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 25, 2002

James A. Boling, Ph.D.
Acting Vice President for Research
University of Kentucky
201 Gillis Building
Lexington, KY 40506-0033

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1324

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 ADSU
Principal Investigator: Frederick A. Schmitt, Ph.D.
IRB Protocol #: 95-30295
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. Boling:

The Office for Human Research Protections (OHRP) has reviewed the University of Kentucky's (UK's) March 14, 2002 report that was submitted in response to OHRP's February 5, 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 5, 2002 letter, OHRP expressed concern that the UK IRB may have failed to ensure that this requirement was satisfied for the above-referenced research.

OHRP finds that UK has adequately responded to this concern. Furthermore, OHRP acknowledges that the UK IRBs have implemented procedures to ensure consideration of 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.

(a) OHRP acknowledges that (i) the UK IRB approved a separate informed consent document for the lumbar puncture (LP) procedure; and (ii) all subjects enrolled in the research at UK declined to undergo this procedure. However, OHRP finds that the informed consent document approved by the UK IRB failed to adequately describe the procedure to be followed for performing the LP.

(b) OHRP finds that the IRB-approved informed consent documents failed to describe 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; and (ii) since the above-referenced research was reviewed by the UK IRB, UK has developed and implemented training and education programs for IRB members that address the required elements of informed consent. OHRP finds this corrective action to be satisfactory and appropriate under the UK MPA.

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 UK's March 14, 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 5, 2002 letter to UK, 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.

UK's report stated the following in response:

> "The alternatives listed in the consent form were commonly accepted standard of care therapies at the time that the study was initiated. At the time the study was initiated, use of estrogen replacement therapy was not an approved standard of care for Alzheimer's disease. The use of estrogen replacement therapy was still considered to be 'experimental'; therefore, it was not deemed appropriate to include it in the 'alternative' section of the informed consent document."

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).

Furthermore, the fact that a given treatment is "experimental" does not necessarily mean it should not be disclosed to subjects as an alternative. 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, even if such use is considered "experimental," it may be appropriate to disclose that use as an alternative treatment to subjects in the informed consent document.

OHRP appreciates the commitment of UK 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: Ms. Helen Cornish, Director, Veterans Affairs Medical Center, Lexington
Ms. Ada Sue Selwitz, Director, Office of Research Integrity, UK
Dr. Thomas Foster, Chairperson, IRB-01, 02, and 03, UK
Dr. Norman Van Tubergen, Chairperson, IRB-04, UK
Dr. Frederick A. Schmitt, UK
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