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 29, 2002

Daniel R. Masys, M.D.
Institutional Official for Human Subjects
University of California, San Diego
9500 Gilman Drive
La Jolla, California 92093-0052

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1274

Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estrogen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease
Principal Investigator: Michael Grundman, M.D.
IRB Protocol #: 950699 and 970777
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. Masys:

The Office for Human Research Protections (OHRP) has reviewed the University of California, San Diego's (UCSD's) March 11, 2002 report that was submitted in response to OHRP's February 6, 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 6, 2002 letter, OHRP expressed concern that the UCSD IRB may have failed to ensure that this requirement was satisfied for the above-referenced research.

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

OHRP notes that HHS regulations at 45 CFR 46.109(e) stipulate that IRBs have the authority to observe or have a third party observe the consent process and the research. OHRP encourages IRBs to use this authority. Furthermore, with respect to the "Draft Procedures for Determining Decisional Capacity in Subjects Participating in UCSD Research Protocols, January 2002," please note that the requirements of HHS regulations at 45 CFR 46.111(b) must be satisfied for all research, not just research involving greater than minimal risk.

(2) 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. In its February 6, 2002 letter to UCSD, OHRP noted that the informed consent document for the above-referenced research was not revised to include a description the risk of thromboembolic disease until 10 months after the UCSD IRB received the third of three reports of subjects experiencing thromboembolic events that were believed by the investigators to be probably or possibly related to the research interventions.

OHRP finds that it would have been appropriate for the UCSD IRB to more promptly require modification of the informed consent document for the above-referenced research.

Corrective Action: OHRP acknowledges that since the above-referenced research was reviewed and approved by the UCSD IRB, the UCSD IRB has implemented more rigorous procedures for reviewing and acting upon reports of adverse events that adequately address the above finding and are appropriate under the UCSD MPA.

(3) 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 UCSD 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.

Corrective Action: OHRP acknowledges that (i) the research has been completed; (ii) since the above-referenced research was reviewed by the UCSD IRB, the UCSD IRB has corrected this deficiency in subsequent protocols. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the UCSD MPA.

(4) OHRP finds that UCSD has adequately addressed the additional concerns raised by OHRP in its 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 UCSD's March 11, 2002 report:

(5) 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 UCSD, 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.

UCSD's report stated the following in response:

> "The specific purpose of the estrogen trial was to determine whether or not estrogen therapy might positively affect the symptomatology and course of the dementing illness in hysterectomized women with [Alzheimer's disease (AD)]. Estrogen replacement therapy was not and is not an approved treatment for AD and it would have been improper for the UCSD investigator to suggest, or consent document to indicate, that AD subjects could also seek therapeutic benefit for their Alzheimer's disease through use of estrogen outside of the study."

OHRP acknowledges UCSD'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 UCSD 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: Mr. Gary Rossio, Director, Veterans Affairs San Diego Healthcare System
Dr. Robert Engler, President, Veterans Medical Research Foundation
Dr. J. Allen McCutchan, Chair, IRB-01A, UCSD
Dr. Richard Kornbluth, Chair, IRB-01B, UCSD
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Sandra Woodruff, Executive Director, Veterans Medical Research Foundation
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