DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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April 3, 2002

Ronald Newbower, Ph.D.
Senior Vice President for Research and Technology
Research Administration - Bartlett Hall 3
Massachusetts General Hospital
55 Fruit Street
Boston, MA 02114

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1331

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 #:	**95-7286**
Principal Investigator:	**John Growdon, M.D.**
HHS Project Number:	**U01-AG10483**

Dear Dr. Newbower:

The Office for Human Research Protections (OHRP) has reviewed the Massachusetts General Hospital's (MGH) June 28, 2000 and March 20, 2002 reports regarding the above-referenced research.

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

(1) OHRP acknowledges that the following three issues of noncompliance were identified in your June 28, 2000 report:

(a) One IRB at MGH failed to conduct continuing review of the above-referenced research on at least an annual basis, as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(e).

(b) The investigator failed to report the first three serious adverse events (which may have represented unanticipated problems involving risks to subjects) to the Institutional Review Board (IRB) as required by HHS regulations at 45 CFR 46.103(b)(5).

(c) One neurologist consented a subject prior to approval of an amendment adding him as a co-investigator, as required by HHS regulations at 45 CFR 46.103(b)(4)(iii).

Corrective Action: OHRP notes that (i) the Quality Improvement and Human Subject Protection Report submitted with your June 28, 200 report recommended that the IRB conduct its continuing review in a more timely fashion; (ii) MGH added two additional IRBs in June 1999 to support the continuing review process; and (iii) the principle investigator has been made aware of the requirements for reporting unanticipated problems involving risks to subjects or others, as well as, requirements for the submission of protocol amendments. OHRP finds that these corrective actions appear to be satisfactory and appropriate under the MGH MPA.

(2) 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 6, 2002 letter, OHRP expressed concern that the MGH IRB may have failed to ensure that this requirement was satisfied for the above referenced research.

OHRP finds that MGH has adequately responded to this concern. Furthermore, OHRP acknowledges that the MGH IRBs have implemented procedures to ensure consideration of additional safeguards for subjects who may be vulnerable as a result of impaired mental capacity.

(3) OHRP finds that MGH has adequately responded to the additional concerns and questions 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:

> (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 MGH, 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.
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> OHRP acknowledges the following statement in MGH's March 20, 2002 report:
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> > "If the drug is routinely used in an 'off label' application it is typically listed under our alternative section in a consent form ... We do not believe that estrogen in 1995 or in 2002 met that standard and therefore do not believe it was warranted that it be formally listed as an alternative therapy for this study"
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> 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).

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: Ms. Rosalyn Gray, MGH
Dr. Elizabeth Hohmann, Partners Human Research Committee
Dr. Delia Wolf, Partners Human Research Committee
Dr. John Growdon, MGH
Commissioner, FDA
Dr. David Lepay, FDA
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Dr. Melody Lin, OHRP
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Mr. Barry Bowman, OHRP