DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 301-402-5567
FAX: 301-402-2071
E-mail: mcarome@osophs.dhhs.gov

March 25, 2002

Arthur S. Levine, M.D.
Senior Vice Chancellor for Health Sciences and
Dean, School of Medicine
University of Pittsburgh
M-240 Scaife Hall
3550 Terrace Street
Pittsburgh, Pennsylvania 15213

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1259

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 ADCSU
Principal Investigator: Steven T. DeKosky, M.D.
IRB Protocol #: 950832
HHS Project Number: U01-AG10483

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 Dr. Levine:

The Office for Human Research Protections (OHRP) has reviewed the University of Pittsburgh's (UP's) March 12, 2002 report that was submitted in response to OHRP's February 4, 2002 report 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 46.116(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 informed consent documents approved by the UP Institutional Review Board (IRB) for the above-referenced research failed to include (a) an adequate description of the procedure for performing the lumbar punctures, and (b) a description of the procedure 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 that (i) the research has been completed; (ii) since the above-referenced research was reviewed by the UP IRB, UP has employed six full-time IRB coordinators who provide support to the UP IRBs in reviewing informed consent documents to help ensure the adequacy and accuracy of the information contained within them; and (iii) UP has implemented orientation and training programs for IRB members that address the required elements of informed consent. OHRP finds these corrective actions to be satisfactory and appropriate under the UP 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 4, 2002 letter, OHRP expressed concern that the UP IRB may have failed to ensure that this requirement was satisfied for the above-referenced research.

(a) OHRP finds that UP has adequately responded to this concern. Furthermore, OHRP acknowledges that the UP 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, UP stated the following:

> "As a general rule, all adults, regardless of their diagnosis or condition, should be presumed competent to consent unless there is evidence of serious mental disability that would impair reasoning or judgement. Mental disability alone should not disqualify a person from consenting to participate in research; rather there should be evidence of the individual's incapacity to understand and make a choice before they are deemed unable to consent."

OHRP agrees with this statement. OHRP also 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).

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.

At this time, OHRP provides the following additional guidance in response to UP's March 12, 2002 report:

> (3) 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 4, 2002 letter to UP, 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.
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> UP's report stated the following in response:
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> > "Please note that at the time this research study was conducted no currently marketed estrogen replacement therapy had received [Food and Drug Administration (FDA)] approval for the clinical indication of preventing the onset or progression of [Alzheimer's disease (AD)]. (In fact, it was the purpose of this research study to evaluate the safety and effectiveness of estrogen therapy for such an indication.) By requiring a statement, in the informed consent document, that estrogen therapy is available outside of the research, the UP IRB would, in effect, be promoting the off-label use of an approved drug for which there was no substantive evidence of its safety and efficacy. We are concerned that such would not only greatly mislead the research subject-AD patient, but would also be likely considered inappropriate by the U.S. Food and Drug Administration."
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> OHRP acknowledges UP's statement. OHRP also 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).
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> Furthermore, where a particular marketed drug is being used by healthcare providers to treat patients for an indication which has not been approved by the FDA, it may be appropriate to disclose that use as an alternative treatment to subjects in the informed consent document.

OHRP appreciates the commitment of UP to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Mr. Dennis Swanson, Director, Research Conduct and Compliance Office, UP
Dr. Philip Troen, Chairperson, Institutional Review Board-01, UP
Dr. Steven T. DeKosky, UP
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. George Gasparis, OHRP
Dr. Harold Blatt, OHRP
Mr. Barry Bowman, OHRP