DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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October 4, 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:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of human subject protection procedures at the Oregon Health & Science University (OHSU) on October 2-4, 2002. The evaluation, conducted by four OHRP staff with the assistance of three consultants, included meetings with institutional officials, at least 20 Institutional Review Board (IRB) members, IRB administrative staff, and investigators supported by the Department of Health and Human Services (HHS). The evaluation involved review of IRB files for over 30 protocols, and the minutes of numerous IRB meetings.

In the course of the OHRP review, it was apparent that there is a strong commitment to human subjects protection across OHSU, which is supported by top institutional officials. The IRB chair, IRB members, and IRB administrative staff displayed an enthusiastic and sincere concern for the protection of human subjects and stated that they view themselves as providing a valuable service to subjects and the research community. Investigators demonstrated a culture of respect for the IRB process. IRB procedures for initial and continuing review of research appear to be substantive and meaningful. The IRB administrative staff were helpful and accommodating to OHRP during the site visit.

OHRP is not prepared at this time to present findings related to the SATURN study. OHRP anticipates issuing a determination letter regarding the SATURN study within the next few weeks.

At this time, OHRP makes the following determinations regarding general human subjects protections at OHSU.

(1) 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 Chair or another IRB member designated by the Chair, 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 Chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP found numerous instances in which the IRB failed to conduct continuing review of research at least once per year.

(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. OHRP finds that the IRB inappropriately applied expedited review 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.

(3) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research during the period for which approval is authorized. OHRP finds that the IRB employed expedited procedures to review changes that exceed this limitation. In specific, for protocol #7261, the IRB approved, through expedited review, the waiver of child assent for research after the convened IRB had expressly disallowed the initial request for assent waiver.

(4) OHRP finds that serious or continuing noncompliance with the 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). In particular, the IRB found an incident of "serious noncompliance" and suspended the related protocol, as reported to the site visit team by the Manager for Research Compliance. OHRP has no record that this noncompliance or suspension was reported to OHRP.

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

(6) HHS regulations at 45 CFR 46.101(b)(4) exempt activities involving existing data, documents, records, or specimens. OHRP notes 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 finds an instance where this exemption was applied to activities involving prospective collection of such materials. In specific, for the exempted protocol titled "Prevalence and risk factors for antibiotic resistant organisms in pediatric urinary tract infections in the emergency department," the investigators were collecting data from multiple sources with identifiers and then later removing the identifiers.

(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 finds that investigators initiated human subject research without meeting this requirement. OHRP finds multiple instances where research subjects underwent screening or other research-related procedures prior to signing an informed consent document. For example, for protocol #5971, subjects underwent screening ultrasounds prior to consent for the study, and several protocols included telephone screening in which researchers obtained private identifiable information prior to obtaining informed consent.

(8) OHRP finds 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."

(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 finds that the informed consent document approved by the IRB for several studies included complex language that would not be understandable to all subjects.

(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 <u>voting</u> member. OHRP finds 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.

(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.

(12) OHRP finds that the institution 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. 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.

Additional Questions and Concerns

(13) [redacted]

(14) [redacted]

(15) [redacted]

(16) [redacted]

(17) OHRP is concerned about the adequacy of the IRB's procedures for ensuring prompt reporting to OHRP of unanticipated problems involving risks to subjects or others.

Required Actions: By November 8, 2002, OHSU must submit to OHRP a satisfactory corrective action plan to address the findings and concerns stated in paragraphs (1) to (17) above.

At this time, OHRP provides the following additional 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. OHRP notes that the OHSU affixes approval dates to informed consent documents, but not expiration dates.

(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. OHRP is concerned that, while the IRB checklist utilized during IRB review correctly distinguishes between the criteria for waiving consent and for waiving written documentation of consent, this distinction may be lost in the final approval letter provided to investigators.

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.

OHRP notes that, while the IRB utilizes checklists when reviewing protocols, it is not clear from these checklists that the IRB makes the determinations under the required regulatory categories.

(3) 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 one.

(4) The HHS regulations do not affect any applicable State or local laws or regulations which provide additional protections for human subjects [see 45 CFR 46.101(f)]. OHRP recommends that written IRB procedures describe applicable State and local laws and regulations relevant to the conduct of human subject research, particularly regarding legally authorized representatives.

(5) OHRP notes that the institution is engaged in several tissue banking or repository activities. These activities require the IRB to make determinations concerning (i) the regulatory status and appropriate use of stored biologic samples, and (ii) the informed consent process for research using such samples. OHRP is concerned that the IRB has not developed policies and procedures for oversight of repository activities that ensure compliance with HHS regulations at 45 CFR Part 46 (see OPRR guidance regarding repositories, 11/97 at URL http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm).

OHRP appreciates OHSU's commitment to the protection of human subjects. OHRP is available to assist OHSU in the development and implementation of this required corrective action. 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
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