DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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December 5, 2001

Commander Harold L. Timboe
Brooke Army Medical Center
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RE: Human Research Subject Protections Under Cooperative Project Assurance (CPA) T-3580

Dear Dr. Timboe:

The Office for Human Research Protections (OHRP) has reviewed the October 25 and 27, 2000 letter of Colonel James Lamiell regarding Brooke Army Medical Center's (BAMC) compliance with Department of Health and Human Services (HHS) regulations protecting human research subjects. OHRP has determined that the corrective actions summarized below address the issues raised in OHRP's letter of October 3, 2000, as follows:

(1) In the October 3, 2000 letter, OHRP found that BAMC's continuing reviews were not substantive and meaningful in that: (a) BAMC's continuing review form did not provide the institutional review board (IRB) a sufficient description of the progress of the research for reviewers to consider the criteria listed in 45 CFR 46.111; (b) IRB members did not receive copies of the continuing review reports or the informed consent documents prior to the convened IRB meeting; and (c) individual protocols undergoing continuing review were not routinely discussed nor acted upon separately by the convened IRB.

Corrective Action OHRP finds that BAMC's "Detail Summary Sheet" for continuing review includes a boxed area for investigators to describe the progress of the research. OHRP notes that the limited space available in the box might inhibit discussion of the criteria listed in 45 CFR 46.111, and recommends that BAMC revise its form to indicate that additional information may be supplied as needed.

OHRP further finds that the BAMC IRB's modified continuing review procedures (Standard Operating Procedures [SOP], page 39) appropriately provide for IRB members conducting continuing review (a) to receive Detail Summaries and informed consent documentation in advance of the convened meeting, and (b) to discuss and act upon protocols undergoing continuing review individually.

(2) In the October 3, 2000 letter, OHRP expressed concern that the IRB consistently failed to comply with HHS regulations at 45 CFR 46.115(a)(2), which require documentation of 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 BAMC's IRB minutes prior to October 5, 2000 failed to comply with HHS regulations at 45 CFR 46.115(a)(2).

Corrective Action: OHRP finds that BAMC's October 5, 2000 IRB minutes document protocol and informed consent changes recommended by the IRB. OHRP recommends that the IRB expand discussion in the minutes of suggested changes to research, to include the IRB's analysis of why the changes are needed, and details of the IRB's deliberations concerning such changes.

(3) In the October 3, 2000 letter, OHRP expressed concern that the minutes of BAMC's IRB meetings did not indicate that approval of protocols was based upon consideration of the determinations required under 45 CFR 46.111, including that (i) risks to subjects are minimized; (ii) risks are reasonable in relation to benefits; (iii) selection of subjects is equitable and recruitment procedures appropriate; (iv) privacy and confidentiality of subjects are adequately protected; and (v) appropriate safeguards are in place to protect vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

OHRP finds that the minutes of BAMC's IRB meetings prior to October 5, 2000 did not indicate that approval of protocols was based upon consideration of the determinations required under 45 CFR 46.111.

Corrective Action: OHRP finds that (a) BAMC's initial review policies dated October 24, 2000 require IRB members to determine the criteria set forth at 45 CFR 46.111, and (b) BAMC's October 5, 2000 minutes include the following standard paragraph within the discussion section for each protocol, indicating that for each protocol, the IRB duly considered the requirements of 45 CFR 46.111 and found that they were met:

> The Board felt the investigator has undertaken every effort to minimize risk to the subject and the IRB has judged the risk to subjects reasonable in relation of the potential benefit. The members of the Board were satisfied with the investigators's provision for subject privacy and confidentiality. Recruitment of potential subjects was judged to be equitable. The Board felt the investigator's methods safeguarded the rights of vulnerable subjects.

(4) OHRP expressed concern that BAMC's arrangement with Wilford Hall Medical Center to permit the IRB from either institution to review and approve certain HHS-supported cooperative research projects had not been approved by OHRP, as required under HHS regulations at 45 CFR 46.114.

Corrective Action: On October 27, 2000, BAMC submitted to OHRP a Cooperative Amendment to its assurance to enable either BAMC's IRB or Wilford Hall Medical Center's IRB to approve cooperatively conducted research.

(5) In the October 3 letter, OHRP expressed concern that the BAMC IRB did not have written policies, as required at 45 CFR 46.103(b)(4) and (5), for (a) conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; and (b) ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of (i) any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

OHRP finds that prior to October 24, 2000, the BAMC IRB did not have written policies, as required at 45 CFR 46.103(b)(4) and (5), for (a) conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; and (b) ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of (i) any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

Corrective Action: OHRP finds that BAMC developed written policies for conducting initial and continuing review of research and for reporting findings and actions to the investigator and institution, as required by 45 CFR 46.103(b)(4) (SOP pages 36-40). OHRP recommends that BAMC expand these policies to include a description of review outcomes (approval, deferral, etc.) and procedures for review of protocols that were previously reviewed but not approved. 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 should 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 under an expedited review procedure.

OHRP further finds that BAMC developed written policies for reporting adverse events to the IRB, including unanticipated problems involving risks to subjects or others, as required by 45 CFR 46.103(b)(5). OHRP recommends that BAMC expand its reporting policies in order to comply fully with this regulation, to include specific procedures for reporting serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and any suspension or termination of IRB approval. Furthermore, OHRP notes that in addition to the IRB, appropriate institutional officials and the Department or Agency head must be notified under 45 CFR 46.103(b)(5).

(6) In the October 3, 2000 letter, OHRP found exculpatory, in violation of HHS regulations at 45 CFR 46.116, BAMC's policy of permitting investigators to ask human research subjects to relinquish "ownership and rights to tissue or fluid."

Corrective Action: OHRP finds that BAMC has removed the policy permitting investigators to ask human research subjects to relinquish "ownership and rights to tissue or fluid" from its SOP.

Presuming full implementation of the corrective actions set forth above, 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 your institution 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.
Compliance Oversight Coordinator
Division of Human Subject Protections

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