DEPARTMENT OF HEALTH & HUMAN SERVICES

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David Ward
Chancellor
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Dear Dr. Ward:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of human subject protection procedures at the University of Wisconsin-Madison (UW-Madison) on August 8-10, 2000. The evaluation, conducted by 5 OHRP staff with the assistance of 4 consultants, involved meetings with senior institutional officials, the Chairs and members of each Institutional Review Board (IRB), IRB administrative staff, and investigators who conduct both biomedical and behavioral research supported by the Department of Health and Human Services (HHS). The evaluation included a review of IRB files for more than 75 protocols and minutes of IRB meetings convened during the past year.

OHRP acknowledges that over the past two years UW-Madison has implemented several actions to enhance its system for protecting human subjects including (i) significant expansion of IRB administrative support and resources, especially with respect to the Health Sciences (HS) IRB; (ii) development of education programs for IRB members, IRB staff, and investigators; and (iii) improved documentation of IRB procedures and activities. Such actions are indicative of significant institutional commitment to the protection of human subjects.

During the course of the OHRP visit, the IRB Chairs, members, and 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. The HS IRB Chair, members, and staff in particular appear to be highly proficient and competent. Investigators demonstrated a culture of respect for the IRB process. Dr. Lois Brako and her staff, as well as the IRB administrative staff, were helpful and accommodating to OHRP throughout the site visit.

OHRP Findings Relative to Systemic Protections for Human Subjects

Based on its evaluation, OHRP makes the following determinations relative to systemic protections for human subjects at UW-Madison:

(1) OHRP acknowledges UW-Madison's plan to standardize the policies and procedures for each of its IRBs. OHRP applauds this goal, but finds that many policies and procedures have not been uniformly implemented across all IRBs. Examples include the following:

(a) It appears that complete and uniform record keeping standards have not been implemented and maintained by the UW-Madison IRBs. In some instances, in particular among the College of Letters and Sciences (L&S) and the School of Education (SoE) IRB files examined by OHRP, and occasionally for the HS IRB files, it was difficult to reconstruct a complete history of all IRB actions related to the review and approval of the protocol.

(b) Where HHS regulations require specific findings on the part of the IRB, such as (i) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (ii) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (iii) approving research involving prisoners (see 45 CFR 46.305-306); or (iv) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP strongly recommends that all required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding. OHRP notes that the HS IRB now routinely documents such findings, whereas the other IRBs do not appear to do so.

(c) OHRP notes that the IRBs do not use consistent terminology to describe IRB actions. For example, the L&S IRB appears to use the term "defer" for an action that corresponds to an "approval pending modification" by the HS IRB.

(d) 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 HS IRB routinely affixes approval and expiration dates on approved informed consent documents, whereas the other IRBs do not appear to do so.

(2) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* for research has been reviewed and approved by the IRB.

(a) OHRP finds that prior to April 2000, the IRBs did not review grant applications for proposed research.

(b) OHRP found instances where there were discrepancies between the research described in an HHS grant application and the corresponding IRB-approved protocol.

(3) Continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects

from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB. Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

OHRP finds that continuing review of research by the L&S, the College of Agricultural Life Sciences (CALS), and the SoE IRBs routinely fail to satisfy these requirements. In particular, the L&S and CALS IRB continuing review forms fail to seek sufficient information from investigators. Furthermore, all three IRBs appear to use an expedited procedure with primary reviewers to conduct most continuing reviews.

(4) OHRP is concerned that the HS, L&S, CALS, and SoE IRBs on occasion approve research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research must be **deferred**, pending subsequent review by the convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB (i.e., under an expedited review procedure).

(5) HHS regulations at 45 CFR 46.116(a) delineate specific elements required for informed consent. OHRP found instances where (a) required elements were omitted; and (b) there were discrepancies between the protocol application and the informed consent documents regarding the research procedures, risks, and benefits of the research.

(6) HHS regulations at 45 CFR 46.116(a)(7) require that the informed consent provide an explanation of whom to contact for answers to questions about research subjects' rights. OHRP finds that this information was not routinely included in informed consent documents approved by the L&S, CALS, and SoE IRBs.

(7) OHRP is concerned that the current memberships of all IRBs appear to lack the diversity, including consideration of race and cultural backgrounds and sensitivity to such issues as community attitudes necessary 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). OHRP believes that UW-Madison could and should recruit greater minority representation for its IRBs.

(8) 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 the IRB 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 finds that the L&S and SoE IRB failed to meet this requirement when reviewing research projects involving prisoners. In specific, the L&S IRB has a prisoner representative consultant who is not a voting member, and the SoE IRB did not have a prisoner representative when it reviewed research involving prisoners.

(9) It appears that UW-Madison has failed to certify to OHRP, acting on behalf of the Secretary of Health and Human Services, that the IRBs have fulfilled their duties stipulated by HHS regulations at 45 CFR 46.305(a) for all active HHS-supported research approved for involvement of prisoners as subjects, as required by HHS regulations at 45 CFR 46.305(c) and 46.306(a)(1).

(10) OHRP is concerned that the Chair and members of the L&S, CALS, and SoE IRBs appear to lack a detailed understanding of the specific requirements of the HHS regulations for the protection of human subjects.

(11) OHRP is concerned that the HS IRB is overburdened by the large volume of research for which it has oversight responsibility. In particular, OHRP is concerned that adherence to a two-hour time limit at convened meetings, given the volume of research reviewed, provides insufficient time for substantive dialogue and may inhibit IRB members from raising important issues. For example, at its July 3, 2000 meeting (starting at 4:09 PM and ending at 6:15 PM), the IRB reviewed 1 previously deferred protocol, 60 protocols undergoing continuing review, 27 protocol amendments, 7 adverse events, and 29 new protocols.

OHRP anticipates that the volume of research overseen by the HS IRB will only increase in the future. It is OHRP's experience that such a large volume of human subjects research warrants either more than one fully functional IRB, longer IRB meetings, or more frequent meetings.

(12) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP's discussions with IRB members and its review of IRB documents reveal scant evidence that the L&S, CALS, and SoE IRBs consistently make the required findings when reviewing research involving children.

(13) OHRP finds that the L&S, CALS, and SoE IRBs do not have written IRB policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4):

> The procedures which the IRB will follow for (i) conducting continuing review of research; and (ii) determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

Required Corrective Actions and Recommendations

Action 1 - Required: Each IRB must inventory and audit its records for all active Federally supported research protocols to determine whether the IRB received and reviewed a copy of the applicable Federal grant application. Where review of the grant application did not occur, at least one IRB member should compare the content of the grant application and the IRB-approved research protocol. Where the grant application and the IRB-approved protocol are discrepant in any way, the IRB must re-review the research protocol in conjunction with the grant application.

By November 30, 2000 UW-Madison must submit to OHRP a report describing the outcome of this audit and IRB review.

Action 2 - Required: For any IRB that reviews research proposing involvement of prisoners as subjects, UW-Madison must submit to OHRP a membership roster designating a prisoner or prisoner representative as a voting member.

Action 3 - Required: UW-Madison must inventory and audit the IRB records for all HHS-supported research involving prisoners and must immediately suspend involvement of prisoners in any HHS-supported research project that has not satisfied the certification requirement at 45 CFR 46.305(c) and 46.306(a)(1). For any project affected by this suspension action, enrollment of new prisoner subjects must cease immediately except in extraordinary cases approved in advance by OHRP (OHRP would expect approval requests for such cases to be rare). Furthermore, research activities involving previously enrolled prisoner subjects may continue only where it is in the best interests of individual subjects. The suspension must continue for each affected protocol until (i) UW-Madison has submitted to OHRP the required certification; and (ii) OHRP has notified UW-Madison that OHRP has judged the research to satisfy the criteria of one or more permissible categories stipulated by HHS regulations at 45 CFR 46.306(a)(2). By September 8, 2000, UW-Madison must submit to OHRP a report describing the outcome of this audit and IRB review.

Action 4 - Required: By September 8, 2000, UW-Madison must provide to OHRP a list of any research protocols for which enrollment of prisoners has been suspended. This list should identify those research projects where research activities involving previously enrolled prisoner subjects has been allowed to continue because UW-Madison judged it to be in the best interests of individual subjects.

Action 5 - Required: UW-Madison must inventory and audit the IRB records for all active Federally supported research projects approved by the L&S, CALS, and SoE IRBs to determine whether the IRB review is in full accordance with all requirements of HHS regulations at 45 CFR Part 46. OHRP suggests that the All-Campus IRB oversee this audit process. UW-Madison must consult with OHRP concerning the need to suspend individual research protocols for which IRB review has been found to be deficient. By November 30, 2000, UW-Madison must report to OHRP the outcome of this review and the corrective actions taken in response to any identified deficiencies.

Action 6 - Required: By November 30, 2000, UW-Madison must submit to OHRP a written response which satisfactorily addresses all OHRP concerns cited above.

Action 7 - Recommended: OHRP recommends that UW-Madison consider consolidation of the L&S, CALS, and SoE IRBs given (i) the relatively low volume of research overseen by each; and (ii) the potential for improved efficiency and quality of review. If UW-Madison chooses not to consolidate these IRBs, OHRP strongly recommends that the membership of each be expanded to include greater diversity of professional expertise and background.

Action 8 - Recommended: OHRP strongly recommends that additional education and training regarding the regulatory requirements for human subjects protections be provided to the Chairs, members, and administrators of the L&S, CALS, and SoE IRBs.

Action 9 - Recommended: OHRP recommends that the IRBs consider adopting procedures for determining when the informed consent process should be independently monitored.

OHRP appreciates the commitment of UW-Madison to the protection of human subjects. OHRP is available to assist UW-Madison in the development and implementation of its corrective action plans. Do not hesitate to contact us should you have any questions.

Sincerely,

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Division of Human Subject Protections

Michael A. Carome, M.D.
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