- Women 35-59 years of age with a composite increased breast cancer risk, based on the following factors, sufficient to justify study entry:
  - Number of first-degree relatives with breast cancer
  - One or more previous breast biopsies, including FNA of a non-cystic lesion
  - Previous diagnosis of atypical hyperplasia
  - Age at first live birth
  - Nulliparity
  - Age at onset of menarche
- Life expectancy of at least 10 years
- Breast examination with no evidence of malignancy; mammogram within 180 days prior to study entry with no evidence of malignancy
- Adequate hematologic, hepatic, renal function
- No concurrent anticoagulation therapy with Coumadin
- Must agree to use adequate contraception
- After July 8, 1994, participants were required to have endometrial sampling prior to randomization
- Other criteria addressed acceptable concomitant medications, which included lipid-lowering medications, low-fat diet, aspirin, persantin, vitamin D, fluoride, calcitonin, biphosphonates, thyroid medication; and acceptable prior events, such as hysterectomy, oophorectomy, MI, stroke

8.4.2 Exclusion criteria

The following exclusion criteria were listed:

- Less than age 35
- Life expectancy less than 10 years
- Prior or suspected breast cancer of any type (invasive breast cancer; DCIS; or LCIS treated with mastectomy, radiation, or systemic adjuvant therapy)
- Participation in other breast cancer prevention studies involving pharmacologic interventions
- Prior malignancy less than 10 years ago, except CIS cervix or basal/squamous cell carcinoma of the skin
- Existing nonmalignant disease which precludes the use of tamoxifen
- Prior history of deep vein thrombosis (DVT) or pulmonary embolus (PE)
- Performance status (PS) that restricts normal activity for a significant portion of each day
- Estrogen or progesterone replacement therapy, oral contraceptives, androgens; women who discontinued these medications could enter the trial 3 months after stopping the ancillary medications
- Psychiatric disorder that would preclude giving informed consent or complying with the study
- Pregnancy
- Prior use of tamoxifen

- Concurrent use of Coumadin
- Prior history of macular degeneration (protocol amendment)
- Concurrent use of chemotherapy for benign disease (protocol amendment)
- For participants randomized after July 8, 1994 with an intact uterus, refusal to undergo endometrial sampling or unsuccessful sampling

Reviewer Comment:

1. Information about the number of pregnancies on study was requested by the FDA reviewer and is described in the safety section.

8.4.3 Enrollment

Thirteen thousand three hundred eighty-eight women were enrolled on the study, 6707 on placebo and 6681 on tamoxifen. The average follow-up time is 3.6 years, and 57% of patients have been followed for 4 years or more.

The NSABP collected data on the number of eligible Risk Profile forms submitted by each site, the number of Entry/Eligibility forms submitted, the number and percent of participants at each center who were eligible to enter the trial, and the number randomized. The overall results are summarized below:

Table 3. Summary of study screening, accrual, and follow-up information (Table 1, P-1 submitted manuscript)

Screening, Accrual, and Follow-up Information	Placebo	Tamoxifen	Total
Breast cancer risk assessments			98, 018
Women who met risk eligibility requirement			57, 641
Medical eligibility assessments			14, 453
Women who met both risk and medical eligibility requirements			13, 954
Women randomized	6707	6681	13, 388
Without follow-up	137	137	274
Included in analysis	6570	6544	13, 114
Average follow-up time (mo)	43.8	43.8	43.8
Median follow-up time (mo)	50.6	50.1	50.4
Percent followed for > 36 months	73.3	73.2	73.2
Percent followed for > 48 months	58.6	58.3	58.5
Percent followed for > 60 months	21.3	20.7	21.0

Approximately 60% of the women screened were eligible for the trial based on breast cancer risk. Of the 57,641 eligible women, 14,453 women agreed to undergo further medical evaluation. Of these women, 13,954 were medically eligible for trial entry, and 13,388 of these women entered the trial and were randomized to study drug.

Twenty-two sites never randomized a participant. In general, these sites screened small numbers of potential participants, most of whom were ineligible.

Reviewer Comment:

1. Sixty percent of the group of women who submitted assessments were eligible based on breast cancer risk. Of the eligible women, 25% (or 15% of the women who submitted risk assessment forms) agreed to undergo medical evaluation. Ninety-seven percent of medically evaluated women were eligible, and 96% of these women were randomized. The randomized group represents 14% of the originally assessed population. Overall, although many women who initially submitted forms were not eligible or did not wish to pursue participation, women who committed to undergo medical screening were highly likely to undergo randomization.
2. A list of sites, accrual by site, sequential dropout at each stage of the screening procedure, and the principal investigator at each site was not provided in the submission. This information was requested from the sponsor and was sent July 1. The majority of centers carefully screened potential participants and submitted data for eligible participants over 90% of the time, and most centers went on to randomize over 90% of eligible participants. The study was comprised of highly motivated, well-screened women who completed a complex multistep entry procedure.
3. A request was made to provide copies of the slides used by Larry Wickerham, M.D. at the ASCO presentation at the Plenary Session. The following slide gives additional information about the length of follow-up of the participants:

Table 4. Distribution of BCPT participants randomized by length of follow-up (NSABP slide, ASCO 1998 Plenary Session)

Length of Follow-up (mo)	Participants	
	Number	Percentage
≤12.0		12.4
12.1-24.0		9.5
24.1-36.0		6.4
36.1-48.0		14.5
48.1-60.0		36.7
≥ 60.1		20.6
TOTAL		100.0

Information on the length of follow-up was not included in the submission. *The median follow-up on study, submitted 10/13/98, was 50.4 months.*

4. No randomization logs were provided. During the teleconference of July 23, 1998, the NSABP explained that all randomization was performed centrally with a

computer program; all information was stored in a data file. Because of the large size of the study and the lack of imbalance between arms with multiple subset analyses by the reviewers, we did not request submission of the randomization computer files.

8.5 Removal from study, unblindings, and protocol violations

8.5.1 Removal from study

Patients were to be removed from study for:

- Invasive breast cancer
- Non-breast primary cancers
- Pulmonary embolus, definite or probable
- Deep vein thrombosis
- Depression (discontinued for definite event; may be put back on study if resolves; off study permanently for a second occurrence)
- Non-cataract ophthalmic toxicities (retinal changes, corneal scarring)
- Pregnancy (participant may resume therapy after completion/termination of pregnancy or lactation)

Specifically, patients could have therapy interrupted but not discontinued for the following events:

- Non-invasive breast cancer (LCIS or DCIS)
- Basal or squamous cell cancer of the skin; CIS of the cervix
- MI
- Fracture
- Cholecystitis/cholelithiasis
- Cataracts
- Endometrial complex hyperplasia with or without atypia, or simple hyperplasia with atypia

Reviewer Comment:

1. While not a goal of this trial, it will be interesting to compare outcome in patients diagnosed with DCIS on the tamoxifen and placebo arms who continued on study therapy. *This point was addressed during the course of the review and was not feasible. Please see Reviewer Comment 3a in section 9.2.*
2. Review of the CRFs indicated that most participants with non-invasive breast cancer discontinued study drug. This point will be clarified with the sponsor.

8.5.2 Unblinding

Unblinding was allowed by protocol in the following circumstances:

- Occurrence of invasive breast cancer
- If the knowledge of the treatment arm is necessary for the treatment of an intercurrent medical condition

8.5.3 Protocol violations

Protocol violations included unblindings not specified in the protocol, non-allowed concomitant medications, and other. Withdrawal for non-protocol designated reasons is detailed in section 8.7.1, Compliance.

8.5.3.a Non-protocol unblindings

Non-protocol unblindings included unblindings performed at the insistence of the treating physician or the patient. Unblinding treatment occurred in 123 women on placebo and in 120 women on tamoxifen. For 105 of these women (54 placebo, 51 tamoxifen), the treating physician indicated that the information was required to treat a new condition. These conditions included complex endometrial hyperplasia/atypia, endometrial cancer, ovarian cancer, lung cancer, other cancer, liver function abnormalities anti-factor VIII antibodies, stroke/CVA, phlebitis, macular degeneration, other vision problem, and other conditions. In the remaining 138 women (69 placebo and 69 tamoxifen), the patient insisted on knowing her treatment.

Reviewer Comment:

1. Information on unblinding was provided in summary form in the ERSMAC report. The sponsor provided additional information at FDA request on July 16, 1998. A total of 126 official unblindings were reported on the placebo arm and 122 on tamoxifen. An additional "unofficial" unblinding occurred on the placebo arm; one participant's husband, who is a chemist, analyzed her study tablets. The reasons for unblinding are summarized in the following table:

Table 5. Treatment unblindings, excluding an invasive breast cancer event

Reason	Placebo	Tamoxifen
Participant's insistence	**69**	**68**
Physician's insistence:	**54**	**52**
Complex endometrial hyperplasia with atypia	3	0
Endometrial cancer	4	15
Ovarian cancer	5	0
Lung cancer	3	1
Other cancer	10	7
Liver function abnormality	4	2
Anti-factor VIII Abs	1	0
Stroke/CVA	3	3
Phlebitis	1	2
Macular degeneration	1	1
Other vision problem	2	1
Non-invasive breast cancer	10	4
Possible PE	0	3
Postmenopausal bleeding	1	3
Ovarian mass	0	1
DVT	0	3
Lupus	0	1
Endometriosis	0	1
Hip fracture	0	1
Participant death; info needed for organ donation	0	1
Abnormal PAP	0	1
Wanted to prescribe tamoxifen	0	1
TIA	1	0
Nipple discharge	1	0
Low platelets	1	0
Fibroids	1	0
Vasculitis	1	0
Headaches	1	0
Other Reasons:		
Child found bottle and consumed several pills	2	0
Insistence of family member	1	2
TOTAL	**126**	**122**

Imbalances in reasons for unblinding generally followed the event: for example, more women on the tamoxifen arm were unblinded because of the occurrence of endometrial cancer, which was more common on the tamoxifen arm. Similarly, more

women on placebo were unblinded because of the occurrence of non-invasive breast cancer, which was more common on placebo.

2. Overall, the number of unblindings was balanced, whether based on participant "need to know" or on physician's insistence. It is unlikely that unblinding influenced the outcome of the study.

8.5.3.b Non-allowed concomitant medications

The sponsor submitted information about non-allowed medications on 7/28/98. This information was limited to the use of hormone therapy, oral contraceptives, open-label tamoxifen, and raloxifene. The date of first administration was given, but the duration of therapy, reason for therapy, and repeated use of the medication (such as several courses of progesterone for dysfunctional uterine bleeding) were not documented according to NSABP.

Table 6. Non-allowed medications

Non-allowed medication	Placebo: All violations	Placebo: Violations on study drug	Tamoxifen: All violations	Tamoxifen: Violations on study drug	Total**
Hormonal*	606	61	667	71	1273
Oral contraceptives (OC)	9	0	9	0	18
Tamoxifen	15	3	1	0	16
Raloxifene	0	0	0	0	0
Hormones and OC	1	0	5	0	6
Hormones and tamoxifen	2	0	1	0	3
OCs and tamoxifen	0	0	0	0	0

*Estrogens, progestogens, androgens, hormone replacement therapy
** 9 patients took more than one disallowed medication

For disallowed hormone therapy, 1 participant on placebo and 3 on tamoxifen were on therapy within 3 months of study entry. For oral contraceptives, 1 participant on tamoxifen was on therapy within 3 months of study entry.

Reviewer Comments:

1. The use of disallowed medication was balanced between arms, with the exception of open-label tamoxifen. Fifteen participants on placebo took open-label tamoxifen, compared to 1 participant randomized to tamoxifen.

The participant on tamoxifen was unblinded because of M.D. request, although the specific reason and the condition treated with open-label tamoxifen is not known.

Of the 15 participants randomized to placebo who took open-label tamoxifen, 5 developed invasive breast cancer and took tamoxifen after the diagnosis of invasive breast cancer and after removal from study. Only 1 of the 15 was unblinded, due to the

participant's insistence. An additional participant was inadvertently given tamoxifen as detailed below:

> Admitted to the hospital for knee replacement and subsequent complications. Told the admitting physicians she was on a "tamoxifen study" and was given open label tamoxifen in the hospital. Had been randomized to placebo. Received tamoxifen for approximately 5 months.

The reason for tamoxifen use in the remaining 9 participants randomized to placebo is unknown.

2. Upon review of the CRFs, it was apparent that additional participants received hormonal therapy but were not recorded in the database. Some women who took hormonal therapy after removal from study were included in the database; the following, found during review of the selected CRFs, were not in the database, but took hormonal therapy on study:

Placebo:

> Randomized to placebo 6/2/93. Treated with Provera for dysfunctional uterine bleeding (12/2/94); not reported in database. Removed from study 1/5/95 for laboratory abnormalities
> Randomized to placebo 10/5/92. Treated with estrogen from 10/7/92 to 11/18/92. Not reported in database. Last study drug treatment 11/18/92
> Randomized to placebo 9/1/92. Developed an enlarged uterus with spotting in January 1995 and received at least 2 doses of IM Lupron. She was removed from study 4/20/95 for a diagnosis of endometrial cancer

Tamoxifen:
None found

The following women were found, during CRF review, to have taken hormonal therapy after study drug was stopped:

Tamoxifen:

> Randomized to tamoxifen 8/27/92. Experienced a hemorrhagic CVA 6/12/94 and was removed from study. Began estrogen after discontinuation of study drug

Placebo:
None found

The following participants were removed from study because of a diagnosis of endometrial cancer and received subsequent hormone therapy that was not reported in the database:

Placebo:

Tamoxifen:

After removal from study, participants were asked to consent to follow up in order to collect information on additional endpoints. Because hormone use may be a confounding factor in evaluating subsequent breast cancer events, it should be recorded.

3. Information about other non-allowed medications was not provided. Several protocol violations were noted in the course of the CRF review:

Treated with methotrexate for systemic sclerosis
Had AV node ablation, pacemaker insertion and chronic anticoagulation in 11/92. Went on study 2/24/93 and did not report her Coumadin therapy, a protocol violation. Remained on study despite documentation in the chart of her need for anticoagulation.
Treated with Coumadin for 3 weeks at the time of a knee replacement; randomized to tamoxifen
Admitted for a hysterectomy for dysfunctional uterine bleeding and had a postoperative CVA. Begun on Coumadin. All events after completing 5 years of study drug with tamoxifen

4. Several participants should have been removed from study for protocol-specified endpoints but remained on the trial:

DCIS:

DCIS was described in the protocol as a reason to temporarily discontinue medication, but not to be removed from study.

Diagnosed with DCIS 9/22/94; continued on study drug until 9/15/95. Randomized to tamoxifen

DVT:

Six protocol violations were noted, one on the placebo arm and 5 on the tamoxifen arm. These participants remained on study drug for one to seven months after the diagnosis of a DVT. One PI signed a note acknowledging the DVT and stating that the participant was given additional study medication. The majority of these violations, however, were because the BCPT treatment center was unaware that the participant had experienced an event until the next scheduled visit.

Placebo arm:

Subclavian vein clot 3/28/94; kept on study drug until 7/25/94

Tamoxifen arm:

DVT 3/22/97; on study drug until 7/14/97
DVT 12/8/95; on study drug until 7/9/96
DVT 10/21/94; on study drug until 5/2/95
DVT 7/20/94; on study drug until 8/26/94
DVT 2/19/97; on study drug until 6/3/97

5. At least one participant reported a prior history of a pulmonary embolism, but was entered on study nonetheless. She was randomized to placebo. *Addenda: The sponsor submitted documentation 9/17/98 that the report was an error; the participant had no such past history.*

6. Overall, the protocol violations may have affected participant safety (i.e., continuing tamoxifen in the face of a DVT) but are unlikely to have affected study outcome because of the small number of participants involved. Approximately 1% of women took hormone therapy while still on study medication. However, based on FDA review of selected CRFs, the sponsor's submission of data on hormone use appears incomplete. There are undoubtedly more protocol violations that have not been reported, since we did not receive information on the use of other medications prohibited by protocol, or continuation of drug therapy in participants who should have been removed from study.

Reviewer Addendum:

Other protocol violations were not reported. For example, on August 19, the sponsor, while replying to a request for baseline mammograms on selected participants, noted that Stanford University informed NSABP that they do not have a copy of the baseline mammogram report for

8.6 Patient characteristics

The demographic characteristics of the participants are summarized in the following table (derived from Access queries of subsequent submissions of the electronic database and information from ASCO/NSABP slides). In the submitted manuscript, the NSABP reported these criteria only on patients with follow-up included in their analyses. The following table differs from the NSABP manuscript in that it describes the entire randomized population.

Table 7. Participant characteristics

Characteristic	Placebo n=6707		Tamoxifen n=6681		Total population n=13,388
	Number	Percent	Number	Percent	
Age					
35-39		2.8		2.5	351
40-49		36.5		36.8	4910
50-59		30.6		30.8	4111
60-69		24.1		23.9	3214
70+		6.0		6.0	802
Race					
White		96.2%		96.5%	12,902
Black		1.7%		1.7%	227
Other		2.1%		1.8%	259
Prior hysterectomy					
No		63.5		62.4	8428
Yes		36.5		37.6	4960
Menses ceased:					
No		33.6%		32.9%	4449
Yes		66.4%		67.1%	8939
Weight:					
≤ 125 lbs		12.6%		12.3%	1664
126-150		32.4%		33.5%	4408
151-175		26.8%		25.5%	3499
176-200		15.4%		15.3%	2055
201-225		7.0%		7.1%	947
226-250		3.5%		3.6%	473
251-275		1.4%		1.5%	193
≥ 276		0.6%		0.8%	95
Unknown		0.3%		0.5%	54
Educational level					
< High school					5%
High school					17%
Some college/ vocational school					33%
College					20%
Post-graduate					25%

The distribution of the population in the prospectively stratified age groups is as follows:

Table 8. Age distribution of BCPT participants

Age Range (years)	Percent of Study Participants
35-49	40%
50-59	30%
≥ 60	30%

The risk factors of the population are summarized in the following table:

Table 9. BCPT participant risk factors

Risk Factor	Placebo N=6707		Tamoxifen N=6681		Total population N=13,388
	Number	Percent	Number	Percent	
Menarche					
≤11		26.2%		27.0%	3557
12-13		54.9%		55.0%	7356
≥14		19.0%		18.0%	2475
Age of first live birth:					
None		18.2%		18.5%	2451
<20		14.0%		14.4%	1900
20-24		37.3%		37.5%	5004
25-29		21.4%		20.9%	2826
≥30		9.2%		8.8%	1207
Number of breast biopsies					
None		44.5%		44.6%	5969
1		27.9%		28.3%	3763
≥2		27.6%		27.0%	3656
Presence of AH					
No		90.8%		91.2%	12, 182
Yes		9.2%		8.8%	1206
Presence of LCIS					
No		93.8%		93.7%	12,554
Yes		6.2%		6.3%	834
No. 1° relatives with breast cancer					
None		24.1%		23.4%	3191
1		56.6%		57.0%	7606
2		16.5%		16.2%	2193
3		2.1%		2.7%	325
4		0.4%		0.4%	58
≥5		0.1%		0.1%	15
Five-year predicted breast cancer risk/100*					
≤2.00		25.0%		24.8%	3272 (25%)
2.01-3.00		30.9%		31.3%	4077 (31%)
3.01-5.00		27.2%		26.1%	3494 (27%)
≥5.01		16.9%		17.8%	2271 (17%)

*Obtained from manuscript; based on evaluable patients, not entire population