DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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April 12, 2002

Dr. Robert Schneider
Director of Informatics and Research Compliance
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Stony Brook, New York 11794-3368

Human Research Subject Protections Under Federal Wide Assurance (FWA) 00000125

Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estrogen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease (IRB #97-2950)
Principal Investigator: Dr. Rachel Schindler
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. Schneider:

The Office for Human Research Protections (OHRP) has reviewed the State University of New York at Stony Brook's (SUNY-SB's) April 3, 2002 report that was submitted in response to OHRP's February 27, 2002 report regarding the above-referenced research.

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

(1) Department of Health and Human Services (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 UP Institutional Review Board (IRB) for the above-referenced research failed to include (a) an

adequate description of the procedure for performing the lumbar punctures, and (b) 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 (i) that the research has been completed, (ii) that neither of the two subjects involved in this research at SUNY-SB received a lumbar puncture procedure, and (iii) SUNY-SB's stated intention to alert the IRB concerning these two omissions in informed consent documentation for the above research. OHRP further acknowledges that SUNY-SB is making considerable efforts to improve its overall system for protecting human research subjects, including (i) formation of an oversight program for auditing human subject protocols on a not-for-cause basis through the mail, and (ii) providing formal training to faculty and students on the protection of human subjects involved in research. OHRP finds these corrective actions to be satisfactory and appropriate under the SUNY-SB FWA.

(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 27, 2002 letter, OHRP expressed concern that the SUNY-SB IRB may have failed to ensure that this requirement was satisfied for the above-referenced research.

OHRP finds that SUNY-SB has adequately responded to this concern. Furthermore, OHRP acknowledges that (i) SUNY-SB's Guidelines on the Capacity to Provide Consent for Research (Including Research Involving Subjects with Diminished Capacity), and (ii) the practice of using an independent, board certified neuropsychologist to evaluate the mental status of subjects potentially lacking the capacity to make informed decisions about participating in research, promote consideration of additional safeguards for subjects who may be vulnerable as a result of impaired mental capacity. OHRP further acknowledges that SUNY-SB is considering use of independent consent monitors to supervise the informed consent process under certain circumstances.

(3) HHS regulations at 45 CFR 46.103(b) and 46.109(a) require that an IRB must review and approve all non-exempt human subject research covered by an assurance. Furthermore, HHS regulations at 45 CFR 46.109(e) require that an IRB conduct continuing review of research not less than once per year. OHRP finds that the SUNY-SB IRB conducted continuing review of the above research on August 27, 1998. OHRP further finds that due to investigator failure to respond to consent form revisions required by the IRB at its August 27, 1998 meeting, the IRB did not reapprove the research as required by HHS regulations, although one subject remained on protocol through March 17, 1999.

OHRP acknowledges that SUNY-SB, following discovery of the lapse in its approval of the

above research, endorsed recommendations (i) to issue a letter to the investigator, with a copy to the departmental chair, regarding this violation and clarification of institutional policy, and (ii) to conduct a compliance review of other active IRB protocols of the investigator. OHRP further acknowledges SUNY-SB's April 3, 2002 statement in its letter to OHRP that these recommendations were not implemented because the investigator subsequently resigned her full-time faculty status at SUNY-SB.

Corrective Action: OHRP acknowledges that SUNY-SB has developed a continuing review policy of asking investigators to supply several documents to the IRB, including a redacted copy of the consent form signed by the last subject enrolled in the research activity, and any existing reports from external audits or monitoring visits. In addition, OHRP acknowledges that since September of 2000, SUNY-SB has taken steps to educate faculty and students concerning the protection of human research subjects, including conducting lectures, developing an on-line training program, and issuing memoranda from the Office of Research Compliance. OHRP finds that these actions should enable SUNY-SB to ensure that investigators comply with the requirements and determinations of the IRB. OHRP finds these corrective actions to be satisfactory and appropriate under the SUNY-SB FWA.

At this time, OHRP provides the following additional guidance in response to SUNY-SB's April 3, 2002 report:

(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 27, 2002 letter to SUNY-SB, 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.

SUNY-SB's report stated the following in response:

> "[SUNY-SB] maintains that estrogen replacement therapy outside of the research was not FDA-approved or indicated in Alzheimer patients for treatment of their cognitive deficits."

OHRP acknowledges SUNY-SB's statement. However, 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 FDA, it may be appropriate to disclose that use as an alternative treatment to subjects in the informed consent document.

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.

OHRP appreciates the commitment of SUNY-SB to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Carol J. Weil, J.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

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