DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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April 1, 2005

Mark A. Emmert, Ph.D.
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RE: Human Research Subject Protections Under Federalwide Assurance FWA-6878

Dear Dr. Emmert:

The Office for Human Research Protections (OHRP) conducted a Not-for-Cause on-site evaluation of the University of Washington's (UW) system for protecting human research subjects from February 23 to February 25, 2005.

OHRP provides oversight on all matters related to the protection of human subjects participating in research conducted or supported by the U.S. Department of Health and Human Services (HHS). OHRP helps ensure that such research is carried out in accordance with the highest ethical standards and in an environment where all who are involved in the conduct or oversight of human subjects research understand their primary responsibility for protecting the rights, welfare, and well-being of subjects.

OHRP is sending this letter to you instead of sending it to Dr. Craig Hogan, who is both the UW Vice Provost for Research and the Institutional Official designated on the UW Federalwide Assurance, because of OHRP's concern expressed in item (8) on page 7.

The above-referenced on-site evaluation, conducted by two OHRP staff with the assistance of two consultants, included meetings with institutional officials, institutional review board (IRB) chairpersons, the administrative staff of the IRBs, members of the various IRBs, and a limited number of principal investigators who submit protocols to the IRBs. The evaluation also involved a review of IRB files for approximately 38 open protocols, approximately 30 exempt studies, and the minutes of IRB meetings held from 1998 to 2005.

During the site visit, the IRB chairpersons, IRB members, and IRB administrative staff displayed

an enthusiastic and sincere concern for, and commitment to, the protection of human subjects. The staff of the IRB office were helpful and accommodating to OHRP during the site visit.

Findings of Noncompliance Relative to Systemic Protections for Human Subjects:

Based on its evaluation, OHRP makes the following determinations:

(1) OHRP finds 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 by the convened IRB of responsive material.

Based on its discussions with IRB chairpersons, IRB members and IRB administrative staff, OHRP notes that the UW IRBs often seem reluctant to defer approval of a study. Instead, studies were approved contingent upon receipt of additional information and upon revision of the consent form. The questions asked in the contingent approval letter were often substantive questions bearing on the risk/benefit determination required under HHS regulations at 45 CFR 46.111 in order to approve a study. In addition, it was often unclear if the investigator's responses were reviewed by the convened IRB or approved by the IRB chairperson or the IRB administrative staff.

OHRP would like to acknowledge and commend the UW IRBs for successfully identifying many critical issues about research reviewed, and for asking detailed questions to solicit information from the investigators. However, many of these issues and questions should have been reviewed and resolved *prior to* the IRB's approving the study. In order to approve, or to contingently or conditionally approve a study, the IRB must make the required determinations under HHS regulations at 45 CFR 46.111.

For example, OHRP notes the following:

(a) HHS regulations at 45 CFR 46.111(a)(1) require that in order to approve research covered by the HHS regulations, an IRB shall determine that risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

The study entitled "Optimizing Iron Status in Preterm Neonates," approved by Committee D on May 9, 2003, is one example of research approved by the IRB contingent upon receipt of and action taken on a number of substantive issues and questions. The IRB inquired in the contingent approval letter dated May 19, 2003, whether the infants on placebo would receive adequate supplementation.

OHRP finds that the IRB did not fully determine that risks to subjects were minimized prior to approving the study. It was inappropriate to grant approval, contingent or otherwise, prior to the convened IRB's receipt and evaluation of the information requested, as the information relates to the determination of risk level for the placebo group.

(b) HHS regulations at 45 CFR 46.111(a)(2) require that in order to approve research covered by the HHS regulations, an IRB shall determine that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result. In the following example, the questions asked and issues raised in the contingent approval letter indicate that the IRB did not make the required determination in 46.111(a)(2) prior to approval of the research.

The study entitled "Phase I/II Trial of the Anti-HIV Activity and Safety of Mifepristone (VGX-410) at Three Dose Levels in HIV-1 Infected Individuals (ACTG 5200, Version 1.0)" was approved by Committee B on December 7, 2004, contingent upon receipt of and action taken on a number of issues and questions contained in the contingent approval letter dated December 11, 2004.

Question #7 states, "What treatment would this group of subjects usually receive as part of standard of care? Will they be denied standard care if they take part in the study? This is of particular concern as subjects will not receive benefit if they take part in this research. Subjects who receive the study drug will not receive active medication (any lowering of the HIV level in the blood will be temporary). Subjects who are assigned to one of the placebo arms will not receive any medication during the study."

OHRP finds that the IRB did not fully determine that risks to subjects were reasonable in relation to anticipated benefits, because the questions asked in the contingent approval letter refer to issues and information that the IRB needed in order to make this determination properly. OHRP notes that these questions posed by the IRB also appear to be directly relevant to determining that risks to subjects are minimized.

(c) HHS regulations at 45 CFR 46.111(a)(4) require that the IRB 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 46.116. HHS regulations at 45 CFR 46.116 state, in pertinent part, that an "investigator shall seek such consent only under circumstances that provide the

prospective subject with sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence."

OHRP reviewed contingent approval letters for a number of studies that asked

questions related to the informed consent process, such as how the investigator planned to recruit subjects, and how the investigator planned to contact potential subjects. OHRP finds that the UW IRB inappropriately granted contingent approval without fully evaluating these important elements of the informed consent process.

(d) HHS regulations at 45 CFR 46.111(a)(6) require that the IRB determine that, when appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

The study entitled "Phase I/II Trial of the Anti-HIV Activity and Safety of Mifepristone (VGX-410) at Three Dose Levels in HIV-1 Infected Individuals (ACTG 5200, Version 1.0)" was approved by Committee B on December 7, 2004, contingent upon receipt of and action taken on a number of issues and questions contained in the contingent approval letter dated December 11, 2004.

Question #1 in the contingent approval letter states, "Please describe the data safety and monitoring plan for the study. Page 52 of the protocol states that there is a mechanism for early stopping due to prohibitively high toxicity/intolerance rates. Please describe the criteria that will be used to make this determination. Who will make the decision? Describe the pause rules and state how often the data will be reviewed."

OHRP finds that the IRB did not fully determine that the research plan contained adequate provisions for monitoring the data collected to ensure the safety of subjects.

(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 disapproving research; and a written summary of the discussion of controverted issues and their resolution. OHRP finds that IRB minutes often did not meet these requirements.

Contingent approval letters often required changes to the research before final approval was to be granted but, the minutes lacked any indication of the basis for requiring those changes. In addition, OHRP finds that the contingent approval letters often seem to reflect the outcome of discussions of controverted issues, but the minutes lack any summary of the discussion itself. In addition, discussion with IRB members indicated that in certain instances the IRB asked that certain information come back to the convened IRB for review, but this is not recorded in the meeting minutes.

(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 the protocol was reviewed by the convened IRB, not on the anniversary of the date the IRB chairperson or his (or her designee) verifies that IRB-specified conditions for approval have been satisfied. OHRP finds 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.

The OHRP guidance document entitled "Guidance on Continuing Review," dated July 11, 2002, clearly sets forth OHRP's position on this issue. Please see the section entitled "How is the continuing review date determined?" at http://www.hhs.gov/ohrp/humansubjects/guidance/contrev2002.htm.

OHRP found numerous instances in which the IRB failed to conduct continuing review of research at least once per year. OHRP notes that the following examples are indicative of a UW IRB policy that incorrectly assigns anniversary dates for continuing review to studies granted contingent approval.

(a) The study entitled "HIV-1 Specific Cellular Immune Response in HIV-1 Uninfected Mother-Infant Pair: A Control Study" was granted contingent approval by UW Committee A on November 6, 2002, at a convened meeting. The contingencies were signed off on February 26, 2003. The date that the IRB chairperson or designee confirmed that the contingencies were met (Feb. 26, 2003) was incorrectly used as the anniversary date for continuing review, instead of using the date of the convened meeting (Nov. 6, 2002). As a result, the study was not reviewed by the IRB at least annually, and there was a three-month period in which there was no valid IRB approval.

(b) The study entitled "Violent Parental Death: The Impact on Children of Family Help Seeking Behavior" was granted contingent approval by UW Committee G on June 19, 2003, at a convened meeting. The contingencies were signed off on August 20, 2003, by the IRB chairperson or designee. August 20, 2003 was incorrectly used as the anniversary date for continuing review, instead of using the date of the convened meeting (June 19, 2003). As a result, the study was not reviewed by the IRB at least annually, and there was a two-month period in which there was no valid IRB approval.

Given the large number of studies to which the UW IRBs have granted contingent approval, OHRP is concerned that numerous studies have experienced lapses in IRB approval.

(4) OHRP finds 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 subjects' confidential contact information was used inappropriately by a member of the study staff. To date, OHRP has not received a report about this unanticipated problem.

(5) OHRP finds that UW does 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.

(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.

HHS regulations at 45 CFR 46.305(c) require that an institution shall certify to OHRP (acting for the Secretary of HHS) that the IRB made the required findings in 45 CFR 46.305(a). The study entitled "Long-term Follow-up Focus on Families" (HHS award # 1-R01 DA017908-01, investigator Richard Catalano) received contingent approval on August 5, 2004 and December 9, 2004, from UW Committee C. The study received final approval on February 11, 2005, related to the enrollment of prisoners. To date, OHRP has not received certification from the University of Washington that Committee C made the required findings in 46.305(a).

OHRP notes that Subpart C prisoner certifications were received from UW Committee C in early November 2004, for two studies involving prisoners that were reviewed and approved on Oct. 28, 2004. OHRP has not yet responded to these certifications, and is awaiting the submission of a complete packet of materials. Please confirm that no prisoners have been involved in these two studies while UW has been awaiting OHRP's response.

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

Additional OHRP Concerns and Questions

OHRP has the following concerns and questions:

(8) [Redacted]

(9) [Redacted]

(10) [Redacted]

(11) [Redacted]

(12) [Redacted]

(13) [Redacted]

(14) [Redacted]

Required Action: By April 28, 2005, please provide OHRP with a corrective action plan that addresses all of the above findings, questions, and concerns. Furthermore, with respect to finding (3), UW must assess whether any studies are currently lapsed in approval due to the assignment of an incorrect anniversary date. These studies must stop, unless the IRB finds that it is in the best interest of subjects to continue participating in the research interventions or interactions.

OHRP Guidance:
OHRP would like to provide the following guidance:

(1) OHRP recommends that IRBs affix the approval and expiration dates to all approved informed consent documents and stipulate that copies of these dated documents must be

used in obtaining consent. This procedure helps ensure that only the current, IRB-approved informed consent documents are presented to subjects and serves as a reminder to the investigators of the need for continuing review.

(2) HHS regulations at 45 CFR 46.116(d) require that the IRB make and document four findings when approving a consent procedure which does not include, or which alters, some or all of the required elements of informed consent, or when waiving the requirement to obtain informed consent. OHRP recommends that when approving such a waiver for research reviewed by the convened IRB, these findings be documented in the minutes of the IRB meeting, including *protocol-specific* information justifying each IRB finding.

Similarly, where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (b) approving research involving pregnant women, human fetuses, or neonates (see 45 CFR 46.204-207); (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP recommends that for research approved by the convened IRB, all required findings be fully documented in the minutes of the IRB meeting, including *protocol-specific* information justifying each IRB finding.

For research reviewed under an expedited review procedure, these findings should be documented by the IRB chairperson or other designated reviewer elsewhere in the IRB record.

(3) Written IRB policies and procedures should provide a step-by-step description with key operational details for each of the procedures required by HHS regulations at 45 CFR 46.103(b)(4) and (5). Important operational details for these procedures should include the following:

(a) A description of any primary reviewer system used for initial review, continuing review, review of protocol changes, and/or review of reports of unanticipated problems involving risks to subjects or others or of serious or continuing noncompliance.

(b) Lists of specific documents distributed to primary reviewers (if applicable) and to all other IRB members for initial review, continuing review, review of protocol changes, and review of reports of unanticipated problems involving risks to subjects or others or of serious or continuing noncompliance.

(c) Details of any process (e.g., a subcommittee procedure) that may be used to supplement the IRB's initial review, continuing review, review of protocol changes, and/or review of reports of unanticipated problems involving risks to subjects or others or of serious or continuing noncompliance.

(d) The timing of document distribution prior to IRB meetings.

(e) The range of possible actions taken by the IRB for protocols undergoing initial or continuing review and protocol changes undergoing review.

(f) A description of how expedited review is conducted and how expedited approval actions are communicated to all IRB members.

(g) A description of the procedures for: (i) communicating to investigators IRB action regarding proposed research and any modifications or clarifications required by the IRB as a condition for IRB approval of proposed research; and (ii) reviewing and acting upon investigators' responses.

(h) A description of which institutional office(s) and official(s) are notified of IRB findings and actions and how notification to each is accomplished.

(i) A description, if applicable, of which institutional office(s) or official(s) is responsible for further review and approval or disapproval of research that is approved by the IRB. Please note that, in accordance with HHS regulations at 45 CFR 46.112, no other institutional office or official may approve research that has not been approved by the IRB.

(j) A specific procedure for how the IRB determines which protocols require review more often than annually, including specific criteria used to make these determinations (e.g., an IRB may set a shorter approval period for high-risk protocols or protocols with a high risk-to-potential benefit ratio).

(k) A specific procedure for how the IRB determines which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review, including specific criteria used to make these determinations (e.g., such criteria could include some or all of the following: (i) randomly selected projects; (ii) complex projects involving unusual levels or types of risk to subjects; (iii) projects conducted by investigators who previously have failed to comply with the requirements of the HHS regulations or the requirements or determinations of the IRB; and (iv) projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources).

(l) A description of what steps are taken to ensure that investigators do not implement any protocol changes without prior IRB review and approval, except when necessary to eliminate apparent immediate hazards to subjects (e.g., this might be addressed through training programs and materials for investigators, specific directives included in approval letters to investigators, and random audits of research records).

(m) A description of which office(s) or institutional official(s) is responsible for promptly reporting to the IRB, appropriate institutional officials, any supporting Agency or Department heads, and OHRP any (i) unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval.

(n) A description of the required time frame for accomplishing the reporting requirements in the preceding paragraph.

(o) The range of possible actions taken by the IRB in response to reports of unanticipated problems involving risks to subjects or others or of serious or continuing noncompliance.

(p) Institutions may wish to consider including additional pertinent information in their written IRB procedures, such as: (a) important definitions (e.g., the definition of *research, human subject*, and *minimal risk)*; (b) a description of procedures for implementing other relevant Federal regulations that apply to human subject research (e.g., FDA and HIPAA regulations); (c) procedures for selecting and appointing the IRB chairperson and members in order to satisfy the requirements of HHS regulations at 45 CFR 46.107; (d) procedures for training and educating IRB members and staff and investigators; (e) a description of the required elements of informed consent and criteria for waiving or altering these requirements; and (f) procedures for ensuring that the IRB possesses sufficient knowledge of the local research context.

(4) OHRP strongly recommends that institutions develop and distribute a handbook of IRB guidelines for research investigators. The handbook should include detailed information concerning (a) federal and institutional requirements for the protection of human research subjects; (b) the IRB's role and responsibilities; (c) the requirements and procedures for initial and continuing IRB review and approval of research; (d) the rationale and procedures for proposing that the research may meet the criteria for expedited review; (e) the requirements and procedures for verifying that research is exempt from IRB review; (f) the responsibilities of investigators during the review and conduct of research; (g) the requirements and procedures for notifying the IRB of unanticipated problems or events involving risks to the subjects, as well as any other expected or unexpected adverse events; (h) an explanation of the distinction between FDA requirements for emergency use of test articles versus HHS regulations for the conduct of human subjects research; (i) relevant examples and user-friendly forms for providing information to the IRB; and (j) a copy of the institution's OHRP-approved assurance, the HHS humans subjects regulations (45 CFR part 46), and *The Belmont Report*. Where appropriate, OHRP also recommends that IRBs develop written operating procedures to supplement their guidelines for investigators.

(5) OHRP recommends that each revision to a research protocol be incorporated into the written protocol. This practice ensures that there is only one complete protocol, with the revision dates noted on each revised page and the first page of the protocol itself. This procedure is consistent with the procedure used for revised and approved informed consent documents, which then supersede the previous ones.

OHRP appreciates the commitment of UW to the protection of human subjects. Please feel free to contact me should you have any questions.

Sincerely,

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

cc: Dr. Craig Hogan, Institutional Official, Vice Provost, UW
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