DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE

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March 25, 2002

Carl J. Getto, M.D.
Dean and Provost for JoAnn Argersinger
Southern Illinois University at Carbondale
-Southern Illinois University School of Medicine
P.O. Box 19230
Springfield, IL 26794

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1311

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: Robert E. Becker, M.D.
Protocol Number: 95-107

Dear Dr. Getto:

The Office for Human Research Protections (OHRP) has reviewed the Southern Illinois University School of Medicine's (SIUSM) report dated March 8, 2002 regarding 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 determinations 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 SIUSM IRB may have failed to ensure that this requirement was satisfied for the research.

OHRP finds that SIUMS has adequately responded to this concern. In particular, OHRP acknowledges that the SIUMS IRB has developed required procedures for the inclusion of cognitively impaired subjects in research, including requiring IRB review and approval of procedures for evaluating capacity to consent, procedures for obtaining consent, and consideration of independent consent monitors to supervise the informed consent process. OHRP has the following comments about these procedures: The procedures state that "[t]ypically a spouse or adult child of such persons consents to their medical care, but no one is their legally authorized representative. The extent to which family members may legally consent to the involvement of such persons in research.... is not clear." The procedures also state "[t]he selection of an appropriate representative to consent on behalf of those unable to consent for themselves must be accomplished without clear guidance from statutes, case law, or regulations...." OHRP notes that under 45 CFR 46.116, only a subject or this or her legally authorized representative may consent to participation in research, unless informed consent is appropriately waived under the regulations. When a legally authorized representative does not exist under applicable law for a prospective subject who lacks capacity to consent, then no one may consent for their involvement in research.

(2) OHRP finds that the informed consent documents reviewed and approved by the SIUSM IRB for this study failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): an explanation of the purposes of the research, and a complete description of the procedures to be followed, and identification of any procedures which are experimental. In particular, OHRP notes the following:

(i) 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.

(ii) There was no mention in the informed consent document about the role of the caregiver in filling out quality-of-life and pharmacoeconomic questionnaires related to the subject's condition and care.

(iii) The informed consent document stated that genetic testing is optional, but there does not appear to be a separate informed consent document for genetic testing or a way to opt out.

(b) Section 46.116(a)(8): A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or

loss of benefits to which the subject is otherwise entitled. The informed consent document stated "I know I can refuse to participate, or may end my participation at any time...withdrawing from the study would not change the care that I would be given for my memory problem." There could be penalties of loss of benefits other than care the subject would be given for their memory problem.

Corrective Action: OHRP acknowledges that the SIUSM IRB has revised its template document to require investigators to include such information in informed consent documents. This template also clearly indicates which language to delete or omit when appropriate.

(3) Continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

When conducting research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above referenced documentation.

OHRP finds that, up until sometime in August of 2001, continuing review by the SIUSM was not substantive and meaningful. In particular, OHRP notes the following:

(a) The minutes of the IRB meetings stated "The committee unanimously approved the following continuing reviews:" and then provided a list of protocols with no documentation of discussion or changes.

(b) The continuing review form did not solicit the current informed consent document or research summary, nor information regarding complaints or current literature.

Corrective Action: OHRP acknowledges that the SIUMS IRB has improved its continuing review procedures, implementing a primary and secondary reviewer system and ensuring that all members get the recommended material for each protocol. The SIUMS has implemented use of a new continuing review form. The minutes of the SIUMS IRB meetings are now being

recorded to document separate deliberations, actions, and votes for each protocol undergoing continuing review.

OHRP finds that these corrective actions adequately addresses the above findings and are appropriate under the SIUSM MPA. As a result, 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.

OHRP has the following guidance regarding the human subject protections at SUIMS.

(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 5, 2002 letter to SIUMS, 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 notes that where a particular marketed drug is being used by healthcare providers to treat patients for an indications which has not been approved by the FDA, it may be appropriate to disclose that use as an alternative treatment to subjects in the informed consent document.

(5) The minutes of the August 8, 2001 IRB meeting include a discussion with Dr. Moticka in which he questioned the IRB's role in determining scientific merit of protocols. Dr. Moticka recommended that the IRB send protocols to him for scientific review when there are questions regarding scientific merit. OHRP notes that assessment of scientific merit is within the purview of the IRB under HHS regulations at 45 CFR 46.111(a)(1) and (2).

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. Allison C. Laabs, SIUSM
Dr. Elvin G. Zook, IRB Chair, SIUSM

Dr. Robert E. Becker, SIUSM
Commissioner, FDA
Dr. David Lepay, FDA
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