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: 301-435-0668
FAX: 301-402-2071
E-mail: pmcneilly@osophs.dhhs.gov

April 29, 2002

Chi Van Dang, M.D., Ph.D.
Vice Dean for Research
The Johns Hopkins University
School of Medicine
Administration Building, Room 124
720 Rutland Avenue
Baltimore, MD 21205-2196

Ronald R. Peterson
President
The Johns Hopkins Hospital
Houck Building, Room 160
600 North Wolfe Street
Baltimore, MD 21287-1160

Michael Klag, M.D.
Vice Dean for Clinical Investigation
The Johns Hopkins University
School of Medicine
Administration Building, Room 124
720 Rutland Avenue
Baltimore, MD 21205-2196

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1011

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 #:	**HBV95-07-05-02**
Principal Investigator:	**Claudia Kawas, M.D.**

HHS Project Number: U01-AG10483

Dear Dr. Dang, Dr. Klag, and Mr. Peterson:

The Office for Human Research Protections (OHRP) has reviewed the Johns Hopkins School of Medicine's (JHU's) April 26, 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 JHU IRB may have failed to ensure that this requirement was satisfied for the above-referenced research.

OHRP finds that JHU has adequately responded to this concern. Furthermore, OHRP acknowledges that the JHU 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 JHU 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 JHU corrective action plan submitted following OHRP's July 2001 site visit adequately addresses the above finding.

(3) OHRP finds that JHU 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 JHU, 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 statement in JHU's April 26, 2002 report:
>
> > "The use of estrogens for dementia was unproven and not approved fro the treatment of dementia. Although estrogen treatment was theoretically available, it did not seem to be a realistic alternative, as it was not being used in the community for this purpose. If included as an alternative in the consent form it would have to be described as an experimental 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 FDA, 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: Dr. Martha Hill, Interim Dean, School of Nursing, JHU
Dr. Jacquelyn Campbell, School of Nursing, JHU
Dr. Gary W. Goldstein, President, Kennedy Krieger Institute

Ms. Karen Cox, Research Administrator, Kennedy Krieger Institute
Dr. Darrell R. Abernethy, Clinical Director, NIA
Dr. Vincent L. Pisacane, Director, Institute for Advanced Science and Technology in Medicine, Applied Physics Laboratory
Mr. David Grant, Applied Physics Laboratory
Ms. Barbara L. Starklauf, Administrator, Human Subjects Committees, JHUSOM
Dr. Lewis Becker, Chairman, JCCI -I, JHUSOM
Dr. David R. Cornblath, Chairman, JCCI-II, JHUSOM
Dr. Paul Lietman, Chairman, JCCI-III, JHUSOM
Dr. Hayden Braine, Chairman, JJJC-IV, JHUSOM
Dr. Gary Briefel, Chairman, JHBMC-1 IRB
Dr. Claudia Kawas, JHU
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Greg Koski, OHRP
Dr. Melody Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. George Gasparis, OHRP
Dr. Harold Blatt, OHRP
Mr. Barry Bowman, OHRP