DEPARTMENT OF HEALTH & HUMAN SERVICES

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October 15, 2001

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Daniel L. Longo, M.D.
Scientific Director
National Institute on Aging
5600 Nathan Shock Drive, Room 1E07
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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1011

Research Project:	**Effects of Sex Hormones on Cognition and Mood in Older Adults**
Protocol #:	**RPN 95-12-15-05**
PI:	**Dr. Pauline Maki**

Dear Dr. Dang and Dr. Longo:

The Office for Human Research Protections (OHRP) has reviewed your January 9, 2001 report involving the above-referenced research. OHRP notes the following:

(1) OHRP acknowledges that the inclusion criteria for the above-referenced research included a requirement for a score of greater than the 25th percentile for age and education on the Mini-Mental State Exam. Potential subjects with serious memory problems should be excluded from participation in the research. Even with the use of the Mini-Mental State Exam, OHRP continues to have concerns about the possibility of the enrollment of subjects with diminished cognitive function.

OHRP also notes that as part of the annual renewal form dated October 27, 1999 for the above-referenced research, a subject in the testosterone arm of the study was ordered withdrawn from the study by the Clinical Director of the National Institute on Aging due to concerns about the subject's competency to consent. This withdrawal was ordered even though the subject may have met the criteria for inclusion in the study. This suggests that it is possible to have problems with the ability to consent without being diagnosed with dementia.

(2) HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, the IRB must review proposed research at convened meetings at which a majority of the members are present, including at least one member whose primary concerns are in nonscientific areas. OHRP finds that the Johns Hopkins University (JHU) Institutional Review Board (IRB) failed to review the research, which was not eligible for expedited review under HHS regulation at 45 CFR 46.110(b), at a convened meeting. As a result, the JHU IRB failed to ensure that all criteria required for IRB approval under HHS regulations at 45 CFR 46.111 were satisfied. Of note, the minutes of the JHU IRB meetings on August 13, 1996 indicated that no review took place at the convened meeting for the initial review of this protocol.

OHRP notes that the issue of failure to review research at a convened meeting of the IRB is currently being addressed by JHU as part of its corrective action plan in response to OHRP's determination letter of July 19, 2001.

(3) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116 require that information given to the subject or their representative shall be in language understandable to the subject or representative. OHRP notes that the informed consent documents approved by the JHU IRB for use from January 23, 1996 through November 24, 1998 included the following statements:

> (a) "Nonhysterectomized women will also receive Provera, a progestin compound."
>
> (b) "Studies show that women who take only estrogen as a hormone replacement will, on average, have twice the risk of developing endometrial cancer as women who take no estrogen. However, if progestins are taken along with estrogen and women are carefully followed by their physician, the risk of endometrial cancer is

not increased. If you have not had a hysterectomy you will receive both estrogen and progestin."

(b) "You may find some neuropsychological tests to be anxiety-provoking or frustrating."

(c) "Those who select the androderm patch form of administration will then be given a 3-month supply of either androderm patch or placebo."

OHRP finds that the language of the informed consent documents approved for use by the JHU IRB from January 23, 1996 through November 24, 1998 is complex and would not be understandable to many of the subjects. Furthermore, OHRP notes that 36 subjects were enrolled during this time frame. OHRP also notes that all informed consent documents approved after November 24, 1998 for the above-referenced research appear to meet the requirements of 45 CFR 46.116.

Additionally, OHRP notes that during the initial review process for this protocol one member of the IRB raised a question regarding the use of the term "nonhysterectomized women" in the informed consent document. This concern was not brought to the principal investigator's attention in the January 4, 1996 letter from Dr. Becker to Dr. Brandt. As a result, this issue was not addressed by the IRB in any subsequent correspondence or meeting.

(4) Based on the following information, OHRP finds that the informed consent document prior to April 5, 1999 for the above-referenced research failed to provide an adequate description of the reasonably foreseeable risks or discomforts to the subjects as required by HHS regulations at 45 CFR 46.116(a)(2).

(a) A copy of the protocol submitted as part of your January 9, 2001 report states, "Some women experience vaginal bleeding, breast tenderness, headache, mood changes, nausea, bloating, weight changes, changes in sleeping patterns, or changes in sex drive."

(b) None of these problems were mentioned in the informed consent document prior to April 5, 1999.

(c) The third year renewal form dated October 15, 1998 indicated that three women were withdrawn from the study due to breakthrough endometrial bleeding.

(5) Based on the following information OHRP finds that the informed consent document for the above-referenced research failed to adequately describe the reasonable expected benefits from the research as required by HHS regulations at 45 CFR 46.116(a)(3):

(a) The informed consent document approved for use by the JHU IRB from January 23, 1996 through November 24, 1998 for the above- referenced research states, "Testosterone may increase bone density and improve sexual function. In addition, it may decrease serum HDL-cholesterol, but this decrease is generally less than 5%."

(b) The duration of testosterone replacement during the study is three months, which is unlikely to significantly alter bone density in these subjects.

OHRP is aware that the above referenced research is closed to enrollment and all subjects have completed the study. As a result of changes made to the informed consent documents during the course of the research and the actions of the JHU IRB as part of JHU's corrective action plan in response to OHRP's determination letter of July 19, 2001, there should be no need for further involvement of OHRP in this matter.

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: Mr. Ronald R. Peterson, President, The Johns Hopkins Hospital
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