**DEPARTMENT OF HEALTH & HUMAN SERVICES**

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**Office of Public Health and Science**

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October 24, 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 October 7, 2005, submitted in response to OHRP's letter dated September 9, 2005. OHRP's September 9, 2005 letter indicated that UW's corrective actions adequately address the seven findings and concerns identified in the April 27, 2005 letter regarding the February 23-25, 2005 on-site evaluation of human subject protections.

OHRP notes that the additional corrective actions taken by UW as a result of suggestions and comments in items 1, 2, 8, and 12 of OHRP's Sept. 9, 2005 letter appear to be adequate under UW's Assurance.

OHRP makes the following additional determinations of noncompliance, previously expressed as additional concerns in its Sept. 9, 2005 letter, based on its review of the institutional review board (IRB) files for the study entitled "Genetic Analysis in Hereditary Neuropathy," principal investigator Phillip Chance.

(1) Continuing review of research must be substantive and meaningful. Department of Health and Human Services (HHS) regulations at 45 CFR 46.111 set forth the criteria

that must be satisfied in order for the IRB to approve research. OHRP finds that UW Committee B failed to conduct substantive and meaningful continuing review of the protocol entitled "Genetic Analysis in Hereditary Neuropathy" when it failed to question the investigator about enrollment totals presented at continuing review that did not correspond to the anticipated enrollment approved at initial review, and about enrollment numbers that did not follow from year to year.

The principal investigator indicated that he anticipated enrolling 100 normals/controls of all ages and 100 patients/cases of all ages in the IRB application for initial review in 1998. Below is the enrollment information listed on each renewal application.

1999 renewal:

# of subjects enrolled in study to date - 200 normals and 200 patients
# of subjects added during past year of approval - **15 normals and 10 patients**
# of subjects continuing participation - **100 normals and 100 patients**
# of subjects who will join study over the next year - 20 normals and 20 patients

OHRP notes that the IRB did not question the principal investigator as to why he enrolled 200 normals and 200 patients during the preceding year, when he indicated at initial approval that he anticipated enrolling 100 normals and 100 patients. There is no indication in the IRB file that the investigator obtained prior approval to exceed the enrollment limits approved at initial IRB review.

2000 renewal:

Total # of subjects enrolled in study to date - **"approximately 300**"

2001 renewal:

# of subjects you are approved to enroll - **"unlimited"**
# of subjects enrolled since initial approval - 150 normals and 150 patients
# of new subjects since last approval - 50 normals and 50 patients
# of subjects actively enrolled - 200 normals and 200 patients

OHRP notes that the investigator was not given prior approval to enroll an "unlimited" number of subjects. OHRP further notes that the IRB did not question the investigator about the increase from 200 total subjects at initial approval to an "unlimited" number of subjects.

2002 renewal:

# of subjects you are approved to enroll - "unlimited"

# of subjects enrolled since initial approval - **225 normals and 225 patients**
# of new subjects since last approval - 75 normals and 75 patients
# of subjects actively enrolled - 300 normals and 300 patients

2003 renewal:
# of subjects you are approved to enroll - "unlimited"
# of subjects enrolled since initial approval - 300 normals and 300 patients
# of new subjects since last approval - 20 normals and 80 patients
# of subjects actively enrolled - 320 normals and 380 patients

2004 renewal:
# of subjects you are approved to enroll - "unlimited"
# of subjects enrolled since initial approval - 320 normals and 380 patients
# of new subjects since last approval - 80 normals and 80 patients
# of subjects actively enrolled - 400 normals and 460 patients

Nov. 23, 2004 renewal:
# of subjects you are approved to enroll - "unlimited"
# of subjects enrolled since initial approval - **320 normals and 600 patients**
# of new subjects since last approval - 80 normals and 220 patients
# of subjects actively enrolled - 400 normals and 600 patients

OHRP notes that the enrollment numbers from one application to the next cannot be reconciled.

**Corrective Actions:** OHRP acknowledges UW's response as follows:

> The currently reviewing IRB has established and documented enrollment figures to the mutual satisfaction of the IRB and researcher. The researcher has committed to providing accurate documentation in the future. The IRB has committed to follow up on any inconsistencies in the future. In-service education is being provided to IRB members and staff regarding the importance of obtaining, reviewing, and documenting information about enrollment totals.

(2) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP is concerned that the principal investigator failed to obtain IRB review and approval to increase enrollment limits prior to enrolling additional subjects in 1999, 2000, and 2001.

**Corrective Actions:** OHRP acknowledges UW's response as follows:

> The principal investigator has been counseled (9-30-05) on the requirement to request IRB review and approval before making any changes in his research and has agreed to comply with this process in future. The IRB will conduct a post-approval monitoring visit of the study and its records during the coming year of approval to follow up on this and other concerns. Information for researchers on how to report and request changes in enrollment will be enhanced as our policies and procedures undergo revision for accreditation.

(3) HHS regulations at 45 CFR 46.111(a)(4) require that in order to approve research covered by the HHS regulations, the IRB shall determine that informed consent will be sought from each prospective subject or the subject's legally authorized representative in accordance with and to the extent required by HHS regulations at 45 CFR 46.116. HHS regulations at 45 CFR 46.117 require that informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative.

There is no indication that the IRB asked the investigator who was obtaining informed consent at UW or at the collaborator sites. The only reference in the IRB application to the process of informed consent at collaborator institutions was provided in response to IRB application section "B. Research Procedures Involved," in which the investigator stated: "In the case of collaborators at other institutions, IRB-approved consent forms from their institutions will be used where available."

OHRP finds that the IRB failed to obtain sufficient information to make the required findings regarding informed consent in accordance with HHS regulations at 45 CFR 46.111(a)(4) for this research.

**Corrective Actions:** OHRP acknowledges UW's response as follows:

> The re-review of this project has resulted in a number of new consent forms, each one appropriate for the targeted subject population. The IRB currently reviewing this activity is in the process of documenting that each of the new consent forms includes all the required elements plus additional information required by the IRB. IRB members are receiving consent form checklists so that they can more easily determine whether an element of consent has been omitted from the consent process (see also response to item #12). No new subjects will be enrolled in the research until the consent forms have been reviewed and approved.

(4) HHS regulations at 45 CFR 46.111(a)(3) require that in order to approve research covered by the HHS regulations, the IRB shall determine that the selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted. OHRP finds that the IRB failed to obtain sufficient information about the recruitment of subjects into the above-referenced research.

Below are examples in which the IRB asked the investigator to respond to specific questions about the recruitment of prospective subjects, followed by the investigator's response. OHRP notes that there is no documentation in any of the examples below that the principal investigator's responses received further review by UW IRB Committee B.

(a) The UW IRB application for initial IRB review contains the following question: "Source of subjects (attach letters of cooperation from agencies, institutions or others involved in subject recruitment)." The principal investigator responded as follows: "Collaborator, medical genetics and MDA clinics at UWMC."

(b) In response to IRB application section "B. Research Procedures Involved," the principal investigator responded, in pertinent part:

> "Research subjects will include both affected and unaffected family members from pedigrees segregating genes for hereditary neuropathies.... It is frequently necessary to include unaffected persons, including spouses of affected and at-risk persons in order to obtain useful information from genetic studies, including linkage analyses.
>
> "In most cases only blood samples will be obtained from persons in which an accurate clinical diagnosis of neuropathy can be reliably established through clinical exam and neurophysiological testing. The sources of patients will include both the Medical Genetics and Muscular Dystrophy Association Clinics at the Univ of Washington Medical Center, referrals from the national MDA office, local physicians, and collaborators at other institutions...."

(c) In response to the application question, "Who will approach subjects and how? Explain what steps you will take to avoid coercion and protect privacy," the principal investigator stated the following: "The Principal investigator and relevant collaborators. In most cases, these individuals will be neurologists, geneticists, or nursing staff who are caring for a particular patient or family member. All subjects will be informed that their participation is optional."

OHRP notes that the IRB did not require the investigator to thoroughly answer the questions related to equitable selection of subjects and recruitment posed both in the IRB application and in the contingent approval letter. Further, there is no documentation in the IRB file that the principal investigator's responses were reviewed by the convened IRB. Therefore, OHRP finds that the IRB failed to obtain sufficient information to make the required determination under 45 CFR 46.111(a)(3) for this research.

**Corrective Actions:** OHRP acknowledges UW's response as follows:

> The IRB currently reviewing this project is in the process of documenting

recruitment procedures for all research sites. The researcher has been informed (9/6/05) that if he adds additional sites, he must provide information about how subjects will be recruited and consented at each new site. All researchers are informed at the time of initial and continuing review that any changes in sites, recruitment, consenting, or other study procedures that are substantive must be reviewed and approved by a convened IRB before implementation. We are in the process of refining our policies and procedures to be more explicit about what constitutes minor changes versus changes that require full IRB review.

(5) HHS regulations at 45 CFR 46.116(a) delineate specific elements required for the informed consent document. OHRP finds that the informed consent document approved in February 1998 for the above-referenced study failed to include and/or adequately address the following elements required by HHS regulations at 45 CFR 46.116(a)(1):

(a) Section 46.116(a)(1): A complete description of the procedures to be followed. For example, the following are questions included in the contingent approval letter issued by the IRB on January 20, 1998, and the corresponding response from the principal investigator included in a letter to the IRB chair dated February 6, 1998:

(i) IRB contingent approval letter, Question #21: "Under 'Other Information,' state that the samples will only be used for looking at genes involved in diseases discussed in the consent form."

Principal investigator response: "As mentioned in the consent form, individuals are invited to participate in studies which aim to identify and study the genes which cause disorders of peripheral nerves. This statement alone implies that DNA samples obtained from patients will not be used for other purposes."

OHRP notes that the principal investigator failed to include the specific language in the consent form mandated by the IRB.

(ii) IRB contingent approval letter, Question #22: "Under 'Other Information,' state whether blood samples will be used to make permanent cell lines (explain in lay terms.) Explain how long samples will be stored and/or how long cell lines will be maintained. Inform subjects as to whether they may withdraw their samples if they choose to."

Question #23: Under 'Other Information,' in the appropriate place, state, "You may at any time request that your sample, together with any descriptive information in the registry, be permanently removed."

Question #24: "Under 'Other Information,' describe the registry. State that identifying information will be stored with samples, and describe

what information will be included (e.g., name, phone number, descriptive information about the subject.) Include the sentence, "In the future, other scientists who study disorders similar to the one in your family may use the information in the registry to contact you to invite you to participate further in this or a similar study." If possible, give an indication as to what other studies might be conducted using the samples. Assure subjects that they will be approached again to sign a new consent form for the new genetic studies and that they are free to refuse to take part in any study. In addition, give the subjects a choice as to whether they want to be in the registry. For example, after explaining the registry, you might include two check boxes...."

Principal investigator response to questions #22 , #23 and #24: "This information will be added to the consent form."

OHRP notes that the consent form was not revised as required by the IRB. It does not contain an explanation in language that would be understood by a layman regarding the use of blood samples to establish cell lines, nor was it revised to add language concerning the duration of storage of samples or cell lines. There is no statement that subjects may withdraw their descriptive information. There is no mention of a registry, and no indication that subjects have a choice as to their participation in the registry. There was no mention of new consent forms for additional genetics studies using the previously collected samples.

(b) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts.

The following question is included in the January 20, 1998 IRB contingent approval letter, Question #16: "Under 'Risks, Stress and Discomfort' [in the consent], inform subjects of the risks of learning genetic information, including emotional stress."

Principal investigator response included in February 6, 1998 response to IRB chair: "In many cases, a discussion of emotional stresses resulting from merely learning about genetic information would be unnecessary (or even inappropriate), given the nature of the diseases under study."

OHRP notes that the Principal investigator failed to revise the consent form as directed by the IRB. In addition, his response contradicts a statement he made in response to IRB contingent approval letter, Question #9: "I am very sensitive to the stigma attached to having an inherited disorder and go to great pains to avoid any humiliation or bad feelings that someone might suffer through an embarrassing contact." OHRP also notes that the IRB-approved consent form section entitled "Risks, Stress and Discomfort" contains merely one sentence, as

follows: "The most likely risks of blood drawing from a vein are brief discomfort, bruising, and a slight chance of infection."

OHRP finds that the investigator's response did not satisfactorily address the issue raised by the IRB. OHRP additionally finds that the IRB chair approved the investigator's response on February 17, 2000, without further review by the convened IRB.

**Corrective Actions:** OHRP acknowledges UW's response as follows:

The re-review process has included a revision of all consent materials. The IRB is in the process of documenting that all required elements of consent are addressed appropriately, including the elements at 45 CFR 46. 116(a)(1), (2), (7). IRB members have received updated consent form checklists (last revised 7/12/05 and sent to you with our last letter) so that they can more easily determine whether an element of consent has been omitted from the consent process.

(6) HHS regulations at 45 CFR 46.111(a)(7) require that in order to approve research covered by the HHS regulations, an IRB shall determine, when appropriate, that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

The following are questions included in the contingent approval letter issued by the IRB on January 20, 1998, and the corresponding responses from the principal investigator included in a letter to the IRB chair dated February 6, 1998:

(a) IRB contingent approval letter, Question #4: "Confidentiality is a critical issue with respect to genetic studies. This means protection of data from family members, as well as from insurance companies, employers and other individuals or organizations. Please describe under what circumstances you would reveal study data to any of these individuals or organizations."

Principal investigator response: "I completely agree that confidentiality is a critical issue. Under no circumstances has information ever been communicated, nor will it ever be communicated, to insurance companies, employers, or other individuals who might be in a position to use that information for discriminatory purposes. Again, the nature of the disorders under study in my laboratory is not such that these would be likely points of discrimination...."

OHRP notes that the Principal investigator did not address the issue of protection of data from family members.

(b) Question #19: "Under 'Other Information' [in the consent], please state something like, 'It is theoretically possible that participation in this genetics study

might hurt your access to health insurance if information about your involvement and/or results of the study become part of your medical record. Therefore, we will keep all study data out of your medical record by keeping this information completely separate.'"

Principal investigator response to #19: "Again, no results have been, nor will ever be, communicated to insurance companies."

OHRP notes that the Principal investigator did not address the issue or indicate that he would make the required modification to the consent form. The consent form was not revised to conform to the IRB requirement.

(c) Question #20: "Under 'Other Information' [in the consent], please explain to subjects how you will protect the confidentiality of the study data. Describe how that data will be coded and stored. Inform subjects that the investigators themselves will not tell family members the results of other family members' tests. Inform subjects of what precautions you will take to keep genetic information out of their medical records."

Principal investigator response: "As mentioned in the consent form, numbers are used to identify specimens. These usually consist of a pedigree number followed by a series of numbers to coordinate a particular blood sample with a cell line with a DNA sample. As mentioned earlier, participation is held strictly confidential. This is an encompassing statement, and it means that results will not be discussed with other family members, nor will they be added to medical records or transmitted to uninvolved, disinterested parties."

OHRP notes that the Principal investigator did not agree to revise the consent to indicate that the investigators themselves will not tell family members the results of other family members' tests. This is a significant omission, given that the Principal investigator had elsewhere stated that subjects would include affected and unaffected persons in families, and that family members would be asked to recruit other family members. In addition, the principal investigator does not explain how data will be stored.

OHRP finds that the IRB failed to obtain sufficient information to make the required finding regarding confidentiality. OHRP notes that there is no documentation that the principal investigator's responses were reviewed by the convened UW IRB Committee B.

**Corrective Actions:** OHRP acknowledges UW's response as follows:

> The IRB currently reviewing this activity has obtained the necessary information regarding confidentiality and has reviewed the researcher's responses at a convened meeting. The IRB is in the process of documenting that correct information about confidentiality of research data is included in the new consent documents. No subjects will be enrolled until the consent forms have been reviewed and approved. At its convened meeting of 10-5-05, the IRB requested that the researcher make additional revisions to the consent forms regarding confidentiality.

(7) HHS regulations at 45 CFR 46.103(a) require that each institution "engaged" in human subjects research provide OHRP with a satisfactory assurance to comply with the regulations, unless the research is exempt under 45 CFR 46.101(b). (Please see OHRP guidance at http://ohrp.osophs.dhhs.gov/humansubjects/assurance/engage.htm.) An institution becomes "engaged" in human subjects research when its employees or agents (i) intervene or interact with living individuals for research purposes; or (ii) obtain individually identifiable private information for research purposes [45 CFR 46.102(d),(f)].

The initial IRB application submitted for the above-referenced research included numerous references to "collaborators." Attached to the application were letters from nine such collaborators. These collaborators agreed to obtain blood samples to be sent to the UW investigator for analysis. Six of the collaborators confirmed the continuation of ongoing collaborations with the UW investigator. One of the collaborators stated, "We will send these blood samples to you for linkage studies and provide up-to-date clinical information about family members for correlation to further facilitate this effort." Another stated, "I will send the remaining samples as soon as I have examined the Ohio family members. I am sending clinical information and pictures on the Wyoming branch." Another stated, "I also will be pleased to provide blood samples from patients with recurring, episodic, seemingly sporadic brachial plexus neuropathy, with the assumption that a subset of these individuals have the inherited form of the disorder." Another stated, "I have already shared material from these families with you and will continue to do so. I am also searching for additional families with this disorder."

The contingent approval letter dated January 20, 1998 did not require the investigator to provide any additional information about the collaborators, nor did it require documentation of an OHRP-approved assurance or IRB approval at the collaborator sites. OHRP notes that UW IRB Committee B did ask the following question in the contingent approval letter that resulted from a January 18, 2005 review of the investigator's response to questions posed in an IRB letter dated October 15, 2004 about a modification request:

> In reference to the collaboration with the two new sites; we will need documentation of IRB approval from the Cleveland Clinic site and the

> Netherlands if research procedures including obtaining informed consent for a blood draw and physical exam, will be conducted at the sites. Point #3 in the letter from the Committee asked where research procedures take place; however the response does not state specifically where procedures take place. Unless subjects are coming to the University of Washington for all study procedures, documentation of approval from each site is necessary.

It is noteworthy that the principal investigator wrote a letter to Dr. Craig Hogan, the Institutional Official, on February 3, 2005, in which he stated, "Instead of reviewing our protocol in light of this single modification request, Committee B has continued to take the opportunity to press me to establish a cell repository, and to raise issues regarding physical exams, coding of samples, etc. that have been discussed and approved in earlier actions. Of particular concern is the requirement that I now have dual IRBs covering samples that I receive from clinicians at other universities." The investigator requested that "...oversight of my IRB protocol be referred to another committee. I am wondering if the treatment I am receiving from Committee B reflects, in part, a punitive response." He also requested "...that I not be asked to establish a cell repository or to demonstrate dual IRBs without just cause."

OHRP notes that UW IRB Committee A reviewed the entire file for this study in March 2005 as a result of the reassignment by Dr. Hogan of this study from Committee B to Committee A, in response to an appeal by the investigator. It is noteworthy that another UW IRB also had concerns about the receipt by the UW investigator of samples and data from collaborators. The March 24, 2005 Committee A letter that detailed the IRB findings from the March 23, 2005 Committee A meeting stated, "The application references numerous 'collaborators' at other institutions who appear to be conducting research under this application. There is no documentation that this is being done with their institutions' approval and oversight." It further states, "The committee was unable to determine if samples, clinical and family pedigree information transferred to Dr. Chance by 'collaborators' have been obtained with appropriate subject consent and IRB approval of the participating institutions."

OHRP finds that the "collaborators" for the above-referenced research were engaged in HHS-supported human subject research, and that UW IRB Committee B failed to ascertain whether the collaborator sites possessed or obtained an OHRP assurance.

**Corrective Actions:** OHRP acknowledges UW's response as follows:

> We agree that, despite the IRB's documented concerns about the approval of "off-site" research activities related to this research, the IRB failed to obtain appropriate documentation of the sites' OHRP Assurance status. In the process of re-review, the IRB has requested documentation of IRB approval

for each of the sites engaged in research associated with this project. The IRB has also requested that the researcher provide documentation of current approval at each continuing review of this activity.

OHRP notes that UW stated that it is planning and implementing the following additional changes in its overall human research protection program:

(1) UW is preparing to implement mandatory education in the protection of human subjects for all researchers who seek review and approval of research involving humans. UW is enhancing its electronic management system (UWise) so that the IRB can determine whether or not a researcher has received the required education. UW currently offers training in three modalities – web-based (Collaborative IRB Training Initiative), CD-ROM (OHRP's "Investigator 101), and in-person tutorials conducted at three locations on a regular basis. UW is considering additional types of education and training.

(2) IRB staff are delivering in-service training to each IRB to stress the importance of follow-through on all compliance issues. Staff are also implementing procedures the IRBs should use when dealing with non-responsive researchers, to be completed by 11/1/05. The UW is co-sponsoring a two-day education and training conference, in addition to scheduled in-services, for IRB members, chairs, and staff on October 17-18, 2005, during which these concerns will be addressed.

(3) UW will sponsor a workshop for IRB members and researchers to promote open discussion and constructive collaboration between researchers and the IRB in the review of genetic research. This workshop has been scheduled for April, 2006.

(4) UW's Office of Research has hired a Post-approval Monitor whose responsibilities include developing and implementing a system to assure post-approval safety and compliance and to assist the IRBs in resolving compliance concerns.

OHRP finds that the corrective actions described above adequately address the above additional determinations of noncompliance.

As a result of these 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 that might alter this determination.

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, 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
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Dr. Donald Sherrard, IRB #6 Chairperson, UW
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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
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Ms. Janet Fant, OHRP