.23	2.13

*Derived from SEER data

Derived by multiplying SEER-derived risks by 1.73

These calculations were used as the basis of eligibility for the P-1 study.

Reviewer Comment:

1. The Gail model has limitations:

- It does not take into account the age at diagnosis of a family member with breast cancer
- It does not include data that suggest a hereditary cancer syndrome, such as breast cancer in male family members or second-degree relatives, the incidence of second breast primaries, or the presence of ovarian cancer in family members
- It includes the number of breast biopsies as a risk factor, which instead may measure the intensity of the participant's follow-up and/or the participant's or health care provider's anxiety about the development of breast cancer
- Additional well-documented risk factors, such as age of menopause, are not included
- It has been shown to overestimate risk in women who do not receive regular breast examinations and yearly screening mammography (JNCI 86; 1994: 620-625; JNCI 86; 1994: 600-607)

2. Despite these limitations, it is the best available model for the reasons outlined in the protocol document. The results from this trial will need to be considered in the context of the population entered on study and the methods used to determine eligibility.

8.2.2 Trial entry

Subjects who fulfilled the eligibility criteria were entered into the trial in a multistep sequence designed to ensure their understanding of and commitment to the trial. The first phase was the recruitment phase, during which participants received general information about the trial, completed the Breast Cancer Risk Assessment Form (which collected information about the parameters in the Gail model), and scheduled a second visit to discuss the Risk Assessment Profile generated by the NSABP. The Risk Assessment Profile was a computer assessment of the participant's risk using the Gail model and was produced for each patient in Phase I by the NSABP Biostatistical Center.

In Phase II, the Protocol Eligibility Assessment, the subject discussed the results of the Risk Assessment with personnel at the recruitment site, reviewed the protocol and

the protocol requirements, and gave informed consent. The eligibility examinations were then completed, and the participant completed the Entry/Eligibility Form. The NSABP Biostatistical Center verified the patient's eligibility, the presence of a signed/witnessed/dated consent form, and confirmed that there were no contraindications to study entry. A visit for study enrollment was then scheduled.

In the final phase, the Study Enrollment Phase, test results and protocol requirements were reviewed with the participant. The Randomization Form was completed. The Randomization Form specifically asked whether there were changes to the Entry/Eligibility Form, checked whether the Demographic and Lifestyle Questionnaire and the Quality of Life Questionnaire were complete, whether blood samples for the serum bank and for lipid determinations had been drawn, and whether the participant's consent had been re-confirmed. The NSABP Biostatistical Center centrally randomized all women to receive tamoxifen or placebo. Randomization was stratified by clinical center, race (black/white/other), age (35-49, 50-59, 60+), presence or absence of LCIS, and risk (RR <2.5, 2.5-3.9, > 4.0). The patient was then given the drug and an appointment for a 3-month follow-up visit. Prior to the first follow-up visit, study personnel contacted the participant by telephone after 1 month of study drug administration.

The study drug was administered as 2 10-mg tablets once a day for 5 years. In premenopausal women, initiation of study drug began during a menstrual period or after a negative β-HCG to minimize the possibility of fetal exposure to tamoxifen.

The table of required on-study evaluations is included in Appendix A. At baseline, patients were required to have a history, including detailed assessments of breast cancer, cardiovascular, and osteoporosis risk factors; a detailed family history of breast and cardiovascular disease, demographic information, and symptoms. A complete physical examination, a clinical breast examination "...documented by progress note or letter..." (protocol document, section 8.3), a gynecologic examination "...documented by progress note or letter..." (protocol document, section 8.4), a bilateral mammogram, laboratories, fasting blood for cholesterol and triglycerides, an ECG if age 55 or greater, and a quality of life assessment were also required. After study entry, participants were monitored at 3 months, at 6 months, and then every 6 months for the duration of the trial. In addition to general medical assessments and evaluations for the development of breast and endometrial cancer, the following special toxicity assessments were performed: questions about visual complaints, blood for lipid levels, ECG at baseline and at 3 and 6 years for women aged 50 and over at study entry.

Results of all breast biopsies and cytologies, whether benign or malignant, were recorded. Pathology reports for malignant lesions were required submissions.

When the protocol was amended to require endometrial sampling, an insufficient sample was deemed, per protocol, as a negative sample. If two attempts to obtain a sample were unsuccessful, a transvaginal sonogram was required. Again, biopsies were to be recorded and pathology reports forwarded to the NSABP.

Tumor tissue samples were also to be submitted, either as blocks or slides.

Reviewer Comment:

1. The protocol was deliberately designed to require multiple sequential visits prior to study entry. The design ensured entry of a group of highly motivated compliant women. In general use, it is unlikely that patients will receive counseling of this intensity, and unlikely that all will be as motivated. This issue raises concerns about the need for careful counseling, monitoring, and follow-up and should be addressed in the label. A Patient Package Insert will help address these points.
2. Eligibility and level of risk were determined using the Gail model and a computer program; both medical and risk-related eligibility was double-checked by the local investigator and centrally by the NSABP Biostatistical Center. Although the NCI plans to distribute the Gail model software (the "risk disk"), it may not be available for use in all practice settings because of time or technical constraints. It will be important to carefully assess risk and benefit in subgroups of risk strata, if possible, and to provide written materials to guide health care providers and women at risk for breast cancer.
3. The advent of 20-mg tablets of tamoxifen may increase compliance.

8.2.3 External monitoring

Safety monitoring was performed by the Endpoint Review Safety Monitoring and Advisory Committee (ERSMAC). The members of this committee are listed below:

Table 2. Members of the ERSMAC Committee

Committee Member	Position	Affiliation
Theodore Colton, Sc.D., Chair	Chair, Epidem. and Biostat.	Boston University School of Public Health
Martin D. Abeloff, M.D.	Director, Cancer Center	Johns Hopkins Oncology Center
Michele A. Carter, Ph.D.	Clinical ethicist	Univ. Texas Instit. For Medical Humanities
Polly Feigl, Ph.D.		Southwest Oncology Group
Laurence S. Freedman, B.A., M.A.		Dept. Critical Epidemiology, Chaim Sheba Medical Center, Israel
Barbara S. Hulka, M.D., M.P.H.	Professor, Dept. Epidemiology, School of Public Health	UNC, Chapel Hill
Howard Judd, M.D.	Chairman, OB-GYN	Olive View-UCLA
Elliot Rapaport, M.D.	Prof. of Medicine, Cardiology service	Univ. CA San Francisco General Hospital
Carol Redmond, Sc.D.*	Prof., Biometry and Epidemiology	Medical Univ. South Carolina
Barbara C. Tilley, Ph.D.	Div. Head, Biostat. and Research Epidem.	Henry Ford Health Sciences Center

* Non-voting member

The members of the BCPT staff who participated were Joseph Costantino, R. Day, H. Sam Wieand, and Walter Cronin. The committee met twice a year to evaluate safety and efficacy endpoints of the trial. The specific responsibilities of the committee included:

- Review of interim treatment-blinded reports (recruitment, accrual, compliance, monitoring of treatment effects)
- Advising the Steering Committee on protocol changes, policy decisions, and operational procedures that affect the quality of the trial
- Assuming responsibility for external review of the Biostatistical Center and other areas of the NSABP

Summaries of accrual, compliance, distribution of baseline risk factors, toxicity and data quality were prepared for the overall population and by study center. This information, with the exception of "serious toxicities", was presented in blinded fashion to the ERSMAC. The toxicity data included the occurrence of endometrial cancer, thromboembolic disorders, hot flashes, nausea, and vomiting. A prospectively defined increased rate of breast cancer in the tamoxifen group relative to placebo (standardized difference of 1.4) was also planned to trigger an ERSMAC review, as well as significant decreases in breast cancer incidence and/or cardiovascular mortality on the tamoxifen

arm. For further details, see Section 8.9, Statistical Considerations. Presentation of information using a global index in order to assess relative risks and benefits from competing events was also performed. Although the global monitoring was not prospectively described in the protocol, the tool was requested by the ERSMAC and implemented before the first interim analysis.

Reviewer Comment:

1. The oversight committee included representation from many medical disciplines and was appropriate.

2. The global monitoring tool was used in order to assess outcomes from competing events; the timing of its implementation did not bias the study results.

3. This summary report comprised the major portion of the sNDA submission.

8.3 Protocol amendments

The original protocol was written May 20, 1992. The following is a list of protocol amendments:

- August 25, 1992
  - Exclusion of participants with macular degeneration
  - Consent form changes to clarify liver toxicity and to document participant agreement for banking of blood samples
- July 30, 1993
  - In order to reduce the risk of pregnancy, medication was initiated during a menstrual cycle. For women with irregular menses, a negative β-HCG was determined to be an acceptable alternative. The consent form was revised to reflect these changes.
  - Dose delays for hepatic toxicity: the occurrence of grade 2 or greater toxicity called for discontinuation of the drug for at least 4 weeks; drug therapy could resume when the toxicity returned to 0. Rechallenge for participants with grade 3 or 4 toxicity could only be performed after careful consideration. The consent form was modified to clarify liver function test monitoring.
  - Dose delays for hematologic toxicity: as for hepatic toxicity
  - Dose delays for other toxicity: as for hepatic toxicity
  - Women participating in any cancer prevention study were ineligible for this study
  - Use of chemotherapy for benign disease was added as an exclusion criteria
  - An additional blood sample was collected at the time of an event
  - Investigators were asked to submit fresh frozen tumor specimens or slides of cancers on study to the NSABP tumor bank; pathology reports were also required
  - Lowered platelet or white blood cell counts were added to the consent form
  - Other modifications consisted of clarifications without significant changes
- 12/24/93 Additional information about uterine cancer risk

- 1/14/94 Consent form added detailed patient information about uterine cancer risk, liver cancer risk, ovarian cysts, hair thinning, and the risks of pregnancy
- 4/16/94 "Dear participant" letter describing the scientific fraud in Montreal; detailing uterine cancer and pregnancy risks
- 9/24/94
    - Requirement for annual endometrial screening on study, and for endometrial sampling prior to study entry
    - Risks of non-uterine cancers
    - Updated information on risk-benefit analysis for the BCPT
    - Requirement for documentation of a complete physical examination
    - Procedures for unblinding
- 11/17/94
    - Re-initiation of sites
    - Endometrial sampling logistics
- 10/7/96 Formal decrease in the sample size to 13,000
- 3/11/97 Updated information on tamoxifen and the eye
- 4/8/98 Press release about the unblinding of the trial

Reviewer Comment:

1. Most of the protocol amendments were designed to provide more information to participants in the informed consent. The amendments that changed the conduct of the trial were the addition of endometrial sampling, which might have increased the number of detected uterine abnormalities, but should have had the same effect in both arms; and the change in the sample size. The change in the sample size was based on the observed increase in the number of invasive cancer events and was appropriate.
2. The original submitted database did not permit assessment of the number of women entered on study with macular degeneration prior to the change in eligibility criteria, the number of women who developed macular degeneration on study, or the outcome in these women. Data on macular degeneration were submitted 8/4/98 at the request of the FDA.

8.4 Eligibility and enrollment

8.4.1 Inclusion criteria

Inclusion criteria included:

- Women $\geq$ 60 years of age with or without additional risk factors
- Women $\geq$ 35 years of age with a histologic diagnosis of LCIS treated with local excision alone