DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

FOR US POSTAL SERVICE DELIVERY:

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August 1, 2001

William Tasman, M.D.
Ophthalmologist-in-Chief
Wills Eye Hospital
900 Walnut Street
Philadelphia, PA 19107-5598

Gerald Litwack, Ph.D.
Vice Dean for Research
Thomas Jefferson University
1020 Locust Street, M-5
Philadelphia, PA 19107-6799

RE: Human 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: Dr. David Andrews

Dear Dr. Tasman and Dr. Litwack:

The Office for Human Research Protections (OHRP) has received your June 6 and June 7, 2001 letters requesting that the Director of OHRP review the findings made by OHRP's Division of Compliance Oversight in its April 23, 2001 letter regarding the above referenced research activity.

OHRP recognizes that the distinction between research and clinical practice is often blurred and the application of innovative therapy in the management of patients does not necessarily make such

activities research. Of note, the Belmont Report states the following regarding the boundaries between research and clinical practice:

> (1) "The distinction between research and practice is blurred partly because both often occur together."
> (2) "Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; *the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects."* (Emphasis added)

With the principles expressed by the Belmont Report in mind, I have reviewed OHRP's findings regarding the above referenced matter and the basis for the findings. My evaluation included (i) a review of key documents previously submitted to OHRP by Thomas Jefferson University (TJU) and Wills Eye Hospital (WEH) in August 1999; TJU's letters of April 20, May 2, and June 6, 2001; and WEH's letter of June 7, 2001; and (ii) discussions with OHRP's compliance oversight staff.

Based upon my review, I concur with the findings and required actions stipulated by OHRP in its April 23, 2001 letter. In particular, I concur with the finding that the activities involving fractionated stereotactic radiosurgery for treatment of large arteriovenous malformations for 14 patients treated prior to approval of protocol #97.9011 under the direction of Dr. Andrews represented research involving human subjects.

I appreciate the willingness of TJU and WEH to develop and implement appropriate substantive corrective actions to address the areas of noncompliance identified by OHRP and strengthen their programs for protection of human subjects. In light of the recommendations made in TJU's Report of the Ad Hoc Investigation Committee dated January 31, 2001, TJU and WEH may wish to consider establishing clear policies and procedures, and perhaps a committee, to independently review proposed innovative therapeutic interventions in order to determine in advance whether a particular intervention involves human subject research and should be conducted under an Institutional Review Board approved protocol. Some medical centers have already done this, and others are doing so, recognizing the need for greater clarity in this area.

OHRP appreciates your institutions' commitment to the protection of human subjects. Please feel free to contact me if you have additional questions regarding this matter.

Sincerely,

Greg Koski, Ph.D., M.D.

Director
Office for Human Research Protections

cc: Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Patrick McNeilly, OHRP