DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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August 28, 2000

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

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:

The Office for Human Research Protections (OHRP) has received the enclosed Food and Drug Administration (FDA) inspection letter that appears to document serious noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46).

The noncompliance appears to involve the following:

(1) Failure of the institution to maintain written Institutional Review Board (IRB) policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate

apparent immediate hazards to the subject.

(b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and Department or Agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

(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).

Continuing IRB review of research must be substantive and meaningful and conducted at intervals appropriate to the degree of risk and not less than once per year. 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 (i)the number of subjects accrued; (ii) 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; (iii) 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 (iv) 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 (see OPRR Reports 95-01). Furthermore, the minutes of IRB meetings should document separate deliberations and votes for each protocol undergoing continuing review by the convened IRB.

(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. OHRP emphasizes that any actions taken at meetings lacking a quorum must be considered invalid.

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

Consistent with its obligations under HHS regulations at 45 CFR 46.103(b)(5) and your CPA, I am requesting that your institutions investigate this matter and forward to OHRP a written report of the investigation (see enclosed Compliance Oversight Procedures dated April 27, 2000).

Please include the following with the report:

(1) A detailed response to each of the above citations of apparent noncompliance.

(2) A copy of any written reports or letters submitted to the FDA in response to its August 14, 2000 Warning Letter.

(3) A copy of the minutes of all IRB meeting convened during the past 12 months.

(4) A copy of any written description of IRB policies and procedures.

(5) A copy of any IRB guidelines for investigators involved in human subjects research.

(6) A copy of the IRB application and protocol forms used at your institution.

(7) A complete list of all active research projects involving human subjects, including the project title, principle investigator name, IRB project number, source of support, HHS project number, if applicable, date of initial IRB approval, and date of most recent continuing review.

(8) If your investigation reveals noncompliance, a description of any corrective actions that have been or will be taken by your institution to prevent such noncompliance from recurring.

(9) A description of your institution's program for ensuring that all IRB members, all IRB staff, and all research investigators are appropriately educated, on an ongoing basis, about the regulatory requirements for the protection of human subjects.

Please forward your report so that OHRP receives it no later than September 25, 2000.

Furthermore, under the requirements of HHS regulations at 45 CFR Part 46 and your CPA, I am requesting that your institutions take the following actions:

Suspend immediately enrollment of new subjects in any HHS supported research projects that (i) have not received appropriate initial review and approval by the IRB in accordance with all requirements of HHS regulations at 45 CFR Part 46 (including Subparts A thru D); or (ii) if initially approved by the IRB more than one year ago, have not received substantive continuing review and approval by the IRB subsequent to August 29, 1999, in accordance with HHS regulations at 45 CFR 46.109(e). For any project affected by this suspension, enrollment of new subjects must cease immediately except in extraordinary cases approved in advance by OHRP (OHRP would expect requests for approval of such cases to be rare). Furthermore, research activities involving previously enrolled subjects should continue only where the IRB finds that it is in the best interests of individual subjects to do so. For each affected protocol this suspension must remain in effect

until the protocol has undergone appropriate review by the IRB.

Any such suspensions of research should be promptly reported to OHRP, appropriate institutional officials, and appropriate officials at the funding HHS Division or Agency in accordance with HHS regulations at 45 CFR 46.103(b)(5).

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

Enclosures: (1) August 14, 2000 FDA Warning Letter
(2) OPRR Reports 95-01
(3) April 27, 2000 OPRR Compliance Oversight Procedures

cc with enclosures:
Dr. Michael Hansen, Chairperson, IRB, St. Francis Health System

cc without enclosures:
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Mr. Steven M. Niedelman, FDA
Ms. Joan Mauer, CTEP, NCI
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. J. Thomas Puglisi, OHRP
Mr. George Gasparis, OHRP
Ms. Helen Gordon, ORHP