**DEPARTMENT OF HEALTH & HUMAN SERVICES**

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**Office of Public Health and Science**

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September 9, 2005

Mark A. Emmert, Ph.D.
President
University of Washington
Office of the President
301 Gerberding Hall
Box 351230
Seattle, Washington 98195-1230

**RE: Human Research Subject Protections Under Federalwide Assurance FWA-6878**

**Research Project: Genetic Analysis in Hereditary Neuropathy**
**Principal Investigator: Phillip Chance**
**Project Number: 28-0342-B**

Dear Dr. Emmert:

The Office for Human Research Protections (OHRP) has reviewed the University of Washington's (UW) letter dated April 27, 2005, submitted in response to OHRP's letter dated April 1, 2005, that contained the findings from the February 23-25, 2005 on-site evaluation of human subject protections.

In its April 1, 2005 letter, OHRP made the following findings:

(1) OHRP found that the IRB frequently approves research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. OHRP notes that when the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111, IRB approval of the proposed research should be deferred, pending subsequent review of responsive material by the convened IRB.

**Corrective Action:** UW indicated in its April 27, 2005 response that all researchers with current IRB-approved projects were informed via email about the restriction of contingent approvals to "minor changes." UW also indicated that UW plans to revise its policies

and procedures to indicate that approval of a proposed research activity must be deferred when there are substantive concerns about the activity, and that approval will be subject to the convened IRB's review of the investigator's responses to the questions posed. UW stated that the Human Subjects Division "has modified its procedures by requiring that all research about which the IRBs have substantive concerns *regarding the safety and welfare of subjects* [emphasis added] will be re-reviewed at a convened meeting of the IRB after a response from the researcher has been received."

HHS regulations at 45 CFR 46.111(a) require the IRB to make seven determinations in order to approve proposed research. HHS regulations at 45 CFR 46.111(b) require the IRB to make an additional determination for research involving subjects who are likely to be vulnerable to coercion or undue influence. OHRP notes that except for research eligible for expedited review, these determinations must be made by the IRB at a convened meeting. OHRP suggests that UW procedures be modified to indicate that if the IRB has substantive concerns or requests substantive clarifications related to *any* of the required determinations under 45 CFR 46.111, the study may not be approved and must be re-reviewed at a convened meeting of the IRB after a response from the researcher has been received.

(2) HHS regulations at 45 CFR 46.115(a)(2) require that, among other things, minutes of IRB meetings be in sufficient detail to show actions taken by the IRB; the basis for requiring changes in or for disapproving research; and a written summary of the discussion of controverted issues and their resolution. OHRP found that IRB minutes often did not meet these requirements.

**Corrective Action**:
UW indicated in its April 27, 2005 response that it is modifying the template for meeting minutes to include the required elements in 46.115(a)(2), as well as an indication of what information should come back to the IRB for review at a convened meeting.

OHRP notes that the draft minutes template includes a general entry entitled "Summary of Discussion." However, OHRP notes that the template does not contain an entry for the documentation of specific IRB findings or any indication of how findings will be documented.

(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 chairperson or another IRB member designated by the chairperson, continuing review must occur no more than one year after the date on which the protocol was reviewed by the convened IRB, not on the anniversary of the date on which the IRB chairperson or his or her designee verified that IRB-specified conditions for approval have been satisfied. OHRP found that the IRB consistently assigns an anniversary date that is one year from the date that an IRB member verifies that

contingencies have been satisfied, rather than using the date of the convened meeting at which approval occurs.

**Corrective Action:** UW indicated in its response dated April 27, 2005 that a database search was performed to identify all studies that were assigned anniversary dates more than 365 days from the date of the IRB meeting in which they were approved. The principal investigators of the lapsed studies were contacted, were asked to submit a continuing review application by April 17, 2005, and were informed that research activities could continue only if the IRB determined that it was in the best interest of the subjects to continue participating in the research interventions or interactions.

(4) OHRP found that the following unanticipated problem involving risks to subjects or others was not promptly reported to OHRP, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5): On October 20, 2004 and November 17, 2004, UW IRB Committee A reviewed a Modification Form containing a report of an unanticipated problem for a study entitled "Immune Determinants Favoring Non-Progression in HIV-1 Infection." The IRB reviewed the information provided about the problem, as well as various versions of a letter to be sent to study participants. After an investigation, the institution determined that confidential subject contact information was inappropriately used by a member of the study staff.

**Corrective Action:** OHRP received a report dated July 25, 2005 regarding the above unanticipated problem involving risks to subjects or others.

(5) OHRP found that UW did not have written IRB procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

> (a) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.
>
> (b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any department or agency head, and OHRP of: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

**Corrective Action:** OHRP acknowledges that UW has developed the following draft policies and procedures to address the above findings: IRB-D.6.0, entitled "Reporting to Institutional Official and External Regulatory Agencies," and IRB-D.9.1, entitled "Verification of research activities since previous IRB review."

(6) HHS regulations at 45 CFR 46.305-306 require specific findings on the part of the IRB for approval of research involving prisoners. OHRP's discussions with IRB members and its review of IRB documents revealed little evidence that the IRB makes

the required findings when reviewing such research.

**Corrective Action:** UW provided information in its April 27, 2005 letter about three studies that proposed to enroll prisoners. In one study, "Role of Attachment in Early Onset of Conduct Problems," at least seven incarcerated subjects were interviewed prior to subpart C certification and a response from OHRP. UW stated that the principal investigators were notified that all activity with incarcerated subjects must cease until OHRP received and responded to the Subpart C prisoner certifications. OHRP notes that it has received and has responded to prisoner certifications for these three studies.

While OHRP acknowledges your statement that all three studies were reviewed in the presence of a prisoner advocate, OHRP notes that HHS regulations at 45 CFR 46.305(a)(1) - (7) enumerate additional duties of the IRB when prisoners are involved. OHRP acknowledges that UW has implemented an electronic system and a checklist that will prompt the investigators to provide information about the involvement of prisoners in research, and will prompt the IRBs to make and document the required findings in Subpart C.

(7) HHS regulations at 45 CFR 46.115(a) require that the institution prepare and maintain adequate documentation of IRB activities. In numerous instances found in the IRB files that OHRP examined, it was difficult to reconstruct a complete history of all IRB actions related to the review and approval of the protocol.

**Corrective Action:** UW has developed an information sheet outlining how the files are constructed.

OHRP finds that the corrective actions described above adequately address the corresponding seven findings above, and that they are appropriate under UW's Assurance.

OHRP expressed the following concerns in its April 1, 2005 letter:

(8) Based on its discussions during the site visit and on OHRP's courtesy copy of a letter dated March 24, 2005 that was sent to the Institutional Official from the Chairperson and Administrator of UW IRB Committee A, regarding a report of continuing noncompliance and the suspension of new enrollment for the study entitled "Genetic Analysis in Hereditary Neuropathy," OHRP expressed concern that Dr. Craig Hogan, the Institutional Official for the UW FWA, may have inappropriately interfered with the authority of Committee B to require modifications to and to disapprove research activities, when he reassigned protocol review from Committee B to Committee A. In addition, OHRP expressed concern that Dr. Hogan may have undermined the independence of the IRBs when he failed to support and facilitate the UW IRBs' federally mandated authority and decisions in the above action.

**Corrective Action:** UW stated in its April 27, 2005 response that the reassignment of the study from Committee B to Committee A did not comply with UW policy. UW stated that it will develop and provide enhanced regulatory education and training for all

IRB members, Human Subjects Division staff, investigators, and others, as appropriate; and that the enhanced training will encompass education on issues raised in #8 abovand #9 below.

OHRP notes that, according to the terms of your Assurance with OHRP, the Institutional Official is responsible for:

- Setting the tone for an institutional culture of respect for human subjects;
- Ensuring effective institutionwide communication and guidance on human subjects research;
- Ensuring that investigators fulfill their responsibilities under the assurance;
- Facilitating participation in human subject education activities;
- Serving as a knowledgeable point of contact for OHRP, or designating another individual to serve in his or her capacity;
- Providing the IRB with necessary resources and staff; and
- Supporting IRB authority and decisions.

OHRP recommends that the Institutional Official be included in regularly scheduled and enhanced education and training made available to others at UW.

(9) OHRP expressed concern that the UW policy above entitled "Appeal Process" does not seem to conform to the regulatory requirements in 45 CFR 46.112. The appeals process outlined in the UW policy seems to attempt to inappropriately grant approval authority to a committee other than the IRB, when research has not been approved by the IRB.

**Corrective Action:** OHRP acknowledges UW's statement in its April 27, 2005 response that it has developed a new appeals process that is internal to each UW IRB and that clarifies that, in the case of a decision by an IRB to disapprove, suspend, or terminate a project, the IRB decision may not be reversed by the Institutional Official or any other official or agency of UW. UW stated that this draft policy is currently implemented on a provisional basis.

(10) OHRP asked UW to explain the manner in which the IRBs ensure that they make the required findings in subpart D of 45 CFR 46 (Additional Protections for Children Involved as Subjects in Research).

**Corrective Action:** OHRP acknowledges UW's statement in its April 27, 2005 response that the electronic submission system to which UW is converting will contain an application that elicits information from the investigator about the involvement of children in research. UW also stated that it has developed a Subpart D checklist that will ensure that the IRB makes and documents the required findings.

(11) OHRP expressed concern that some IRB members appear to lack a detailed understanding of the specific requirements of the HHS regulations for the protection of human subjects. As a result, IRB determinations at times may have deviated from these

requirements. OHRP requested a description of the continuing education that individuals involved in the support and review of human subjects research at UW receive regarding the specific regulatory provisions of 45 CFR part 46.

**Corrective Action:** UW described in its April 27, 2005 response its current and planned initial and continuing education for IRB chairpersons, members, and staff.

(12) OHRP expressed concern that there appears to be boilerplate informed consent formatting that may be confusing to subjects. For example, the benefits section is often appended to the purpose section. In addition, alternatives to participation are often difficult to locate in the informed consent document.

**Corrective Action:** OHRP acknowledges UW's statement in its April 27, 2005 response that it has drafted a revised consent form template to address the concerns above, and that this template is now posted on the UW Web site.

OHRP would like to comment on the following statement made by UW: "HSD staff has been instructed to be even more attentive to the clarity of the consent materials with regard to the potential benefits of the research and the alternatives to participation as well as all the other required elements of consent." OHRP suggests that the above-referenced instruction be directed toward IRB members.

(13) HHS regulations at 45 CFR 46.116(d) require that the IRB find and document four specific criteria when approving a waiver or alteration of some or all of the required elements of informed consent. HHS regulations at 45 CFR 46.117(c) require specific findings on the part of the IRB in order to grant a waiver of the usual requirement that the investigator obtain a signed consent form from all subjects.

Citing a specific example, OHRP expressed concern that the IRB does not adequately understand the difference between the waiver of informed consent and the waiver of the documentation of informed consent. Regarding the specific example cited, OHRP acknowledges UW's statement in the April 27, 2005 response that "although the appropriate findings were made by the IRB, they were not appropriately documented in the IRB's approval letter to the researcher or in the minutes of the meeting."

OHRP finds that the UW Committee C did not document the required findings for waiver of informed consent in the study entitled "The Middle School Literacy Coach: Roles, Contexts and Influence on Teaching."

**Corrective Action:** OHRP acknowledges UW's statement in its response that two review checklists have been developed to ensure that the IRB has made and documented the appropriate findings.

(14) OHRP finds that IRB members were not advised of (a) research protocols approved at the time of initial or continuing review under an expedited review procedure, or (b) minor changes in research protocols approved under an expedited review procedure, as

required by HHS regulations at 45 CFR 46.110(c).

**Corrective Action:** OHRP acknowledges UW's statement in its April 27, 2005 response that it expects by July 1, 2005 to have put in place a method to inform IRB members of the various items approved using an expedited review procedure.

OHRP finds that the corrective actions summarized above for items #8 - 14 above adequately address the concerns expressed in UW's April 1, 2005 letter and are appropriate under the UW Assurance.

**Additional OHRP Concerns**

Based on its review of the IRB files for the study entitled "Genetic Analysis in Hereditary Neuropathy," principal investigator Phillip Chance, OHRP would like to express the following additional concerns regarding the IRB reviews conducted by UW IRB Committee B between 1998 and 2004.

(15) [Redacted]

[Redacted]

(16) [Redacted]

(17) [Redacted]

(18) [Redacted]

[Redacted]

(19) [Redacted]

[Redacted]

[Redacted]

(20) [Redacted]

[Redacted]

(21) [Redacted]

[Redacted]

**Required Action:** Please provide responses to the findings, questions, and concerns in items #15 - 21 above by October 15, 2005.

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,

Karena Cooper, J.D., M.S.W.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Craig Hogan, Vice Provost, UW
Mr. David Thorud, Acting Provost, UW
Mr. Weldon E. Ihrig, Executive Vice President, UW
Ms. Helen McGough, HPA, UW
Dr. Zane A. Brown, IRB #1 Chairperson, UW
Dr. Alan J. Wilensky, IRB #2 Chairperson, UW
Dr. Patricia C. Kuszler, IRB #3 Chairperson, UW
Ms. Rebekah J. Rein, IRB #4 Chairperson, UW
Dr. Nancy M. Robinson, IRB #5 Chairperson, UW
Dr. Donald Sherrard, IRB #6 Chairperson, UW
Commissioner, FDA

Dr. David Lepay, FDA
Dr. Lana Skirboll, NIH
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Kristina Borror, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Janet Fant, OHRP