DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

FOR US POSTAL SERVICE DELIVERY:
Office for Human Research Protections
6100 Executive Boulevard, Suite 3B01
National Institutes of Health (MSC 7507)
Rockville, Maryland 20892-7507

FOR HAND DELIVERY OR EXPRESS MAIL:
Office for Human Research Protections
6100 Executive Boulevard, Suite 3B01
Rockville, Maryland 20852

Telephone: 301-435-5654
FAX: 301-402-0527
E-mail: sandy_leikin@nih.gov

October 11, 2000

Sister M. Rosita Wellinger
President and Chief Executive Officer
St. Francis Health System
4401 Penn Avenue
Pittsburgh, PA 15224

Michael Hansen, M.D.
St. Francis Medical Center
400-45th Street
Pittsburgh, PA 15201-1198

RE: Human Research Subject Protections Under Cooperative Project Assurance (CPA) T-3970

August 14, 2000 Food and Drug Administration (FDA) Warning Letter

Dear Sister Wellinger and Dr. Hansen:

The Office for Human Research Protections (OHRP) has reviewed the September 22, 2000 report from St. Francis Health System (SFHS) that was submitted in response to OHRP's August 28, 2000 letter.

OHRP finds that SFHS has developed adequate corrective action plans to address each of the following areas of apparent noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects that were cited in OHRP's August 28, 2000 letter:

(1) Failure of the institution to maintain adequate written Institutional Review Board (IRB) policies and procedures as required by HHS regulations at 45 CFR 46.103(b)(4) and (5).

Corrective Action: SFHS is drafting new, detailed IRB policies and procedures. Please see additional OHRP guidance below regarding the draft SFHS IRB policies and procedures.

(2) Failure of the IRB to conduct adequate and timely continuing review of research involving human subjects, as required by HHS regulations at 4CFR 46.109(e).

Corrective Action: SFHS has developed a continuing review procedure that should ensure timely, substantive, and meaningful continuing review of research. Furthermore, SFHS has developed a new IRB computer database to track the status of all active research protocols.

(3) The convened IRB reviewed and approved many research protocols without a majority of members being present, in contravention of the requirements of HHS regulations at 45 CFR 46.108.

Corrective Action: SFHS has implemented IRB procedures for ensuring that a majority of members are present whenever the convened IRB reviews and acts upon research protocols.

(4) Failure of SFHS and its IRB to maintain the documents stipulated by HHS regulations at 45 CFR 46.115.

Corrective Action: SFHS has implemented IRB procedures for ensuring that the IRB maintains the documents stipulated by HHS regulations at 45 CFR 46.115.

OHRP acknowledges that (i) SFHS temporarily suspended four active HHS-supported research protocol involving human subjects; (ii) all four projects were re-reviewed and approved by the IRB at an appropriately convened meeting; and (iii) five additional HHS-supported research protocols that only involve on-going data analysis are to be re-reviewed by the IRB at its October 2000 meeting.

Additional OHRP Concerns, Questions and Guidance

Based upon its review of your report, OHRP has the following additional concerns and questions, and provides the following additional guidance:

(1) OHRP notes that the SFHS CPA expired on April 27, 1999. In January 1999, OHRP notified SFHS of the impending expiration of the CPA and requested that SFHS submit a renewal CPA document. OHRP has no record of receiving a CPA renewal document from SFHS. Furthermore, based upon the list of active IRB-approved research protocols being conducted by SFHS, it appears that SFHS is not involved in the conduct of any OHRP-recognized Cooperative Protocol Research Program (CPRP) clinical trials (e.g., the National Cancer Institute sponsored oncology group clinical trials). As such, it may be appropriate for OHRP to deactivate the SFHS CPA. Please respond.

(2) HHS regulations at 45 CFR 46.103(a) require that an institution engaged in HHS-supported research involving human subjects must have an OHRP-approved Assurance applicable to the research, unless the research is exempt under HHS regulations at 45 CFR 46.101(b). OHRP notes that the SFHS CPA applies only to CPRP research protocols.

Each of the HHS-supported research projects referenced in your report would require an OHRP-approved Single Project Assurance (SPA), unless the research was determined to be exempt. In reviewing its records, OHRP was unable to identify an applicable SPA for each of the HHS-supported research projects being conducted by SFHS. Please respond. In your response, please provide the number of any applicable OHRP-approved SPA or other applicable Assurance. **Please note that any HHS-supported research project involving human subjects, including those involving data analysis only, for which OHRP has not approved an applicable Assurance must be suspended until OHRP has approved an Assurance for the research.**

(3) Based upon its review of the minutes of recent IRB meetings, OHRP is concerned that little substantive review takes place at convened IRB meetings and IRB approval of research may not be consistently based on consideration of the determinations required under HHS regulations at 45 CFR 46.111. In specific, the IRB appears not to consider systematically and rigorously such issues as equitable selection of subjects and subject recruitment, privacy and confidentiality protections, and special protections required for vulnerable subjects. Please respond.

(4) Where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (b) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP strongly recommends that all required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

(5) OHRP notes that IRBs frequently approve research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research must be **deferred**, pending subsequent review by the convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

(6) Regarding the draft revision of the IRB Policy and Procedures, please note the following:

(a) Pages 5-6, section D.2 - This section should be revised to indicate that copies of any applicable HHS-grant applications and Clinical Investigator's Brochures are to be submitted to the IRB.

(b) Page 9, section F, discussion of "parental consent" for research involving children - This section is not consistent with the requirements for obtaining parental permission stipulated by HHS regulations at 45 CFR 46.408. In specific, parental permission must be obtained for all HHS-supported research involving children, regardless of the degree of risk, unless the IRB has waived the requirement for obtaining informed consent in accordance with the requirements of HHS regulations at 45 CFR 46.116(d) or 46.408(c). Please revise this section of the draft IRB Policy and Procedures accordingly.

(c) Page 21, Continuing Review procedure - This section should be revised to include a description of the documents that are provided to the primary reviewer(s) and all other IRB members prior to convened IRB meetings.

OHRP again emphasizes that continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB. Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

When conducting research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above referenced documentation.

(d) Page 24, Changes in study protocol or consent form - OHRP notes the following statement in this section:

> "If a Principal Investigator wishes to make significant changes in the study protocol or consent form he/she MUST submit these changes for approval by the IRB PRIOR to the implementation of the changes.

Please note that in accordance with HHS regulations at 45 CFR 46.103(b)(4)(iii), the IRB, must review and approve **all** proposed changes in a research activity prior to initiation of the changes, not just "significant" changes. Please revise this section of the draft IRB Policy and Procedures accordingly.

(e) The draft IRB Policy and Procedures should be expanded to include a description of the procedures for ensuring prompt reporting to appropriate institutional officials, the HHS agency head, and OHRP any of the following events related to HHS-supported research, as required by HHS regulations at 45 CFR 46.103(b)(5):

> (i) Any unanticipated problems involving risks to subjects or others.
>
> (ii) Any serious or continuing noncompliance with the requirements of HHS regulations at 45 CFR Part 46 or the requirements or determinations of the IRB.
>
> (iii) Any suspension or termination of IRB approval.

(7) OHRP is concerned that the protocol application form used by SFHS fails to provide the IRB with sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, the protocol application form appears to include only minimal information regarding (a) risk and minimization of risk; (b) subject recruitment and enrollment procedures; (c) the equitable selection of subjects; (d) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (e) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable. Please respond.

Please submit a report responding to the above concerns and questions no later than November 10, 2000. Please include the following with your report:

(1) A copy of the final draft of the IRB Policy and Procedures.

(2) The minutes of any IRB meetings convened since September 20, 2000.

OHRP appreciates the commitment of your institution to the protection of human subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Sanford Leikin, M.D.
Compliance Oversight Coordinator
Division of Human Subject Protections

cc: Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Mr. Steven M. Niedelman, FDA
Dr. Jean Toth-Allen, FDA
Ms. Joan Mauer, CTEP, NCI
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Jeffrey M. Cohen, OHRP
Dr. Clifford C. Scharke, OHRP
Dr. J. Thomas Puglisi, OHRP
Ms. Roslyn Edson, OHRP
Ms. Helen Gordon, ORHP
Mr. Barry Bowman, ORHP