Table 62. Age at the time of DVT with annual hazard rates

Event	Number of Events		Rate/1000 Women		Risk Ratio	95% CI
	Placebo	Tamoxifen	Placebo	Tamoxifen		
DVT:	19	30	0.79	1.26	1.59	0.86-2.98
≤ 49	6	9	0.64	0.97	1.52	0.48-5.19
≥ 50	13	21	0.89	1.44	1.62	0.77-3.51

When age at event is examined, women over age 50 had a greater increase in the absolute number of events than did women under the age of 50. However, both women under 50 and women over age 50 experienced a 50% increase in the number of events. None of the increases, whether measured in the total population, by age at randomization, or by age at event, was statistically significant.

If one looks only at women with DVT on study drug or within 1 month of stopping study drug by age:

Table 63. Age at the time of DVT while on study drug or within 1 month of stopping study drug

Age at DVT	Placebo	Tamoxifen	Increase
≤ 49	3	9	3-fold
≥ 50	5	21	4-fold

This analysis supports the following observations:

- Clots are more commonly seen in postmenopausal women but still occur at a significant frequency in premenopausal women; the relative risk is the same although the absolute risk is greater in the postmenopausal setting
- Premenopausal women may become postmenopausal during the period of tamoxifen therapy, and this issue should be included in a risk-benefit discussion with a potential participant

7. An additional concern that emerged during review of the CRFs was the delay in diagnosis of deep vein thromboses. The tamoxifen prevention study was well-publicized with open discussion of potential adverse events in both the medical literature and in the lay press. Participants were required to sign a multi-page consent form that clearly outlined potential risks, including the risks of thrombotic events. However, one woman with a DVT on the placebo arm (5%) and seven women with DVTs on the tamoxifen arm (23%) had delays in diagnosis ranging up to 4 weeks that can be attributed to their physicians, not to participant non-compliance or participant's failure to seek medical care. With one exception, it was not possible to determine from the CRFs whether women informed the treating physician that they were on the NSABP P-1 study. The woman on placebo and 5 of the 7 women on tamoxifen had clot in the thigh, with an increased risk of pulmonary embolus. These cases are detailed below:

Placebo:

Participant presented to the ER with leg pain after a fall. The ER physician felt her exam was unremarkable and performed a diagnostic study at the insistence of the participant. The study was positive for deep vein thrombosis. Site: thigh.

Tamoxifen:

Participant had a history of lower extremity calf pain. Was seen by an orthopedist and a neurosurgeon with negative examinations and was given the diagnosis of a slipped disc. The diagnosis of a DVT was made 4 weeks after initial evaluation when the participant presented to the ER with increasing swelling, warmth, and pain. Site: calf

Called physician on call with complaints of pain and swelling in the calf and behind the knee. Was advised to elevate the leg and take non-steroidal anti-inflammatory drug and to go to the ER if the pain increased. The participant sought medical attention within a few hours and was found to have a DVT. Site (thigh versus calf) not reported.

Called physician with leg pain; was told to elevate leg. She called back with increasing pain and was told to go to the ER, where a diagnosis of DVT was made. Site: thigh

Called with 3-day history of leg swelling and pain. Was told to elevate leg and apply heat TID before undergoing diagnostic evaluation. Time interval between phone call and diagnosis not stated in the CRF. Site: thigh

Participant was seen by the PI of the BCPT at that site with complaints of unilateral lower extremity swelling. As documented in the record, the coordinator "encouraged a work-up with her local physician." The records indicate that this visit date was the last date of study drug administration. The participant was not seen by her local physician until 3 weeks later, when she was found to have a clot extending to the popliteal vein.

Participant was advised over the phone by the physician on call to take non-steroidal anti-inflammatory drugs for complaints of redness, swelling, and pain in the leg. Six days later she was diagnosed with a DVT in the femoral vein. Site: thigh

Participant was diagnosed with SCCA of the vulva and on the same day was given the diagnosis of superficial thrombophlebitis. Twelve days later, on her preoperative evaluation prior to radical vulvectomy, she was diagnosed with an extensive LE clot that extended from the calf into the thigh. Site: thigh

These cases underscore the need for careful monitoring during tamoxifen therapy. Women and their physicians should recognize the increased risk of thrombosis and should be prepared to have a low threshold for implementation of a diagnostic work-up. Women should be instructed to inform any treating physician that they are on tamoxifen. A Patient Package Insert will be helpful in underscoring this point.

7. 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. Details can be found in section 8.5.3, Protocol violations.

Reviewer Comments: Pulmonary Embolus

1. In the course of reviewing CRFs for death, the reviewer found another pulmonary embolus in a patient on tamoxifen which resulted in her death.

> This participant was a 65 year old woman at study entry whose other risk factors included a first degree relative with breast cancer. She had a biopsy-proven diagnosis of idiopathic pulmonary fibrosis made in 1994, prior to study entry. She began study drug on 9/6/96. On 3/4/97, study drug was discontinued because of increasing respiratory difficulties. She was placed on Imuran for the pulmonary fibrosis. She was admitted to the hospital 4/15/97 because of increasing shortness of breath, increased cough, and a history of a fever which resolved, and anemia with neutropenia attributed to the Imuran. She improved with antibiotics and transfusions, recovered her counts fully, and was afebrile off all antibiotics for 4 days. She then became acutely febrile and tachypneic with a sudden requirement for 50% oxygen supplementation. On 5/5/97, she was found cold and pulseless; resuscitation measures did not succeed. The provisional autopsy results indicated pulmonary fibrosis, possible right pulmonary artery thrombosis pending microscopic examination, mediastinal adenopathy with anthracosis, and LVH. The NSABP review coded her death as "idiopathic pulmonary fibrosis."

The reviewer was concerned that the participant had instead experienced a pulmonary embolus which, superimposed on her reduced pulmonary function, resulted in her death. We requested the final autopsy report from the sponsor, which was sent July 17, 1998. The final autopsy report noted a right pulmonary artery thromboembolus, with organizing microthrombi in smaller vessels. In addition, there was evidence of a transmural acute myocardial infarction, estimated to be between 3 and 10 days old. A small collection of malignant cells was found in one section taken from the right middle lobe.

The sponsor agreed with the reviewer that the participant experienced a fatal pulmonary embolus. There were therefore a total of 18 pulmonary emboli on the tamoxifen arm, 3 of them fatal.

2. Ninety-six percent of the pulmonary emboli were diagnosed in women aged 50 or more: 5 of the 6 PE in the placebo group and 18 of 18 diagnosed on tamoxifen.

3. Of the PE reported on the trial, all on the placebo arm occurred while the participants were on study drug. For the tamoxifen group, 6 PEs occurred 46 days to 29

months after discontinuing study drug. One of the events on the tamoxifen arm occurred in a participant who had been removed from study for a DVT. One occurred in the participant discussed in point 1, who was removed from study for a pulmonary event, but the pulmonary event was not identified as a PE until the autopsy.

4. Predisposing factors are summarized below.

Table 64. Predisposing factors for pulmonary emboli

Predisposing factor	Placebo	Tamoxifen
Surgical procedure	4	5
Comorbid condition	0	2*
Malignancy	0	3#
No predisposing events	2	8
Tobacco:		
Ever smoked	0	9
Currently smoke	0	3^
Weight:		
< 155 lbs	1	6
156-175 lbs	1	6
> 175 lbs	4	6

*CVA, pulmonary fibrosis leading to immobility

Pancreatic cancer; 2 breast cancers—one woman was receiving adjuvant chemotherapy at the time of the event

^ These women are included in the "Ever smoked" category

Women on tamoxifen with a PE were more likely to smoke (3/18) than women on placebo (0/6). Five of 6 women on placebo (83%) and 12/18 women on tamoxifen (67%) with PE were above the median weight in the trial.

5. It is reported in the medical literature that the incidence of pulmonary embolus is probably underreported for a variety of reasons. First, many physicians may not pursue the diagnosis of a PE in a patient with a documented DVT, as it adds expense and potential risk to a patient, if an angiogram is required, but does not change the management. Second, many pulmonary emboli are asymptomatic. Third, patients with PE may have significant comorbid illnesses that complicate or obviate additional work-up. The following cases were identified during the CRF review and may represent additional cases of "missed" PE.

Placebo:

The participant was 65 years old at study entry with a history of a first-degree relative with breast cancer. She began study drug 12/18/92 (randomized to placebo) and discontinued therapy 5/15/94 because of adverse publicity about the trial. She was diagnosed with a glioblastoma 11/26/96. A DVT of the thigh with extension through the calf vessels was diagnosed 12/3/96 and is included in the DVT listings supplied by the sponsor. A filter was inserted to prevent PE because of her CNS lesion

and contraindication to anticoagulation. On 12/7/96, she became acutely hypotensive and acidotic with prolonged PT and PTT levels and thrombocytopenia. The physician's note indicates that her cardiovascular parameters were not consistent with cardiogenic shock. She went on to develop renal and respiratory failure and expired. The cause of death was reported as glioblastoma multiforme.

This 48 year old participant entered the trial with a history of one first-degree relative with breast cancer and 2 biopsies. She began study drug 9/21/92 and was randomized to placebo. A diagnosis of pancreatic cancer metastatic to the liver was made 2/24/97. On 4/26/97 she was found to have a DVT in the left superficial femoral, common femoral, and popliteal veins with extension into the iliac system. A V/Q scan was indeterminant: there were mismatched defects, but the perfusion defects were matched by radiographic abnormalities, such as pleural reaction and interstitial air space disease. She died 4/28/97 after rapidly progressive respiratory failure. Her death was attributed to pancreatic cancer.

Tamoxifen:

This participant was 47 years old with a history of 1 biopsy in the past, who began study drug 10/14/92 and was randomized to tamoxifen. She was diagnosed with a DVT 9/3/96 extending from the common iliac to the popliteal vein. She presented with right lower pleuritic chest pain and was found to have a pulse oximetry of 87%. Additional work-up for PE was not pursued.

A 59 year old participant with a first-degree relative with breast cancer was entered on the trial and randomized to tamoxifen. A brother also had breast cancer, but male relatives are not counted in the Gail model. She developed sharp left-sided pleuritic chest pain, but completed a scheduled cross-continental plane trip to California followed by a 5-hour car trip to her destination. She then developed calf swelling and presented for medical evaluation. A Doppler study showed a DVT in the left superficial femoral vein that extended through the popliteal vein. A V/Q scan showed patchy diffuse changes on both the ventilation and the perfusion scans. The radiologist felt the pattern was consistent with COPD. The chest X-ray demonstrated hyperinflation consistent with this interpretation. The participant had a 40 pack-year history of smoking and had quit 5 years prior to the event.

There may have been underreporting of PE in this trial, comparable to what occurs in clinical practice. However, the size of the study and the double-blind randomized design makes it unlikely that over-reporting occurred on one arm of the study and accounts for the difference in the incidence of thromboembolic events between the two arms.

6. Overall, tamoxifen increased the risk of pulmonary emboli and increased the risk of fatal pulmonary emboli. This event was limited, in the current study, to postmenopausal women. Smoking and obesity were associated with an increased risk, but did not account for all of the events.

Reviewer Comments: All thromboembolic events

1. The reported listings do not count multiple events in the same participant as separate events. Participants were always listed as the worst event, i.e., pulmonary embolus. These multiple events may be categorized as follows:

a. Recurrent DVT

On the placebo arm, four women experienced two or more clots. One of these women was the previously discussed participant with protein S/protein C deficiency.

No women randomized to tamoxifen experienced two or more DVTs without a PE.

b. Five participants, 3 on placebo and 2 on tamoxifen, presented with a simultaneous diagnosis of DVT and PE.

c. Two participants experienced DVT and PE, separated in time:

Tamoxifen:

This 50 year old woman (age at study entry) had a history of a first-degree relative with breast cancer and 1 biopsy. She began study drug 10/1/93 with tamoxifen and was diagnosed with breast cancer 8/11/95, causing her to be removed from study. She received 6 months of adjuvant CMF. She presented 1/19/96 with "pleurisy" and was felt to have pneumonia. A V/Q scan was obtained and was read as intermediate probability. She was treated conservatively. On 2/26/96 she was diagnosed with a DVT in the superficial femoral and popliteal veins. On 5/18/96, she presented with severe chest pain and a pO_2 of 68. A V/Q scan showed a segmental defect in the right mid-chest, called low probability for PE by the radiologist. The NSABP evaluated this finding and called the event a PE; she is reported among the PE events on study. The reviewer agrees with this assessment. She therefore experienced 2 documented events, DVT and PE, separated by 3 months. It is possible that the event of 1/19/96 was a PE, but there is no documentation to support this diagnosis.

This participant was 50 years old at study entry with a history of a first-degree relative with breast cancer and 1 biopsy for breast cancer. She began study drug 12/10/92 with tamoxifen. On 1/14/93, a clinical diagnosis of superficial phlebitis was made and she was treated with NSAID. On 2/9/93, a Doppler study showed a popliteal clot and a V/Q scan was read as high probability for PE. She was taken off study drug and treated with Coumadin until 12/22/93. On 1/6/94, a venogram demonstrated a new lower extremity clot. She required hospitalization and anticoagulation. The second DVT was not reported as a separate event in the database. Whether one considers the second DVT directly attributable to tamoxifen therapy or secondary to the initial clot, it should be considered as a long-term complication of the initial event.

2. Complications of a thrombotic event have not been discussed.

Among women reported to have DVT, no participant randomized to placebo experienced a long-term complication independent of second events. On the tamoxifen

arm, two women experienced chronic venous insufficiency that did not resolve during the period of observation in the study. One woman experienced a lower gastrointestinal bleed secondary to over-anticoagulation and required 5 units of PRBC and additional transfusions of fresh frozen plasma.

Among the participants with pulmonary emboli, one randomized to tamoxifen 6/24/93, was diagnosed simultaneously with a DVT and a PE 10/27/95 after presentation with pulmonary edema, right ventricular failure, hypotension, ventricular tachycardia, and renal insufficiency. The DVT involved the tibial, popliteal, and right superficial femoral veins. The PE was demonstrated by pulmonary angiogram to have blocked all flow to the right lung. She was treated with intra-arterial urokinase with restoration of blood flow to the lung followed by conventional anticoagulation. She was then found to have a large retroperitoneal bleed with a hemoglobin of 8.2 mg/dl. She required transfusions (number not given in the CRF). At the time of the bleed, the PT was 13.6 and the PTT was 68.3. A filter was placed.

3. Other thrombotic events

In section 10.5.2, Other Ophthalmologic Events, there are 2 safety reports of retinal vein occlusions that occurred in premenopausal healthy women without concomitant medical illnesses both randomized to tamoxifen. One occurred in a woman who had discontinued study drug 1 year previously; this event is unlikely to be related to tamoxifen administration. The other is temporally related and resulted in permanent vision deficit. There may be additional thrombotic complications of tamoxifen that have not been fully described or recognized in the course of the study. These events support increased risk in premenopausal women.

Reviewer Summary of Thromboembolic Disease:

1. Tamoxifen administration resulted in an increased risk of thromboembolic events. While the majority of events were seen in postmenopausal women, it appears that the relative increase in events for DVT was the same in both pre- and postmenopausal women, although the absolute difference was smaller for premenopausal women. Pulmonary emboli were predominantly seen in postmenopausal women. With the small number of PEs observed in the study, however, the reviewer does not feel that the risk of PE in premenopausal women can be discounted.

2. As with any thromboembolic event, a woman remains at increased risk for a second event, because of the underlying disorder that led to the first event (coagulopathies, obesity, tobacco use) in addition to anatomic abnormalities caused by the first event (altered venous architecture). Women considering tamoxifen for prevention of breast cancer should be apprised of the potential for complications of therapy-related and secondary events.

10.5 Ophthalmologic events

10.5.1 Cataracts

Evaluation of ophthalmic events on NSABP B-14 (tamoxifen versus placebo for estrogen receptor positive node negative breast cancer patients) suggested that tamoxifen administration might be associated with an increased incidence of cataracts. NSABP P-1 was designed to specifically examine this question in healthy women. Data regarding cataracts and cataract surgery, as described in the ERSMAC report, are presented in the following table.

Table 65. Relative risk of cataract surgery by baseline cataract status (Table 5, ERSMAC report, 1/31/98)

Cataract Status at Baseline	Participant status	Placebo	Tamoxifen	Rate Ratio	95% CI
Without cataracts at baseline	No. randomized	6230	6199		
	No. developed cataracts	483	540		
	Annual rate of cataracts/1000 participant-years	22.5	25.41	1.13	1.00-1.28
	No. cataract surgeries	63	101		
	Annual rate of surgery/1000 participant-years	31.43	46.62	1.48	1.08-2.03
With cataracts at baseline	No. randomized	477	482		
	No. cataract surgeries	66	100		
	Annual rate of surgery/1000 participant-years	46.20	72.89	1.58	1.16-2.15
Total	No. randomized	6707	6681		
	No. cataract surgeries	129	201		
	Annual rate of surgery/1000 participant-years	37.58	56.81	1.51	1.21-1.89

The manuscript submitted for the NSABP P-1 trial evaluated only randomized participants with follow-up:

Table 66. Average annual hazard rates of cataracts and cataract surgery among participants (Table 9, NSABP P-1 manuscript)

Event	Placebo	Tamoxifen	Rate/1000 Women		Risk Ratio	95% CI
			Placebo	Tamoxifen		
Without cataracts at randomization	6105	6073				
Developed cataracts	483	540	22.51	25.41	1.13	1.00-1.28
Developed cataracts and underwent cataract surgery	63	101	2.83	4.57	1.62	1.17-2.25

The authors noted that there was a 13% increased risk, of marginal statistical significance, of developing cataracts on tamoxifen treatment. Women who entered the trial with cataracts or who developed cataracts on study had a 62% increase in the need for cataract surgery.

Reviewer Comments:

1. Some women developed cataracts while followed on study, but after discontinuing study drug. Sixty-nine women on placebo and 99 women on tamoxifen had cataracts diagnosed 6 days to 5 years after stopping study drug. Fourteen and 16 participants respectively had cataract surgery 2 days to 3 years after stopping study drug.
2. Predisposing factors for cataract formation include age, diabetes mellitus, and some cholesterol-lowering drugs. A wide array of other etiologic factors is cited in the literature, but these factors were unlikely to occur in significant numbers of the study population. Tobacco use has also been questionably linked to cataract formation. These factors for the group of participants with cataracts at any time during the study are summarized below.

Table 67. Potential risk factors for women with cataracts at baseline or on study

Risk Factor	Placebo (n=960)	Tamoxifen (n=1022)	Total (n=1982)
Age:			
≤49	79	73	152
50-59	184	188	372
≥60	697	761	1458
Diabetes mellitus:			
No	887	941	1828
Yes	73	81	154
Past/current use of cholesterol-lowering medications:			
No	808	865	1673
Yes	152	157	309
Tobacco use:			
Ever smoked			
No	537	580	1117
Yes	423	442	865
Current smoker			
No	879	930	1809
Yes	81	92	173
Any one of the above (except age)			
No	428	456	884
Yes	532	566	1098

Age was the most common factor observed in women with cataracts. There were no imbalances between the treatment arms, and no factors other than age that appeared to predict cataract formation.

3. The incidence of cataract surgery by age was evaluated.

Table 68. Incidence of cataract surgery by age

Age	Placebo (n=129)	Tamoxifen (n=201)	Total (n=330)
≤49	6	8	14
50-59	18	28	46
≥60	105	165	270

Women over the age of 60 had the highest incidence of cataract surgery, as expected. Approximately half of the operations in each age group occurred in women with cataracts at study entry, and half in women who developed cataracts on study.

4. The cataract data suggest that tamoxifen may increase the incidence of cataracts. The 95% confidence interval for this calculation includes 1.00, and the observation is at the border of significance. These data also suggest that tamoxifen increases the risk of requiring cataract surgery. These observations imply that tamoxifen may accelerate cataract formation. Steroids have been associated with cataract formation; it is possible that the steroid characteristics of tamoxifen are responsible for this finding.

10.5.2 Other Ophthalmologic Events

The blank CRF contained a Report of Vision Abnormalities or Examinations form. This form reported the date of a vision exam and specifically asked about the development of cataracts, deterioration in previously-diagnosed cataracts, deterioration in the cornea, development of macular degeneration, or other problems, with space to specify the problem. Information on therapeutic interventions was also solicited. However, the NSABP stated in several meetings/teleconferences that only information on cataracts and cataract surgery was collected. At the request of the FDA, the NSABP submitted copies of safety reports made to the FDA on 7 individuals who experienced eye problems during the course of the study. These cases are described below:

Placebo:

This participant was randomized on 1/5/93 at age 52 to study drug (randomized to placebo). On 8/20/97, at age 57, she complained of black spots and wavy lines in the field of vision. She was diagnosed by her ophthalmologist with a retinal hole and underwent argon photocoagulation surgery to correct the problem.

This 66 year old began study drug 12/23/92 and was diagnosed with glaucoma 8/94.

Tamoxifen:

This participant began study drug 5/7/93 with tamoxifen at age 44 and complained of blurred vision in the left eye 11/93. Study drug was stopped at this time because of problems with gastritis and mouth ulcers. On 1/10/95 she was diagnosed with a small branch vein occlusion.

This 47 year old participant began study drug 4/29/96 (randomized to tamoxifen). In 8/96, she noted cloudiness in her eye and vision loss, as well as bleeding in the left eye. On 8/24/96, her ophthalmologist diagnosed a non-ischemic venous occlusion. Study drug was discontinued 8/24/96. No therapy was instituted, and no improvement in her vision was noted. This participant was healthy, with no history of diabetes or hypertension, and was on no medications. Her PT, PTT, glucose, cholesterol, and platelet count were normal at the time of the event.

This participant began study drug 10/1/92 (randomized to tamoxifen) at age 60. On 7/25/96, at the age of 64, she was found to have macular degeneration of the left eye on routine examination. Study drug was discontinued.

This participant began study drug in September 1992 (randomized to tamoxifen) at the age of 62. In October 1996, she noted difficulty reading. In December, cataract surgery with lens implant was performed. In February 1997, a macular hole in the left eye was diagnosed at the age of 67. Surgery was scheduled for 2/24/97. Study medication was discontinued 2/9/97.

This participant began study drug 10/17/93 (randomized to tamoxifen) at age 65. In June 1994, she was diagnosed with early cataracts and mild age-related macular degeneration. In December 1996, she saw an ophthalmologist for complaints of blurred vision (she was age 69). In the opinion of the ophthalmologist, the changes were age-related, not tamoxifen-related. She continued on study drug.

This 68 year old participant was randomized 5/16/93 to study drug (tamoxifen). Because of complaints of decreased vision, she saw her ophthalmologist 5/19/97 at the age of 72 and was found to have early cataracts and age-related macular degeneration.

This 76 year old woman was randomized to tamoxifen and began study drug 5/11/93. Glaucoma was diagnosed 11/20/96, requiring trabeculectomy. She remained on therapy as of 12/11/97.

This 72 year old was randomized to tamoxifen and began study drug 9/18/92. Medication was discontinued 11/23/94 because of a diagnosis of glaucoma.

A database table of participants who reported a diagnosis of macular degeneration on study was provided 8/4/98. The database includes the participants listed above with macular degeneration.

Table 69. Macular degeneration in participants on NSABP P-1

Age	Placebo (n=65)	Tamoxifen (n=64)	Total (n=129)
≤ 49	12	4	16
50-59	13	10	23
≥ 60	40	50	90

Reviewer Comment:

1. Despite the structure of the form that included questions about a variety of ophthalmic complaints, not all of this information was incorporated into the database. In addition, participants were not required to have annual eye examinations.

2. The sponsor stated that cataracts and cataract surgery were the only eye findings noted during the trial. In the course of review of the CRFs, the following eye events were noted:

This 66 year old participant was diagnosed with macular degeneration 8/1/94, after starting study drug on 3/3/94. She went off-study at her request 10/30/95 because of her concerns about decreasing vision and worsening macular degeneration. She was randomized to tamoxifen.

This 56 year old participant was randomized to study drug with tamoxifen 3/14/94. She was noted on eye exam 2/3/95 to have corneal pitting. Study drug was stopped 11/5/95 because of a diagnosis of cancer of unknown primary.

The participant with macular degeneration was not listed in the database. If she is included, the number of women with macular degeneration on each arm of the study is equal.

3. The 7 MedWatch reports include 5 participants who have been reported in the database and in the above table for macular degeneration. The other 2 cases describe a venous occlusion of the eye, 1 that occurred on study drug and one that occurred after study drug discontinuation. These cases were discussed in Section 10.4.3, Thromboembolic events, and are likely to be related to the increased thrombogenesis associated with tamoxifen.

4. Review of available data does not demonstrate an increased risk of macular degeneration in participants on tamoxifen.

5. There is insufficient information to determine whether women are at increased risk of other, non-cataract- and non-macular degeneration-related eye events.

6. The consultation from the Division of Ophthalmologic Drug Products (Wiley A. Chambers, M.D.) noted the following:

- *The definition of cataract, the method of detection, the frequency of examination, type of cataract, and the reason for cataract extraction were not uniform throughout the study*
- *Despite these limitations, the finding of an increased rate of cataract extraction should not be ignored*
- *From review of the B-14 ophthalmologic substudy, clear differences in color vision testing and in the frequency of posterior subcapsular cataracts were observed. Posterior subcapsular cataracts are the most common drug-induced type of cataract.*
- *Recommendations for labeling were made*

10.6 Pregnancy

Women were required to indicate at several points during the pre-study evaluation that they were willing to use adequate contraception in order to enter the study. A warning about the risks to the fetus from tamoxifen was included in the consent form. Nonetheless, it is possible in a trial of this size and duration that pregnancies might occur.

At the FDA's request, the sponsor submitted information about pregnancies on study. This information is summarized below:

Table 70. Pregnancies during NSABP P-1

Patient Number	Treatment	Duration of Treatment; Pregnancy Outcome
	Placebo	Never started therapy; delivery Oct or Nov 1993
	Placebo	Started therapy 3/21/94 and continued until study unblinded. Pregnancy reported 5/95; miscarriage 5/26/95
	Placebo	Therapy started 5/25/94; continued until study unblinded. Positive home pregnancy test with request for unblinding; had elective abortion 8/28/95
	Placebo	Therapy started 9/23/93; found to be 9 wks pregnant 1/24/94. Drug stopped until 2/17/94. Had miscarriage 2/12/94. Back on study drug until unblinding
	Tamoxifen	On study drug 11/13/92 to 12/17/92. Became pregnant 9/97. Pregnancy outcome unknown; more information pending

Reviewer Comment:

1. Overall, 5 women out of the 13,388 participants (0.04%) became pregnant, a sign of the highly motivated women in this trial.

2. During review of the CRFs, at least one participant (who did not become pregnant) was noted by a nurse to practice rhythm as a means of birth control

Rhythm is not considered an effective means of birth control.

3. The sponsor sent information about She delivered a healthy baby boy January 26, 1998. Postpartum exam was normal. No reported problems with the infant as of 5/28/98.

4. It will be important to include a detailed section in the label warning physicians and women about the potential risks of pregnancy with this drug. A Patient Package Insert will be helpful.

10.7 Adverse Events

10.7.1 Hematologic/Systemic adverse events

Adverse events were solicited from the Quality of Life forms, which included 42 symptoms. Participants filled out these forms, rating each event in severity from 0-4. Bloodwork was obtained at each visit, specifically WBC, platelet count, SGOT or SGPT, bilirubin, creatinine, and alkaline phosphatase. These results were then recorded on the

ADR form by the study coordinator at each site. The specific symptoms were placed in NCI CTC categories with grades at the local site. Forms were reviewed centrally.

Information is taken from the ERSMAC report that was presented March 24, 1998 and included patient data up to January 1, 1998 and from the database tables containing grade 3-4 adverse events from the ADR forms (sent 7/29/98), grade 3-4 gynecologic symptoms (sent 8/3/98), and grade 3-4 laboratory values (sent 7/31/98). Only participants with follow-up, not all randomized participants, were included in the analysis by the NSABP. The results are summarized in the following table. Neuro-mood scores are discussed in Section 11.0, Quality of Life.