DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 301-435-8072
FAX: 301-402-2071

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Sharon A. Brown, Ph.D.
Associate Vice President for Research
University of Texas – Austin
101 East 27th Street
P.O. Box 7426
Austin, Texas 78713

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 2030

Dear Dr. Brown:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of human subject protection procedures at the University of Texas at Austin (UTA) on May 20-22, 2003. The evaluation, conducted by two OHRP staff and with the assistance of one consultant, included meetings with institutional officials, 17 current Institutional Review Board (IRB) members, IRB administrative staff, and numerous research investigators. The evaluation involved review of IRB files for over 20 protocols, and the minutes of over 10 IRB meetings.

In the course of the OHRP review, the IRB chair, IRB members, and IRB 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. Investigators demonstrated a culture of respect for the protection of human subjects and for the IRB process. IRB procedures for continuing review of research appear to be substantive and meaningful. Every individual interviewed expressed the sentiment that the institution has a very strong commitment to the protection of human subjects. The IRB administrative staff were helpful and accommodating to OHRP during 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 UTA:

(1) In accordance with Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b) and 46.109(a), the 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.

(2) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require that the institution have written IRB procedures that adequately describe the following activities: The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any Department or Agency head, and OHRP of: (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 finds that UTA has not reported to OHRP certain unanticipated problems involving risks to subjects or others, serious or continuing noncompliance and suspensions or terminations of IRB approval. In specific, the IRB chair and IRB members informed OHRP about events that were not reported to OHRP, such as a suspension of research involving an investigator who was conducting a medical procedure without current standing orders from a physician; the serious noncompliance noted above in the protocol entitled "Evaluation of the Exceptional Care Pilot Project;" and an unanticipated problem involving perception research in which a mother complained that her child was traumatized as a result of participating in the research

(3) OHRP finds that the IRB frequently approves research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. In specific, the IRB requested substantive modifications to and clarifications regarding the following protocols reviewed at the indicated meetings which were subsequently reviewed in an expedited manner: 2002-11-0030 on November 25, 2002; 2002-09-0068 and 2002-10-0031 on October 28, 2002; 2002-10-0081 and 2003-01-0004 on January 27, 2003.

OHRP recommends the following guidelines in such cases: When the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111, IRB approval of the proposed research should be **deferred**, pending subsequent review by the convened IRB of responsive material. 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 under an expedited review procedure.

(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 finds 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 notes 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.

(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.

(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.

(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.

(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.

Required Actions:

UTA must develop a satisfactory corrective action plan to address the above determinations.

OHRP is available to assist UTA in the development and implementation of these corrective action plans. Do not hesitate to contact me should you have any questions.

OHRP Questions and Concerns Relative to Systemic Protections for Human Subjects

(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. Please clarify. In your response please specify the procedures for IRB review of HHS grant applications.

(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 is concerned 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. Please respond.

For detailed guidance on appropriate mechanisms for ensuring that the IRB has adequate knowledge of the local research context, please see:
http://ohrp.osophs.dhhs.gov/humansubjects/guidance/local.htm

At this time, OHRP provides the following additional guidance:

(1) The UTA Template for Consent Forms, in response to the boilerplate question "what if you are injured in the study," addresses only physical risks. UTA may wish to consider adding psychological risks in the boilerplate instructions, along with an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(2) Interviews with the IRB chair, IRB members, staff and investigators indicated that UTA conducts a high percentage of research involving students as participants. UTA may wish to consider adding a student member to the IRB.

(3) OHRP recommends that each revision to a research protocol be incorporated into the written protocol. This practice ensures that there is only one complete protocol with the revision dates noted on each revised page and the first page of the protocol itself. This

procedure is consistent with the procedure used for revised and approved informed consent documents which then supersede the previous one.

(4) HHS regulations at 45 CFR 46.116(d) require that the IRB make and document four findings when approving a consent procedure which does not include, or which alters, some or all of the required elements of informed consent or when waiving the requirement to obtain informed consent. OHRP recommends that when approving such a waiver for research reviewed by the convened IRB, these findings be documented in the minutes of the IRB meeting, including *protocol-specific* information justifying each IRB finding.

Similarly, where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (b) approving research involving pregnant women, human fetuses, or neonates (see 45 CFR 46.204-207); (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), OHRP recommends that the IRB document such findings. OHRP recommends that for research approved by the convened IRB, all required findings be fully documented in the minutes of the IRB meeting, including *protocol-specific* information justifying each IRB finding.

For research reviewed under an expedited review procedure, OHRP recommends that these findings be documented by the IRB chair or other designated reviewer elsewhere in the IRB record.

OHRP appreciates your institution's commitment to the protections of human subjects.

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
Ms. Carol Weil, OHRP
Dr. Patrick McNeilly, OHRP

Ms. Shirley Hicks, OHRP
Ms. Melinda Hill, OHRP