DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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March 25, 2002

Alison F. Richard
Provost
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New Haven, Connecticut 06520-8236

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1452

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 Disease Cooperative Study Unit
Principal Investigator: Christopher H. van Dyck, M.D.
IRB Protocol #: 8988
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. Richard:

The Office for Human Research Protections (OHRP) has reviewed the Yale University's (YU'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 regarding the above referenced-research:

(1) 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 5, 2002 letter, OHRP expressed concern that the YU IRB may have failed to ensure that this requirement was satisfied for the above-referenced research.
OHRP finds that YU has adequately responded to this concern. Furthermore, OHRP acknowledges that the YU 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.

OHRP finds that the informed consent documents approved by the YU IRB 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 (i) the research has been completed; (ii) since the above-referenced research was reviewed by the YU IRB, YU has implemented procedures to ensure that informed consent documents approved by the IRB adequately address all required elements of informed consent. OHRP finds this corrective actions to be satisfactory and appropriate under the YU MPA.

(3) OHRP finds that YU adequately addressed the additional concerns raised by OHRP in its February 5, 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.

At this time, OHRP provides the following additional guidance in response to YU's March 14, 2002 report:

(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 5, 2002 letter to YU, 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.

YU's report stated the following in response:

> "The informed consent document did not describe [estrogen replacement therapy (ERT)] as an alternative treatment for [Alzheimer's disease (AD)] outside of the research study because the condition being studied was AD and ERT was not an approved therapeutic treatment for AD."

OHRP acknowledges YU'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).

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 YU 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: Dr. Suzanne K. Polmar, Director, Grant and Contract Administration, YU
Dr. Maurice J. Mahoney, Chair, IRB-01 and -02, YU
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