DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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July 2, 2003

Sharon A. Brown, Ph.D.
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RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 2030

Dear Dr. Brown:

The Office for Human Research Protections (OHRP) has reviewed your letter dated June 24, 2003. OHRP has determined that the corrective actions summarized below adequately address the findings and concerns in OHRP's June 4, 2003 site visit letter and are appropriate under the University of Texas at Austin (UTA) FWA:

(1) In accordance with Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b) and 46.109(a), the Institutional Review Board (IRB) must review and approve all non-exempt human subject research covered by an assurance before the research may be conducted. OHRP found that certain human subjects research covered under UTA's assurance was conducted without IRB review. In specific, the research project entitled "Evaluation of the Exceptional Care Pilot Project" was conducted without prior IRB review and approval, as noted in the minutes of the December 16, 2002 IRB meeting.

Corrective Action: OHRP acknowledges that UTA has notified OHRP of the above-referenced noncompliance. In addition, a new electronic database will allow the Office of Sponsored Projects to access and verify IRB approval for all studies; projects that have not been approved by the IRB will not be implemented and an account set-up will not be authorized. Several educational efforts have been offered to train investigators about the human subjects research approval process and the Vice President will send a responsibility memo to all principal investigators delineating their responsibilities for protecting human subjects.

(2) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) and the UTA FWA require that UTA promptly report to OHRP (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. OHRP found that UTA had not reported to OHRP certain unanticipated problems involving risks to subjects or others, serious or continuing noncompliance and suspensions or terminations of IRB approval.

Corrective Action: OHRP acknowledges that the UTA IRB has since reported these incidents to OHRP. In addition, UTA has developed a web-based form to enable prompt reporting of noncompliance and adverse events, and the UTA IRB Procedure Manual is being revised to delineate a time frame and reporting structure for reporting to institutional officials and OHRP on a monthly basis instances of unanticipated problems involving risks to subjects or others, serious or continuing noncompliance with the regulations or requirements or determinations of the IRB, and suspension or termination of IRB approval. OHRP notes that more prompt reporting may be warranted in certain circumstances.

(3) OHRP found that the UTA IRB frequently approves research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB.

Corrective Action: OHRP acknowledges UTA's statement that protocols requiring substantive modifications will be subject to another IRB review prior to approval, and the Procedure Manual is being revised to clarify instances when it would be appropriate to defer approval of the proposed research.

(4) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. OHRP found that the UTA IRB minutes failed to meet these requirements regarding (a) the basis for requiring changes in research and (b) a written summary of the discussion of controverted issues. In addition, OHRP noted that the attendance appears to change during the meetings, as reflected in the votes, which in some cases appeared to exceed the attendance at the meeting. However, the minutes do not document that the quorum is maintained, that additional members entered the meeting, nor that guests such as investigators are present.

Corrective Action: OHRP acknowledges that the UTA IRB has developed a more detailed method involving a matrix of reporting IRB members' attendance/votes, and key points of discussion will be documented. In addition, regulatory requirements for vulnerable populations and for documentation of informed consent will be added to the review sheets.

(5) 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.
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> (b) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.
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> (c) The procedures for ensuring prompt reporting to the appropriate institutional officials and OHRP of: (a) any unanticipated problems involving risks to subjects or others; and (b) any suspension or termination of IRB approval.

Corrective Action: OHRP acknowledges that the UTA IRB Procedure Manual will be revised to address these procedures.

(6) 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.

Corrective Action: OHRP acknowledges that the UTA IRB will implement a process by which copies of the updated database entry for the study will be placed into the file as each IRB action is completed and documented, and the database will trace all these activities electronically. In addition, a monthly audit of IRB files is being conducted to verify current, complete documentation of each file.

(7) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* or proposal for research covered by the assurance has been reviewed and approved by the IRB. In reviewing IRB records, and in discussions with IRB members and IRB administrators, it was not clear that the IRB consistently reviews the HHS grant application for proposed research.

Corrective Action: OHRP acknowledges that the Chairman of the IRB reviews the HHS grant applications and signs a Certificate of Consistency. UTA's Office of Sponsored Projects will not release the grant funds unless they confirm on the IRB database that a Certificate of Consistency has been signed by the IRB Chairman or Vice Chairman.

(8) HHS regulations at 45 CFR 46.103(d) require that the adequacy of IRBs be evaluated in light of, among other things, the anticipated scope of the institution's research activities, the types of subject populations likely to be involved, and the size and complexity of the institution. The HHS regulations at 45 CFR 46.107(a) further require, among other things, that IRBs be (a) sufficiently qualified through the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel; and (b) able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. Institutions have a profound responsibility to ensure that all IRBs designated under an OHRP-approved assurance possess sufficient knowledge of the local research context to satisfy these requirements. OHRP expressed concern that the IRB members and chair stated that they rely upon the investigator to provide the IRB with knowledge of the local research context for research conducted in international settings, and therefore may not meet the requirements of 45 CFR 46.103(d) and 46.107(a), regarding knowledge of the local context.

Corrective Action: OHRP acknowledges that the IRB will identify countries in which research involving human subjects is conducted and will develop a consultant list of individuals to contact regarding the appropriateness of the research to be conducted in specific countries and/or cultures.

As a result, OHRP anticipates no need for further involvement in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

OHRP appreciates your institution's commitment to the protections of human subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C Borror, Ph.D.
Director, Division of Compliance Oversight
Office for Human Research Protections

cc: Dr. Clarke A. Burnham, UTA IRB Chair
Dr. Lisa Leiden, UTA
Dr. Bernard Schwetz, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP

Ms. Yvonne Higgins, OHRP
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