DEPARTMENT OF HEALTH & HUMAN SERVICES **PUBLIC HEALTH SERVICE**

Office for Human Research Protections
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November 30, 2001

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Christian LaMantia
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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1521
Research Project: Methionine and Homocysteine Metabolism in Alzheimer's Disease Patients and Controls
Principal Investigator: Robert P. Friedland, M.D.
Protocol Number: 02-00-04

Dear Mr. Wagner, Ms. Walters, and Ms. LaMantia:

The Office for Human Research Protections (OHRP) has reviewed the Case Western Reserve University's (CWRU) and University Hospitals of Cleveland's (UHC) report dated November 8, 2001

regarding the above-referenced research. Based on the review, OHRP makes the following determinations:

(1) OHRP found no evidence to substantiate the concerns referenced in OHRP's August 10, 2001 letter that:

(a) UHC IRB and the investigators failed to ensure that risks to subjects were minimized, as required by HHS regulations at 45 CFR 46.111(a)(1).

(b) CWRU failed to ensure that an unanticipated problem involving risks to subjects or others was promptly reported to OHRP, as required by HHS regulations at 45 CFR 46.103(b)(5).

(2) OHRP finds that when reviewing this protocol application, the IRB lacked sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. In particular, OHRP notes the following:

(a) There was no mention in the IRB-approved protocol regarding the medical/personal history and lifestyle questionnaire, which the informed consent document stated could last as long as 10 hours. The IRB did not have this questionnaire when reviewing this protocol.

(b) The March 20, 1996 draft of the grant application "The Effects of Cigarette Smoking on the Development of Alzheimer's Disease: International Epidemiological and Neurobiological Studies" included a "Refusers Report." This report analyzed demographic data from individuals who refused participation in the trial. When reviewing this protocol, the IRB was unaware of the inclusion of "refusers" in the research.

Corrective Action: OHRP notes that the questionnaire and information from the Alzheimer's Registry were reviewed by the IRB for a separate protocol (#01-87-35). OHRP acknowledges that the IRB will re-review the registry protocol to ensure that it meets current regulatory standards, and that the investigator has been advised that all questionnaires referred to in a consent document require review. In addition, the IRB has been reminded that they should ensure that all questionnaires and research instruments are reviewed for each protocol.

(3) HHS regulations at 45 CFR 46.116 require that the information that is given to subjects must be in language understandable to the subject. OHRP finds that the informed consent document approved by the IRB for this study included complex language (e.g., atherosclerosis, vascular abnormalities, ingest, intravenous catheter) that may not be understandable to all subjects.

Corrective Action: OHRP acknowledges that CWRU and UHC have reminded all the IRBs

under MPA-1521 of the importance of readability and comprehension of approved consent form. In addition, informed consent seminars have and will emphasize the importance of readability and comprehension of consent forms.

OHRP finds that the above-referenced corrective actions adequately address the findings and are appropriate under the CWRU MPA. 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 has the following additional guidance regarding the above-referenced research and UHC's IRB policies and procedures:

(4) OHRP notes that the Alzheimer Center Family History Questionnaire used for this research requests information from the subject regarding family members, including first and last names, year of birth, occupation, health problems and smoking patterns. OHRP notes that when investigators conducting research obtain indentifiable private information about living individuals, those individuals are human subjects. Unless waived by the IRB, researchers must obtain informed consent from such subjects, regardless of how the indentifiable private information was obtained (or from what sources).

(5) OHRP recommends that written IRB policies and procedures should provide the **operational details** for each of the following procedures required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4) and (5):

(a) 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.

(b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, OPRR 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.

(6) HHS regulations at 45 CFR 46.116(a)(8) require the inclusion of the following element when obtaining informed consent of subjects: A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. Although the regulations do not require this exact language, the UHC template informed consent document states that "I understand that my

decision to participate or not to participate in this study will not alter my usual health care." OHRP notes that there could be other penalties or loss of benefits besides alteration of usual health care.

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.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Mr. Terry R. White, MetroHealth System
Mr. William D. Montague, Louis Stokes Dept of VA Medical Center
Dr. William Dahms, IRB Chair, UHC
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
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Mr. George Gasparis, OHRP
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