DEPARTMENT OF HEALTH & HUMAN SERVICES **PUBLIC HEALTH SERVICE**

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 301-435-8072
FAX: 301-402-2071
E-mail: borrork@od.nih.gov

March 26, 2002

James Wagner
Interim President
Case Western Reserve University
10900 Euclid Avenue
Cleveland, OH 44106-7004

Farah M. Walters
President and CEO
University Hospitals of Cleveland
11100 Euclid Avenue
Cleveland, OH 44106-5001

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1521

Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estorgen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease
Research Publication: Estrogen Replacement Therapy for Treatment of Mild to Moderate Alzheimer Disease: A Randomized Controlled Trial, Mulnard, et al. JAMA 2000; 283: 1007-15.
Principal Investigator: Elisabeth Koss, Ph.D.
Protocol Number: 07-95-46

Dear Mr. Wagner and Ms. Walters:

The Office for Human Research Protections (OHRP) has reviewed the Case Western Reserve University's (CWRU) and University Hospitals of Cleveland's (UHC) report dated March 10, 2002, that was submitted in response to OHRP's February 5, 2002 letter to CWRU regarding the above-referenced research. Based upon its review, OHRP makes the following determinations regarding the above-referenced research:

(1) 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 5, 2002 letter, OHRP expressed concern that the CWRU IRB failed ensure that this requirement was satisfied for the above-referenced research.

OHRP finds that CWR and UHC have adequately responded to this concern. In particular, OHRP acknowledges that the UHC IRB now specifically requests additional information regarding vulnerable populations and reviews this documentation of additional safeguards in the protocol to ensure that these subjects are adequately protected. In addition, education of investigators via written materials and seminars include information on protecting vulnerable subjects. OHRP also acknowledges that it has been standard practice of the Alzheimer Center to conduct baseline mental capacity assessments for all subjects included in the Alzheimer Center Research Registry.

(2) OHRP finds that the informed consent documents reviewed and approved by the IRB for this study failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116 (a):

> (a) Section 46.116(a)(1): an explanation of the purposes of the research, and a complete description of the procedures to be followed, and identification of any procedures which are experimental. In particular, OHRP notes the following:
>
> > (i) The informed consent document did not mention that one of the purposes of the research was to determine the safety and tolerability of the intervention. OHRP acknowledges that the UHC investigators and IRB believed that determining the safety and tolerability was not one of the purposes of the research. However, the IRB-approved protocol clearly stated that an objective of the study was "to establish the safety and tolerability of ERT in elderly female AD patients."
> >
> > (ii) There was no mention in the informed consent document about the role of the caregiver, in filling out quality-of-life and pharmacoeconomic questionnaires related to the subject's condition and care. OHRP acknowledges that in 1996-1997 it became standard practice in the Alzheimer Center to include a separate section or a separate consent form for caregivers and that caregivers were fully informed of their participation. OHRP notes that providing the caregiver with a separate consent is not sufficient to ensure informed consent from the primary subject. The primary subject should have been informed in the informed consent document that others will be providing information about her for the research.

Required Action: By April 23, 2002, please provide OHRP with a satisfactory corrective action to address the above findings. In addition, please provide a copy of the caregiver informed consent document for this research and clarify whether it was reviewed and approved by the UHC IRB.

(3) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB Chair or another IRB member designated by the Chair, continuing review must occur no more than one year after the date the protocol was reviewed by the convened IRB, not on the anniversary of the date the IRB Chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP finds that the UHC IRB apparently failed to conduct continuing review of this research at least once per year. The protocol was initially reviewed and approved August 1, 1995. The next continuing review did not occur until November 19, 1996 (more than a year later.)

Corrective Action: OHRP acknowledges UHC's assertion that the process and timeliness for continuing review of approved protocols has been significantly improved, and that the current practice of the UHC IRB is to send reminder notices to investigators ten and six weeks prior to the expiration of their protocols. In addition, UHC policy dictates that protocols that have passed their expiration dates and have not received appropriate continuing review receive deferment and termination notices. This corrective action adequately addresses the finding and is appropriate under the CWRU and UHC MPA.

(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 5, 2002 letter to UK, 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.

UK's report stated the following in response:

> The benefits of estrogen replacement therapy (ERT) to treat the symptoms and progressions of Alzheimer's disease were not known at the time of the study. Approved indications for the use of ERT included only vasomotor symptoms associated with menopause and osteoporosis prevention...Thus, at the onset of the estrogen study, the use of ERT in the treatment of Alzheimer's disease did not have an established indication and its risk/benefit ratio for Alzheimer's disease was not established.

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, the fact that a given treatment's risk/benefit ratio for a given indication is not known does not necessarily mean it should not be disclosed to subjects as an alternative. 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 looks forward to receiving UHC's and CWRU's response to the above determination by April 23, 2002.

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,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Christian LaMantia, CWRU
Mr. Terry R. White, MetroHealth System
Mr. William D. Montague, Louis Stokes Dept of VA Medical Center
Dr. William Dahms, IRB Chair, UHC
Mr. Philip A. Cola, UHC
Dr. Elisabeth Koss, CWRU
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
Dr. Michael A. Carome, OHRP
Dr. Melody H. Lin, OHRP
Mr. George Gasparis, OHRP
Dr. Harold Blatt, OHRP