DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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April 30, 2002

Neal Nathanson, M.D.
Vice Provost for Research
University of Pennsylvania
Room 215, College Hall
Philadelphia, PA 19104-6381

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1025

Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estrogen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease (IRB Number 1568-0)
Principal Investigator: Christopher M. Clark, M.D.
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. Nathanson:

The Office for Human Research Protections (OHRP) has reviewed the University of Pennsylvania's (UP's) April 19, 2002 report that was submitted in response to OHRP's February 15, 2002 letter to UP regarding the above-referenced research.

Based upon its review, OHRP makes the following determinations regarding the above-referenced research:

(1) Department of Health and Human Services (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 15, 2002 letter, OHRP expressed concern that the UP institutional review board (IRB) may have failed to ensure that this requirement was satisfied for the above-referenced research.

OHRP finds that UP has adequately responded to this concern. In particular, UP described the following additional safeguards the IRB may require to protect the rights and welfare of subjects with diminished mental capacity: (i) witnessing of assent/informed surrogate consent by a third party; (ii) assessment by an independent third party of subjects' ability to assent or surrogates' ability to consent, (iii) and independent documentation of the informed consent process.

(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 informed consent documents approved by the UP IRB for the above-referenced research failed to include 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 the research has been completed. OHRP further acknowledges UP's statements that (i) in the above research, the subjects' consent documentation, in addition to the caregivers' consent documentation, should have described the quality-of-life and pharmacologic questionnaires, (ii) since the time of this study, UP has amended its human subject protection policies to deal with this deficiency, and (iii) the current UP IRB would ensure that subject consent and assent forms clearly describe the role of third parties involved in the research. OHRP finds these corrective actions to be satisfactory and appropriate under the UP 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 UP's April 19, 2002 letter:

(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 15, 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.

In UP's April 19, 2000 report in response to OHRP, UP stated that it would have been improper for consent documents to indicate that subjects could also seek therapeutic benefit for

their Alzheimer's disease by obtaining estrogen off study because estrogen replacement therapy was not an approved treatment for Alzheimer's. The April 19 report further stated that discussion of other approved and accepted therapeutic uses of estrogen, even if potentially beneficial to the subject, would have been improper and unrelated to the focus of the study.

OHRP acknowledges UP's statements. 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, where a particular marketed drug is being used by healthcare providers to treat patients for an indication which has not been approved by the Food and Drug Administration, it may be appropriate to disclose that use as an alternative treatment to subjects in the informed consent document.

(4) In its April 19 report, UP stated that the UP IRB would not require additional safeguards to protect vulnerable subjects involved in low risk research. OHRP notes that the level of risk of research has no bearing upon subjects' vulnerability to coercion or undue influence, or the requirement to provide additional safeguards to protect vulnerable subjects under HHS regulations at 45 CFR 46.111(b).

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,

Carol J. Weil, J.D.
Compliance Oversight Coordinator

cc: Dr. Nicholas Kefalides, Executive IRB Chair, UP
Dr. Joseph Sherwin, Director of Regulatory Affairs, UP
Dr. Christopher Clark, Director, Memory Disorders Clinic, UP
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. Harold Blatt, OHRP

Mr. George Gasparis, OHRP
Mr. Barry Bowman, OHRP