DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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April 10, 2007

Myron Rosenthal, Ph.D.
Vice Provost for Human Subject Research
University of Miami
1500 N.W. 12th Avenue, Suite 1002
Miami, FL 33136

RE: Human Research Subject Protections Under Federalwide Assurance (FWA)2247

Research Project: Research involving the collection and analysis of data on the use of intravitreal Avastin for treatment of patients with age-related macular degeneration and other retinal diseases
Principal Investigators: Phillip Rosenfeld. M.D.

Dear Dr. Rosenthal:

The Office for Human Research Protections (OHRP) currently is investigating allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) involving the above-referenced research.

As you know, OHRP conducted an on-site evaluation of the human subject protections system at the University of Miami, Florida (UM) from March 13-15, 2007. The evaluation, conducted by six OHRP staff and with the assistance of three expert consultants, included meetings with senior institutional officials, the chairpersons of the UM Institutional Review Boards (IRBs), IRB members, IRB administrative staff, and five research investigators. The evaluation involved the review of IRB files for 42 protocols, as well as the minutes of numerous IRB meetings.

In the course of the OHRP review, the IRB chairpersons, IRB members, and IRB administrative staff displayed a sincere commitment to the protection of human subjects. Furthermore, the volume of research reviewed and the amount of time and effort devoted to IRB activities by the IRB chairs and staff indicate great dedication to the mission of the IRB. The IRB administrator and staff were very helpful and accommodating to OHRP during the site visit.

OHRP notes that there have been substantial improvements in the operations of the UM IRBs

over the past 1-2 years. The IRB staff members were clearly enthusiastic about their jobs and their role in the protection of human subjects. These improvements were commented on by many individuals interviewed during the course of the visit, including IRB members and research investigators.

OHRP Findings

Based on the review of materials submitted in UM's March 28, 2006, December 19, 2006 and February 23, 2007 correspondence, interviews and materials reviewed during its March 13-15, 2007 site visit, as well as the UM March 16, 2007 documents clarifying a concern voiced during the March 15 exit interview, OHRP makes the following determinations:

(1) It was alleged that Dr. Rosenfeld's administration of intravitreal Avastin to patients with age-related macular degeneration and other retinal disorders and subsequent collection and analysis of data from their medical records constituted (a) the conduct of non-exempt human subjects research without prior IRB review and approval, in contravention of HHS regulations at 45 CFR 46.103 (b) and 46.109(a); (b) a failure to ensure that risks to subjects were minimized, as required by HHS regulations at 45 CFR 46.111(a)(1); and (c) a failure to obtain legally effective informed consent prior to initiating human subjects research, in contravention of HHS regulations at 45 CFR 46.116.

OHRP notes the following:

(a) The UM IRB reviewed and approved research protocol 20053304, entitled "Review of Clinical Outcomes Following the Intravitreal Injection of Bevacizumab (Avastin)," on August 1, 2005. This protocol called for the "retrospective" review of charts for patients who were clinically treated with intravitreal injections of Avastin by multiple physicians at UM. This protocol was first submitted on June 5, 2005 to the UM IRB and underwent review via the expedited review procedure under expedited review category 5. The IRB-approved research protocol included a plan to collect and analyze data from the medical records of patients who had undergone intravitreal Avastin injection prior to IRB approval of the protocol and on patients who were to undergo that procedure subsequent to the IRB approval. The sections of the UM IRB-approved informed consent document related to research procedures, risks, and potential benefits only addressed the procedures, risks, and benefits of the collection of data from medical records.

(b) Dr. Rosenfeld stated that the other UM physicians who treated patients with intravitreal Avastin were not doing so under his direction. Dr. Rosenfeld also stated that the activities described in protocol 20053304 did not affect his use of intravitreal Avastin and that he had been using this procedure in patients prior to submitting protocol 20053304; however, he stated that the results of the chart review might reasonably affect his and other physicians' use of intravitreal Avastin in the future. He asserted that patients who were treated with intravitreal Avastin would have

received the same treatment with intravitreal Avastin without being enrolled in protocol 22053304. Dr Rosenfeld therefore maintained that he was researching the outcome of medical treatment and that the treatment itself was clinical care administered by multiple independent physicians and not part of the research protocol.

(c) Dr. Rosenfeld pioneered the use of intravitreal Avastin use in May of 2005, and OHRP understands that it is now considered routine clinical care for the treatment of macular degeneration in the ophthalmological community even though intravitreal Avastin is not approved by the Food and Drug Administration (FDA) for the treatment of any ophthalmologic disorder. Dr. Rosenfeld stated that intravitreal Avastin treatment was performed by multiple physicians at UM and now throughout the world.

(d) UM's investigative committee that was established to evaluate the allegations regarding Dr. Rosenfeld stated the following in its report:

> "It is not possible to verify independently the intention [*sic*] Dr. Puliafito or Dr. Rosenfeld. However, based on the information and statements reviewed, it appears the intent was to provide a therapy to individuals in danger of losing their vision. Therefore, it is the conclusion of the Compliance Officers that it is unlikely that Dr. Puliafito or Dr. Rosenfeld were conducting research without IRB approval."

(e) During OHRP's March 14, 2007 interview with Dr. Rosenfeld, he defined "retrospective" to mean "after the clinical treatment." In the case of protocol 20053304, data was collected and analyzed on many patients who had received intravitreal Avastin after the UM IRB review and approval of the protocol.

OHRP finds that with respect to the research activities involving the collection and analysis of data from the medical records of patients who had undergone intravitreal Avastin injection, the complainant's allegations were not substantiated.

With respect to the complainant's allegations that the use of intravitreal Avastin itself was a research intervention performed without IRB approval or appropriate informed consent of the subjects, OHRP found no definitive evidence to refute Dr. Rosenfeld's assertion that the use of intravitreal Avastin in patients with age-related macular degeneration and other retinal disorders was solely for clinical purposes and not for research. On the other hand, OHRP in retrospect is unable to definitively confirm Dr. Rosenfeld's assertion. Therefore, at this time OHRP makes no findings regarding this aspect of the complainant's allegations.

OHRP notes that the HHS protection of human subject regulations permit research involving the prospective collection and analysis of data on innovative treatments used

by clinicians solely to treat patients without the innovative treatments being considered part of the research. OHRP recognizes that the application of innovative therapy in the management of patients does not necessarily make such activities research, and also recognizes that the distinction between research and clinical practice is often blurred. Of note, the Belmont Report states the following regarding the boundaries between research and clinical practice:

> "The distinction between research and practice is blurred partly because both often occur together….
>
> "When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is 'experimental,' in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project."

UM may wish to consider establishing a formal process to independently review proposed innovative therapeutic interventions at an early stage in order to determine whether a particular intervention involves, or should involve, human subject research that requires IRB review and approval.

(2) 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, but 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. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB Chair or another IRB member designated by the Chair, continuing review must occur no later than one year after the date the protocol was reviewed by the convened IRB, not on the anniversary of the date the IRB Chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP finds that the UM IRB failed to conduct continuing review of research at least once per year. In specific OHRP notes the following:

(a) In protocol 20030724, "Human T-cell response to SM-auto-antigen," initial approval was granted on February 23, 2004 but continuing review did not occur until March 28, 2005 , and then again not until April 26, 2006.

(b) In protocol 20030496, "Failure rate for emergency intubations in trauma patients prior to hospital arrival," initial approval was granted on July 17, 2003 with continuing reviews taking place on August 2, 2004 and March 27, 2006.

(c) In protocol 20043542, "Results of treatment of intraocular retinoblastoma with chemotherapy and laser therapy," the initial approval was granted on March 4, 2005; however, continuing review did not take place until April 12, 2006.

(d) In protocol 20040164, "Comparison of intensity/modulated therapy, three dimensional conformal radiotherapy and four-field external beam radiation for patients with prostate cancer," initial approval was granted March 24, 2004; however, continuing review did not occur again until August 16, 2005 and then again until October 11, 2006.

The UM IRBs and investigators must plan ahead to meet required continuing review dates. If an investigator has failed to provide continuing review information to the IRB or the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interest of currently enrolled subjects to continue participating in the research interventions or interactions. The IRB may consider a request for continued participation of all subjects currently enrolled. In any case, enrollment of new subjects cannot occur after the expiration of IRB approval.

OHRP finds that the decision for already enrolled subjects to continue during a period of lapsed approval was made in protocol 20030724, "Human T-cell response to SM-auto-antigen," on April 1, 2006 without adequate justification (i.e., there were no direct benefits to the enrolled subjects). OHRP further finds that this decision was made by a person who was not an IRB member.

Corrective Actions: OHRP acknowledges that the written UM IRB procedures more clearly define that it is the principal investigator's responsibility to submit timely reports and requests for continuing review as well as the IRB's procedures for alerting the investigators of impending review and renewal dates; nonetheless, there appeared to be 4 of 42 protocols reviewed by OHRP where the UM IRBs failed to conduct continuing review of research at least once per year apparently without suspending the research during periods when IRB approval had not been granted. By May 30, 2007, please provide a corrective action plan that will further address this finding.

(3) HHS regulations at 45 CFR 46.103(b)(2) require that institutions provide meeting space and sufficient staff to support the IRB's review and recordkeeping duties. OHRP finds that the UM IRB administrative staff lacks sufficient space to conduct IRB duties.

Required Action: By May 30, 2007, please provide OHRP with a corrective action plan to address this finding.

OHRP has the following additional questions and concerns:

(4) [Redacted]

(5) [Redacted]

(6) [Redacted]

[Redacted]

(7) [Redacted]

(8) [Redacted]

[Redacted]

(9) [Redacted]

(10) [Redacted]

OHRP has the following guidance:

(11) OHRP notes that two individuals are referred to as ex-offico members of the UM IRBs. Additionally, one of these persons referred to themselves as a non-voting IRB member during OHRP's interviews. OHRP further notes that there is no such entity as a non-voting member of the IRB under the HHS regulations at 45 CFR part 46.

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,

Paul J. Andreason, MD
Compliance Oversight Coordinator
Division of Compliance Oversight

Enclosure

cc: Dr. Thomas Sick, Chair, UM IRB #1
Dr. Ofelia Alvarez, Chair, UM IRB #2
Dr. Charles S. Carver, IRB Chair, UM Social and Behavioral Science Committee

Ms. Kelly Insignares, Exec Dir for HSRO, UM
Dr. Carmen Puliafito, UM
Dr. Phillip Rosenfeld, UM
Commissioner, FDA
RADM Linda Tollefson, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Kristina Borror, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Ms. Patricia El-Hinnawy, OHRP