THE CANCER LETTER

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Four Patients In Tamoxifen Treatment Trial Had Died Of Uterine Cancer Prior To BCPT

Four breast cancer patients in a treatment trial of tamoxifen died from endometrial cancer prior to the start of a $65 million prevention trial that is administering the drug to healthy women, according to internal documents obtained by **The Cancer Letter**.

The four patients were enrolled in the National Surgical Adjuvant Breast & Bowel Project's B-14 study, a trial testing tamoxifen versus a placebo in more than 4,000 women diagnosed with breast cancer.

Meanwhile, informed consent forms for the concurrent Breast Cancer Prevention Trial continued to claim that "no deaths from uterine cancer were reported" in large clinical trials using 20 mg of tamoxifen daily. "The uterine cancers that have occurred have been at an early stage and are thought to be curable," according to the form.

The internal documents, from NSABP headquarters and Zeneca Pharmaceuticals Group, portray a cooperative group that was cumbersome

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Pittsburgh Investigates Use Of Resources In Anonymous Mailing To Researchers

Univ. of Pittsburgh facilities and postage discounts may have been used in preparation of an anonymous mailing designed to trigger a letter-writing campaign protesting the removal of Bernard Fisher from chairmanship of the National Surgical Adjuvant Breast & Bowel Project, the university acknowledged.

"The leadership of NSABP discovered that the anonymous letter from the Coalition in Support of Breast Cancer Research was from a group of staff, friends and patients of the NSABP," the university said in a press release.

According to the press release, the coalition may have used NSABP's discounted UPS rates to send out its unsigned mailing that urged cancer researchers to write to Congress and Administration officials to demand Fisher's immediate reinstatement. At least one batch of the coalition's mail was picked up on university premises, the statement said.

The university declined to disclose the names of the individuals under inquiry. However, sources said the inquiry has focused on one faculty member and several members of NSABP staff.

An informal survey by **The Cancer Letter** indicates that the mailing was sent via overnight mail to all principal investigators in NSABP trials,

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Next Week:

NSABP's Plans For Overhaul

NCI's New Audit Procedures

Company Surprised To Learn It Held IND For Treatment Trial

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and slow in reporting and verifying patient deaths, a leadership concerned about negative publicity and reluctant to inform both NCI and the pharmaceutical company that manufactures tamoxifen.

The documents also fill in important gaps in the understanding of the controversy over the treatment and prevention trials of tamoxifen:

●Even after learning about the unexpectedly high mortality from endometrial cancer in 1993, NSABP leadership was reluctant to make annual gynecologic examinations a protocol requirement, disregarding a recommendation from the group's biostatistics director, who expressed "serious legal, ethical and moral concerns."

●Throughout the B-14 trial, investigators waited as long as two years to inform the cooperative group of patient deaths. Compounding the problem, NSABP sometimes took as long as two years to verify a death. In the first endometrial cancer death, it took NSABP two and a half years to make a report to NCI and investigators.

●According to an NSABP chart obtained by **The Cancer Letter**, four endometrial cancer deaths occurred in the B-14 study between June 1991 and April 1992. The prevention trial began April 29, 1992. Two more patients died in the fall of 1992 and the summer of 1993. It is not clear from the chart whether the dates on the chart refer to confirmed deaths from endometrial cancer. *(The chart appears on page 12.)*

● One Zeneca memorandum describes the apprehensions of NSABP chairman Bernard Fisher regarding the company's plans to change the consent forms for a similar prevention trial conducted in the UK. "Dr. Fisher did comment about the potential negative publicity that could occur," the company memorandum said. "In particular, this could be the bullet being sought by the health authority in the UK to stop the European prevention trial. If that is the case, that would have a major effect in the United States." NSABP is not involved in the UK trial.

●Zeneca on several occasions in 1992 and 1993 requested information from NSABP on tamoxifen-related endometrial cancer. According to company documents, Fisher assured the company that consent form changes were not necessary and that the group would soon publish a report on endometrial cancer in the B-14 study.

●Ultimately, in December 1993, the company learned through NCI, not NSABP, about the deaths of patients from endometrial cancer, even though the company required regular reports as a condition of supplying tamoxifen free to NSABP trial participants.

●After the endometrial cancer deaths became known, Fisher, in a meeting with NCI and Zeneca, objected to informing clinical investigators for fear that the news would leak to the press before publication in a professional journal. "Dr. Fisher was extremely reluctant to have this information disseminated for fear that this might leak to the press before the data could be presented in a manuscript where this data could be presented in its proper context," a Zeneca official wrote in a company memorandum.

●Though the B-14 trial began in 1982, memos indicate that Zeneca was not aware until 1993 that it held the investigational new drug application for the use of tamoxifen in the trial. It is the responsibility of the IND holder to inform FDA of all adverse effects in a clinical trial. The documents obtained by **The Cancer Letter** do not explain the cause of the apparent confusion.

Former NSABP chairman Bernard Fisher and NSABP Biostatistical Center Director Carol Redmond declined to comment for this story.

"Both Dr. Redmond and I are reviewing the information which we collected and provided to the [House Energy and Commerce Committee's] subcommittee [on oversight and investigations] and will respond to the issues raised as soon as we have reviewed all the material," Fisher said in a written statement to **The Cancer Letter**. "We would be willing to discuss these with you at a later date."

The subcommittee, chaired by Rep. John Dingell

THE CANCER LETTER

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(D-MI), held a hearing April 13 on the controversy over NSABP. Another hearing, scheduled for June 15, is expected to focus on the tamoxifen issue specifically, Capitol Hill sources said.

A Zeneca spokesman declined to be interviewed for this story. Zeneca is cooperating with the subcommittee's investigation of the NSABP. "It is not appropriate for Zeneca to comment on this information," said Jeffrey Soper, a spokesman for Zeneca Pharmaceuticals Group.

Endometrial Cancer Deaths on B-14

A chart prepared by the NSABP Biostatistical Center listing the endometrial cancer cases in B-14 shows that the institutions involved in the cooperative group delayed notifying the NSABP operations office of patient deaths for months or years. NSABP took months or years to follow up on the reports, other documents show.

According to the chart, 13 cases of endometrial cancer in B-14 had been reported to the group by the end of April 1992.

At an April 29, 1992, press conference in Bethesda announcing the prevention trial, Fisher said six B-14 patients had developed stage I or in situ endometrial cancer. Neither he nor NCI officials present mentioned any deaths from endometrial cancer.

All participants would have routine gynecologic exams and would be asked about uterine abnormalities, Fisher said. If abnormalities were reported, an endometrial exam would be done, he said.

A chronology of the deaths listed in the NSABP charts follows:

First death: June 25, 1991. Reported to NSABP on Aug. 5, 1991. Another NSABP chart obtained by **The Cancer Letter** shows the death was reported to NSABP on Nov. 5, 1991. A third chart shows NSABP approved a summary file containing the death information on Nov. 22.

Fisher told the House oversight and investigations subcommittee that it took two years to determine the cause of death of this patient because he was "unable to obtain autopsy analysis from the hospital," Dingell said at the April 13 hearing.

In January 1992, the group requested slides on the patient, and on Feb. 21, 1992, notified the Zeneca of the death, according to the second chart on the case. NSABP provided first notification of death to Zeneca on Jan. 30, 1992, according to a chart.

The group received the slides on March 16, but no further action took place until September 1993, when NSABP requested the autopsy report. The report was sent to medical review on Nov. 22, 1993, according to the chart.

Broder testified that the cause of death for this patient was originally listed as pulmonary embolism. "Since the diagnosis had pulmonary embolism as a cause of death, I believe there was some legitimate basis for not making a decision," he said. "I believe that early in 1992, certain information about endometrial cancer death could have been provided to us."

Second death: Oct. 15, 1991. NSABP was notified of the death 20 months later, on June 21, 1993, two months after the prevention trial began. The group approved the summary file containing death information on Oct. 8, 1993.

Third death: March 6, 1992. NSABP was notified Sept. 25, 1992. According to another NSABP chart, Zeneca was notified of this death in February 1993. The group approved the summary file Jan. 6, 1993.

Fourth death: April 22, 1992, just six days before the prevention trial began. NSABP was notified one year later, on April 9, 1993. The group approved the summary file June 29, 1993.

Fifth death: Oct. 9, 1992. NSABP was notified four months later, on Jan. 21, 1993. The summary file was approved June 29, 1993.

Sixth death: July 26, 1993. NSABP was notified Aug. 27, 1993.

It is not clear from the charts whether, in the cases reported to Zeneca, the company was informed that the patients had died of endometrial cancer.

"Information Was Not Provided To Us"

NCI did not learn about the endometrial cancer deaths until an NSABP meeting in October 1993, NCI Director Samuel Broder testified to Dingell's subcommittee earlier this month.

"It is my professional judgment that we should have received information on certain facts, and particularly it would be possible to have information on endometrial cancer early in 1992, possibly earlier," Broder testified at the April 13 hearing. "That information was not provided to us until substantially later than that."

The B-14 study enrolled 2,843 patients in the US and Canada from 1982 to 1988. Initial findings were reported in the New England Journal of Medicine in 1989. The study evaluated postoperative tamoxifen

in women with estrogen-receptor positive, invasive breast cancer and histologically negative axillary lymph nodes. Following either lumpectomy and radiation or total mastectomy, patients were randomized to receive either five years of tamoxifen or a placebo.

Later, an additional 1,220 women were registered in the trial to receive tamoxifen for five years, and then were randomly assigned to receive another five years of tamoxifen or placebo. This was done to compare five years to 10 years of tamoxifen.

The NSABP last fall acknowledged that 25 of the B-14 patients had developed endometrial cancer following the administration of tamoxifen, and six died from the disease (**The Cancer Letter**, Feb. 25). Earlier this month, Zeneca sent letters warning doctors of the risk of death from endometrial cancer associated with tamoxifen (**The Cancer Letter**, April 15). NCI instructed investigators conducting trials of tamoxifen to revise consent forms to notify patients.

The Making of a Controversy: A Chronology

When the prevention trial began, Zeneca, then ICI Pharmaceutical Group, was planning to revise its label for tamoxifen to include an update on the incidence of endometrial cancer, according to a June 12, 1992, letter to Fisher and Redmond from Paul Plourde, then director of endocrinology research for ICI.

Plourde, now Zeneca's senior director of clinical research, declined to be interviewed for this story.

"In regards to the B-14 study, I was happy to hear that you are preparing a manuscript with the updated data for publication," Plourde wrote to Fisher on June 12. "I will be expecting the B-14 incidence results. This will then serve as the basis for our revision."

The letter also discussed the company's interest in seeing "timely reports" on serious and life-threatening events in the prevention trial, which had just begun. "I hope you appreciate our need to have ongoing updates on the safety results of this trial," Plourde wrote.

The company wanted to review the procedures of the prevention trial's safety monitoring committee. "A yet to be resolved issue is how and when to inform investigators and the IRB, along with a possible need to revise the consent form if a serious life-threatening adverse event is reported which previously was not included in the label, investigational drug brochure, or consent form."

In a June 18 memo for his files, Plourde summarized a June 10 meeting with Fisher and Redmond, where the three discussed the safety monitoring process for the prevention trial. The safety monitoring committee had decided that "they alone should have access to the data, but according to the protocol NSABP would be tabulating adverse reactions and provide monthly summaries," Plourde wrote.

"A divergent view exists on the reporting of unexpected, life-threatening ADEs [adverse events] to investigators, IRB, and subsequent changes in the consent form," Plourde wrote. "The NSABP insists that this should be decided by the safety monitoring committee. If an association with the drug was seen, reporting to the IRB and investigators would occur.

"It is ICI's policy to report any serious, life-threatening ADE not previously noted in the PIB [patient information brochure] or consent form," Plourde wrote.

At the same meeting, Fisher and Redmond agreed that the tamoxifen label needed to be updated, and promised the B-14 results. "The label change will not impact the prevention trial consent form," Plourde wrote.

A draft of the B-14 paper was to be submitted for peer review "by the end of the summer," Plourde wrote. "Dr. Fisher has agreed to share a preprint with us for internal use only.

"The publication will contain 5-year data which does show a survival and disease-free advantage over placebo," Plourde wrote. "However, the data on registered patients who all received NVX [Nolvadex] for 5 years and were then re-randomized to either NVX or placebo will not be presented; this data is not mature enough."

On July 17, 1992, P.L. Walton, of the Medical Research Dept. at ICI in England, wrote to Ian Jackson and John Patterson at ICI headquarters in Wilmington, DE. He sent copies to Plourde and other ICI officials.

Walton wrote that he had seen a reference to endometrial cancer in the B-14 study in a publication by Craig Jordan. The report noted that, "Seven patients have experienced uterine cancer. Six of these were randomized to tamoxifen and one to placebo. All of these were early-stage disease."

Walton wrote, "Many of us have heard Bernard Fisher talking about the results of this study and referring to freedom from significant ADRs in the Nolvadex treatment group compared to the controls." The endometrial cancer cases "do not appear in the tables" in an NSABP report earlier that year, Walton

wrote. "Any comments?"

Plourde received Walton's memo on July 21, according to a stamp on the document.

On July 21, NSABP statistician Redmond wrote to Plourde with an update on endometrial cancer in B-14. **The Cancer Letter** was unable to obtain a copy of the tables included with the memo. The memo does not mention the number of patients with endometrial cancer.

"I should point out that the estimated relative risk is still unreliable, with 95% confidence intervals ranging from 0.9 to 20," Redmond wrote. "We will keep you informed of future updates on this toxicity."

A spokesman for Dingell said the subcommittee was seeking information about the reporting of the deaths.

"We have asked Dr. Fisher for correspondence with Zeneca which informed Zeneca about deaths with tamoxifen, and they have not provided those documents yet," the spokesman said.

Redmond: More Gyneclogical Follow-up

In 1993, Redmond wrote in memos to Fisher that investigators on tamoxifen trials should be told about the endometrial cancer risk.

"Due to the possible risk of endometrial cancer we have included special gynecological follow-up requirements in the prevention trial," Redmond wrote in a March 24 memo to Fisher. "However, we have not extended these same requirements to our treatment protocols although we have discussed doing so on several occasions. We have also recently had a woman diagnosed with what is reported as a stage III endometrial cancer in B-14.

"I believe that we can not afford to delay implementation of specific protocol guidelines for gynecologic surveillance to ensure that endometrial cancers are detected as early as possible," Redmond wrote. "We must make all investigators on the tamoxifen treatment trials aware of the endometrial cancer risk and ensure that women who experience gynecological symptoms are evaluated promptly and appropriately."

Following is a listing of the events that ensued, according to memos obtained by **The Cancer Letter**:

July 7, 1993: Plourde called Fisher to discuss the association of endometrial cancer with tamoxifen, according to Plourde's account of the call.

"We over the last few weeks have been looking at the association of endometrial cancer with Nolvadex treatment," Plourde wrote. "This was in part initiated because of the Yale publication reporting that the tumors associated with Nolvadex treatment were poorly differentiated tumors resulting in poor prognosis for these patients. Our evaluation from the clinical trial data base as well as from the literature could not confirm this Yale publication. Therefore, we did not feel that we needed to make any changes in our label.

"We will continue to monitor this closely," Plourde wrote. "Dr. Fisher thought that this was appropriate and he himself has initiated some activity within the NSABP to explore this further. He is requesting that slides from the endometrial cancer seen in the B-14 trial be evaluated. He plans on doing this over the next several months."

The company was interested in the "increasing number of patients within the B-14 trial developing endometrial cancer while on Nolvadex," Plourde wrote. "Upon careful review of the data, we felt that there was an increased risk to develop endometrial cancer with Nolvadex and that we will modify our label to reflect this.

"It was impossible to precisely quantitate the relative risk although quantitatively it did appear that there was a slight increased incidence," he wrote.

"I did not see these changes having a great impact on the treatment of patients with confirmed breast cancer and also on the US prevention trial since the protocol did include the B-14 data as well as the Swedish data and that this potential risk was noted on the consent form," Plourde wrote. "However, I did comment that it did have more of an impact on the European trial which would require that the protocol and consent form be modified."

Plourde continued: "Dr. Fisher did comment about the potential negative publicity that could occur. In particular, this could be the bullet being sought by the health authority in the UK to stop the European prevention trial. If that is the case, that would have a major effect in the United States."

The company planned to gather a panel of prevention trial investigators, epidemiologists and gynecologists to examine the issue, Plourde wrote in the confidential memo. "Dr. Fisher did not see any great need for having this panel, since he felt that the issue had been examined and he saw no need to rediscuss this issue," Plourde wrote. "However, he understood our desire to convene this panel and agreed to participate."

Plourde told Fisher that the principal investigator of the European prevention trial planned to hold a

press conference that week about the changes in the consent form, Plourde wrote.

NCI had agreed to send Susan Nayfield of the Div. of Cancer Prevention & Control to the press conference. Fisher said he wanted to discuss these issues with NCI.

Later the same day, Plourde held a conference call with Fisher and Leslie Ford, chief of NCI's Community Oncology & Rehabilitation Branch.

"Dr. Ford...agreed with our approach in regards to the label change," Plourde wrote. "She did not feel that the US needed to make any changes in the consent form or the protocol.... She recognized, however, that this could cause some unnecessary and inappropriate publicity."

Plourde wrote that Ford would instruct Nayfield not to participate in the press conference.

"Overall, this interaction was positive and I believe that both groups felt happy that we were keeping them informed," Plourde wrote.

Ford did not return a reporter's phone call this week.

July 8, 1993: Plourde wrote to Fisher and Ford that Zeneca felt the association between tamoxifen and endometrial cancer "does impact on the assessment of the risk benefit ratio for women participating in the current prevention trials." The company proposed to amend the drug label.

Zeneca would inform the three research groups—US, UK, and Italy—of the changes. "In turn, we require that each group now ensures that this increased risk is appropriately reflected in the trial protocol and consent form and that adequate measures are in place for monitoring the occurrence of endometrial changes during the trial."

He asked Fisher and Ford to re-examine the prevention trial protocol and consent form.

July 15: Joseph Constantino, NSABP statistician on the B-14 study, provided Fisher with a list of 21 patients on B-14 diagnosed with endometrial cancer and the date of diagnosis.

"Of these 21 cases, eight blocks/slides were received several months ago and sent to Ed [Fisher, NSABP's pathologist and Bernard Fisher's brother]," Constantino wrote. "An additional eight specimens have been received and are at the Biostatistical Center. There are still five patients from whom we have not received specimens."

In one case, a pathologist "refuses to send the material," Constantino wrote. Slides for two cases were to be sent to the group shortly.

"Institutions for the remaining two cases have also been contacted and they have indicated that they will send the specimens as soon as possible," he wrote.

Aug. 5: Fisher and NSABP staff met with Plourde. Fisher said he did not think consent form changes for the prevention trial were necessary, Plourde wrote in Aug. 5 minutes of the meeting.

NSABP assured Plourde that the group is "exploring the endometrial cancer risk more closely" and will submit a paper to a journal within "the next couple of months," Plourde wrote.

Aug. 9: In a letter to Fisher, Plourde said he was concerned by the discovery that the B-14 trial and two other trials were actually under Zeneca's IND.

"Because of our standard operating procedure, we would need to monitor the trials in order to be in compliance," Plourde wrote. "Although I fully acknowledge that the NSABP are compulsively monitoring the trials, it may not satisfy our regulatory requirements. Having these trials under our IND requires additional resources, therefore, I am exploring the possibility for these studies to be transferred to your IND."

Aug. 17: In a memo to Plourde, Zeneca's John Patterson expressed concern that NSABP was not providing safety reports to the company on a regular basis, which was one condition of drug supply.

"I am aware of the difficulty in dealing with Dr. Fisher but it seems that we must insist on our conditions of supply of material being met in full," Patterson wrote.

Aug. 17: Plourde wrote to Redmond thanking her for agreeing to provide information on second primary tumors, particularly in the liver and the endometrium. Plourde requested information on "age, time onset, histology and staging at diagnosis, treatment and outcome."

Aug. 19: Redmond wrote a memo to Fisher, titled "Follow-up of Patients Receiving Tamoxifen on NSABP Protocols":

"I have just reviewed your July 26 memorandum to NSABP investigators on the above named subject. I personally and professionally have serious legal, ethical and moral concerns regarding your decision that annual gynecologic examinations on these protocols are merely a protocol recommendation rather than a protocol modification/requirement. There is general consensus that tamoxifen increases the risk of developing endometrial cancer. Only by

requiring that all protocols which involve tamoxifen therapy include an annual gynecological examination, can we be assured that the risks are minimized.

"We, as the investigators, are obligated to ensure that women are adequately informed about their risks. I am concerned that a 'recommendation' that examinations be done does not fulfill our obligations to the women involved in these trials.

"I strongly propose the following immediate course of action:

"a) All protocols which involve tamoxifen or tamoxifen/placebo should have a formal protocol modification in the body of the protocol and consent form with an accurate description of the risk of endometrial cancer.

"b) We should require that we are informed that the IRB's have approved the protocol modification.

"c) For all patients still being treated with tamoxifen or tamoxifen/placebo on protocols B-12, B-14, B-16, B-18, B-20, B-22, B-23, B-24 and B-25, we should require that each individual patient sign an protocol addendum and that a copy of that addendum be submitted to NSABP....

"The Biostatistical Center staff will support this process by generating lists of patients still on therapy, providing the lists to the involved institutions and recording the receipt of the signed protocol addenda."

The Cancer Letter was unable to determine whether Fisher responded to the memo.

Sept. 7: Plourde, Patterson and NSABP staff held a conference call to discuss the B-14 endometrial cancer data. "Dr. Fisher reviewed the B-14 endometrial cancer data," Plourde wrote. "A lot of data was transmitted which unfortunately was difficult to capture over the phone. However, the conclusions were as follows:

"There is a slight increase incidence in endometrial cancer although the exact quantification is not possible. The relative risk is estimated to be approximately 5 with a confidence interval of 1.9-18.7."

The risk factors for developing endometrial cancer while on Nolvadex were not determined, Plourde wrote. About half of the patients had received prior hormone replacement therapy. "The majority of patients had stage 1 disease with favorable histological and nuclear grading." This was "encouraging," Plourde wrote, because the data did not support the conclusion of the Yale study, which had reported that tamoxifen-associated endometrial cancers appeared to have poorer prognoses.

Plourde wrote that the company needed the B-14 data "to convince the UK Working Party on the Prevention Study that the risk of developing endometrial cancer needed to be mentioned in the consent form." However, since the data was not published, the UK group would not include the information in the consent form.

"This is unacceptable to us, therefore we requested permission to have the B-14 data," Plourde wrote. "Dr. Fisher does not want to release this information until it is published. He hopes to get a draft manuscript written within two weeks and submitted to a journal in a short period of time.

Another item discussed was FDA's request for a labeling change to recommend prolonged follow-up of offspring exposed to tamoxifen in utero. FDA wanted this information in the prevention trial consent form, but Fisher refused.

Dec. 9: In an internal memo, Plourde reported a Dec. 8 phone conversation with Karen Johnson, of NCI, who informed him about the data presented at a Nov. 1 NSABP meeting. One death from endometrial cancer was reported, Plourde wrote.

"This information was conveyed to Dr. [Samuel] Broder, director of the NCI. Dr. Broder was concerned and requested that the consent form be modified to reflect this new information. In addition, he asked whether this data had been submitted to the FDA.

"I told Dr. Johnson that we had not been provided with this B-14 data although the number of patients developing endometrial cancer had been sent to us. Therefore, this death had not been reported to the FDA and had not been included as part of the prevention trial consent form.

"I agreed with Dr. Johnson that the consent form needed to be modified and that this information needed to be provided to the FDA."

Plourde wrote that he then called Fisher and Redmond. "Dr. Fisher acknowledged that they had not submitted this information to us," he wrote. The information would be provided to the company and then to FDA, he wrote.

The group is reviewing the consent form and "will make the modification," Plourde wrote. "In particular, all protocols dealing with tamoxifen will be re-examined and modified to include the endometrial cancer data."

Dec. 13: Fisher and Redmond wrote to Plourde, listing the endometrial and other second primary cancers reported on B-14.

Six patients who took tamoxifen had died of endometrial cancer, out of a total of 25 cases,

according to a table included in the letter.

"We have received two additional cases during the past week and are in process of collecting all relevant information so that headquarters staff can assess and confirm whether or not these are endometrial cancers," they wrote.

Dec. 21: Fisher and NSABP colleagues traveled to Bethesda to update NCI on the endometrial cancer in B-14, according to a memo written by Ford to DCPC Director Peter Greenwald.

"Among the randomized tamoxifen population, there were 15 cases of uterine cancer. Five of these patients are dead, but it is important to note the circumstances," Ford wrote. "One of the five was randomized but never received any tamoxifen. A second randomized patient who took tamoxifen for five months died later of a cardiovascular event. Although she was reported to have had stage IA endometrial cancer, the diagnosis was not confirmed at a central pathology review, which found no malignancy on the slides.

"Of the three remaining cases, one died of abdominal carcinomatosis (73 months after cessation of tamoxifen), one after a diagnosis of stage IV papillary endometrial cancer, and the other of post-operative complications following hysterectomy for a stage IIB carcinosarcoma. There was one death from eight cases of endometrial cancer in the registered population. This patient was diagnosed after only nine months of tamoxifen therapy, raising the question of a pre-existing condition. This may also apply to five other cases where the diagnosis occurred after less than one year of tamoxifen therapy.

"The accumulating information about endometrial cancer in B-14 has immediate implications for that trial and other treatment trials that use tamoxifen. When B-14 was started, there was no requirement for gynecologic evaluation and follow-up. In July, a directive went out from NSABP to all its investigators advising them of the need for careful monitoring and follow-up of gynecologic symptoms and increased surveillance for uterine cancer in patients on tamoxifen treatment trials."

NSABP investigators were modifying the protocols and consent forms for the treatment trials, she wrote.

"From the latest risk-benefit analysis, it is clear that the prevention of breast cancer recurrence, contralateral breast cancer, and other benefits from tamoxifen greatly outweigh the number of endometrial events observed in B-14," Ford wrote. "The risk-benefit ratio that was calculated for the Breast Cancer Prevention Trial with tamoxifen was based on a twofold increase in uterine cancer in the tamoxifen arm of the trial. Even though there are now some additional cases of uterine cancer, the overall risk-benefit ratio is not substantially changed by the latest information.

"The consent form is being revised immediately to remove the statement that no deaths from endometrial cancer have been reported in patients receiving 20 mg of tamoxifen daily in clinical trials," Ford wrote. "Other than notification of investigators and appropriate modification of protocols and consent forms, the attendees at the meeting agreed that NSABP would continue to coordinate both the data collection and its 'public' presentation."

Dec. 22: NCI, NSABP and Zeneca held a meeting to discuss the endometrial cancer data, Plourde wrote in a Dec. 30 memo. "Of the six patients who died, two died as a direct consequence of uterine cancer, one died from the surgery to treat the endometrial cancer, and the other three died of other causes," he wrote.

The risk-benefit ratio for the prevention trial was reviewed. "The patients entering the study have a much higher risk of developing breast cancer than expected," Plourde wrote. "Hence, the benefits of the study are much greater than were originally calculated despite the higher endometrial cancer rate.

"This was very convincing and the participants at this meeting all agreed that the endometrial cancer risk does not require the termination of the prevention trial."

NCI's Div. of Cancer Treatment expressed "urgency" in modifying the consent forms of all tamoxifen protocols the division was sponsoring, Plourde wrote.

"Dr. Fisher was extremely reluctant to have this information disseminated for fear that this might leak to the press before the data could be presented in a manuscript where this data could be presented in its proper context," Plourde wrote. "It was decided that Dr. Fisher would issue a draft revision of the consent form used in various treatment trials."

Jan. 12, 1994: NCI notified investigators of the B-14 data (**The Cancer Letter**, Feb. 25).

Jan. 18: Fisher sent the protocol and consent form changes for the prevention trial to Plourde.

"The level of increased risk of uterine cancer associated with tamoxifen is still uncertain," according to the new text in the uterine cancer section of the consent form. "After an average of eight 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 two per 1,000 women. (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 have subsequently died from uterine cancer. Most of the uterine cancers that have occurred have been diagnosed at an early stage when treatment is highly effective."

April 6: An article by Fisher on endometrial cancer in the B-14 trial was published in the Journal of the National Cancer Institute (**The Cancer Letter**, March 25).

April 8: Zeneca issued a letter to doctors notifying them of changes in the package insert for tamoxifen to update the toxicity information.

Mysterious Coalition Found To Have University Links

(Continued from page 1)

members of the National Cancer Advisory Board and several physicians who appear to have been selected on the basis of their prominence.

"It would be a violation of university policy to use university facilities, equipment, personnel, funds or other resources for personal activities," the statement said. The inquiry is being conducted by Donald Trump, NCAB's executive officer, in consultation with the university's general counsel.

"Ronald Herberman [NSABP's interim chairman] inquired, was told and believes, along with the university leadership, that Bernard Fisher was not involved with this effort," the statement said. "Herberman was told that this mailing was done with personal funds and on personal time."

The Cancer Letter obtained a shipping document from the coalition's mailing. The document indicated that the mailing was sent via UPS Next Day Air Letter. At $9 per letter, the coalition's mailing costs alone could have been as high as $4,500. NSABP's volume discount would have cut these costs in half.

Pennsylvania law enforcement officials said to **The Cancer Letter** that the coalition may have violated state consumer protection laws by listing its mail box as a "suite" on the stationery. The fines for such misrepresentations can be as high as $1,000 for every letter sent.

An anonymous caller claiming to represent the coalition acknowledged to **The Cancer Letter** that the group's address was indeed a box at a franchise of Mail Boxes Etc., located near the NSABP headquarters.

The coalition's 12-page mailing included an unsigned cover letter dated April 5 and addressed to "Dear Colleague," a sample letter to be sent to legislators and Administration officials, as well as sample letters to be given out to breast cancer patients and patients enrolled in the prevention trial.

"I am a woman at high risk of getting breast cancer," the latter piece of correspondence begins. "I have lived all my life waiting for the day when breast cancer will strike me down."

The rest of the mailing consisted of addresses and telephone numbers of legislators and government officials.

The Cancer Letter contacted 15 principal investigators in NSABP trials in the US. Thirteen of the 15 said they had received the mailing.

One said he had been traveling and did not know whether he had received the letter and one said he must have been excluded from the mailing because of his long-standing criticism of NSABP.

Of those who received the mailing, seven said it had arrived via overnight mail, while the rest said they had not seen the envelope.

The Cancer Letter also contacted five NCAB members, four of whom said they had received the mailing. One of the four said the envelope had arrived via overnight mail.

A survey of one NSABP site indicated that the mailing was received only by the PI. However, at two other sites, investigators who were not PIs reported having received the mailing.

The persons who had planned the mailing appeared to have had a more than casual familiarity with the NSABP PIs. One investigator contacted by **The Cancer Letter** said he must have been excluded from the list because of his rivalry with NSABP leadership.

"I didn't receive anything," Phillip Bretz of the Desert Breast Institute in Rancho Mirage, CA, said to **The Cancer Letter**. "Why would I write a letter in support of Dr. Fisher?"

Prior to the start of the Breast Cancer Prevention Trial, Bretz, a surgeon, unsuccessfully sought FDA approval to conduct a trial of tamoxifen in post-menopausal patients at high risk of developing breast cancer. Bretz is a candidate for the seat being vacated

by Rep. Al McCandless (R-CA).

Last Sunday, a caller who identified herself as a member of the Coalition in Support of Breast Cancer Research, said to **The Cancer Letter** that the ad hoc group was formed in response to recent events at NSABP.

The caller, who said she was a health care professional practicing in Pittsburgh, said the group conducts no fundraising.

Participants in the coalition's activities finance those activities, the caller said. "It's sort of like me going to a grocery store, getting my groceries and choosing to do with them as I like," she said.

Asked how the mailing was financed, the caller said, "I don't know the sources of funds... I wasn't a part of that mailing."

The caller declined to give the names of any of the group's members. "The real key in terms of anonymity is that we are talking as a group, not as individuals," she said. "There are other groups that have adopted this policy, such as Alcoholics Anonymous."

Confirming that the group's address was a box at Mail Boxes Etc. rather than a "suite," the caller said the box had been rented for some time before the coalition was created.

"There was no intention of being deceptive," she said.

NCI Suspends Tulane, LSU Due To 'Missing Data' In Audit

Two institutions belonging to the National Surgical Adjuvant Breast & Bowel Project have been suspended from new patient accrual in the group's clinical trials due to missing data.

The action suspending Louisiana State Univ. and Tulane Univ. was taken March 18, a week before NCI placed NSABP on probation because of concerns about the quality of the group's auditing process for its clinical trials.

NCI sent audit teams to LSU and Tulane after becoming concerned about the conclusions of NSABP audits of the institutions in late 1992, according to an NCI statement last week. The audits were reported to NCI in December 1993.

NSABP could not provide NCI with plans for follow-up with the institutions to correct the problems that had been identified in the audits, NCI said.

"Because there was so much data missing, we couldn't establish the eligibility of a majority of patients at these two sites," said Bruce Chabner, director of NCI's Div. of Cancer Treatment.

The NCI audits were arranged with little notice to either institution and were conducted, in part, in response to data manipulations at other sites in NSABP, according to NCI.

At Tulane, where about 75 patient charts for a variety of studies were audited between 1976 and 1994, NCI auditors could confirm patient eligibility in less than 20 percent of the charts. There was insufficient documentation to confirm eligibility in about half of the cases and about five percent were ineligible, NCI said.

An acceptable informed consent document could not be verified in about a quarter of the cases and there were several protocol violations, NCI said.

Monitoring of cooperative group clinical trials was begun by NCI in 1982. Each group member is audited at least once every three years.

"At this time, NCI does not challenge the basic integrity of these institutions, but further site visits and audits will be necessary," according to the statement.

LSU and Tulane are developing written plans to correct the problems, NCI said. NCI will review the plans and decide whether to resume accrual.

No Evidence Of Systematic Fraud In NCI Audit Of NSABP

NCI auditors have not found evidence of systematic manipulation of data in clinical trials of the National Surgical Adjuvant Breast & Bowel Project, the Institute said last week.

Completing the first phase of an audit of primary medical records of patients entered into NSABP trials, there is nothing to indicate fraud or scientific misconduct, NCI said in a April 21 statement.

However, NCI found "unacceptably high rates of missing or unconfirmed data" in some institutions during a review of NSABP's audits reports for the past four years. NCI plans to audit these institutions over the next few months.

NSABP has begun a complete overhaul of its data management and auditing procedures, with the advice of an oversight committee. Accrual to NSABP studies will not resume until a functioning audit program is in place, NCI said.

NCI's review should be considered preliminary, according to the statement. Medical records review requires interpretation and clinical and scientific

judgment, NCI said. Additional analysis is required. Access to records that have been archived may resolve some differences, NCI said.

NSABP has submitted to NCI a draft plan for improving its audit procedures.

Original Findings Confirmed

An NCI contractor, EMMES Corp., of Potomac, MD, completed an independent analysis of the NSABP electronic analysis file for the B-06 study of lumpectomy with or without radiation versus mastectomy. The analysis excluded the patients entered by Roger Poisson of St. Luc Hospital in Montreal. Poisson was found by NIH to have committed scientific misconduct.

The original findings of the B-06 study were confirmed, NCI said. The EMMES reanalysis of studies B-13 and B-14 also confirmed the original findings.

NCI plans to audit the patient charts in the B-14 study.

"There is a general consensus in the scientific community that breast-sparing procedures are valid," NCI said. "The value of the procedures has been confirmed by independent studies."

B-06 began in 1976 and completed accrual more than 10 years ago. Still, a high proportion of the data used in the independent reanalysis of the study results were verified by direct comparison to patient charts. Nine data points used in the reanalysis and 25 eligibility elements were examined in the NCI audit.

The audit was conducted on 975 B-06 charts, representing 53 percent of the patients entered on the trial. A preliminary analysis of the audit results on more than 700 of the patients confirmed the accuracy of greater than 92 percent of the data entries for eight of nine data categories evaluated, including date of surgery, presence of positive lymph nodes, and date of death.

The auditors' findings disagreed with NSABP data entries in two percent or less of the cases for all categories examined.

There was a 7 percent disagreement for date of last follow-up. Follow-up data available in the charts had not been sent to NSABP for some cases, NCI said. There was 4 percent disagreement for site of first recurrence. In this category, patients with second primary breast cancer in the other breast were classified as recurrences by some investigators in their initial reports.

Most patient eligibility items were verified in the 975 patient charts reviewed. Complete verification was obtained in 60 percent of the cases. The most frequent reason for not meeting all protocol eligibility requirements was the lack of a signed, dated, or witnessed informed consent form.

However, NCI auditors could clearly document that informed consent, either oral or written, had been obtained in 92 percent of patient records examined, although a properly executed document that would meet current standards was found in only 60 percent.

The B-06 study was begun in April 1976. Regulations about informed consent procedures were not completely formalized until 1981, NCI said.

Many charts were scattered because the audits were conducted with little prior notice to the institutions and because the B-06 study had been closed to accrual for so long, NCI said. The purpose of the audits was to determine whether there was evidence of systematic manipulation of the data that would indicate fraud or major problems with data quality. Such problems have not been found, NCI said.

Community-Based Trials

"These rates of NSABP data confirmation, while lower than those reported in the recent audit experience of other cooperative groups, such as the Eastern Cooperative Oncology Group and the Cancer & Leukemia Group B, likely result from the community-based nature of the trials, the many years between inception of the B-06 trial and the current audit, and the urgency with which the audit was conducted," NCI said.

NSABP studies are more community-based that those of other cooperative groups, NCI said. This has been considered one of the group's strengths because the results of studies are likely to reflect the actual standard of practice in the community.

The full reports of the reanalyses are available on NCI's CancerFax service, on CancerNet, which provides information via Internet, and on PDQ News.

To use CancerFax, dial 301/402-5874 using the handset on a fax machine, and request document 400027 for the B-06 reanalysis, and document 400028 for the B-13 and B-14 reanalyses. CancerNet may be accessed by electronic mail message to cancernet@icicb.nci.nih.gov. Include code numbers cn-400027 and cn-400028 on separate lines in the body of the message. The items will be returned via electronic mail usually within 10 minutes, NCI said. To obtain the reports from PDQ news, consult a medical librarian, NCI said.

B-14 ENDOMETRIAL CASES: AVAILABLE PRE-DIAGNOSTIC HISTORY, DATES OF DIAGNOSES AND REPORTS

STUDY NUMBER	DATE OF FIRST GYNECOLOGIC SYMPTOM	DESCRIPTION	PREVIOUS TESTS AND DATES	DATE OF DIAGNOSIS OR ENDOMETRIAL CANCER	DATE REPORTED TO NSABP	DATE OF DEATH (IF APPLICABLE)	DATE DEATH REPORTED TO NSABP
14-0134-123	08-26-91	Bleeding	N.R.	09-20-91	01-06-92		
14-3137-905	08-??-90	Bleeding	Unknown (D+C)	09-13-90	10-22-90		
14-0310-137	N.R.		N.R.	11-10-82	10-26-92		
14-0627-053	N.R.		N.R.	04-09-91	11-20-91	03-06-92	09-25-92
14-0760-078	07-??-89	Discharge	N.R.	01-12-90	04-11-90		
14-0984-026	11-??-91	Bleeding	N.R.	11-22-91	03-08-93	04-22-92	04-09-93
14-1073-407	02-16-93	Bleeding	02-17-93 (PAP)	02-16-93	03-23-93		
14-1270-097	10-??-85	Irregular Menses	N.R.	08-04-86	02-24-87		
14-2102-039	03-??-88 02-03-89	Excess. Menses Bleeding	N.R.	02-06-89	04-12-89		
14-2444-055	N.R.		N.R.	01-09-92	04-27-92	07-26-93	08-27-93
14-3251-444	11-??-90 02-22-91	Spotting Bleeding	02-22-91 (CT)	03-06-91	03-18-91		
14-4211-014	01-??-88 ??	Irregular Menses Discharge	Unknown (BX)	04-18-90	07-18-90		
14-4675-014	??	Endo. Thickening	Per Discharge Summary (MRI)	09-30-92	06-07-93	10-09-92	01-21-93
14-4862-629	01-??-90	Bleeding	04-??-90 (PAP, D+C)	05-01-90	07-13-90		
14-2915-084	N.R.		N.R.	03-09-93	04-14-93		
14-3461-073	08-01-93	Bleeding	10-02-90 (PAP) 11-03-92 (GYN)	08-06-93	08-16-93		
14-2002-066	09-25-86	Bleeding	09-30-86 (D+C)	09-30-86		10-15-91	06-21-93
14-2236-444	??	Bleeding		06-13-88	08-11-88		
14-3877-196	N.R.	N.R.	N.R.	03-01-89	11-05-91	06-25-91	08-05-91
14-4726-104	10-27-89	Bleeding	N.R.	12-15-89	02-20-90		
14-5546-065	??	Bleeding		09-29-89	10-15-92		
14-5550-097	??	Enlarged Uterus on P.E.		11-13-90	06-03-91		
14-5596-043	01-??-92	Bleeding	02-??-92 (D+C)	02-06-92	06-25-92		
14-5909-064	02-??-91 11-??-91 01-??-92 05-??-92	2 Periods After None for Years Missed Periods Heavy Flow Heavier Flow		05-28-92	12-14-92		
14-4475-406	10-??-92	Bleeding	04-??-92(PAP) 07-??-92(PAP) 10-17-92 (Neg. BX)	03-05-93	04-29-93		