DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for HumanResearch Protections
The Tower Building
1100 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 301-402-3006
FAX: 301-402-2071
E-mail: rmeyer@osophs.dhhs.gov

April 3, 2002

Christine M. Maziar, Ph.D.
Vice President for Research and
Dean of the Graduate School
University of Minnesota
420 Johnston Hall
101 Pleasant Street, S.E.
Minneapolis MN 55455-0421

RE: Human Research Subject Protections Under Federal Wide Assurance (FWA) FWA-00000312 and Multiple Project Assurance (MPA) M-1167

Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estrogen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease: A Pilot Study of the Alzheimer's Cooperative Study Unit (ADCSU)
Principal Investigator: David Knopman, M.D.
IRB Number: 9508M10106

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)
HHS Project Number: U01-AG10483

Dear Dr. Maziar:

The Office for Human Research Protections (OHRP) has reviewed the University of Minnesota's

(UM's) March 21, 2002 report that was submitted in response to OHRP's February 14, 2002 letter to UM regarding the allegations of possible noncompliance with the Department of Health and Human Services (HHS) regulations for 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 46.116 stipulate that, except as provided elsewhere under the HHS regulations, 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. In its February 14, 2002 letter, OHRP expressed concern that UM Institutional Review Board (IRB) may have failed to ensure that this requirement was satisfied for the above-referenced research since the principal investigator attested to only obtaining "assent" from the subject for research participation.

OHRP acknowledges that the research has been completed. OHRP also acknowledges that the UM IRB did not approve (a) the enrollment of subjects who were incapable of giving legally effective informed consent; and (b) an assent procedure with an written assent form for the above-referenced research. OHRP further acknowledges UM's plans to investigate this matter further with the principal investigator and UM's overall plan to re-evaluate its procedures and standards for research subject protection. OHRP finds these corrective actions to be satisfactory and appropriate under the UM MPA.

(2) HHS regulations at 45 CFR 46.111(b) stipulate that in order to approve research, the 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 14, 2002 letter, OHRP expressed concern that the UM IRB may have failed to ensure that this requirement was satisfied for the above-reference research.

(a) OHRP finds that UM has adequately responded to this concern. Furthermore, OHRP acknowledges that the UM IRBs have implemented procedures to ensure consideration of additional safeguards for subjects who may be vulnerable as a result of impaired mental capacity.

(b) In its discussion of additional protections for subjects likely to be vulnerable to coercion or undue influence, UM stated the following:

> "An absolute study entry requirement was that the subject in fact be competent to act as his or her own consent authority. Thus, if subject selection was going well, there would BE no vulnerable subjects."

OHRP notes that certain individuals with mental disability, while being able to consent to research on their own behalf, can be vulnerable to coercion or undue influence. In such circumstance, the IRB should determine that additional safeguards have been included in the study to protect the rights and welfare of such subjects, in accordance with HHS regulations at 45 CFR 46.111(b).

(3) HHS regulations at 45 CFR 46.116(a)(1) require that when seeking informed consent, each subject be provided with a description of the procedures to be followed and identification of any procedures which are experimental.

(a) OHRP finds that the UM IRB-approved informed consent documents for the subject and the subject's caregiver failed to describe the procedure for having the subject's caregiver (i) accompany the subject to all clinic visits; (ii) administer the study drug to the subject; and (iii) fill out quality-of-life and pharmacoeconomic questionnaires related to the subject's condition and care.

UM's report stated the following in response:

> "We agree with OHRP that the consent forms approved for this study would have been better if they had a fuller explanation of the caregiver's expected contribution."

Corrective Action: OHRP acknowledges UM's statement. OHRP further acknowledges UM's overall plan to re-evaluate its procedures and standards for research subject protection. OHRP finds this corrective action to be satisfactory and appropriate under the UM MPA.

(b) OHRP expressed concern that the UM IRB-approved informed consent document**s** failed to include an adequate description of the procedure for performing the lumbar puncture.

(4) 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.

OHRP expressed concerned that the UM IRB-approved informed consent document**s** failed to adequately describe the risk of the lumbar puncture procedure.

With regard to (3)(b) and (4) above, OHRP acknowledges UM's report that (a) the performance of lumbar punctures for cerebrospinal fluid collection was not included as a component of the subject research at UM; and (b) a lumbar puncture procedure was not performed on the enrolled subject at UM.

(5) 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 of courses of treatment, if any, that might be advantageous to the subject. In its February 14, 2002 letter to UM, OHRP expressed concern that the IRB-approved informed consent document for the above-referenced research did not describe the alternative of receiving estrogen replacement therapy outside of the research.

UM's report stated the following in response:

> "Of course we agree with OHRP that there is a regulatory and ethical mandate that there be disclosure to prospective research subjects of potentially-advantageous alternatives to study participation. We also agree that receiving the studied therapy outside the study context may be such an alternative and may require disclosure. This concept is specifically presented in both slides and handout materials to our investigators in the introductory course on regulatory affairs and research ethics; requiring such disclosure is the ordinary practice of this IRB."

OHRP acknowledges UM's statement. OHRP notes that it may have been appropriate to disclose in the informed consent document the alternative of receiving estrogen replacement therapy outside of the research context for known standard indications in the study population (i.e., treatment of menopausal vasomotor symptoms, atrophic vaginitis, and osteoporosis).

(6) OHRP finds that UM has adequately addressed the additional concerns raised by OHRP in its February 14, 2002 letter.

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 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,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Moira A. Keane, UM
Dr. David Guay, Chair, IRB-01, UM
Dr. James Anderson, Chair, IRB-02, UM
Dr. Charles E. Furman, Chair, IRB-03, UM
Ms. Bonnie LeRoy, Chair, IRB-04, UM
Dr. David Adson, Chair, IRB-05, UM
Dr. Susan Berry, Chair, IRB-06, UM
Dr. John Mather, Director, Office of Research Compliance and Assurance, Veterans Health Administration
Commissioner, FDA
Dr. David A. Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Jeffrey M. Cohen, OHRP
Mr. George Gasparis, OHRP
Dr. Harold Blatt, OHRP
Mr. Barry Bowman, OHRP