DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 301-435-8072
FAX: 301-402-2071
E-mail:kborror@osophs.dhhs.gov

December 10, 2002

Peter O. Kohler, M.D.
President
Oregon Health & Science University
3181 SW Sam Jackson Park Rd L101
Portland, OR 97201-3098

RE: Human Research Protections Under Federal Wide Assurance FWA-161

Dear Dr. Kohler:

The Office for Human Research Protections (OHRP) has reviewed your November 15, 2002 report regarding the above-referenced research conducted at the Oregon Health & Science University (OHSU) that was submitted in response to OHRP's October 4, 2002 site visit letter.

In its October 4, 2002 letter OHRP made the following determinations regarding general human subjects protections at OHSU.

> (1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the Institutional Review Board (IRB) at intervals appropriate to the degree of risk and not less than once per year. OHRP found numerous instances in which the OHSU IRB failed to conduct continuing review of research at least once per year.
>
> **Corrective Action:** OHRP acknowledges that the OHSU IRB and the Office of Research Integrity (ORIO) have implemented a new procedure by which all newly submitted protocols and all continuing reviews now specify the period of approval on the cover memo. The IRB determines the approval period for each protocol, which starts as of the date of the IRB meeting. To assure continuing reviews occur at intervals of no more than 12 months, the electronic database lists the date that the convened board reviewed and approved the protocol. All studies are then flagged for continuing review two months prior to the lapse date. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the OHSU FWA.

(2) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364--60367 that involves no more than minimal risk. OHRP found that the IRB inappropriately applied expedited review procedures to research that involves greater than minimal risk. In specific, for protocol #4566, the IRB approved, through expedited review, bone marrow aspiration in children with Fanconi's Anemia solely for research purposes.

Corrective Action: OHRP acknowledges that the OHSU IRB has developed an IRB Triage Form to provide two levels of oversight to assure that expedited review procedures are followed. An IRB analyst first reviews the protocol and any investigator request for an expedited review, then completes the Triage Form, which is provided to the IRB chair with the protocol and other supporting information. The IRB chair makes the final determination regarding expedited review and the appropriate category. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the OHSU FWA.

(3) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited review procedures for review of minor changes to previously approved research during the period for which approval is authorized. OHRP found that the IRB employed expedited review procedures to review changes that exceed this limitation.

Corrective Action: OHRP acknowledges OHSU's statement that a waiver of child assent for research was not granted for the protocol in question, #7261, as OHRP had indicated. OHRP also acknowledges that the implementation of the IRB Triage Form should enhance compliance with the regulations pertaining to expedited review. OHRP finds that this corrective action is appropriate under the OHSU FWA.

(4) OHRP found that serious or continuing noncompliance with the HHS regulations or the requirements or determinations of the IRB, and suspension or termination of IRB approved research, were not reported to OHRP as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

Corrective Action: OHRP acknowledges that, although the Manager for Research Compliance reported to the site visit team that the IRB had found an incident of "serious noncompliance" and suspended the related protocol, OHSU stated in its November 21, 2002 letter to OHRP that this particular incident was not determined to be a "major protocol violation" and therefore not reportable. However, OHRP notes that both the Manager for Research Compliance and the November 21 letter indicate that the IRB did suspend this protocol, which does need to be reported to OHRP under HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). OHRP acknowledges that the OHSU IRB has revised its protocol violation policy and procedure to include reporting to OHRP any serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB. The

process has been further amended to include tabulation and reporting of any protocol violations in the process of conducting a continuing review, which actively solicits information regarding protocol violations. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the OHSU FWA.

(5) 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 found that letters were sent by the investigator to prospective subjects for protocol #4158 without IRB approval.

Corrective Action: OHRP acknowledges that OHSU has instituted a Responsible Conduct of Research education program which makes it clear to investigators that any changes to approved research must be approved before implementation and requested by a Protocol Revisions/Amendment Form. In addition, OHSU will remind investigators of this requirement via two electronic newsletter and monthly live education sessions. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the OHSU FWA.

(6) HHS regulations at 45 CFR 46.101(b)(4) exempt research activities involving existing data, documents, records, or specimens. OHRP noted that the information must be **recorded by the investigators** in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. OHRP found an instance where this exemption was applied to activities involving prospective collection of such materials.

Corrective Action: OHRP acknowledges OHSU's statement that implementation of the IRB Triage Form should prevent recurrence of such noncompliance. In addition, the IRB has re-emphasized the need to carefully review applications for qualifications related to exempt and expedited categories. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the OHSU FWA.

(7) HHS regulations at 45 CFR 45.116 state that, except as provided elsewhere in the regulations, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. OHRP found that investigators initiated human subject research without meeting this requirement. OHRP found multiple instances where research subjects underwent screening or other research-related procedures prior to signing an informed consent document.

Corrective Action: OHRP acknowledges that OHSU has revised its telephone screening policy and is providing training for study staff and investigators. OHSU states that "investigators are not allowed to conduct screening procedures unless '…informed consent [is]

obtained prior to initiation of any clinical procedures that are performed solely for the purpose of determining eligibility for research….'" OHRP notes that HHS regulations at 45 CFR 46.116 (d) and 46.117 allow for waiver or alteration of informed consent or waiver of a written consent document under certain circumstances. Such waivers may be appropriate for some minimal risk screening procedures.

(8) OHRP found that the informed consent documents reviewed and approved by the IRB for numerous studies failed to include or adequately address the following elements required by HHS regulations at 45 CFR 46.116 (a):

(a) Section 46.116(a)(1):

(i) An explanation of the purposes of the research. In specific, in protocol #0602, the purpose of the study was to assess the feasibility and toxicity of the intervention but the informed consent document stated that the purpose was to evaluate the safety and effectiveness of the intervention.

(ii) A complete description of the procedures to be followed, and identification of any procedures which are experimental. For example, the informed consent document for protocol #1609 did not state that subjects would have repeat interventions at 6, 12, 24, and 48 months; and the informed consent document for #6688, a chemotherapy study, stated "All tests and procedures in this study are part of standard care for your disease. You would have all the same tests and procedures if you were not taking part in this experiment," even though the research intervention was a procedure that was not part of standard care.

(b) Section 46.116(a)(3): A description of any benefits to the subject or others that may *reasonably* be expected from the research. In specific, the informed consent document for protocol #4566, which involved procurement of bone marrow from children for research purposes, stated "I may benefit from this procedure by having my stem cells available for future gene therapy study."

(c) Section 46.116(a)(8): A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(i) Virtually all OHSU informed consent documents that OHRP reviewed included the following or similar statement: "you may refuse to take part or withdraw from this study at any time without affecting [your] relationship with or treatment at the Oregon Health Sciences University." OHRP notes that there could be penalties or

loss of benefits other than a subject's relationship with OHSU, and that the statement as required by the regulations should be in the informed consent document.

(ii) Numerous informed consent documents reviewed and approved by the OHSU IRB included a statement allowing continued use of genetic samples after withdrawal of consent if the "withdrawal jeopardizes the success of the entire project."

Corrective Action: OHRP acknowledges that the IRB is re-reviewing these protocols and may require reconsent of subjects in some or all of these protocols. The OHSU IRB also has changed the language in the model consent document to include the language required by HHS regulations at 45 CFR 46.116(a)(8). In addition, the IRB Reviewer Summary forms solicit review of all the required elements of informed consent under HHS regulations at 45 CFR 46.116(a). OHRP notes OHSU's disagreement with findings (8)(a)(ii) and 8(b). OHRP acknowledges that the site visit team may have been missing information that could have refuted these findings. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the OHSU FWA.

(9) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. OHRP found that the informed consent document approved by the IRB for several studies included complex language that would not be understandable to all subjects.

Corrective Action: OHRP acknowledges OHSU's statement that the OHSU IRB members are aware of the need to replace technological and medical terms with lay terms and are diligent in their efforts to do so. The informed consent template posted on the OHSU website contains statements that help to improve the understandability of these documents. Also, an education module has been devoted to the informed consent process and advises investigators to write informed consent documents so that they are understandable at a sixth to eighth grade level. Guidance is given to investigators on using a word processor tool to determine grade level readability. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the OHSU FWA.

(10) HHS regulations at 45 CFR 46.304 require modification of IRB membership for review of research involving prisoners. In specific, at least one member of an IRB that reviews the research shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity. When the convened IRB reviews research involving prisoners (including initial review, continuing review, review of protocol modifications, and review of unanticipated problems involving risks to subjects or others), the prisoner or prisoner representative must be present as a voting member. OHRP found that the IRB failed to meet this requirement when conducting the first continuing review, and review of all project amendments for protocol #5981, a research project involving prisoners.

Corrective Action: OHRP acknowledges OHSU's statement that the study in question does not involve prisoners, and upon further consultation with legal counsel, OHRP concurs with this assessment. Therefore, no corrective actions are necessary.

(11) 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 by OHRP, it was difficult to reconstruct a complete history of all IRB actions related to the review and approval of the protocol. In some instances, OHRP could not determine what the IRB actually approved.

Corrective Action: OHRP acknowledges that the OHSU IRB has created a new regulatory action tracking form that will be inserted inside the study file, and will summarize all activity related to the study. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the OHSU FWA.

(12) OHRP found that the institution 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. For example, 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.
>
> (b) The procedures for ensuring prompt reporting to the 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. For example, the procedures should include a description of which office(s) or institutional official(s) is responsible for promptly reporting such events.

Corrective Action: OHRP acknowledges that the OHSU policies and procedures have been revised to include most of these requirements. OHRP notes, however, that these revisions still do not seem to address the procedures for ensuring prompt reporting to any Department or Agency head and OHRP of any suspension or termination of IRB approval. **Please provide OHRP with revised written procedures to address these reporting requirements.**

Additional Questions and Concerns

(13) [Redacted]

(14) OHRP expressed concern that the current IRB membership appeared to lack the diversity, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects, as required under HHS regulations at 45 CFR 46.107(a).

Corrective Action: OHRP acknowledges that OHSU is sensitive to the issue of ethnic, gender, and age diversity of its IRB membership. The Provost's office and OHSU's Office of Diversity and Multicultural Affairs are working with the IRB to enhance these efforts. Additionally, OHSU is requesting that investigators who interact with these communities keep in mind the potential for recruitment of representatives to the IRB. OHRP finds that these corrective actions adequately address the above concern and are appropriate under the OHSU FWA.

(15) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. OHRP expressed concern that minutes of IRB meetings consist of handwritten notes by three different IRB staff. OHRP strongly recommended that these handwritten notes be summarized in a single written record that includes discussion of controverted issues and their resolution.

Corrective Action: OHRP acknowledges that the OHSU IRB has implemented a new system for recording the minutes of IRB meetings. One of the two analysts assigned to each board will collect the three sets of handwritten minutes and summarize them into a single, typed record of

the discussion. This summary will include the discussion of controverted issues and their resolution. The analyst who performs this summary will assemble the minutes for each meeting by placing this summary along with the handwritten notes, the IRB member summary sheets, and a copy of the review summary sent to the investigator, into a single packet for that meeting. The OHSU IRB also has obtained guidance from a commercial IRB on how best to translate the discussions around the IRB meeting table into printed minutes. **Please provide OHRP a copy of the minutes of the most recent IRB meeting.**

Please submit to OHRP the information requested in paragraphs (12), (13) and (15) above by January 21, 2003.

OHRP appreciates OHSU's commitment to the protection of human subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Human Subject Protections

cc: Dr. Gary T. Chiodo, OHSU IRB#1 & #3 Chair
Dr. Susan Hansen, OHSU IRB#2 Chair
Dr. William C. Jacobs, Western IRB Chair
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Jeff Cohen, OHRP
Mr. George Gasparis, OHRP
Dr. Kamal Mittal, OHRP
Mr. Barry Bowman, OHRP