DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 301-435-0062
FAX: 301-402-2071

May 9, 2002

Dr. Thomas Q. Morris
Vice President, Health Sciences Division
Columbia University College of Physicians and Surgeons
630 West 168th Street, P & S 3-460
New York, NY 10032

Mr. Herbert Pardes, President and CEO
New York-Presbyterian Hospital
161 Fort Washington Avenue
14th Floor
New York, NY 10032

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1356

Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estrogen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease (IRB Number 7306)
Principal Investigator: Mary Sano, Ph.D.
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. Sohn and Mr. Pardes:

The Office for Human Research Protections (OHRP) has reviewed Columbia Presbyterian Medical Center's (CPMC's) March 26, 2002 report in response to OHRP's February 19, 2002 letter to CPMC concerning the above research study.

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) and (2) require that when seeking informed consent each subject be provided with, among other things, (i) a description of the procedures to be followed, (ii) identification of any procedures which are experimental, and (iii) a description of any reasonably foreseeable risks or discomforts to the subject. OHRP finds that informed consent documents approved by the CPMC's Institutional Review Board (IRB) for the above-referenced research failed to include (a) a description of the procedure and risks for performing 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 none of the eight subjects enrolled in this research at CPMC received a lumbar puncture procedure, and (iii) CPMC's statements that consent documentation approved by the IRB should have described the procedure and risks of lumbar puncture and the procedures for caregivers to complete questionnaires related to the subject. OHRP further acknowledges that (i) CPMC's informed consent template states that any potential discomfort or risk most be included in the consent documentation and (ii) CPMC has added a second IRB to facilitate more thorough IRB review of informed consent documentation. OHRP finds these corrective actions to be satisfactory and appropriate under the CPMC MPA.

(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 19, 2002 report OHRP expressed concern that the subjects of the above-described research, because of their potentially impaired mental state, were likely vulnerable to coercion or undue influence.

OHRP finds that CPMC has adequately responded to this concern. OHRP acknowledges that CMPC's policies and procedures call for IRB consideration of additional safeguards for subjects with degenerative mental disease who are able to give informed consent initially but subsequently become incompetent. These protections include: (i) an independent assessment of mental capacity, (ii) ongoing monitoring and reassessment of capacity, and (iii) use of a legally authorized representative, health care proxy or advocate to protect subjects' ability to withdraw from a study.

(3) OHRP finds that CPMC adequately responded to the additional concerns raised in OHRP's February 19, 2002 letter to CPMC.

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 CPMC's March 26, 2002 report:

(4) HHS regulations at 45 CFR 46.103(a) and 103(b)(4)(iii) require that institutions have written IRB procedures for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject. OHRP notes that CPMC's policies and procedures do not identify which office or institutional official is responsible for promptly reporting to the IRB, appropriate institutional officials, any supporting Agency or Department heads, and OHRP any (i) unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval.

OHRP appreciates the commitment of CPMC to the protection of human research subjects. Please do not hesitate to contact me if you have any questions.

Sincerely,

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

cc: Mr. Paul Papagni, IRB Executive Director, CPMC
Dr. Andrew Witt, IRB 1 Vice Chair, CPMC
Dr. James Garven, IRB 2 Vice Chair, CPMC
Dr. Mary Sano, CPMC
Dr. Richard Sohn, CPMC
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Jeffrey Cohen, OHRP
Ms. Yvonne Higgins, OHRP
Mr. George Gasparis, OHRP
Mr. Barry Bowman, OHRP