DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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April 4, 2002

James W. Patrick, Ph.D.
Vice President and Dean of Research
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Office of Research
One Baylor Plaza, 600D
Houston, TX 77030

RE: Human Research Subject Protections Under Federalwide Assurance FWA 00000286 and Multiple Project Assurance (MPA) M-1060

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 #:	**H-4194**
Principal Investigator:	**Rachelle Smith Doody, Ph.D., M.D.**
HHS Project Number:	**U01-AG10483**

Dear Dr. Patrick:

The Office for Human Research Protections (OHRP) has reviewed Baylor College of Medicine (BCM) March 20, 2002 report in response to OHRP's letter of February 7, 2002 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 7, 2002 letter, OHRP expressed concern that the BCM IRB may have failed to ensure that this requirement was satisfied for the above-referenced research.

OHRP finds that BCM has adequately responded to this concern. Furthermore, OHRP acknowledges that the BCM 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 Institutional Review Board (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 the system for the protection of human subjects at BCM is undergoing reorganization. BCM has committed to enhance the education components of its human subjects protection program to ensure that all informed consent documents detail the required elements. In addition, BCM is currently making changes to its system for the protection of human subjects including the following:

(a) Expansion of the number of IRBs.

(b) Increasing the number of staff in the Assurance and Compliance (A&C) Services in the BCM Office of Research.

(c) Appointment of a faculty liaison to facilitate communication with the A&C staff.

(d) Development of a system for the electronic submission of research protocols.

(e) Creation of a new position of human research educator.

(f) Conduct of random and for-cause regulatory audits.

(g) Ongoing review and updating of IRB policies and procedures

OHRP finds these corrective actions to be satisfactory and appropriate under the BCM MPA.

(3) OHRP finds that BCM's report adequately responded to the additional concerns raised in OHRP's 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 BCM'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 7, 2002 letter to BCM, 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.

BCM's report stated the following in response:

> (a) "Please note that estrogen replacement therapy was not an approved treatment for Alzheimer's Disease. Alternative treatments for Alzheimer's Disease were listed in the alternatives section of the informed consent document"
>
> (b) "BCM is concerned, however, that suggesting to subjects that they may be able to get a medication 'off study' through their family doctor, when the medication is not approved for the condition under study, might mislead subjects to believe that the medication has been demonstrated to be efficacious and safe for the condition."

OHRP acknowledges BCM's statements 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

cc: Dr. Kathleen Motil, BCM
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