DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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February 5, 2002

Alison F. Richard
Provost
Yale University
P.O. Box 208236
New Haven, Connecticut 06520-8236

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 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) June 28, 2000 report that was submitted in response to OHRP's May 15, 2000 letter to YU presenting allegations of noncompliance with the Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46) involving the above-referenced research.

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

(1) HHS regulations at 45 CFR 46.116 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. OHRP acknowledges your report that informed consent was obtained from, and documented for, each of the nine subjects enrolled in the above-referenced research at YU.

(2) Continuing Institutional Review Board (IRB) review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

OHRP finds that continuing review of the research by the YU IRB was not substantive and meaningful.

Corrective Action: OHRP acknowledges that the research has been completed. Furthermore, OHRP acknowledges that YU previously has implemented appropriate corrective action under its MPA to ensure the continuing review of research by the YU IRB is substantive and meaningful.

(3) OHRP finds that when the YU IRB conducted its initial review of the research on August 14, 1996, the IRB approved the research contingent upon substantive modifications or clarifications directly relevant to the determinations required under HHS regulations at 45 CFR 46.111 without requiring additional review by the convened IRB. For example, the IRB requested that the investigator provide the following substantive clarifications, among others:

> "Please explain how you will deal with the loss of capacity to consent (in some patients) during the 15 month study. What will be done to assure their continuing freedom to withdraw?"

OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research should be **deferred**, pending subsequent review by the convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

(4) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be in sufficient detail to show, among other things, the vote on all actions taken by the IRB, including the number of members voting for, against, and abstaining. OHRP finds that IRB minutes failed to meet this requirement when the YU IRB conducted its continuing review of the research on September 10, 1997, and September 23, 1998.

Corrective Action: OHRP acknowledges that YU previously has implemented appropriate corrective action under its MPA to ensure the minutes of all IRB meetings document the vote on all actions taken by the IRB, including those actions related to continuing review.

OHRP has the following additional questions and concerns regarding the above-referenced research:

(5) 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. OHRP is concerned that (a) the subjects of the research, because of their potentially impaired mental state, may have been likely vulnerable to coercion or undue influence; and (b) if so, the YU IRB failed ensure that there were additional safeguards included in the study to protect the rights and welfare of these vulnerable subjects.

In particular, OHRP notes a lack of important details in the IRB records regarding the procedures for recruitment and enrollment of subjects, and finds no evidence in the IRB-approved protocol or other relevant IRB records that additional safeguards were included during the subject recruitment and enrollment process. Please respond in detail. In your response, please describe the types of additional safeguards, if any, the YU IRB requires for research involving adults with impaired mental capacity. For example, does the IRB ever consider requiring procedures such as: (a) inclusion of a mental capacity assessment by someone independent from the research team at the time of enrollment and during a subject's participation in such research if mental capacity is likely to diminish; and (b) independent consent monitors to supervise the informed consent process?

(6) 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 is concerned 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. Please respond.

(b) OHRP notes that the research at most other study sites involved lumbar puncture procedures for research purposes at baseline and at 6 months. Please clarify whether lumbar puncture procedures were planned or conducted on subjects enrolled at YU. If so, please provide the IRB-approved informed consent documents related to these research procedures.

(7) 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 notes that deep vein thrombosis (DVT) was noted in a subject as early as October of 1996, but the informed consent document was not changed until the Alzheimer Disease Cooperative on May 21, 1998 requested that this risk be included in the informed consent document.

Furthermore, OHRP notes that subject #9 at YU started taking the investigational agent on September 12, 1997. OHRP is concerned that there is no evidence that the YU IRB required the investigators to provide this subject with additional information regarding the risk of DVT and thromboembolic disease. Please respond. In your response, please clarify whether or not this subject was undergoing research interventions at the time the Alzheimer Disease Cooperative requested the change in the informed consent document regarding DVT, and whether or not the subject was informed of this new risk.

(8) 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. OHRP is concerned that the informed consent document did not describe the alternative of receiving estrogen replacement therapy outside of the research. Please respond.

Please submit YU's response to the questions and concerns in (5)-(8) above so that OHRP receives it no later than March 15, 2002. If upon further review of the questions and concerns YU identifies additional instances of noncompliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

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
Dr. Douglas Olsen, Chair, IRB-03, YU
Dr. Robert C. Lange, Chair, IRB-04, YU
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Dr. John Mather, Director, Office of Research Compliance and Assurance, Veterans Health Administration
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