DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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April 3, 2002

Larry J. Goodman, M.D.
President & CEO
Rush-Presbyterian-St. Luke's Medical Center
1653 West Congress Parkway
Chicago, Illinois 60612-3833

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1385

Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estrogen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease: A Pilot Study of the Alzheimer's Disease Cooperative Study Unit (ADSCU) - Project D
Principal Investigator: Concetta M. Forchetti, M.D.
ORA Number: 95080581

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)
HHS Project Number: U01-AG10483

Dear Dr. Goodman:

The Office for Human Research Protections (OHRP) has reviewed Rush-Presbyterian-St. Luke's Medical Center's (RPSLMC's) March 21, 2002 report that was submitted in response to OHRP's February 11, 2002 letter to RPSLMC regarding the allegations of possible noncompliance with the Department of Health and Human Services (HHS) regulations for protection of human subjects (45

CFR Part 46) involving the above referenced research.

Based upon its review, OHRP makes the following determinations:

(1) 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 11, 2002 letter, OHRP expressed concern that the RPSLMC Institutional Review Board (IRB) may have failed to ensure that this requirement was satisfied for the above-referenced research.

OHRP finds that RPSLMC has adequately responded to this concern. Furthermore, OHRP acknowledges that the RPSLMC has developed a policy guideline and initiated training and education programs for IRB members and investigators that address 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 a description of the procedures to be followed and identification of any procedures which are experimental.

(a) OHRP finds that the RPSLMC IRB-approved informed consent documents failed to include a description of the procedure for having the subject's caregiver (i) accompany the subject to all clinic visits; (ii) administer the study drug to the subject; and (iii) fill out quality-of-life and pharmacoeconomic questionnaires related to the subject's condition and care.

Corrective Action: OHRP acknowledges that the research has been completed. OHRP also acknowledges RPSLMC plans to implement an education program for IRB members that addresses the required elements of informed consent. OHRP finds this corrective action to be satisfactory and appropriate under the RPSLMC MPA.

(b) OHRP expressed concerned that the informed consent documents approved by the RPSLMC IRB failed to include an adequate description of the procedure for performing the lumbar punctures.

(3) 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.

OHRP expressed concerned that the informed consent documents approved by the RPSLMC IRB failed to adequately describe the risk of the lumbar puncture procedures.

With regard to (2)(b) and (3) above, OHRP acknowledges RPSLMC's report that (a) the performance of lumbar punctures was not included as a component of the subject research at RPSLMC; and (b) lumbar puncture procedures were not performed on the two enrolled subjects at RPSLMC.

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 guidance in response to RPSLMC's March 21, 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 of courses of treatment, if any, that might be advantageous to the subject. In its February 11, 2002 letter to RPSLMC, OHRP expressed concern that the RPSLMC IRB-approved informed consent document did not describe the alternative of receiving estrogen replacement therapy outside of the research.

RPSLMC's report stated the following in response:

> "OHRP was concerned that the Rush IRB-approved consent document did not describe the alternative of receiving estrogen replacement therapy outside the context of this particular research study. Although the FDA did not approve estrogen therapy for this purpose, the investigators at the Rush site routinely informed patients and their caregivers that they could seek estrogen replacement therapy without enrolling in this study. Exercise of this option was one of the main reasons so few subjects enrolled in the study."

OHRP acknowledges RPSLMC's statement. OHRP 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.

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,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Henry R. Black, Associate Vice President for Research, RPSLMC
Dr. David C. Clark, Ph.D., Director, Research Compliance, RPSLMC
Dr. Allen Korenblit, Chair, IRB-01, RPSLMC
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