DEPARTMENT OF HEALTH & HUMAN SERVICES **PUBLIC HEALTH SERVICE**

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May 7, 2002

Nathan Kase, M.D.
Dean (Interim)
Mount Sinai School of Medicine
Dean's Office
One Gustave Levy Place
Box 1475
New York, NY 10029

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1155
Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estorgen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease
Research Publication: Estrogen Replacement Therapy for Treatment of Mild to Moderate Alzheimer Disease: A Randomized Controlled Trial, Mulnard, et al. JAMA 2000; 283: 1007-15.
Principal Investigator: Deborah Marin, M.D.
Protocol Number: 91-208PS/VA

Dear Dr. Kase:

The Office for Human Research Protections (OHRP) has reviewed the Mount Sinai School of Medicine's (MSSM) report dated April 26, 2002 that was submitted in response to OHRP's February 5, 2002 letter to MSSM presenting allegations of noncompliance with the Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46) involving the above-referenced research.

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

(1) 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 5, 2002 letter, OHRP expressed concern that the MSSM IRB may have failed to ensure that this requirement was satisfied for the above-referenced research.

OHRP finds that MSSM has adequately responded to this concern. Furthermore, OHRP acknowledges that the MSSM 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 purpose of the research and the procedures to be followed and identification of any procedures which are experimental. OHRP finds that the informed consent documents approved by the IRB for the above-referenced research failed to include the following:

(a) A complete description of the purpose of the research. In specific, OHRP notes that the informed consent document did not mention that one of the purposes of the research was to determine the safety and tolerability of the intervention. OHRP acknowledges MSSM's statement that determining the safety and tolerability was not one of the purposes of the research. However, the IRB-approved protocol clearly stated that an objective of the study was "to establish the safety and tolerability of estrogen replacement therapy in elderly female Alzheimer's disease patients."

(b) A description of the procedure for having the subject's care giver fill out quality-of-life and pharmacoeconomic questionnaires related to the subject's condition and care.

(c) Nothing in the informed consent document states that genetic testing is optional (which the protocol implies it is), but there does not appear to be a separate informed consent document for genetic testing or a way to opt out.

Corrective Action: OHRP acknowledges that (i) the research has been completed; (ii) since the above-referenced research was reviewed by the MSSM IRB, MSSM has implemented numerous steps to improve its system for protecting human subjects following OPRR's on-site evaluation in 1999 that adequately address the above finding.

(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 5, 2002 letter to MSSM, 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.

OHRP acknowledges that the current MSSM IRB Guidelines and Policies Manual includes the following suggestion for "alternative to participation" in the informed consent document: "treatment comparable to that being proposed in the context of this study is/is not available to you outside of this study."

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 MSSM's April 26, 2002 report:

(4) The March 2002 MSSM IRB Guidelines and Policies Manual stated "New York State has not codified a policy for acceptable surrogates to consent for research. However, the MSSM IRB believes that there are situations and research projects where it would be appropriate and potentially beneficial to an individual with diminished or absent capacity to be enrolled in a research project. Accordingly, the MSSM IRB has approved the following hierarchy of acceptable individuals who may be used as surrogates for consent to participate in human subject research projects: (1) previously designated health care proxy; (2) previously appointed guardian; (3) spouse/domestic partner; (4) children....."

HHS regulations at 45 CFR 46.116 stipulate that, except as provided elsewhere under the HHS regulations, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. HHS regulations at 45 CFR 102(c) define a legally authorized representative as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. MSSM should ensure that there is a sound legal basis under applicable New York State law for permitting surrogates to consent on behalf of a prospective subject to participate in research.

(5) The March 2002 MSSM IRB Guidelines and Policies Manual describes the termination of projects by the IRB when review has not occurred at least annually, and states that such terminations should be reported to the funding department. Please note that when continuing review does not occur by the date specified by the IRB, IRB approval <u>expires</u> automatically. Such expiration of IRB approval does not need to be reported to OHRP as a suspension or termination of IRB approval under HHS regulations.

OHRP views "suspension" or "termination" of IRB approval as an active process whereby the

IRB suspends or terminates its approval prior to the end of the current IRB approval period. This most commonly occurs when the IRB either identifies noncompliance by the investigator(s) or determines that serious unanticipated problems involving risks to subjects or others are occurring (e.g., the frequency and severity of serious adverse events is occurring at a higher rate than expected). Such a suspension or termination does need to be reported to OHRP under HHS regulations.

(6) The form "Request for Modification in Documentation of Informed Consent" stated that "...would the consent document be the only identifiable link between the subject and the research, and would there be potential harm to the subject if the confidentiality of the consent document were breached?" OHRP notes that the requirements at HHS regulations 45 CFR 46.117(c)(1) for waiver of documentation of informed consent state that the IRB must find, among other things, that the **principal** risk would be a potential harm resulting from a breach of confidentiality.

(7) OHRP recommends that the MSSM IRB Policies and Procedures Manual be updated to include the revised Subpart B (Federal Register: November 13, 2001 (Volume 66, Number 219), Rules and Regulations, Page 56775-56780).

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,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Jane Tsambis, MSSM
Dr. Ruth G. Abramson, MSSM
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