DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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Gerald Litwack, Ph.D.

RE: Human Research Subject Protections Under Multiple Project Assurances (MPA) — M-1231 and M-1115

Research Project: Phase I Dose Escalation Study of Multiple Fraction Stereotactic Radiotherapy for the Treatment of Intracranial Arteriovenous Malformations
Principal Investigator: David W. Andrews

Dear Dr. Tasman, Mr. Kessler, Dr. Litwack and Mr. Lewis:

The Office for Human Research Protections (OHRP) has reviewed the reports from Wills Eye Hospital (WEH) and Thomas Jefferson University (TJU) dated June 6, 2001 and June 7, 2001, respectively, that were submitted in response to OHRP's determination letter of April 23, 2001.

(1) In reviewing the documents submitted by WEH and TJU, OHRP notes the following:

(a) The proposed plan for contacting subjects involved in the above-referenced research included the following components:

(i) An initial contact with the subjects during a follow-up visit scheduled by Dr. Rosenwasser.

(ii) Each subject being sent a letter requesting an in-person or telephone interview.

(iii) Each subject being informed of his or her participation during the scheduled interview.

(b) The Draft Rosenwasser contact letter (Exhibit 15) stated "Please be aware that this interview is not related in any way with the outcome of the clinical care you received."

(c) The "Draft [Stereotactic Radiosurgery (SRS)] SRS Script" (Exhibit 17) includes the following statements:

(i) "OHRP looked at your treatment and believes that it should have been recognized as a research study and submitted to our [Institutional Review Board (IRB)] IRB for approval."

(ii) "The consent form you signed before receiving SRS disclosed many of the specific medical risks associated with this form of treatment. That consent form was a valid treatment consent form."

(iii) "However, whether or not a particular treatment is or is not research is a complex issue. A committee at Thomas Jefferson University, including an outside expert conducted an independent review and found that the SRS you received was treatment and not research."

(2) OHRP finds that the proposed TJU/WEH plan for debriefing subjects involved in the above referenced research is not adequate. OHRP expects that the debriefing text to include at a minimum the following elements:

(a) An accurate explanation of the purpose of the research.

(b) A simple, complete, and accurate description of all research procedures that the subjects underwent.

(c) A description of the reasonably foreseeable risks and discomforts of the research.

(d) A description of any benefits to the subjects or others that may have resulted from the research.

(e) A statement of the appropriate procedures or courses of treatment that might have been advantageous to the subject.

(f) An explanation of whom to contact if the subject has any questions about their

rights as a research subject.

(g) A statement that the data from the subject was published in an abstract describing the research.

(h) A statement that the consent form signed by the subject was not adequate for use in a research protocol.

(3) The TJU/WEH plan for contacting subjects fails to take into consideration the possibility that a subject may not schedule a follow-up visit and therefore may not receive the initial notice from Dr. Rosenwasser. TJU/WEH in conjunction with its IRBs should develop a proactive plan to contact all subjects involved.

(4) The SRS script included the statement: "That consent form was a valid treatment consent form." Subjects would not be in a position to assess the accuracy of this statement and also would not be able to determine the difference between a treatment and research consent form. It would be appropriate for this statement to be removed from the SRS script.

(5) OHRP notes that the minutes of the TJU/Methodist Hospital IRB meeting held June 5, 2001 indicated that a motion was passed by the IRB calling for the deletion of the statement in the SRS script which reads, "A committee at TJU, including an outside expert, conducted an independent review and found that the SRS you received was treatment and not research." OHRP finds no evidence that this motion by a TJU IRB was taken into consideration when developing the SRS script. OHRP agrees with the position of the TJU/Methodist Hospital IRB and agrees that this statement should be deleted from the SRS script.

(6) OHRP notes that the minutes of the May 17, 2001 special meeting of the combined on-campus IRBs acknowledged that fourteen subjects are surviving but it appears that the plan for contacting subjects includes only thirteen subjects. This point was also evident in the June 5, 2001 meeting of the TJU/Methodist Hospital IRB which indicated that thirteen subjects were to be contacted. OHRP requires that efforts be made to contact **all** subjects as part of the required action 1 of its April 23, 2001 letter.

Action 1 - Required: By November 16, 2001, TJU and WEH must submit to OHRP a revised plan for contacting subjects who were involved in the above-referenced research prior to IRB approval. The revised plan must address all of the concerns raised in items 1-6 above.

(7) 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. Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol that requires continuing review by the convened IRB.

Based upon OHRP's review of the June 6 and June 7, 2001 reports, as well as information provided during a conference call with TJU officials on August 15, 2001, OHRP finds that continuing review of research by the convened TJU IRBs has not been substantive nor meaningful. Nearly all protocols undergoing continuing review have neither individually been presented nor discussed at a convened meeting of the TJU IRBs.

OHRP acknowledges the recent implementation of a new continuing review policy for the TJU IRBs. OHRP has reviewed a copy of this policy which was included as part of TJU's August 15, 2001 letter to OHRP. This new policy should ensure substantive and meaningful continuing review by the TJU IRB.

Action 2 - Required: TJU must suspend immediately any Federally supported research projects (as well as any other research protocols covered by MPA M-1115) that were not eligible for an expedited review procedure and did not undergo substantive and meaningful continuing review by the convened IRB during the past one year period. 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.

By November 16, 2001, TJU must submit to OHRP a list of all research activities which have been suspended as a result of this action.

(8) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the 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 finds that the TJU IRB's procedure for reviewing protocol modifications is inadequate. OHRP's review of minutes of IRB meetings along with discussions during a conference call with TJU officials on August 15, 2001 indicated that changes to protocols are reviewed by a subcommittee of the IRB and are voted on in a block fashion without substantive discussion at IRB meetings.

(9) OHRP is concerned about the recording of votes during TJU IRB meetings. It is

OHRP's understanding that for other than initial review of protocols, each IRB votes separately on continuing reviews and amendments. The votes from each IRB are then tallied. OHRP is concerned that having each TJU IRB separately act and vote upon the same research may not provide for full discussion by the IRB. For example, OHRP in unclear of (i) how members of one IRB are made aware of concerns by another IRB; (ii) if one IRB has approved a protocol can the second IRB overrule the decision; and (iii) how are such conflicts resolved.

Action 3 - Required: By November 16, 2001, TJU and WEH must submit to OHRP a corrective action plan to adequately address items 8 and 9 above.

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,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. David G. Brock, Chairperson, IRB-01, TJU
Dr. Stephen P. Weinstein, Chairperson, IRB-02, TJU
Dr. Gregory Mokrynski, Chairperson, IRB-03XB, TJU
Dr. Larry Donoso, IRB Administrator, WEH
Dr. Carl Regillo, Chairperson, IRB, WEH
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