DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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March 17, 2003

Michael M. Gottesman, M.D.
Deputy Director for Intramural Research
National Institutes of Health
Building 1, Room 114
Bethesda, MD 20892

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1000

Research Project: Positron Emission Tomographic (PET) Scanning of Sympathetic Innervation and Function in Patients with Neurocardiologic Disorders
Project Number: 94N-0186
Principal Investigator: David S. Goldstein, M.D., Ph.D.

Dear Dr. Gottesman:

The Office for Human Research Protections (OHRP) has reviewed the National Institute of Neurological Disorders and Stroke (NINDS)/National Institutes of Health's (NIH) February 4, 2003 report regarding the above-referenced research that was submitted in response to OHRP's December 30, 2002 letter to NIH.

Based upon its review of your report, OHRP makes the following determinations regarding the above-referenced research:

(1) OHRP finds that the informed consent documents reviewed and approved by the NINDS institutional review board (IRB) for this project failed to adequately address a description of the reasonably foreseeable risks and discomforts, as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.116 (a)(2). In particular, OHRP notes the following:

(a) The informed consent documents do not include the risk of headache from yohimbine.

(b) The informed consent documents list the risks of cardiac catheterization as "clotting, bleeding, infection, abnormal heart rhythms, and even knotting of the plastic tubes in the blood vessels." The informed consent documents did not explain the clinical significance of any of these risks or possible outcomes (e.g., heart attack, pulmonary embolism, requirement for surgery to remove knotted tubes).

Corrective Actions: OHRP acknowledges that the informed consent document for this study has been amended to include of the risk of headache from yohimbine-induced increased blood pressure, and that the protocol already had been amended to exclude cardiac catheterization. These corrective actions adequately address the above finding and are appropriate under the NIH MPA.

(2) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. OHRP finds that the informed consent documents approved by the IRB for this study included complex language that would not be understandable to all subjects. For example, the informed consent documents include undefined words such as vascular, untoward, contraindicated, vanishingly, auspices, pharmacological, adverse, and evoke.

Required Action: By April 28, 2003, please provide OHRP with a corrective action to address this finding.

(3) OHRP finds that prior to January 2003 the NINDS did not have written IRB procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow for conducting its continuing review of research.

(b) The procedures which the IRB will follow for determining which projects require review more often than annually.

(c) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(d) The procedures which the IRB will follow 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.

(e) The procedures for ensuring prompt reporting to OHRP of: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

Corrective Action: OHRP acknowledges that the most current NINDS IRB written procedures address most of these required elements. However, OHRP finds that the written procedures do not adequately address the procedures which the IRB will follow 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. The procedures should provide a step-by-step description with key operational details the IRB will follow to ensure that such reporting will occur. OHRP notes that this might be addressed through training programs and materials for investigators, specific directives included in approval letters to investigators, and random audits of research records. By April 28, 2003, please provide OHRP with a corrective action to address this finding.

Please provide your response to the above findings so that OHRP receives it no later than April 28, 2003.

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: Dr. David S. Goldstein, NINDS
Dr. Alan L. Sandler, Director, OHSR, NIH
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
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