DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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April 2, 2002

George E. Walker, Ph.D.
Vice President for Research and
Dean of the Graduate School
Indiana University
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Bryan Hall, Room 104
Bloomington, Indiana 47405-1201

Stuart A. Kleit, D.D.S., M.D.
Executive Vice President
Clarian Health Partners, Inc.
Fesler Hall, Room 302
1120 W. South Drive
Indianapolis, Indiana 46202-5113

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1167

Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estrogen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease
Principal Investigator: Martin R. Farlow, M.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. Walker and Dr. Kleit:

The Office for Human Research Protections (OHRP) has reviewed Indiana University's (IU's) March 14, 2002 report that was submitted in response to OHRP's February 7, 2002 letter to IU regarding the allegations of possible noncompliance with the Department of Health and Human

Services (HHS) regulations for protection of human subjects (45 CFR Part 46) involving the above-referenced research.

Based upon its review, OHRP makes the following determinations:

(1) 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 7, 2002 letter, OHRP expressed concern that the IU Institutional Review Board (IRB) may have failed to ensure that this requirement was satisfied for the above-referenced research.

OHRP finds that IU has adequately responded to this concern. Furthermore, OHRP acknowledges that the IU 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 a description of the procedures to be followed and identification of any procedures which are experimental. OHRP finds that the informed consent document approved by the IU IRB for the above reference research failed to include a description of the procedure for having the subject's caregiver (a) accompany the subject to all clinic visits; (b) store and administer the study drug to the subject; and (c) fill out quality-of-life and pharmacoeconomic questionnaires related to the subject's condition and care.

(3) HHS regulations at 45 CFR 46.116(a)(2) require that when seeking informed consent, each subject be provided with a description of any reasonably foreseeable risks and discomforts. OHRP finds that subject BH was not provided with the IRB-approved consent document that was updated to include the added risk of deep vein thrombosis associated with estrogen therapy.

Corrective Action: OHRP acknowledges that the research has been completed. OHRP also acknowledges that the current IU IRB procedures now require that (i) if a subject's participation is contingent upon another person's involvement in the research procedures (e.g., caregiver), a statement must be included to inform the subject regarding what will be expected of the other participant; and (ii) if new risks are identified during the course of the research, the enrolled subjects will be notified and asked to sign an updated consent document outlining such risks. OHRP further acknowledges that IU has developed and implemented training and education programs for IRB members that address the required elements of informed consent. OHRP finds these corrective actions to be satisfactory and appropriate under the IU MPA.

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 IU's March 14, 2002 report:

(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 of courses of treatment, if any, that might be advantageous to the subject. In its February 7, 2002 letter to IU, OHRP expressed concern that the IRB-approved informed consent document for the above-referenced research did not describe the alternative of receiving estrogen replacement therapy outside of the research.

IU's report stated the following in response:

> "OHRP is correct that this alternative was not included in the informed consent document. However, the whole purpose of the estrogen trial was to determine whether or not estrogen therapy might positively affect the symptomatology and course of the dementing illness in hysterectomized women with Alzheimer's Disease. Estrogen replacement therapy was not an approved treatment for Alzheimer's Disease and it would have been improper, in the IRB's view, for the informed consent documents to indicate that subjects could also seek therapeutic benefit for their Alzheimer's disease through estrogen use outside of the study. Further, for the investigator or the informed consent document to discuss other approved and accepted therapeutic uses of estrogen (e.g., bone protection, cardiovascular benefit, bladder support) would also have been

improper and unrelated to the focus of this investigation and irrelevant for subjects wishing to participate in a study related to their diagnosis of Alzheimer's Disease."

OHRP acknowledges IU's statement. 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 subjects in the informed consent document.

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

Sincerely,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Mark L. Brenner, Vice Chancellor for Research and Graduate Education, Associate Vice President for Research, IU
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