DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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April 2, 2002

Mr. John H. Herrell
Vice President, Board of Trustees
Mayo Foundation
200 First Street SW
Rochester, MN 55905

Mr. Robert M. Walters
Secretary, Board of Governors
Mayo Clinic Jacksonville
4500 San Pablo Road
Jacksonville, FL 32224

Mr. Jeffrey O. Korsmo
Secretary, Board of Governors
Mayo Clinic Rochester
200 First Street, SW
Rochester, MN 55905

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1006

Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estrogen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease
Principal Investigators: Dr. Ronald C. Petersen (Rochester) and Dr. Neill R. Graff-Radford (Jacksonville)
HHS Project Number: U01-AG10483
IRB Project Numbers: 724-X-95 00 (Rochester) and 717-X-95 (Jacksonville)

Research Publication: Estrogen Replacement Therapy for Treatment of Mild to Moderate Alzheimer Disease: A Randomized Controlled Trial (Mulnard, et al. JAMA. 2000;283:1007-1015)

Dear Mr. Herrell, Mr. Korsmo and Mr. Walters:

The Office for Human Research Protections (OHRP) has reviewed Mayo Foundation's March 11, 2002 report that was submitted in response to OHRP's February 6, 2002 letter regarding the above-referenced research.

Based upon its review, OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111(b) stipulate that in order to approve research, the Institutional Review Board (IRB) shall determine that when some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of the subjects. In its February 6, 2002 letter, OHRP expressed concern that the Mayo Foundation IRB may have failed to ensure that this requirement was satisfied for the above-referenced research.

OHRP finds that the Mayo Foundation has adequately responded to this concern. Furthermore, OHRP acknowledges that the Mayo Foundation IRBs consider additional safeguards for subjects who may be vulnerable as a result of impaired mental capacity.

(2) HHS regulations at 45 CFR 46.116(a)(1) require that when seeking informed consent, each subject be provided with, among other things, a description of the procedures to be followed and identification of any procedures which are experimental. OHRP finds that the IRB-approved informed consent documents failed to describe the procedures for having the subject's caregiver fill out quality-of-life and pharmacoeconomic questionnaires related to the subject's condition and care.

Corrective Action: OHRP acknowledges (i) that the research has been completed; and (ii) Mayo Foundation's has stated that if the study were to be submitted today, the Mayo Foundation's IRB would require a clear description of the procedures for having the subject's caregiver provide quality of life and pharmacoeconomic information about the subject. OHRP finds this response to be satisfactory and appropriate under the Mayo Foundation's MPA.

(3) HHS regulations at 45 CFR 46.116(a)(2) require that when seeking informed consent each subject be provided with a description of any reasonably foreseeable risks and discomforts. In its letter of February 6, 2002, OHRP questioned whether the Mayo Foundation IRB required investigators to provide the two subjects remaining in the study with information regarding the risk of thromboembolic disease, following the Executive Committee of the Mayo Foundation's IRB review and approval of a modification to include the complication of thromboembolic phenomena in the consent form.

OHRP finds that the Mayo Foundation has adequately responded to this concern. Furthermore, OHRP acknowledges that the Mayo Foundation IRB has implemented procedures to ensure that when new risks are discovered, investigators are required to reconsent the study subjects within 30 days if treatment is ongoing. Under this policy, if study treatment has been completed but the risk of injury still exists, investigators are required to send subjects an informational letter describing the risk.

(4) HHS regulations at 45 CFR 46.116(a)(4) require that when seeking informed consent, each subject be provided with a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. In its February 6, 2002 letter to the

Mayo Foundation, OHRP expressed concern that the IRB-approved informed consent documents for the above-referenced research did not describe the alternative of receiving estrogen replacement therapy outside of the research protocol.

OHRP finds that the Mayo Foundation has adequately responded to this concern. In addition, OHRP acknowledges that the Mayo Foundation has implemented procedures to ensure that the informed consent documents disclose when appropriate alternative procedures or courses of treatment can be obtained outside of the research protocol.

As a result of the above determinations, 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 commitment of Mayo Foundation 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: Dr. Michael B. Wood, President and CEO, Mayo Foundation
Mr. John Mills, Legal Counsel, Mayo Clinic
Mr. Bonnie A. Edwards, Chair, Division of Research Services, Mayo Clinic Rochester
Mr. Jeffrey G. Scheffel, Chair, Division of Research Services, Mayo Clinic Jacksonville
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