THE CANCER LETTER

Vol. 20 No. 14
April 8, 1994

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NCI To Require Prompt Publication Of Data Affected By Falsification In Future Grants

NCI is developing a policy that would require grantees to meet specified deadlines for analyzing and publishing data that has been affected by falsification or error, Institute officials said last week.

The policy, to be included in the terms of award for cooperative agreements that support clinical trials, is under development by NCI's grants management staff, Institute officials said at an emergency meeting of the leaders of the NCI-funded cooperative groups last week.

The new terms spell out NCI's authority to step in and reanalyze suspect data whenever a grantee fails to do so.

The deadlines are the result of NCI's frustration over the delay by the

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In Brief

Bast To Head M.D. Anderson Medicine Div.; Ozer Named Emory Cancer Center Director

ROBERT BAST JR., director of the Duke Comprehensive Cancer Center since 1987, will take the position as head of the Div. of Medicine at the Univ. of Texas M.D. Anderson Cancer Center as of July 1. Bast replaces **Irwin Krakoff**, who has retired. Bast, who went to Duke in 1984, collaborated with Robert Knapp in developing the CA-125 blood test for early detection of ovarian cancer. At M.D. Anderson, Bast plans to continue the CA-125 research, as well as oversee the center's chemotherapy and bone marrow transplant trials. . . . **HOWARD OZER** was named director of the Winship Cancer Center at Emory Univ. Ozer is the former chief of medical oncology at the Univ. of North Carolina School of Medicine and associate director of the Lineberger Comprehensive Cancer Center. Last year, Emory received a planning grant to apply for an NCI cancer center support grant. . . . **REP. WILLIAM NATCHER** (D-KY), chairman of the House Appropriations Committee and its subcommittee on Labor, HHS and Education died last week. He was 84. . . . **REP. DAVID OBEY** (D-WI), who was recently named the committee's acting co-chair, is expected to succeed Natcher as chairman. . . . **REP. NEAL SMITH** (D-IA) is expected to succeed Natcher as chairman of the Labor, HHS panel. . . . **NANCY BRINKER**, founding chairman of the Susan G. Komen Breast Cancer Foundation, received the James Ewing Layman's Award at the annual meeting of the Society of Surgical Oncology, in Houston. The award is presented every year to a non-physician for distinguished contributions in support of cancer research.

NCI Proposes Stricter Rules For Grantee Fraud Reporting

(Continued from page 1)

National Surgical Adjuvant Breast & Bowel Project in publishing a reanalysis of data from several studies, including the landmark study comparing lumpectomy to mastectomy for breast cancer.

The NIH Office of Research Integrity found in February 1993 that the lumpectomy study and 13 other NSABP studies contained falsified data submitted by Roger Poisson, a surgeon at St. Luc Hospital in Montreal.

NSABP did not act on two letters and several verbal requests from NCI urging the publication of a reanalysis of the lumpectomy and other affected trials, NCI officials said. The first request followed NSABP's presentation of a reanalysis to NCI and ORI in March 1992, sources said.

NCI urged NSABP Chairman Bernard Fisher in writing in January 1993 to "finalize" a reanalysis, according to a March 23 letter from Rep. John Dingell (D-MI) to HHS Secretary Donna Shalala. Dingell has scheduled an April 13 hearing of the House Subcommittee on Oversight and Investigations to look into the NSABP controversy.

Emergency Session of Group Chairmen

"There is such a large pool of ethical investigators, [that] it makes it that much harder to detect the criminal," said Michael Friedman, director of NCI's Cancer Therapy Evaluation Program. "We cannot hold the rest of the research hostage. We must strike a balance."

Friedman spoke at a meeting of leaders of NCI-sponsored cooperative groups in Bethesda last week.

THE CANCER LETTER

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Subscription $225 per year North America, $250 elsewhere. ISSN 0096-3917. Published 48 times a year by The Cancer Letter Inc., also publisher of The Clinical Cancer Letter.

Much of the rewriting of the terms of award is expected to clarify existing NCI policies in the event of scientific misconduct such as the case at St. Luc Hospital, Friedman and other NCI officials said at the meeting.

Most important, Friedman said, is the principle that any non-compliance with guidelines and any suspected fraud must be reported to NCI immediately, so that NCI can alert the Office of Research Integrity and the Food & Drug Administration.

"Research is damaged in two ways: fraudulent data and sloppy data," said Friedman. "Ask your executive committees to define what you consider fraud and what you consider sloppy."

NCI is considering the following clarifications in the terms of award:

- Immediate notification of NCI of any irregularities found during auditing of institutions.

Some grantees in the past have thought it was acceptable to inform their institutions or cooperative groups. However, NCI needs to be informed as well, Friedman said to the group chairmen.

In addition, NCI will require cooperative groups to inform them any time an audit has taken place, to ensure that audits are being conducted on schedule.

- Establishment of deadlines for reanalysis of falsified or erroneous data, and submission of results of the reanalysis for publication.

"If there is any expectation that manuscripts include potentially fraudulent data, it is reasonable to put a hold on them," said Bruce Cheson, head of the Medicine Section in CTEP's Clinical Investigations Branch. If a presentation of the data is to be made and a reanalysis has not been done, there should be a disclaimer at the time of presentation, he said.

- Following a finding of scientific misconduct, the grantee is responsible for notifying all collaborators and sponsors in a timely manner.

This includes notification of scientific journals that published the research. The New England Journal of Medicine never was informed about the falsifications in the lumpectomy study, according to news reports. NCI will inform journal editors as well, Friedman said.

- NCI has the right to recover federal funds used to support fraudulent or falsified research, or where federal policies, including terms of award, have not been adhered to.

The NCI is pursing the recovery of funds from

St. Luc Hospital. In addition, NIH has established a committee to develop more precise policies on funds recovery, according to Leo Buscher Jr., chief of NCI's Grants Administration Branch.

NCI is considering "some recovery of funds" from the Univ. of Pittsburgh, the headquarters of the NSABP, Buscher said to the group chairmen.

Friedman added that this was at an "early stage of discussion."

Sharon Murphy, chairman of the Pediatric Oncology Group, said her university's grants management office would "break out into hives" at the prospect of being held legally and financially accountable for the actions of an investigator at another institution.

The cooperative group system depends on hundreds of smaller institutions, hospitals and physicians' offices for enrollment of patients on clinical trials.

•NCI has the right of immediate access to data when requested, in a usable and accessible format. This can be done without compromising patient anonymity, NCI officials said.

The group chairmen noted that data files are constantly being updated, and archiving large data sets could be expensive. Charles Coltman, chairman of the Southwest Oncology Group, suggested that the groups maintain a library of data used to prepare each publication. "When a question arises, we can send you a file fixed in the time it was used."

What About The Patients?

Friedman asked the group chairmen for assistance in developing a policy for notifying patients who participated in trials that are later found to report fraudulent data.

"What should we say to the women who participated in study B06?" the NSABP lumpectomy study, Friedman said.

Cooperative groups also should consider ethics training for data managers and support staff, NCI officials said.

Poisson's falsification was carried out with the help of his data managers, ORI investigators said. However, the data managers were not held responsible because they were following Poisson's directions, ORI said.

Data managers need to be told that: "Your job is to put down the truth," Friedman said. "We want them to understand the seriousness of this. It is a violation of federal law."

Although ORI exonerated the data managers, the funding for St. Luc Hospital was lost as a result of the falsifications and which terminated the support of the data managers. "They lost their jobs," said Richard Ungerleider, chief of the Clinical Investigations Branch.

Ungerleider also expressed concern about auditing of large intergroup studies, including the trial of Proscar (finasteride) for prostate cancer. The trial is coordinated by the Southwest Oncology Group.

"We think the sudden influx of 10,000 patients on the Breast Cancer Prevention Trial may have overwhelmed the NSABP operations office," Ungerleider said.

Coltman said SWOG has a full staff in its operations office. In the Proscar trial, each group will audit its own patients, and there is funding for audit expenses. The first audit of all randomized patients at one of the medical centers involved in the trial will take place this month.

Dingell To Challenge NCI, NSABP Handling of Fraud

NCI officials are preparing for a Congressional hearing where Rep. John Dingell (D-MI) is expected to challenge the handling of scientific fraud by the Institute and the National Surgical Adjuvant Breast & Bowel Project.

At the April 13 hearing of his Subcommittee on Oversight and Investigations, Dingell is expected to grill the Institute officials as well as representatives of NSABP on the details of the fraud and its aftermath.

NSABP's chairman Bernard Fisher, who is on administrative leave from the cooperative group, has been declining comment on the controversy pending his planned appearance at the hearing.

A list of questions submitted by Dingell, chairman of the subcommittee as well as of the full Committee on Energy and Commerce, offers a glance at the direction his inquiry could take. The following are excerpts from Dingell's letter to HHS Secretary Donna Shalala:

"We are concerned because there have been serious problems in this major study, because there have been significant delays in addressing these problems, and because no reassessment of the data has yet been published," Dingell wrote in the letter dated March 23.

"This episode is yet another example of how

scientific misconduct, coupled with an inadequate federal government response, can undermine efforts to improve the health and safety of the public.

"Women with breast cancer—the persons most vitally affected by the results of the NSABP studies—are widely reported to be 'devastated' and 'enraged,' with their confidence shaken both by the fraud and the inexplicable delay in its revelation. Clearly, the public trust has not been well served," he wrote.

NCI officials admonished staff of the National Surgical Adjuvant Breast & Bowel Project to tighten the cooperative group's auditing procedures 18 months ago, Dingell wrote.

In October 1992, NCI officials wrote that the NSABP's audit policy "contributed to the delay in detecting significant data irregularities" by Roger Poisson at St. Luc Hospital in Montreal.

In a January 1993 letter to Fisher, NCI officials again wrote that the NSABP audit procedures "will be under close scrutiny and open to possible criticism," and "strongly urging" NSABP to "review its present audit procedures and sample size selected for review," Dingell wrote.

Dingell's 13 Questions

1. From March 1992 to the present, did any ORI, NCI or NIH official perform the elementary step of examining the NSABP "reanalysis" to determine its reliability and accuracy vis-à-vis the published papers, and to substantiate the NSABP claim that exclusion of the St. Luc data did not change the studies' conclusions?

2. From 1991 to the present, has anyone other than the NSABP staff examined the research data to determine the accuracy and reliability of the data "reanalysis"?

3. When did NCI request the "updated" reanalysis, provided by Dr. Fisher to NCI in February 1994? Why did NCI request this update and why did NCI wait so long to do so? How does the update differ from what was presented in March 1992?

4. What steps, if any, did NCI take from 1992 to the present to ensure that results of the reanalyses were published in a timely fashion? Did NCI inform any of the affected scientific journals or the co-sponsor of the studies (the American Cancer Society) about the problems with the St. Luc data?

5. Were any papers containing the St. Luc data submitted or published by the NSABP after the 1991 reporting of the fraud at St. Luc? ... Did the papers reveal the problems with the St. Luc data?

6. Why did NCI wait until February 1994 to initiate steps to recover funds expended for the fraudulent research?

7. Does NCI possess a copy of the NSABP research data, either electronic or hard copy? ... If NCI does not possess the data, how did NCI perform "its own confirming reanalysis" as reported by NCI in its March 15 press release?

8. Why did NCI wait nearly two years after accepting the conclusions of the March 1992 NSABP verbal briefing on the data "reanalysis" to seek independent reviews of the reanalysis? What instructions were given to the three statisticians commissioned by NCI to conduct these reviews? Please identify these statisticians and describe how they were selected to conduct the reviews. What materials were the statisticians given to enable them to perform their task? Were they provided with any research data?

9. Why is it that, until the past few days, NCI never recognized the apparent problems in the NSABP reanalysis? Why, despite having recognized the significant deficiencies in the NSABP reanalysis, is NCI continuing to assert that "the original results and conclusions of the trials were confirmed?" ... Please provide a copy of the plan for the NCI reanalysis of the NSABP data.

10. What changes, if any, have been made in NSABP audit procedures, in response to NCI's October 1992/January 1993 critiques? When were these changes, if any, made?

11. Given the failure of the NSABP audits to detect the fraud at St. Luc, what confidence is there concerning the authenticity and reliability of any of the NSABP data?

12. What has been done to determine responsibility for the delays by NCI and NIH? Who is accountable?

13. How will HHS act to restore public confidence in the NCI and NSABP, and in the scientific data that have direct, profound consequences for the well-being of millions of women in this country and abroad?

Pittsburgh Vows To Make Changes To Keep NSABP

Univ. of Pittsburgh officials said they are determined to correct any problems in the National Surgical Adjuvant Breast & Bowel Project and are working to strengthen the project to keep its $7 million

annual funding.

Following NCI's demand that the cooperative group install new leadership, Ronald Herberman, director of the Pittsburgh Cancer Institute, was appointed interim principal investigator for NSABP.

In another appointment, Donald Trump, deputy director of PCI, was named interim executive officer.

Bernard Fisher, the cooperative group's chairman and principal investigator, is on administrative leave.

NCI accused NSABP of delays in conducting audits and failure to report irregularities. The NSABP had not conducted an audit of any of its member institutions in at least 12 months, and possibly longer, sources said to **The Cancer Letter**.

The delays, and lack of rigorous auditing, may have contributed to the group's failure to detect the falsifications by Roger Poisson of St. Luc Hospital, and an irregularity discovered at St. Mary's Hospital Center, another institution in Montreal that enrolled patients on NSABP studies, sources said.

Intent On Keeping NSABP

University officials said they stand by Fisher, 75, whose studies changed the standard of care for women with breast cancer.

"We are very concerned that Dr. Fisher's pioneering research has been lost sight of," Herberman said to **The Cancer Letter**. "We support Dr. Fisher 100 percent."

In the next month, Herberman and Trump will develop a plan for reorganization of the NSABP's operations office, according to the university's statement.

"We are trying to understand where the problems arose," Herberman said. "We are intent on doing everything possible to preserve the integrity of the NSABP, strengthen the NSABP, and keep the headquarters at Univ. of Pittsburgh."

NCI officials said they were pleased with the university's quick response.

"I am encouraged by the efforts that the new NSABP leadership is demonstrating," Richard Ungerleider, chief of NCI's Clinical Investigations Branch, said to **The Cancer Letter**. "They appear to be devoted to maintaining and enhancing the NSABP as a valuable resource for the country."

Traditionally, NSABP operations have been separate from those of PCI. However, with PCI officials taking over the top posts in the cooperative group, that separation has in effect eroded.

Moreover, long before the allegation against Fisher became public, PCI was developing the technology that would allow it to manage a large cooperative group.

In February, PCI, Univ. of Pittsburgh Medical Center and Magee-Womens Hospital announced a venture with Westinghouse Electric Corp. and Carnegie Group Inc. to create a network to gather and organize data on patient diagnoses, treatment and research findings, and patient outcomes in breast cancer (**Cancer Economics**, February 1994).

The system, based on technology Westinghouse developed for military use, will link diagnoses, treatment options and plans, research findings, tissue and serum bank resources, and treatment outcomes.

A logistics component of the network will enable rapid collection, transport, archiving and redistribution of tissue and fluid specimens.

The software for the PCI breast cancer program could be in place in a few months, Herberman said. The cancer center is working with its collaborators to expand the system and link it to the NSABP's data operations, he said.

"This system is well suited to handle the complex array of data including alarms and alerts needed in the conduct of NSABP clinical trials," Herberman said to **The Cancer Letter.** "We are working as quickly as possible to try to tie this in with the NSABP."

Much of the NSABP's data collection and recordkeeping is done on paper, Herberman said.

"Lookng on the bright side, we are optimistic that we will turn these unfortunate events into a process that strengthens the efforts of the cooperative group," Herberman said.

Herberman came to Univ. of Pittsburgh in 1985 to establish and lead PCI, according to the university's statement. From 1966 to 1985, he worked at NCI, serving as chief of the Laboratory of Immunodiagnosis in the Biological Therapeutics Branch, and was acting director of the Biological Response Modifiers Program.

NCI Letter Details Deficiencies In NSABP Operations Office

In a letter to the Univ. of Pittsburgh last week, NCI officials detailed the deficiencies that the Institute said "must be corrected" if the National Surgical Adjuvant Breast & Bowel Project operations office is to remain at the university.

"The NCI believes that the credibility of the

NSABP is at stake and the integrity of the entire NCI-supported clinical trials program may be jeopardized," NCI chief grants management officer Leo Buscher Jr. wrote to Michael Crouch, director of the Office of Research at the university.

A copy of Buscher's letter, dated March 29, was obtained by **The Cancer Letter**.

The letter withdrew NCI's approval of Bernard Fisher as principal investigator for the NSABP. "The problems that have been identified demonstrate serious management and scientific deficiencies for which the current principal investigator is responsible," Buscher wrote.

The full text of the letter follows:

There have been numerous incidents arising in the management of the National Surgical Adjuvant Breast & Bowel Project, of which Bernard Fisher, M.D., is Group Chairman, that are cause for grave concern to the National Cancer Institute. Even after NSABP discovered Dr. Roger Poisson's scientific misconduct at Saint Luc Hospital in Montreal, mismanagement problems and lack of judgment continue to occur. For example:

1. After this clear and acknowledged case of fabrication, NSABP staff have been extremely slow to submit manuscripts for publication that correct for fraudulent data. Moreover, they have not adequately informed the membership of the NSABP and other parties who would need to know the facts of the fraud and fabrication.

2. Despite a new system for auditing, a record that identified a data irregularity sat unattended in the NSABP Operations Office in Pittsburgh since September 1993. NSABP staff not only failed to notify the NCI immediately upon discovery of the irregularity, but also failed to follow-up with the institution (St. Mary's Hospital Centre, Montreal). This discrepancy was discovered by NCI staff during its on-site inspection of the data in Pittsburgh.

3. NSABP staff have reanalyzed trials B-06, B-13, and B-14 with Saint Luc data omitted. However, they have not reanalyzed other published trials, nor those unpublished but in press or submitted. They also have failed to notify journals, other than The New England Journal of Medicine, which published those trials.

4. Once the fabrication and falsification of the research data had been proven, the NSABP failed to notify Dr. Poisson's patients in the NSABP trials, or to notify appropriate institutional officials within Saint Luc Hospital or in neighboring or allied facilities.

5. NSABP leadership have as yet not established a data and safety monitoring board for treatment trials, which was to be implemented by February 1, 1994, despite repeated requests from NCI dating back to December 1992.

In addition to the above, other deficiencies were noted by a National Cancer Institute team consisting of Richard S. Ungerleider, Chief, Clinical Investigations Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment; Roslyn Bacon, Deputy Grants Management Officer; and Gary Smith, Clinical Trials Monitoring Specialist, Regulatory Affairs Branch, CTEP, who visited the NSABP Operations Office at the University of Pittsburgh on March 23-25, 1994. In particular:

1. The NSABP failed to notify the NCI immediately when data irregularities were identified on-site, to follow up when deficiencies were noted, and to submit audit reports to the NCI within the time period required by NCI guidelines.

2. There have been no audits of cases on treatment trials since April 1993 and there are reports still not submitted to NCI for audits dating back as far as 1991.

3. It appears that the quality control of submitted data to the NSABP Biostatistical Center has been confused with the on-site audit program. The two should have distinct functions.

a. The intent of the on-site quality assurance audit program is to verify submitted data; i.e., the source documentation, mainly the hospital chart, is compared with the submitted data. At the time of the on-site audit, the auditor is also reviewing the hospital chart for protocol compliance.

b. The Biostatistical Center controls the submitted data from participating NSABP institutions. The quality control function reviews the submitted data for completeness, timeliness, and data entry control. The Biostatistical Center should follow up on delinquent data.

4. It appears that there are few staff who are authorized to make decisions or to respond to the NCI's questions. This is especially troubling when there are time constraints. Two recent examples are: 1) When NCI staff in Bethesda discovered audit irregularities in reports from Louisiana State University at New Orleans and from Tulane University, they placed telephone calls to NSABP staff requesting clarification and description of follow-up measures. Neither of these phone calls was returned despite the establishment of definite

deadlines. 2) During the NCI's visit last week, NCI staff asked Operations Office staff if patients at Saint Luc Hospital are being re-randomized to NSABP protocols and which drugs, if any are being provided for patients at Saint Luc. We still have not been provided the answer.

The Code of Federal Regulations, Title 42, Section 52.2(b) defines principal investigators as "a single individual designated by the grantee in the grant application, and approved by the Secretary [this authority has been delegated to NCI] who is responsible for the scientific and technical direction of the project." Under 42 CFR 52.5(a) the competency of the proposed staff is one of the factors evaluated in determining whether awards should be made. The problems that have been identified demonstrate serious management and scientific deficiencies for which the current principal investigator is responsible.

Accordingly, the NCI is amending the awards to withdraw its approval of Dr. Fisher as principal investigator. However, this does not limit the participation of Dr. Fisher in the NSABP as a scientist.

The University of Pittsburgh must propose an interim principal investigator(s) immediately, subject to NCI approval. The interim principal investigator(s) will serve during the period of investigation of apparent data irregularities at Saint Mary's Hospital and oversee implementing the corrective actions discussed below, and until the NSABP can elect a new Group Chair who will be subject to NCI approval.

It is the NCI's decision that the deficiencies must be corrected if the NSABP Operations Office at the University of Pittsburgh is to remain the central office for NSABP. The NCI believes that the credibility of the NSABP is at stake and the integrity of the entire NCI-supported clinical trials program may be jeopardized.

Therefore, effective immediately, the three referenced awards are amended as follows: The NSABP Operations Office is on probation for a three-month period. All actions taken by the interim principal investigator are subject to institutional requirements for prior approval and all correspondence with the NCI must be signed by both the interim principal investigator and the official authorized to sign for the University.

During this probationary period, the following corrective actions must be taken:

1. The University of Pittsburgh must immediately notify all funded and unfunded institutions that participate in clinical trials utilizing NSABP protocols that no new patients are to be entered onto NSABP protocols until further notice. Institutions should be notified that they are expected to continue therapy and follow-up for patients already entered onto NSABP protocols; awarded funds may be used only for these purposes.

2. The University of Pittsburgh must immediately inform the membership of the NSABP of the change in leadership. In addition, the NSABP must propose a suitable plan for transition to a new leadership structure, which will be subject to NCI approval.

3. Within two weeks of the date of this letter, the University of Pittsburgh is to forward a plan to the NCI describing the steps that the NSABP will take to assure continuity of patient care, maintenance of the integrity of the research program, and maintenance of other patient safeguards, including informed consent.

4. NSABP must appoint a group administrator/ executive officer, separate from the scientific leadership of the NSABP, with full authority for all administrative matters pertaining to the operations office. A contact person for the on-site audit program must also be designated.

5. NSABP must implement an improved on-site monitoring and quality assurance program, consistent with NCI guidelines, which includes:

a. The adoption of improved procedures for verification of patient data on-site and for assessment of compliance by the institution in the areas of treatment-specified and protocol-specified clinical evaluations.

The on-site audit quality assurance program must include procedures for review of informed consent documents; review of Institutional Review Board approvals, reapprovals, and amendment approvals; the review of NCI Drug Accountability Records and procedures for an on-site pharmacy inspection.

b. In carrying out all chart audits, procedures for immediate notification to the NCI, by fax or other similar communication, of any differences discovered.

c. The adoption of improved procedures for processing apparent problematic audit reports, which will include:

1) Immediate reporting of apparent problematic findings to the NCI.

2) A system for timely review of all audits by NSABP operations office staff, with requests that the institution audited take immediate corrective action,

and for timely follow-up by the NSABP to ensure that corrective action has been taken.

3) Establishment of a tickler system to monitor responses to requests in #2 above.

4) Procedures for ensuring that the NCI is kept abreast of actions/responses.

5) Submission to the NCI of all correspondence between NSABP and the audited institution regarding problems identified in conjunction with auditing.

6) Establishment of written standards as to what constitutes an adequate audit report and what are the acceptable limits of noncompliance, i.e., number of ineligible patients; number of protocol deviations, i.e., 10%, 15%.

7) Establishment of written procedures to deal with noncompliant institutions and repeat offenders.

8) Establishment of early alert procedures for any noncompliance with data forms submission to trigger timely on-site audit.

d. Compliance with the six weeks limit for report of non-problem audits to NCI.

e. Beginning immediately, provision of audit schedules monthly to the NCI, with immediate notification when changes are made. NCI must be told of the upcoming audits four weeks prior to the scheduled date.

f. Updating and reporting all currently outstanding audits to the NCI immediately.

6. NSABP must establish an independent data monitoring board to cover all NSABP treatment trials, as previously requested by the NCI.

The University of Pittsburgh must ensure that no conflicts of interest exist for the committee members. As consultants, these committee members and all other consultants utilized by NSABP must be covered by the University of Pittsburgh's conflict of interest policy, in accordance with the Public Health Service policy described in the PHS Grants Policy Statement, page 8-19 in addition to any other guidelines established by NSABP. The University of Pittsburgh will also be responsible for ensuring that members serving under consortium agreements are in compliance with their own institution's conflict of interest policies, in addition to any other guidelines established by NSABP.

7. The NSABP must implement procedures to rectify the problems identified at the on-site audits in March 1994 of Louisiana State University at New Orleans and Tulane University. This must be provided to the NCI by April 15, 1994.

8. The NSABP must provide to the NCI by April 9, 1994, an on-site audit schedule which takes into account the backlog of audits from April 1993 to date. NCI staff or their representatives will accompany the NSABP audit team on a majority of these audits.

9. The NSABP must reanalyze all trials containing data from Hospital Saint-Luc, including any papers published or submitted for publication since 1991 within 90 days of the date of this letter. Editors of these journals should be notified of the intentions to submit these reanalyses within 30 days of the date of this letter.

10. The NSABP must submit all NSABP manuscripts to NCI for approval before submission for publication.

With the exception of the due dates indicated above, please provide in writing, within 30 days of the date of this letter, detailed plans for the required remedial actions, the anticipated time frame, and any corrective actions that may have already been taken.

Throughout the probationary period, the NCI will evaluate the NSABP's compliance with the items listed under corrective actions. The NCI will consider the following alternatives:

1. If all deficiencies have been corrected, the NCI will remove the probationary status. In the event that the probationary status is removed, please be aware that further failure to follow NSABP's established procedures may result in withholding support of the next noncompeting continuation applications.

2. If, in the judgment of the NCI, these deficiencies have not been rectified, the NCI will suspend the cooperative agreements and will initiate termination procedures if the remaining deficiencies are not corrected within 30 days.

3. If the NSABP elects a new Group Chair at another site, the NCI would then evaluate transferring the Operations Office and the Research Base to the chair's institution.

The NCI will notify you on or before July 1, 1994, of its decision about continued support for NSABP.

The University of Pittsburgh must choose either to propose an interim principal investigator or request a termination of the cooperative agreements. Please notify me of the University of Pittsburgh's decision by April 12, 1994, otherwise, termination actions will have to be initiated by the NCI because of the absence of an approved principal investigator and lack of appropriate action to correct the deficiencies.

The NCI is prepared to assist the NSABP and the Univ. of Pittsburgh to remedy any of the identified problems.