DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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April 3, 2002

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Ronald G. Evens, M.D.
President
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Ted W. Fry
President
St. Louis Children's Hospital
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St. Louis, MO 63110

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1123

Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estrogen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease

Principal Investigator: John C. Morris, 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. Peck, Dr. Evens and Mr. Fry:

The Office for Human Research Protections (OHRP) has reviewed Washington University School of Medicine's (WUSM's) report of March 13, 2000 that was submitted in response to OHRP's February 7, 2000 letter to WUSM 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 46.116(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 expressed concern that the informed consent documents approved by the WUSM Institutional Review Board (IRB) failed to include an adequate description of the procedure for performing a lumbar puncture.

(2) 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 expressed concern that the informed consent documents approved by the WUSM IRB failed to adequately describe the risks of a lumbar puncture procedure.

OHRP acknowledges WUSM's report that (a) the performance of lumbar punctures for cerebrospinal fluid collection was not included as a component of the subject research at WUSM; and (b) lumbar puncture procedures were not performed on the six enrolled subjects at WUSM.

(3) HHS regulations at 45 CFR 46.116(b)(5) require informed consent documents to include, when applicable, a statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject. The initial and revised IRB-approved consent forms contained the statement:

> "You will be informed of any significant new finding developed during the course of your participation in this research which may have a bearing on your willingness to continue to participate." OHRP finds that enrolled subjects were not provided with additional information regarding the added risks of blood clot formation and stroke associated with estrogen therapy or asked to sign revised consent documents.
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> **Corrective Action:** OHRP acknowledges that the research has been completed. OHRP also acknowledges that the current WUSM IRB policies and procedures now require that enrolled subjects be re-consented should new information become available which may bear upon the willingness of those individuals to continue to participate in the research. OHRP finds this corrective action to be satisfactory and appropriate under the WUSM 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 WUSM's March 13, 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, 2000 letter to WUSM, OHRP expressed concern that the WUSM IRB-approved informed consent document did not describe the alternative of receiving estrogen replacement therapy outside of the research.
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> WUSM's report stated the following in response:
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> > "WUSM investigators did not include estrogen in the informed consent document as an alternative therapy for dementia, because the investigators addressed only those agents approved and available for dementia treatment at the time of the trial.
> >
> > The investigators considered it improper to suggest in the consent document that subjects could seek therapeutic benefit for their Alzheimer's disease through the unapproved use of estrogen outside the study."
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> OHRP acknowledges WUSM'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 WUSM 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: Ms. Patricia M. Scannell, IRB Administrator, WUSM
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