DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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April 4, 2002

Kern Wildenthal, M.D., Ph.D.
President
University of Texas Southwestern Medical Center
5323 Harry Hines Boulevard
Dallas, TX 75235

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1304

Research Publication	**Estrogen Replacement Therapy for Treatment of Mild to Moderate Alzheimer Disease: A Randomized Controlled Trial (Mulnard, et al. JAMA 2000;283:1007-10015)**
Research Project:	**A Multicenter, Double-Blind, Placebo-Controlled Study of Estrogen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease**
IRB Protocol #:	**0795 27900**
Principal Investigator:	**Myron Weiner, M.D.**

HHS Project Number: U01-AG10483

Dear Dr. Wildenthal:

The Office for Human Research Protections (OHRP) has reviewed the University of Texas Southwestern Medical Center's (UTSWMC) March 20, 2002 report that was submitted in response to OHRP's letter of February 6, 2002 regarding the above-referenced research.

Based upon its review, OHRP makes the following determinations:

(1) Department of Health and Human Services 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 6, 2002 letter, OHRP expressed concern that the UTSWMC IRB may have failed to ensure that this requirement was satisfied for the above-referenced research.

(a) OHRP finds that UTSWMC has adequately responded to this concern. Furthermore, OHRP acknowledges that the UTSWMC IRB considers additional safeguards, such as independent monitors to assess the informed consent process, 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, UTSWMC indicated that its IRB considers additional safeguards for research involving vulnerable subjects when the research involves more than minimal risk. Please note that the IRB must ensure that the requirement at 45 CFR 46.111(b) is satisfied for all research, not just research involving greater than minimal risk to the subjects.

(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 UTSWMC Institutional Review Board (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 (i) the research has been completed; (ii) the current practice of the UTSWMC IRB is to address such caregiver questionnaires in the informed consent documents. OHRP finds this corrective action to be satisfactory and appropriate under the UTSWMC MPA.

(3) OHRP finds that UTSWMC's report adequately responded to the additional concerns raised in OHRP's February 6, 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 UTSWMC's March 20, 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 6, 2002 letter to UTSWMC, 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.

UTSWMC's report stated the following in response:

> "... estrogen replacement therapy for AD [Alzheimer Disease] patients is not an approved treatment for AD and should not be included as an alternative to the patient outside of the research protocol."

OHRP acknowledges UTSWMC's statement 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 (FDA) it may be appropriate to disclose that treatment as an alternative to subjects in the informed consent document.

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

Sincerely,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

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