DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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Robert O. Webster, Ph.D.
Associate Provost for Research Administration
Saint Louis University Health Sciences Center
3556 Caroline Street
Room 301
Saint Louis, MO 63104

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1119

Research Projects Involving Neuroimaging in Epilepsy

Dear Dr. Webster:

The Office for Human Research Protections (OHRP) has reviewed the Saint Louis University's (SLU) letters and reports dated March 9, 2000, March 17, 2000, June 22, 2000, and May 20, 2002 that were submitted in response to OHRP's January 14, 2000 letter and April 5, 2002 electronic mail correspondence to SLU presenting allegations of noncompliance with the Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46) involving the above-referenced research.

Based upon its review, OHRP makes the following determinations:

(1) HHS regulations at 45 CFR 46.109(a) require that the Institutional Review Board (IRB) review and approve, require modification to, or disapprove all non-exempt human subject research. OHRP finds that human subject research at SLU involving neuroimaging in patients with epilepsy was conducted without review and approval of the SLU IRB. Specifically, OHRP notes the following statement in SLU's report of March 17, 2000:

> "...[B]ased on a lengthy internal investigation and both internal and external (where appropriate) review, we have to date found . . . [that] Dr. [Edward] Hogan and several Saint Louis University investigators failed to obtain IRB approval before conducting

> retrospective research involving standard clinical care interventions; [and] in two specific instances Dr. Hogan and other investigators engaged in prospective research involving standard clinically justified interventions when, at the time these occurred, the investigators intended to review the charts of patients after the procedure was performed and include the data in abstracts without obtaining IRB approval.... "

Corrective action: OHRP finds that SLU has developed and implemented satisfactory corrective action plans to ensure that investigators are aware of the requirement for IRB review and approval of all non-exempt human subject research, including retrospective and prospective reviews of medical records involving standard clinical care interventions that fulfill the definition of research under HHS regulations at 45 CFR 46.102(d) and involve human subjects as defined under HHS regulations at 45 CFR 46.102(f). Specifically, OHRP notes the following actions that were described in SLU's letter of March 17, 2000:

> (a) In October 1999, the SLU IRB sent letters of admonition to several researchers informing them that they failed to comply with applicable regulations involving the conduct of research at SLU.
>
> (b) The SLU IRB directed the IRB Chair to notify Dr. Hogan that for the next two years: (i) his chairperson must review all of Dr. Hogan's future publications, including abstracts and manuscripts; (ii) the chairperson must sign a statement that the research contained therein was conducted under appropriate IRB approval; (iii) prior to submission, all publications will be submitted to the IRB for review; and (iv) data already collected by Dr. Hogan without IRB approval may not be used prospectively for any further publications.
>
> (c) On January 28, 2000, the President and the Provost of SLU sent a memorandum to SLU faculty members reminding them of their obligations with respect to the conduct of research involving human subjects.

OHRP finds that these corrective actions satisfactorily address the above finding and are appropriate under SLU's MPA.

(2) HHS regulations at 45 CFR 46.116 state that, except as provided elsewhere in the regulations, no investigator may involve a human subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subjects or the subject's legally authorized representative. OHRP finds that SLU investigators initiated human subject research as noted above without meeting this requirement.

Corrective action: OHRP finds that SLU has developed and implemented satisfactory corrective action plans to ensure that investigators obtain legally effective informed consent as required under HHS regulations 45 CFR 46.116. Specifically, SLU has expanded its educational

initiatives to remind and inform SLU researchers of their obligation to obtain informed consent consistent with HHS regulations before engaging in any retrospective or prospective research.

(3) OHRP makes no finding regarding the allegation that subjects have been harmed as a result of their participation in the above-mentioned research. OHRP notes the following information provided by SLU in its letter of March 17, 2000:

> "[SLU] retained [an expert neurologist from another institution], who specializes in epilepsy, to conduct a medical record review. He examined medical records of 30 of 32 patients who received Ictal SPECT and had been included in the abstracts attached to your letter of January 14, 2000...He provided a written report to the Associate Provost confirming that Ictal SPECT has been a standard clinical diagnostic procedure for evaluating epilepsy patients for surgery adjunct to other diagnostic techniques and the physiological information (EEG's)...Finally, [he] concluded that the patients who underwent surgery had excellent outcomes, the postoperative complication rate was 'favorable,' and that 'there was no evidence that any patients suffered harm as a result of having undergone SPECT scans.'"

(4) Regarding the related research publication (Hogan RE, Lowe VJ, Bucholz RD. Triple-technique (MR Imaging, Single-Photon Emission CT, and CT) coregistration for image-guided surgical evaluation of patients with intractable epilepsy. American Journal of Neuroradiology 1999; 20:1054-1058), OHRP makes no finding with respect to the allegation that an investigational "ANALYZE" software program was used in this research to co-register image sets to make clinical decisions during surgery, without the investigator first obtaining approval from the SLU IRB and legally effective informed consent of the subject, as required under HHS regulations. OHRP notes the following statements provided by SLU in its letter of June 22, 2000 with respect to SLU's investigation into this allegation:

> (a) "In conclusion...we have found no additional evidence...that would confirm or refute the possibility that the unapproved software was used clinically. No electronic trail can be followed to verify dates and times images were sent to the StealthStation for use in these surgeries. As noted in our earlier report...Dr. Hogan, the neurologist, believed that the software had so been used, but Dr. Bucholz, the surgeon involved, denied that he had, in fact done so. Moreover, Dr. Bucholz and his technician both stated that such a use in surgery was not technically feasible."
>
> (b) "A review of operative reports of the patients allegedly treated using the ANALYZE program does not indicate that the program was used for clinical or research purposes."
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> (c) "...Drs. Hogan and Bucholz sent a letter to the American Journal of Neuroradiology...explaining the error in the publication and offering to write an addendum outlining the inaccuracies. The Board reviewed the situation and consulted

> with the University's Research Integrity Officer. It concluded that, given the circumstances involved, this letter was adequate to remedy the errors made in publication..."

At this time, OHRP has the following questions and concerns:

(5) [redacted]

(6) [redacted]

Please submit your response to the above questions and concerns to OHRP no later than September 3, 2002.

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

Sincerely,

Leslie K. Ball, M.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Mr. Jesse A. Goldner, Chair, IRB, SLU
Ms. Jamie Nehrt, Director, IRB, SLU
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Dr. David Lepay, FDA
Mr. Neil Ogden, FDA
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