DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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May 8, 2002

Robert M. Glickman, M.D.
Dean
New York University School of Medicine
Office of the Dean
550 First Avenue
New York, NY 10016

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1177

Research Publication: Estrogen Replacement Therapy for Treatment of Mild to Moderate Alzheimer Disease: A Randomized Controlled Trial (Mulnard, et al. JAMA 2000;283:1007-10015)
Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estrogen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease
IRB Protocol #: H6223-01
Principal Investigator: Steven Ferris, Ph.D.
HHS Project Number: U01-AG10483

Dear Dr. Glickman:

The Office for Human Research Protections (OHRP) has reviewed the New York University School of Medicine's (NYU) April 29, 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 46.111(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 7, 2002 letter, OHRP expressed concern that the NYU IRB may have failed to ensure that this requirement was satisfied for the above-referenced research.

OHRP finds that NYU has adequately responded to this concern. Furthermore, OHRP acknowledges that the NYU 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 procedures to be followed and identification of any procedures which are experimental. OHRP finds that the informed consent documents approved by the NYU IRB for the above-referenced research 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; and (ii) the NYU IRB will include descriptions of the involvement of caregivers in the informed consent documents for future studies. OHRP finds that this corrective action adequately addresses the above finding.

(3) HHS regulations at 45 CFR 46.116 require that informed consent be in language understandable to the subject or their legally authorized representative. OHRP finds that certain terminology in the IRB-approved informed consent document for the above- referenced research failed to meet this requirement.

Corrective Action: OHRP acknowledges NYU's commitment to ensuring that informed consent documents are in language understandable to the subject or the subject's legally authorized representative. OHRP also acknowledges that NYU has revised its IRB policies and procedures as well as its standard IRB forms an templates to address this issue. OHRP finds that this corrective action adequately addresses the above finding.

(4) OHRP finds that NYU has adequately responded to the additional concerns and questions raised in OHRP's February 7, 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:

(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 7, 2002 letter to NYU, 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 the following statements in NYU's April 29, 2002 report:

(a) "At the time this clinical trial was conducted, however, estrogen therapy was not recognized as an established, effective treatment for Alzheimer's disease"

(b) "We believe that, under these circumstances, it would have been inappropriate to identify in the consent document what was, at the time, a totally unproven treatment as an alternative therapy."

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 Food and Drug Administration, it may be appropriate to disclose that use as an alternative treatment to the 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,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Mr. Mark Brody, NYU

Ms. Kay Ryan, NYU
Dr. Keith Krasinski, NYU
Dr. Steven Ferris, NYU
Commissioner, FDA
Dr. David Lepay, FDA
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