DEPARTMENT OF HEALTH & HUMAN SERVICES

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OFFICE OF PUBLIC HEALTH AND SCIENCE

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December 11, 2000

Dr. David Ward
Chancellor
University of Wisconsin - Madison
161 Bascom Hall
500 Lincoln Drive
Madison, Wisconsin 53706

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1285

Dear Dr. Ward:

The Office for Human Research Protections (OHRP) has reviewed your letters of September 7, 2000, and November 30, 2000, regarding the protection of human research subjects at the University of Wisconsin-Madison (UW-Madison).

OHRP has determined that UW-Madison has adequately responded to all required corrective actions stipulated in OHRP's letter of August 11, 2000. In specific, OHPR finds the following:

(1) UW-Madison developed and implemented a process for the inventory and audit of records for all active Federally supported research protocols, to determine whether the institutional review board (IRB) reviewed a copy of the applicable federal grant application. Where such review had not occurred, a copy of the grant (and any additional information needed) was obtained from the principal investigator, and an IRB member compared the content of the grant application and the IRB-approved protocol. Reviewers found either no differences between the documents, or minor differences that were satisfactorily clarified by additional information provided by investigators. No discrepancies between any grant application and its associated human subject protocol(s) required review by the full IRB.

(2) On September 7, 2000, UW-Madison submitted to OHRP membership rosters designating prisoner representatives as voting members for the Health Sciences (HS) IRB, the School of Education (SoE) IRB, and the College of Letters and Science (L&S) IRB. UW-Madison informed OHRP at that time that the remaining UW-Madison IRB, the

College of Agriculture and Life Sciences (CALS) IRB, does not review research proposing involvement of prisoners as human subjects. In its report of November 30, 2000, UW-Madison stated that as of December 7, 2000, only the HS IRB and L&S IRBs would be authorized to review and approve protocols for research involving prisoners.

(3) UW-Madison inventoried and audited all IRB files for HHS-supported research projects involving prisoners as subjects, and informed OHRP about two active HHS-supported protocols that had not been certified as required by HHS regulations at 45 CFR 46.306(a)(1). These protocols were suspended until proper certifications were submitted to OHRP.

(4) The All Campus IRB at UW-Madison supervised an inventory and audit of IRB records for all active federally supported research projects approved by the SoE, L&S, and CALS IRBs, to determine whether the IRB review was in full compliance with the requirements of HHS regulations for the protection of human research subjects (45 CFR Part 45). On November 30, 2000, UW-Madison submitted a report to OHRP which described the outcome of this review, and proposed corrective actions for identified deficiencies. That report (page 8) concluded that 43 protocols required re-review by the IRB, and estimated completion of these re-reviews by April 30, 2001. OHRP notes that any federally supported, nonexempt protocols which did not receive IRB review in accordance with HHS regulatory requirements under 45 CFR Part 46 should be suspended until appropriate re-review (full or expedited) has occurred.

(5) UW-Madison has taken several steps to ensure that all IRBs use complete and uniform record keeping standards. These steps include ad hoc file reviews by the All Campus IRB, a semiannual All Campus audit, an IRB minutes checklist provided to all IRBs, and education provided to IRB staff. The All Campus file reviews are designed to ensure: (a) documentation of required specific findings on the part of the IRB, such as (i) approving a procedure which alters or waives informed consent requirements, (ii) approving a procedure which waives the informed consent requirement, or (iii) approving research involving prisoners, or children; (b) use by all four IRBs of consistent terminology to describe IRB actions such as "deferred" and "approval pending modification"; (c) use of expiration dates on all consent documents; and (d) review of grant applications for all federally funded proposed research.

(6) In response to OHRP's concern that the continuing review procedures and forms for the SoE, L&S, and CALS IRBs were deficient, these three IRBs drafted new written policies and procedures for continuing review in accordance with OHRP guidance.

(7) The All Campus IRB adopted a three-pronged approach (in contrast to OHRP's two-pronged approach) for determining when modifications or clarifications requested by the IRB must be reviewed by the full IRB, or by an IRB Chair or a member designated by the Chair. As with OHRP's approach, administrative changes or specific revisions requiring simple concurrence by the PI may be approved by the IRB Chair or Chair's designee, and

substantive revisions requested by the IRB must be returned to the convened IRB for review and approval. The All Campus IRB included a third category of minor consent form changes or minor protocol revisions required by the IRB, which must be returned to the IRB Chair and/or to two IRB members for review who may subsequently approve the revised protocol on behalf of the IRB or may recommend that the protocol be reconsidered by the full IRB. With respect to this third category, so long as the minor changes/revisions required by the IRB are specified verbatim in writing, OHRP would concur with this approach.

(8) The All Campus IRB has taken steps to ensure that the consent documents approved by the other IRBs include: (a) all eight basic elements listed in HHS regulations at 45 CFR 46.116(a); (b) any appropriate additional elements listed at 45 CFR 46.116(b); and (c) an explanation of whom to contact for answers to questions about research subjects' rights. The IRBs have also been instructed to seek out, and resolve, any discrepancies between protocol applications and informed consent documents regarding research procedures, risks, and benefits of research.

(9) Each IRB is making conscious efforts toward ensuring greater diversity with respect to the cultural, ethnic and racial backgrounds and sensitivities in the membership of the UW-Madison IRBs.

(10) The All Campus Committee is designing a workshop, to be scheduled in the early part of 2001, for the chairs and members of the L&S, CALS, and SoE IRBs. The workshop will provide guidance about the requirements of the human subject protection regulations, and best practices for dealing with specific types of human subjects research. All IRB Chairs are also being required to attend a national meeting or other forum relevant to human subjects protection at least every other year, and new members are required to attend such an event in their first year. All IRB members are encouraged to attend campus training programs on a regular basis, and at least one national or regional meeting. The All Campus Committee is also developing a continuing human subjects education credit system for IRB members, whereby members obtain required credits by participating in meetings, workshops, and/or web-based programs on human subjects protection issues.

(11) The HS IRB has expanded the duration of its bimonthly meetings from 2 hours to 2.5-3 hours, in response to OHRP's concern that adherence to a strict 2 hour time limit, given the volume of research reviewed, provides insufficient time for substantive dialogue and may inhibit IRB members from raising important issues.

(12) The L&S, CALS, and SoE IRBs, with assistance from the All Campus IRB, have drafted new policies and procedures on (a) conducting continuing review, and (b) determining which projects need verification that there have been no material changes from sources other than the investigator, in accordance with the requirements of 45 CFR 46.103(b)(4).

(13) UW-Madison is continuing to examine the possibility of further IRB restructuring in order to promote appropriate diversity of professional expertise and background on the IRBs, as well as workload reduction for the HS IRB.

(14) UW-Madison has taken under advisement OHRP's recommendation that the IRBs consider adopting procedures for determining when the informed consent process should be independently monitored.

Presuming full implementation of these corrective actions, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

OHRP appreciates the continued commitment of UW-Madison to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

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

cc: Dr. Michael Carome, OHRP
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