DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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December 6, 2004

Leopold G. Selker, Ph.D.
Senior Vice President
Evanston Northwestern Healthcare
ENH Research Institute
2650 Ridge Ave.
Evanston, IL 60201

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1396 and Federalwide Assurance FWA-3000

Research Project: Advanced Magnetic Resonance Imaging
Principal Investigator: Dr. Robert Edelman
ENH Project Number: ENH01-057

Research Project: A Phase II Investigation of Code 7228 as a Magnetic Resonance Angiography Contrast Agent
Principal Investigator: Dr. Robert Edelman
ENH Project Number: ENH02-123

Dear Dr. Selker:

The Office for Human Research Protections (OHRP) has reviewed Evanston Northwestern Healthcare's (ENH) April 8 and November 9, 2004 reports responding to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) involving the above-referenced research.

In its September 15, 2004 letter, OHRP made the following determinations regarding the above-referenced research:

> (1) HHS regulations at 45 CFR 46.116 state that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. OHRP found that the investigators failed to obtain the legally effective informed consent of the complainant before involving him in protocol number ENH01-057.

(2) HHS regulations at 45 CFR 46.116 require that informed consent be obtained only under circumstances that provide the prospective subject or the subject's representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. OHRP found that the complainant was not given sufficient opportunity to consider whether or not to participate in protocol number ENH01-057.

Corrective Action: OHRP requested a copy of the investigator's written procedures for obtaining informed consent and a corrective action plan to ensure that no ENH investigator involves human subjects in research without first obtaining legally effective informed consent (if not appropriately waived) of the subject, or without allowing the subject sufficient opportunity to consider whether or not to participate. OHRP acknowledges that the ENH Department of Radiology now has detailed procedures for the informed consent process. In addition, new clinical research employees at ENH must undergo training in human subjects protections, with an emphasis on obtaining informed consent, and the ENH has developed an informed consent checklist for those obtaining informed consent to help ensure that the proper forms are used and that subjects are given enough time to consider participating.

(3) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require prompt reporting to OHRP of any suspension or termination of institutional review board (IRB) approval. ENH's April 8, 2004 report indicated that protocol number ENH02-123 was suspended in November 2002, when the IRB discovered that the investigator was enrolling normal volunteers in the study and was using an investigational contrast agent without IRB approval. OHRP has no record that this suspension was reported to our office.

Corrective Action: OHRP acknowledges that ENH now has a policy to require reporting to OHRP of any suspension or termination of IRB approval.

OHRP makes the following additional determinations regarding the above-referenced research:

(4) OHRP finds that when reviewing protocol number ENH01-057, it appears that the ENH IRB lacked sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, the IRB appeared to review only minimal information regarding:

(a) Subject recruitment and enrollment procedures. In specific, the protocol included no description of an enrollment ceiling or how subjects would be recruited, and no inclusion/exclusion criteria were indicated in the protocol.

(b) The equitable selection of subjects.

(c) The exact improvements to MR imaging hardware and software that were to be evaluated.

(d) The justifications for increasing subject enrollment to 1000.

Corrective Action: OHRP acknowledges that the study was closed to enrollment, and that Dr. Edelman was required to submit a protocol revision clarifying the purpose of the study and the alternatives to participation. In addition, the review form for new projects has been revised to include additional detail and direction for submission to the IRB, including soliciting information about subject recruitment and enrollment procedures, equitable selection of subjects, and the procedures to be followed. In addition, a special meeting of the IRB is scheduled for January 2005 to discuss IRB protocol submission requirements.

(5) OHRP finds that the informed consent documents reviewed and approved by the ENH IRB for protocol number ENH01-057 failed to address the following elements adequately, as required by HHS regulations at 45 CFR 46.116(a)(1):

(a) An explanation of the purposes of the research (i.e., specific technical enhancements to MRI were being tested);

(b) How participation in the research would change the expected duration of the subject's MRI;

(c) Identification of any procedures which are experimental (i.e., it was not clearly described which parts of the procedures were for clinical purposes and which were strictly for research purposes).

Corrective Action: OHRP acknowledges that the ENH IRB has developed a consent form template to assist investigators in developing informed consent documents and, as noted above, a special meeting of the IRB is scheduled for January 2005 to discuss IRB protocol submission requirements, including informed consent requirements.

(6) 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 the inclusion of normal volunteers in the study was implemented in project number ENH02-123 without prior IRB review and approval.

Corrective Action: OHRP acknowledges that the IRB discovered in 2002 that the investigator was enrolling normal volunteers in project number ENH02-123 and, as a result, the study was suspended. A new principal investigator was named to the study, and the appropriate changes were made to the protocol and informed consent documents. OHRP recommends that all ENH investigators be reminded that all proposed changes in a research activity must be reviewed and approved by the IRB prior to initiation of such changes.

OHRP finds that the above corrective actions, along with the actions describe in ENH's April 8, 2004 report, adequately address the above findings and are appropriate under the ENH

assurance. OHRP anticipates no further involvement in this matter.

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,

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight

cc:

Mr. Robert L. Stanton, ENH
Dr. Bernard Adelson, Chair, ENH IRB #1
Dr. Robert Edelman, principal investigator, ENH
Commissioner, FDA
Dr. David Lepay, FDA
Ms. Marian Serge, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Ms. Melinda Hill, OHRP
Ms. Patricia El-Hinnawy, OHRP