DEPARTMENT OF HEALTH & HUMAN SERVICES

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November 29, 2000

William R. Tash, Ph.D.
Vice Provost for Research
Temple University
University Services Building, Room 406
Philadelphia, PA 19122

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1442

Research Projects: Radiation Therapy Oncology Group (RTOG) protocols #9202, #9408, and #9413

Dear Dr. Tash:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your July 28, 1999 report regarding the above referenced research projects. OHRP apologizes for the delay in its response to your report.

Based upon its review of your report, OHRP has determined that the Temple University (TU) Institutional Review Board (IRB) did not fail to conduct continuing review at least annually of the above referenced research projects as required by Department of Health and Human Services regulations at 45 CFR 46.109(e). In particular, OHRP acknowledges your report that (i) in August 1997, Dr. Thomas, the principal investigator on RTOG protocols, submitted his resignation from TU, effective February 1998, and informed the RTOG Chair that TU was resigning from the RTOG; and (ii) following Dr. Thomas' departure from TU, all RTOG protocols were administratively closed by the IRB.

As a result of the above determination, there should be no need for further OHRP involvement in this matter. Of course, TU should notify OHRP promptly of any new information that might alter this determination.

At this time OHRP would like to provide the following additional guidance:

(1) The written IRB policies and procedures should be expanded to include additional operational details for each of the following procedures, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

(a) The procedures which the IRB follows for conducting continuing review of research.

(b) The procedures which the IRB follows for reporting their findings and actions to the investigator and the institution.

(c) The procedures which the IRB follows for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(d) The procedure which the IRB follows 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.

(e) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, OHRP and any supporting Department or Agency head of (i) any unanticipated problems involving risks to subjects or others; (iii) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval.

(2) Written IRB policies and procedures should specify the documents and materials that are provided to primary reviewers (if any) and all other IRB members prior to the IRB meetings for protocols undergoing initial or continuing review.

(3) 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. In accordance with this requirement, at least one member of the IRB should receive a complete copy of any applicable Federal grant application or proposal.

(4) 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 (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.

When conducting research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above referenced documentation.

(5) IRBs must determine which protocols require continuing review more often than annually, as appropriate to the degree of risk [see 45 CFR 46.103(b)(4) and 46.109(e)]. OHRP recommends that the minutes of IRB meetings clearly reflect these determinations regarding risk and approval period (review interval) for each protocol that is approved.

(6) HHS regulations at 45 CFR 46.115(a)(2) require that the minutes of IRB meetings document the vote on all IRB actions including the number of members voting for, against, and abstaining. In order to document the continued existence of a quorum, OHRP strongly recommends that votes be recorded in the minutes using the following format: Total = 15; Vote: For-14, Opposed-0, Abstained-1 (NAME). Please note that recording votes as unanimous is not sufficient.

(7) Where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (b) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) 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 appreciates the commitment of TU to the protection of human subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Dr. Friedrich Kueppers, Chairperson, IRB, Temple University Health Sciences Center
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Ms. Joan Mauer, CTEP, NCI, NIH
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. J. Thomas Puglisi, OHRP
Dr. Jeffrey Cohen, OHRP
Dr. Katherine Duncan, OHRP
Ms. Freda Yoder, OHRP
Mr. Barry Bowman, OHRP