DEPARTMENT OF HEALTH & HUMAN SERVICES

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March 25, 2002

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Robert R. Rich, M.D.
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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1426

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
Principal Investigator: Robert C. Green, M.D.; Allan Levey, M.D.
IRB Protocol #: HIC 498-95
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. Johns and Dr. Rich:

The Office for Human Research Protections (OHRP) has reviewed the Emory University's (EU's) March 6, 2002 report that was submitted in response to OHRP's February 5, 2002 letter regarding the above-referenced research.

Based upon its review, OHRP makes the following determinations:

(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 5, 2002 letter, OHRP expressed concern that the EU IRB may have failed to ensure that this requirement was satisfied for the above-referenced research.

OHRP finds that EU has adequately responded to this concern. Furthermore, OHRP acknowledges that the EU 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.

(a) OHRP acknowledges that (i) the EU IRB approved an informed consent document that made reference to the procedure for the lumbar puncture (LP) procedure and described in detail the risks associated with the LP; and (ii) all subjects enrolled in the research at EU declined to undergo this procedure. However, OHRP finds that the informed consent document approved by the EU IRB failed to adequately describe the procedure to be followed for performing the LP.

(b) OHRP finds that the IRB-approved informed consent documents failed to describe 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) since the above-referenced research was reviewed by the EU IRB, EU has developed and implemented training and education programs for IRB members that address the required elements of informed consent. OHRP finds this corrective action to be satisfactory and appropriate under the EU MPA.

(3) 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 EU, 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:

> "It is true that the alternative section did not mention that subjects could receive estrogen outside the protocol. According to our current standards this was an omission. More recently we have been asking Pis, for studies in which all the study agents are approved by the FDA, to include in the alternative section a statement that the patients may receive the drugs off-study."

OHRP finds that EU's response adequately addresses OHRP's concern.

(4) In its February 5, 2002 letter to EU, OHRP expressed concern that the continuing review of research by the EU IRB was not substantive and meaningful. OHRP finds that the continuing review procedures used by the EU IRBs for the past several years have been substantive and meaningful.

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.

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

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Mr. Robert Perreault, Medical Center Director, Atlanta Veterans Affairs Medical Center
Dr. Robert J. Pollett, President, Atlanta Research and Education Foundation
Mr. Antonio J. Laracuente, Atlanta Veterans Affairs Medical Center
Dr. James W. Keller, Chair, IRB, Emory University School of Medicine
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