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April 23, 2001

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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), formerly the Office for Protection from Research Risks (OPRR), has reviewed reports from Wills Eye Hospital (WEH) and Thomas Jefferson University (TJU) dated July 29, 1999 and August 25, 1999, respectively, regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations at 45 CFR Part 46 for the protection of human subjects involving the above referenced research.

In reviewing the documents submitted by WEH, TJU, and their attorneys, OHRP notes the following:

(1) In an abstract published as part of the proceedings of the LINAC Radiosurgery Meeting (December 11-15, 1996) entitled *Treatment of Large AVMs with Hypofractionated Stereotactic Radiosurgery* [HSRS], (D.W. Andrews, *et al*). The authors stated:

(a) "11 females and 3 males with a mean age of 39 years were treated from December, 1994 through July, 1996 with a mean follow-up of 10 ± 1.9 months (range 2 to 20 months)."

(b) "After Institutional review and approval, we initiated a dose seeking toxicity study to evaluate the tolerance of HSRS in patients with AVMs [arteriovenous malformations] judged to either be inoperable, or partially or completely inaccessible to endovascular embolization."

(c) "Eight patients were enrolled in six alternate day treatments of 7 Gy fractions each for a total treatment dose of 42 Gy."

(d) "Two patients experience neurologic deficits related to brain swelling around the nidus both of whom improved on a course of steroids"

(e) "In a third case, the patient experienced edema surrounding the nidus which improved on steroids. In the eleventh month, he sustained a stroke which was attributed to venous hypertension from a prematurely thrombosed vein draining the nidus."

(f) "Given this morbidity, we dropped the fraction dose to 5 Gy and the total dose to 30 Gy."

(g) "We caution that toxicity at higher doses may be related to rapid and premature thrombosis of important draining veins leading to unacceptable morbidity."

(2) Dr. David W. Andrews first submitted a protocol entitled *Phase III Study Evaluating Fixed-Frame Single Fraction Radio Surgery of Small Arteriovenous Malformations and*

Phase I Study Evaluating Multiple Fraction Stereotactic Radiotherapy for the Treatment of Large Arteriovenous Malformations (Protocol # 96.9117) for Institutional Review Board (IRB) review and approval on January 5, 1996. OHRP notes the following regarding this protocol:

(a) The submitted copy of the protocol indicated that it was version 4 and is dated December 21, 1995.

(b) One of the purposes of this study was "To evaluate the immediate, subacute and chronic CNS toxicity of high dose multiple fractionated stereotactic radiotherapy (SRT) in the treatment of large AVMs (>20mm)."

(c) The dose prescription for the Phase I study as indicated in the protocol was "700 cGy fractions every other day over two weeks, for a total of 4200 cGy."

(d) The Risk/Benefit section of the protocol stated: "The major risk of therapy is delayed effects of radiation therapy, notably radiation necrosis. Given all extant data, we anticipate no greater than 3 % morbidity associated with delayed radiation necrosis. Risk of blindness or decreased visual acuity is an additional risk of this procedure for any lesion irradiated near the optic apparatus, as are cranial neuropathies for brainstem lesions."

(e) According to the minutes of the January 5, 1996 TJU IRB meeting, this protocol was tabled by the IRB for extensive revisions to the protocol and consent form. This protocol was discontinued by Dr. Andrews on September 10, 1996 after submitting a subsequent protocol.

(3) The TJU IRB approved a subsequent protocol entitled *Phase I Study Evaluating Multiple Fraction Stereotactic Radiotherapy for the Treatment of Large Arteriovenous Malformations* (Protocol # 96.9011) on July 25, 1996. OHRP notes the following regarding this protocol:

(a) The purpose and radiotherapy dose prescription for this study was the same as that for the protocol listed above under item (2).

(b) The protocol stated, "If two patients experience severe symptoms in the immediate, subacute or chronic period of post-treatment surveillance, the current dose regimen of 7 Gy over six alternate day fractions will be terminated. We will re-initiate SRT for patients who meet the same entry criteria with a dose of 5 Gy over six alternate day fractions. This represents a cumulative dose-reduction from 42 Gy to 30 Gy."

(c) In response to a question on the TJU request for review of research proposal form for this protocol regarding why the risks are reasonable in relation to the anticipated benefits to the subjects (question #6), Dr. Andrews stated, "We feel the multiple fraction treatment will allow a higher dose to be delivered safely to the nidus, and hopefully, a higher rate of angiographic obliteration and a shorter latency period. Since this has never been attempted, we of course must begin with a Phase I evaluation of response to treatment, as outlined in the protocol."

(d) This protocol was approved by the IRB for enrollment of eight subjects.

(4) TJU has provided a list of subjects treated under the protocol described above. This list includes fourteen subjects who participated in the research involving stereotactic radiosurgery from January 9, 1995 through July 15, 1996, prior to TJU IRB approval for the above referenced phase I study (protocol # 96.9011).

(5) A consent document provided by WEH that was signed by a subject (GP) on January 9, 1995 stated:

(a) "I agree to participate in a clinical research study. The study is being carried out at the Wills Neurosensory Institute."

(b) "The purpose of this study is to evaluate the benefits and potential side effects of fractionated radiation given to a small area of the brain for patients with brain lesions that are symptomatic and if untreated, may cause great harm."

(c) "I understand that participation in this study is optional for me."

(6) The first request for continuing review of research Protocol # 96.9011 submitted by Dr. Andrews on September 4, 1997 indicated the following:

(a) Twelve subjects had entered the protocol since the last approval on July 25, 1996.

(b) A total of 26 subjects had entered the protocol to date.

(c) One subject had a major adverse reaction not on the consent form.

(7) According to Dr. Andrews' deposition of October 22, 1998:

(a) It was Dr. Andrews' intention of submitting the research protocol to the IRB for review when he had first written the protocol on November 14, 1994.

(b) Dr. Andrews indicated that, in retrospect, IRB approval should have been obtained prior to treating the first subject.

(c) Dr. Andrews indicated that he had never treated a patient with a large AVM similar to the first subject with fractionated radiosurgery.

(8) According to Dr. Walter Curran's deposition of April 9, 1998:

(a) Dr. Curran indicated that the use of a fractionated radiation dose of 42 Gy for the treatment of large AVMs was a novel therapy.

(b) Dr. Curran indicated that the treatment of the first eight patients undergoing a fractionated radiation dose of 42 Gy was a pilot experience.

(c) Dr. Curran indicated that the reasons for using this fractionated dose regimen was:

(i) The substantial lack of other alternative therapies.

(ii) The available information suggesting that the regimen was well tolerated in another cohort of patients involving intracranial tumors.

(9) The report of the IRB Investigation Committee for Non-Compliance with Human Subjects Regulations provided with your August 25, 1999 letter stated:

(a) "Dr. Andrews treated seven patients between 1/9/95 and 11/13/95 with a dose regimen of 7 Gy over six fractions. From 2/9/96 through 7/15/96 he treated seven additional patients with 5 Gy fractions over 6 treatments. The latter 7 patients were dropped to a lower dose based on a delayed complication in one of the earlier patients."

(b) "Of the total of 31 patients treated both off and on the IRB-approved protocol, 5 of the original 7 patients treated at 7 Gy are cured of their disease without any associated treatment related morbidity. One patient still manifests a small residual nidus on MRI scan, but otherwise remains normal. There was one serious complication in a patient who developed a venous thrombosis 10 months after F/SRT, which led to a severe stroke. This complication had not been seen before and has not been seen since."

(c) "The first indication that Dr. Andrews treated 14 patients prior to IRB approval was in July of 1998 when Dr. Kalf was called to give a deposition in a legal case."

(d) "He [Dr. Andrews] also stated that he did not provide the patient with a copy of the signed consent form unless the patient requested one."

(10) A cooperative agreement between TJU and WEH for the reliance on each others' IRBs was signed and approved by OPRR on March 29, 1995. This cooperative agreement states that any time all of the human subjects of a research activity will be exclusively accrued at only one of the institutions, the IRB of that institution will review for both participating institutions. Additionally, any time human subjects of a research activity will be seen at both institutions, responsible institutional officials shall have the authority to decide which IRB shall review for both institutions.

OHRP Findings Regarding the Above Referenced Activities

Based upon its review of the above referenced materials, OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.102(d) define research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for the purposes of the Federal Regulations at 45 CFR Part 46 whether or not they are conducted or supported under a program which is considered research for other purposes. HHS regulations at 45 CFR 46.102(f) define a human subject as a living individual about whom an investigator conducting research obtains (i) data through intervention or interaction with the individual; or (ii) identifiable private information.

OHRP finds that the activities involving fractionated stereotactic radiosurgery (SRS) for treatment of large AVMs for 14 patients treated prior to approval of Protocol # 96.9001 under the direction of Dr. Andrews unequivocally represented research involving human subjects. Specifically, OHRP finds that Dr. Andrews in a prospective and systematic manner collected clinical data on the safety and efficacy of SRS in the treatment of large AVMs between January 1995 and July 1996.

(2) HHS regulations at 45 CFR 46.109(a) and the WEH and TJU MPAs require that all research involving human subjects that is not exempt be reviewed and approved by the IRB.

OHRP finds that the research involving SRS prior to July 1996 was not exempt under HHS regulations at 45 CFR 46.101(b) and was initiated without review and approval by either the WEH or TJU IRB.

(3) HHS regulations at 45 CFR 46.116 stipulate that, except as provided by the regulations, no investigator may involve a human subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. This regulatory requirement is based upon the principle of respect for persons, one of the three basic ethical principles embraced by WEH and TJU in their MPAs and presented in the Belmont Report, upon which the HHS regulations are premised. In its discussion of this ethical principle, the Belmont Report states that "individuals should be treated as autonomous agents. . . . In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information."

OHRP finds that the research involving SRS for the treatment of large AVMs prior to July 1996 was conducted without the investigators obtaining the legally effective informed consent of the subjects or the subjects' legally authorized representatives as approved by the IRB.

(4) HHS regulations at 45 CFR 46.111(a)(1) and (2) require that in order to approve research covered by the regulations the IRB shall determine, among other things, that risks to subjects are minimized and reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result.

OHRP finds that because Dr. Andrews failed to obtain IRB review and approval for this research these regulatory requirements, among others, were not satisfied.

(5) HHS regulations at 45 CFR 46.102(i) define minimal risk as when the probability and magnitude of harm or discomfort anticipated are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Due to the unique nature of the technique employed and the risks described in the protocol and informed consent document, OHRP finds that this research involved greater than minimal risk to the subjects.

(6) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. OHRP notes the following:

(a) The TJU IRB approved Protocol 96.9011 on July 25, 1996.

(b) The TJU IRB's initial continuing review and approval of protocol #96.9011 occurred on September 11, 1997.

(c) Between July 25, 1997 and September 11, 1997 two subjects were enrolled in the study.

OHRP finds that the TJU IRB failed to meet the requirements at 45 CFR 46.109(e) for performing continuing review on at least an annual basis.

(7) 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 no documentation that the TJU IRB reviewed and approved the following protocol changes prior to their initiation:

(a) According to the continuing review request submitted by Dr. Andrews on September 4, 1997, 12 subjects were enrolled in the IRB-approved research described in Protocol # 96.9011 which was approved for enrollment of only eight subjects.

(b) The IRB-approved protocol indicated " If two patients experience severe symptoms in the immediate, subacute or chronic period of post-treatment surveillance, the current dose regimen of 7 Gy over six alternate day fractions will be terminated. We will re-initiate SRT for patients who meet the same entry criteria with a dose of 5 Gy over six alternate day fractions. This represents a cumulative dose-reduction from 42 Gy to 30 Gy." Evidence from the abstracts by Andrews D.W. et al and Armoda R.A., et al, indicate that the first 8 patients treated before the protocol was submitted to the IRB (from 1/9/95 to 11/13/95) received the 42 Gy total dose but because of severe symptoms, the remaining patients received a total dose of 30 Gy.

(c) The TJU IRB apparently approved the protocol for continued enrollment of human subjects on September 11, 1997 without reflecting these changes to the protocol.

(8) HHS regulations at 45 CFR 46.103(a), 46.103(b)(5), and 46.108(a) require that any unanticipated problems involving risks to subjects or any serious or continuing noncompliance with regulations relating to the protection of human subjects are promptly reported to appropriate institutional officials, appropriate Federal Department of Agency heads, and OHRP.

As was noted above, the TJU IRB received a continuing review report which indicated that Protocol # 96.9011 had enrolled 12 subjects during its first year and had a total of 26 subjects enrolled and in July of 1998 Dr. George F. Kalf, Executive Secretary of the TJU IRB and Assistant Dean for Scientific Affairs, learned that 14 subjects had been enrolled in this study prior to it being given IRB approval.

OHRP finds that the enrollment of 14 subjects into the research study involving SRS for the treatment of large AVMs prior to IRB approval was an example of serious noncompliance with the regulations for the protection of human subjects. Furthermore, OHRP finds that TJU and its IRB failed to take any action, including reporting to OHRP, with respect to this serious noncompliance until May 24, 1999 after Dr. Andrews failed to provide the IRB with a continuing review report for this study.

Additionally, OHRP finds no evidence in the documents submitted by WEH and TJU that any IRB ever reviewed or reported the serious adverse reaction indicated by Dr. Andrews on his September 4, 1997 request for continuing review prior to OHRP's inquiry of June 7, 1999.

OHRP acknowledges that the research involving SRS under Protocol 96.9011 for the treatment of large AVMs was automatically terminated on September 10, 1998 by the TJU IRB for failure to provide a continuing review report.

Action 1 - Required: The WEH and TJU IRBs, in conjunction with its investigators and other officials, must develop a satisfactory plan, including both the means and the content, for contacting all surviving subjects (or the guardians or surviving relatives of subjects who are now incapacitated or deceased) who participated in human subject research referenced in the documents above prior to IRB approval being obtained by the investigators, and informing them of their previous unwitting participation in the research, the risks associated with the research, and the nature of noncompliance by the investigators with the requirements of HHS regulations at 45 CFR 46 Part 46. By June 8, 2001, please submit to OHRP a written report regarding the IRB's determinations and plan for this matter and the documentation underlying these determinations, including relevant IRB minutes and the proposed text for debriefing the research subjects and/or their guardians or survivors.

Action 2 - Required: The WEH and TJU, in conjunction with all of its investigators and clinical practitioners, as well as relevant administrators, must audit and identify all ongoing research projects involving human subjects that are not exempt under HHS regulations at 45 CFR 46,101(b) and confirm that all such research has been reviewed and approved by the WEH and/or TJU IRBs. By June 8, 2001, please provide OHRP with a summary report on the results of this audit and a list of any research activities that have been suspended as a result of this audit.

Action 3 - Required: By June 8, 2001, WEH and TJU must submit to OHRP a detailed plan for ensuring that all research investigators, all IRB members and all IRB staff at their respective institutions are appropriately educated, on an ongoing basis, about ethical principles and regulatory requirements for the protection of human subjects.

Action 4 - Required: By June 8, 2001, the WEH and TJU must provide an updated report on the status of Dr. Andrews compliance with the requirements set forth by the TJU IRB in its Report of the Institutional Review Board Investigation Committee for Non-Compliance with Human Subjects Regulations. Furthermore, WEH and TJU must provide OHRP with an update on the status of any projects for which Dr. Andrews is listed as principal investigator or co-investigator. This update should include any projects that Dr. Andrews has submitted to the IRBs for review along with the actions the IRBs have taken on such projects.

Additional Finding, Concerns, and Guidance Regarding WEH and TJU's Systemic Protections for Human Subjects

(9) HHS regulations at 45 CFR 46.115(a)(2) require that the minutes of IRB meetings be in sufficient detail to show the vote on these actions including the number of members voting for, against, and abstaining; 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 minutes of both the TJU and WEH IRB meetings provided with your reports failed to meet these requirements for protocols undergoing initial and continuing review.

(10) OHRP finds that the informed consent documents reviewed and approved by the TJU IRB on July 25, 1996 failed to include the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) A complete description of the procedures to be followed. For example, the radiation dose was not provided. Additionally, there was an inconsistency regarding the follow-up MRI measurements. On page 1, paragraph 4, it stated "I will undergo an MRI scan at six month intervals after treatment." whereas page 1, paragraph 5 states "... A series of follow-up visit MRI at three month intervals will be required."

(b) A complete description of reasonably foreseeable risks and discomforts to the subject. For example, the discomforts related to transfemoral arterial puncture, use of angiographic dye and pre-imaging sedation were described in the protocol but not in the informed consent document. In the description of risks the protocol

stated "... we anticipate a 7% morbidity associated with delayed radiation necrosis." This information was not provided in the consent form.

(c) A description of appropriate alternative procedures that might be advantageous to the subject. For example, the protocol stated that with observation only "The natural history of AVM is a cumulative 3% bleed rate per year."

(d) The description of the extent to which confidentiality and privacy will be maintained. In addition to physicians it may be necessary to reveal research records to other federal and state regulatory agencies.

(e) An explanation of whom to contact for answers to questions about research subjects' rights, other than the investigators, and whom to contact in the event of a research-related injury is not provided.

(11) It appears that it would have been appropriate for the informed consent documents to include the following additional elements in accordance with HHS regulations at 45 CFR 46:116(b):

(a) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(b) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(c) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(12) HHS regulations at 45 CFR 46.117(a) stipulate that a copy of the written consent form shall be given to the person signing it. OHRP finds that Dr. Andrews failed to provide copies of the informed consent documents to subjects enrolled in research studies.

Action 5 - Required: By June 8, 2001, WEH and TJU IRBs must submit to OHRP a satisfactory corrective action plan that addresses findings (9) - (12) above. The corrective action plan should include revised IRB policies and procedures addressing each of the issues raised in findings (9) - (12) and copies of minutes of IRB meetings which document changes which have been made with respect to documentation of discussions and actions of the IRB.

(13) Based on the IRB minutes provided, it appears that little substantive review takes place at convened meetings of the WEH IRB. Most protocols undergoing continuing review are not individually presented nor discussed at the convened meeting by the IRB as a group. For example, the minutes from the Wills Eye Hospital IRB meeting convened on January 26, 1994 failed to indicate any discussion for most of the new protocols, nor were individual votes recorded for each protocol. Under the section Annual Progress Reports it states "The following Annual Progress Reports have been APPROVED and TERMINATED." There is no evidence that each individual protocol was reviewed, or which ones were approved or terminated. It is stated that the meeting started at 4:08 p.m. and adjourned at 4:25 p.m. A total of 32 protocols required review in that time period. Please respond.

(14) OHRP finds that the IRB frequently approved research contingent upon modifications of the consent forms without requiring additional review by the IRB. 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 must 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.

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
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