DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY
OFFICE OF PUBLIC HEALTH AND SCIENCE

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August 21, 2001

David J. Skorton, M.D.
Vice President for Research
The University of Iowa
201 Gilmore Hall
Iowa City, Iowa 52242

**Re: Human Subject Protections Under Multiple Project Assurance (MPA) M-1080**

Dear Dr. Skorton:

The Office for Human Research Protections (OHRP) has reviewed your correspondence responding to OHRP's November 18, 1999 letter regarding the University of Iowa's (UoI's) human subject protection program. OHRP has concluded that UoI has adequately addressed OHRP's questions and concerns, and is therefore closing its investigation. Specifically, OHRP makes the following findings:

(1) OHRP expressed concern that the UoI institutional review board (IRB) frequently approves research contingent upon substantive modifications, without requiring additional IRB review by the convened IRB. OHRP finds that IRB minutes from 1998 provided to OHRP indicated that the IRB frequently required changes to protocols that it approved without documenting the need to have such changes reviewed by the IRB. OHRP notes that UoI's Standard Operating Procedures comply with regulatory requirements and OHRP guidance, in stating that specific protocol revisions will be reviewed by the IRB chair or his or her designee, and when extensive or general revisions are requested by the convened IRB, the full board will review them.

(2) OHRP expressed concern that the six elements of informed consent listed at Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(b), required to be included in the consent process when appropriate [in addition to the basic informed consent elements required by HHS regulatoins at 45 CFR 46.116(a)] were not fully included in the UoI investigator's guide nor in the informed consent forms provided to OHRP. OHRP finds that UoI revised its investigator's guide and informed consent template to require consideration of the elements listed at 45 CFR 46.116(b). OHRP notes under 45 CFR 46.116(b)(1), subjects are to be advised of **any treatments or**

**procedures** that may involve unforeseeable risks, but that UoI's template limits consideration of unforeseeable risks to unforeseeable **drug** risks. OHRP recommends that UoI broaden this template language to include unforeseeable risks associated with any research intervention.

(3) OHRP expressed concern that the UoI IRB Standard Operating Procedures ("SOP") did not contain written procedures for determining which research projects need verification from sources other than investigators that no material changes have occurred since previous IRB review, as required under 45 CFR 46.103(b)(5). OHRP concurs that the revised SOP address this issue in discussing the need for additional monitoring of approved projects (Section XI, paragraph D).

Regarding the reporting requirements in the UoI SOP, OHRP notes that under 45 CFR 46.103(a) and 46.103(b)(5), there must be prompt reporting to the IRB, appropriate institutional officials and OHRP of "any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with [45 CFR Part 46] or the determinations of the IRB; and any suspension of termination of IRB approval." This standard differs from the requirement in the SOP to report "adverse experiences that are both serious and unanticipated." OHRP expects UoI to modify its reporting requirements accordingly.

(4) Regarding review of minor changes in previously approved research:

(a) OHRP expressed concern that the minutes of IRB meetings revealed approval of an array of protocol modifications, although it was unclear (i) what the changes were, (ii) whether the changes were minor or substantive, and (iii) whether the modification was approved by expedited or full board review. OHRP acknowledges UoI's statement that actions are recorded in greater detail in protocol files, although the IRB attempts to record its actions in the meeting minutes. OHRP notes that documentation of IRB actions in the IRB minutes, including the basis for requiring changes in or disapproving research, is required under HHS regulations at 45 CFR 46.115(a)(2), and expects UoI to adjust its documentation practices as necessary to comply with this requirement.

(b) OHRP expressed concern that UoI had not developed a description of the types of minor changes in previously approved research which could be approved by expedited review in accordance with HHS regulations at 45 CFR 46.110(b)(2). UoI has since developed a specific definition of minor changes which focuses on minimal risk. OHRP notes that the concept of minimal risk would not limit the use of expedited review to changes that are necessarily minor in impact (i.e., changes in study design or exclusion criteria). OHRP recommends that UoI alter its definition of minor change so as to restrict expedited review of protocol amendments to truly "minor" changes such as the names of primary investigators.

(5) OHRP expressed concern that the UoI IRB meeting minutes did not reflect required

findings for approval of research involving children set forth in HHS regulations at 45 CFR 46.404-407. OHRP acknowledges UoI's statement that IRB members have been educated about the need to document required findings regarding vulnerable populations such as children (45 CFR 46.404-407) and prisoners (45 CFR 46.305-306), as well as the need to document the waiver or alteration of informed consent requirements (45 CFR 46.117(c)).

OPRR appreciates the continued commitment of your institution to the protection of human research subjects. Feel free to call me if you have any questions.

Sincerely,

Carol J. Weil, J.D.
Division of Compliance Oversight

cc: Mary Sue Coleman, Ph.D., UoI
David L. Wynes, M.D. UIHC
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