DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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April 17, 2003

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

RE: Human Research Protections Under Federalwide Assurance FWA-161

Research Project: Student Athlete Drug Surveillance Trial (SATURN)
Principal Investigator: Linn Goldberg, M.D.
OHSU IRB Number: 4682
HHS Protocol Number: R01DA012018

Dear Dr. Kohler:

The Office for Human Research Protections (OHRP) has reviewed your December 17, 2002 report regarding the above-referenced research and your January 17, 2003 report regarding general human subjects protections at the Oregon Health & Science University (OHSU) that were submitted in response to OHRP's October 24, 2002 and December 10, 2002 letters, respectively.

In its October 24, 2002 letter, OHRP made the following determinations regarding the SATURN study.

> (1) OHRP found that mandatory drug testing of student athletes is an integral part of the design of the SATURN research protocol.
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> (2) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116 require, among other things, that the investigator shall seek informed consent only under circumstances that minimize the possibility of coercion or undue influence. OHRP found that the circumstances under which subjects were enrolled and the study was conducted failed to meet this requirement.

Corrective Action: OHRP acknowledges that OHSU disagrees with findings (1) and (2). OHRP also acknowledges that the OHSU has proposed a number of corrective actions in response to these findings, including: (a) the OHSU institutional review board (IRB) will re-review the study to determine the adequacy of how the goals of the research are expressed in the informed consent document; (b) the OHSU investigators will withdraw from direct involvement in urine sample collection, will no longer receive drug testing results, and will destroy the drug test results previously collected; (c) no new students will be enrolled in the study and no new consents will be sought; however, if re-consent of previously enrolled students is required by the OHSU IRB, the investigators will ask personnel other than coaches and principals to distribute or collect the informed consent documents from students; and (d) informed consent documents will be returned via mail directly to the investigators by students and their parents, and questionnaires will only be distributed to students for whom parental permission and assent to participate in the study have been obtained and documented.

OHRP finds that, while these corrective actions address several of the concerns inherent in OHRP's findings, they fail to address the central findings. In specific, because under the IRB-approved protocol (a) subjects are randomly assigned in groups (i.e., all student athletes at a particular school) to either mandatory drug testing or no mandatory drug testing; and (b) for student athletes at a school randomized to the mandatory drug testing intervention, continued participation in the school athletic programs is contingent upon participation in the major research intervention, OHRP finds that the proposed corrective actions fail to address the finding that the informed consent of the subjects is not being sought under circumstances that minimize the possibility of coercion or undue influence.

(3) 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 numerous protocol changes were implemented without OHSU IRB review and approval.

Corrective Action: OHRP acknowledges OHSU's statement that no other changes will be implemented in the above-referenced research without prior IRB review and approval. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the OHSU FWA.

(4) HHS regulations at 45 CFR 46.116 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. Under HHS regulations at 45 CFR 46.408(a) and (b), the IRB shall determine that adequate provisions are made for soliciting the assent of children involved as research subjects, when in the judgment of the IRB the children

are capable of providing assent, and, in accordance with and to the extent that consent is required by 45 CFR 46.116, that adequate provisions are made for soliciting the permission of each child's parents or guardian for the children to participate in the research. HHS regulations at 45 CFR 46.117 and 46.408(d) require that informed consent and parental permission be documented by the use of written forms approved by the IRB and signed by the subject, the subject's legally authorized representative, or parents or guardian, unless the IRB waives these requirements in accordance with HHS regulations at 45 CFR 46.117(c). HHS regulations at 45 CFR 46.408(e) require that when the IRB determines that child assent is required, it also shall determine whether and how assent must be documented. Of note, the IRB-approved protocol for this study required that investigators document the assent of the student athletes and permission of their parents with signed assent and parental permission forms.

OHRP found that the SATURN investigators initiated human subjects research without meeting these requirements for some subjects in this research.

Corrective Action: OHRP acknowledges that the student athlete questionnaires will be distributed only to those students who have signed informed consent documents and whose parents have given permission for their participation, as verified by the investigators prior to the administration of the questionnaires. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the OHSU FWA.

(5) OHRP found that the informed consent documents reviewed and approved by the OHSU IRB for the SATURN study 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): A complete description of the procedures to be followed, and identification of any procedures which are experimental. In particular, OHRP noted the following:

(i) There was no statement in the informed consent document that the research involved randomization of high schools to either a prospective drug prevention efficacy arm (using random, mandatory drug surveillance and alcohol testing procedures) or a no-drug-testing control group. Furthermore, the informed consent document may have caused subjects to think that the drug testing is not part of the research design.

(ii) There was no statement in the informed consent document that parents will be notified of positive drug test results.

(iii) There was no description of the "longitudinal study" as referenced in OHSU's July 11, 2001 report to OHRP. This report also stated that "[s]tudents who agree to participate but who wish to recuse themselves from

the longitudinal study may complete a questionnaire anonymously... participation in the study (with longitudinal tracking) is strictly voluntary and will not impact their participation in sports or other school programs." However, this was not clearly described in the informed consent documents.

(iv) Several parts of the informed consent document for the student athletes and materials sent to their parents and schools implied that completion of the questionnaires was the only aspect of the research.

(b) Section 46.116(a)(5): A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. OHRP found that the description of the coding of samples and data, handling of identifiers, and sharing of information in the informed consent document was confusing and inconsistent in places.

Corrective Action: OHRP acknowledges that if the OHSU IRB decides to require re-consent of the enrolled subjects, the informed consent documents will be revised to include a statement that the research team will not receive information about drug test results, a description of the randomization aspect of the study's design, and a more detailed description of the longitudinal study. Until OHRP receives a follow-up report regarding the assessment of the OHSU IRB with respect to the need to re-consent already enrolled subjects, OHRP is unable to assess the adequacy of the proposed corrective actions.

(6) HHS regulations at 45 CFR 46.111(a) state that, in order to approve research covered by the regulations, the IRB shall determine that certain requirements are satisfied. OHRP found that the investigators failed to ensure that the following requirements were satisfied during the conduct of the research:

(a) 45 CFR 46.111(a)(1): Risks to subjects are minimized, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk. It was clear from multiple interviews with the research team and staff from the participating schools that the school-based personnel were inadequately trained by the research team and did not follow uniform procedures for obtaining and documenting parental permission and subject assent and for collecting subject data. Such deficiencies reflected a failure to follow procedures consistent with sound research design.

(b) 45 CFR 46.111(a)(7): When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. Correspondence between the investigators and the schools as well as interviews with research team members indicated that, on at least one occasion, numerous signed informed consent documents were lost by the schools.

Corrective Action: OHRP acknowledges that if the OHSU IRB elects to require re-consent of the enrolled subjects, the informed consent documents will be returned directly to the SATURN researchers. In addition, student-athlete questionnaires will not be administered to any student unless the researchers have received the student's signed informed consent document. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the OHSU FWA.

(7) HHS regulations at 45 CFR 46.103(a) require that each institution "engaged" in human subjects research that is conducted or supported by HHS provide OHRP with a satisfactory assurance of compliance 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)].

OHRP found that (a) all of the participating SATURN high schools were engaged in human subjects research funded by HHS and (b) none of these sites obtained an OHRP-approved assurance for this research.

Corrective Action: OHRP acknowledges that if the OHSU IRB elects to require re-consent of the enrolled subjects, the informed consent documents will be returned directly to the SATURN researchers. However, the randomized research intervention, the drug testing of student athletes, is now being performed by the schools; therefore, the schools are still engaged in human subjects research. For this reason, OHRP finds that the corrective action does not adequately address the above finding.

OHRP Action

In its October 24, 2002 letter, OHRP restricted the OHSU Assurance (FWA-161). Under this restriction, the applicability of FWA-161 to the above-referenced research project (the SATURN study) was suspended until OHSU developed a satisfactory corrective action plan to address all deficiencies and concerns described above as a condition for OHRP consideration of removal of the restriction on the OHSU FWA.

As noted in OHRP's response to the OHSU corrective actions for findings (1), (2), and (7) above, OHRP finds that the OHSU corrective action plan inadequately addresses the findings made by OHRP in its October 24, 2002 letter. In specific, OHRP finds that the plan fails to adequately address the finding that the informed consent of the subjects is not being sought under circumstances that minimize the possibility of coercion or undue influence, as required by HHS regulations at 45 CFR 46.116. As a result, the OHRP restriction on the OHSU FWA remains in effect and the SATURN study must remain suspended until OHSU develops a satisfactory corrective action plan to address these findings. OHRP

notes that the findings noted in paragraphs (1), (2), and (7) may be impossible to address under the current protocol and that a satisfactory corrective action plan most likely will have to include (i) termination of the current study; and (ii) designing a new study that provides for an informed consent procedure which minimizes the possibility of coercion or undue influence.

In its October 24, 2002 letter, the OHRP required the OHSU IRB to re-review the SATURN protocol. This review must include review of the complete grant application, and should consider the need to re-consent already enrolled subjects. Please provide OHRP with a report of this review, including the IRB minutes of the meeting, and all correspondence between the investigators and the IRB.

OHRP finds that the corrective actions that OHSU detailed in its January 17, 2003 letter adequately address the general human subjects protections concerns expressed in OHRP's December 10, 2002 letter and are appropriate under the OHSU FWA.

OHRP encourages OHSU to develop its corrective action plan expeditiously, and forward it to OHRP for review as soon as possible. OHRP is available to assist OHSU in the development and implementation of this corrective action plan. Do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.
Director, Division of Compliance Oversight

cc: Dr. Gary T. Chiodo, OHSU IRB#1 & #3 Chair
Dr. Susan Hansen, OHSU IRB#2 Chair
Dr. William C. Jacobs, Western IRB Chair
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