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: 301-402-5567
FAX: 301-402-2071
E-mail: sandy_leikin@nih.gov

July 12, 2000

Dale M. Landi, Ph.D.
Vice President for Research
University at Buffalo, State University of New York
Office of the Provost
516 Capen Hall
Buffalo, New York 14260-1611

Re: Human Research Protections under Multiple Project Assurance (MPA) # M-1270
Research Projects: Spinal Internal Fixator Trials (SIF-02 and SIF-03)
Principal Investigator: Drs. Edward H. Simmons (SIF-02) and Edward D. Simmons (SIF-03)

Dear Dr. Landi:

The Office for Human Research Protections (OHRP) has reviewed your November 1, 1999 letter responding to concerns raised by OHRP in its letter of October 4, 1999, regarding the University of Buffalo, State University of New York (UB) system for protecting human subjects.

Based upon its review of all previous reports submitted by UB since March 1996, OHRP makes the following determinations regarding the above referenced research projects:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds that Dr. Edward H. Simmons failed to comply with this requirement when he modified his protocol to permit enrollment of a subject by another co-investigator at another performance site without IRB approval.

(2) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. OHRP finds that the investigators conducted human subject research under the above referenced protocols after IRB approval had expired.

(3) OHRP finds that the investigators for the above referenced projects failed to obtain and document the legally effective informed consent of some subjects in accordance with the requirements of HHS regulations at 45 CFR 46.116 and 46.117.

Corrective Action: OHRP finds that UB has taken appropriate corrective actions to address the above findings of noncompliance including: (i) formal counseling of one principal investigator and sanctioning the second principal investigator by prohibiting him from conducting research at UB; (ii) contacting subjects for whom documentation of prospective written informed consent was lacking to inform them of their involvement in the research; and (iii) implementation of new IRB procedures for continuing review (including placement of IRB approval dates and expiration dates on informed consent documents).

Furthermore, OHRP makes the following additional determinations regarding the UB Health Sciences IRB (IRB-01) :

(4) Continuing IRB review of research must be substantive and meaningful. In conducting continuing 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.

OHRP finds that the continuing review report form used by the UB Health Sciences IRB prior to May 1999 was insufficient to achieve substantive and meaningful continuing review of research.

Corrective Action: OHRP acknowledges that the UB Health Sciences IRB has revised its report form to include the items required for substantive and meaningful continuing review of research.

(5) Convened IRBs often set conditions under which a protocol can be approved (OHRP discourages use of the term "Conditional Approvals"). The following guidelines apply in such cases: (i) When the 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. (ii) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chairperson or designated reviewer subsequently approve the research on behalf of the IRB.

Based on review of the minutes of IRB meetings conducted between November, 1998 and October, 1999, OHRP finds that the UB Health Sciences IRB frequently approved research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB.

Corrective Action: OHRP acknowledges your statement that (i) when the convened UB Health Sciences IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research will be **deferred**, pending subsequent review by the convened IRB of responsive material; (ii) the IRB minutes will indicate when IRB approval is deferred pending substantive changes of a research protocol or an informed consent document; (iii) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator will the IRB Chair or designated reviewer subsequently approve the research on behalf of the IRB.

(6) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP's review of IRB documents reveals no evidence that the UB Health Sciences IRB made the required findings when reviewing research involving children prior to October 4, 1999.

Corrective Action: OHRP acknowledges your statement that when reviewing research involving children, the UB Health Sciences IRB will make the specific finding required for the approval of the research involving children, and will include the protocol specific information justifying each IRB finding in the IRB minutes.

(7) HHS regulations at 45 CFR 46.115(a)(2) require that the minutes of IRB meetings document the vote on all IRB actions including the number of members voting for, against, and abstaining.

OHRP finds that the voting on continuing review of each protocol and of each amendment was not recorded in the minutes of the UB Health Sciences IRB meetings prior to October 4, 1999.

Corrective Action: OHRP acknowledges your statement that the UB Health Sciences IRB will document in the minutes all actions, including the voting on the continuing review of each protocol and of each amendment.

The corrective actions described above appropriately address the deficiencies identified by OHRP. As a result, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

OHRP appreciates the continued commitment of your institution to the protection of human research 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: Dr. Melody H. Lin, OHRP
Dr. J. Thomas Puglisi, OHRP.
Dr. Michael A. Carome, OHRP.
Dr. Clifford Scharke, OHRP.
Dr. Katherine Duncan, OHRP
Ms. Freda Yoder, OHRP
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. James B. Lee, Chairperson, UB Health Sciences IRB
Dr. Edward H. Simmons
Dr. Edward D. Simmons