DEPARTMENT OF HEALTH & HUMAN SERVICES

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October 3, 2000

Commander Harold L. Timboe
Brooke Army Medical Center
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Fort Sam Houston, TX 78234-6200

RE: Human Research Subject Protections Under Cooperative Project Assurance (CPA) T-3580
Southwest Oncology Group (SWOG) Clinical Trials

Dear Dr. Timboe:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed Brooke Army Medical Center's (BAMC's) September 22, 1999 report and July 21, 2000 addendum with additional IRB minutes and continuing review documentation, relating to allegations of possible noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects involving the above referenced research.

Based upon its review, OHRP makes the following determinations:

(1) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the Institutional Review Board (IRB) review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP found that certain amendments to SWOG protocols were not submitted to the IRB for review and approval prior to their initiation.

Corrective Action: OHRP acknowledges that (i) all previously unapproved amendments to SWOG protocols referenced in the Clinical Trials Monitoring Branch Final Audit Report have been approved by the IRB; and (ii) BAMC has implemented procedures to ensure that all protocol amendments are reviewed and approved by the IRB in a timely manner.

(2) OPRR finds that the concerns regarding the use of expedited review and the adequacy of informed consent documents were adequately addressed by COL Longfield's report.

(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 prior to the IRB meeting a protocol summary and a status report on the progress of the research, including (i) the number of subjects accrued; (ii) 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; (iii) 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 (iv) 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 (see OPRR Reports 95-01). 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 IRB regularly failed to satisfy these requirements. In specific, OHRP finds that for research requiring continuing review by the convened IRB (a) the continuing review form has routinely failed to provide a description of the progress of the research sufficient to enable reviewers to consider the criteria listed in 45 CFR 46.111; (b) IRB members do 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 are not routinely discussed nor acted upon separately by the convened IRB.

Required Action: BAMC must suspend immediately any HHS-supported research studies that are not eligible for an expedited review procedure, which received initial IRB approval prior to October 3, 1999. OHRP requests that BAMC provide to OHRP with a list of all HHS-supported research projects subject to this suspension.

For any project affected by this suspension, enrollment of new subjects must cease immediately except in extraordinary cases approved in advance by OHRP (OHRP would expect requests for approval of such cases to be rare). Furthermore, research activities involving previously enrolled subjects may continue only where the IRB finds that it is in the best interests of individual subjects to do so. For each affected protocol, this suspension must remain in effect until the protocol has undergone substantive and meaningful continuing review and been re-approved by the convened IRB. OHRP anticipates that implementation of this required action would necessarily include the following steps:

(a) Principal investigators will need to submit new continuing review reports that provide an adequate summary of the progress of the research so that the IRB can make the determinations required by 45 CFR 46.111.

(b) Copies of the continuing review reports and the informed consent documents

should be distributed to IRB members prior to the convened IRB meeting.

(c) Individual protocols requiring continuing review should be individually discussed and acted upon, and the vote on such actions should be recorded in the minutes of IRB meetings in accordance with HHS regulations at 45 CFR 46.115(a)(2).

OHRP has the following additional concerns, questions, and guidance:

(4) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be in sufficient detail to show the basis for requiring changes in or disapproving research and a written summary of the discussion of controverted issues and their resolution. OHRP is concerned that the minutes of IRB meetings provided by BAMC fail to meet these requirements. In specific, OHRP notes the following:

(a) The discussion of protocols undergoing initial review routinely includes only a brief summary of research objectives, and the action taken by the IRB.

(b) The minutes frequently indicate that studies were approved with minor changes, but such changes and the basis for such changes are not documented in the IRB minutes.

Please respond.

(5) HHS regulations at 45 CFR 46.111 require the IRB to ensure that certain criteria are satisfied before research is approved by the IRB, including but not limited to the following determinations: (i) risks to subjects are minimized; (ii) risks to subjects 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 is concerned that the BAMC IRB minutes appear to reveal little evidence that IRB approval of research is consistently based on consideration of the determinations required under HHS regulations at 45 CFR 46.111. In specific, the IRB appears not to consider systematically and rigorously such issues as equitable selection of subjects and subject recruitment, privacy and confidentiality protections, and special protections required for vulnerable subjects. Please respond.

(6) With OHRP approval, the HHS regulations at 45 CFR 46.114 permit an institution participating in a cooperative project to rely upon the review of another qualified IRB. COL Longfield's September 22, 2000 letter indicates that Brooke Army Medical Center and Wilford Hall Medical Center have established procedures under which certain HHS-supported research may be reviewed by either the BAMC or WHMC IRB on behalf of both institutions. OHRP has no record of approving such a procedure. Please respond.

The usual mechanism for obtaining OHRP approval of such a cooperative procedure for IRB review is submission of a cooperative amendment to your Assurances. Please find enclosed a sample cooperative amendment document (the same document can be downloaded from OPRR's website at http://grants.nih.gov/grants/oprr/humansubjects/assurance/mpa-ca.htm).

(7) OHRP is concerned that BAMC does 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) and (5):

> (a) The procedures which the IRB will follow for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution.
>
> (b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and 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.

The Standard Operating Procedures for the above activities should be expanded to include operational details for each of the above procedures. Please submit revised IRB policies and procedures.

(8) HHS regulations at 45 CFR 46.116 prohibit any exculpatory language in the informed consent process through which the subject is made to waive, or appear to waive, any of the subject's legal rights. OHRP notes the following statement in Section 2-5 of the BAMC Administration of the Clinical Investigation Program Standard Operating Procedures:

> "The donor [of tissue or biologic samples for research purposes] may be asked separately to relinquish ownership and rights to tissue or fluid."

This statement appears to be exculpatory and should not be used when obtaining consent from research subjects, even if done separately. Please respond.

Please respond to the above concerns and questions above no later than October 31, 2000. Please note that since these issues and concerns relate to the performance of the IRB, it would be appropriate for someone other than the IRB Chairperson to investigate this matter and respond to OHRP.

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 Compliance Oversight

Enclosure: Sample Cooperative Agreement

cc: Jenice N. Longfield, M.D., BAMC
John R. Caton, Jr., MD, BAMC
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