DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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April 2, 2002

Francis R. Dietz
President
Memorial Hospital of Rhode Island
111 Brewster Street
Pawtucket, RI 02860

**RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1126**

**Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estrogen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease**
**Principal Investigators: Dr. Brian R. Lott and Dr. Margaret C. Lannon**
**HHS Project Number: U01-AG10483**
**IRB Project Numbers: 96-29**

**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 Mr. Dietz:

The Office for Human Research Protections (OHRP) has reviewed the Memorial Hospital of Rhode Island's (Memorial Hospital's) March 20, 2002 report that was submitted in response to OHRP's February 7, 2002 letter 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 Memorial Hospital IRB may have failed to ensure that this requirement was satisfied for the above-referenced

research.

OHRP finds that Memorial Hospital has adequately responded to this concern. Furthermore, OHRP acknowledges that the Memorial Hospital IRB has 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 Memorial Hospital IRB for the above-referenced research failed to include (a) 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 and (b) an adequate description of the procedure for performing lumbar punctures.

**Corrective Action:** OHRP acknowledges that (i) the research has been completed; and (ii) since the above-referenced research was reviewed by the Memorial Hospital IRB, Memorial Hospital has implemented procedures to ensure that appropriate informed consent be obtained for procedures and medical interventions performed during the course of a study. OHRP finds this response to be satisfactory and appropriate under Memorial Hospital's MPA.

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 Memorial Hospital's March 20, 2002 report:

(3) 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 Memorial Hospital, 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 research.

Memorial Hospital's report stated the following in response:

> "After considering this question... we determined that it would have been inappropriate to advise the participants about such alternatives because estrogen replacement therapy was not an approved treatment for Alzheimer's disease."

OHRP acknowledges Memorial Hospital'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 Food and Drug Administration (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 Memorial Hospital to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Leslie K. Ball, M.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Mr. Joseph Cortellini, Memorial Hospital
Dr. Brian R. Lott, Memorial Hospital
Dr. Margaret C. Lannon, Memorial Hospital
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