DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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July 18, 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) has reviewed the University of Miami's (UM) May 24, 2007 response to OHRP's April 10, 2007 letter that presented findings of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR part 46) related to the above-referenced research and UM's system for protecting human subjects.

Based upon its review, OHRP finds the corrective actions described below adequately address OHRP's April 10, 2007 findings and are appropriate under the UM FWA:

(1) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the institutional review board (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 found that the UM IRB failed to conduct continuing review of research at least once per year in four cases.

OHRP found that the decision to allow 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 found that this decision was made by a person who was not an IRB member.

Corrective Actions:
OHRP acknowledges UM's clarifying information that the decision to continue the participation of subjects already enrolled in the study "Human T-cell response to SM-auto-antigen," was to monitor subjects for "local [intravenous line] infection, seizures, low blood pressure, temporary low calcium…" that might result from the previous research intervention. OHRP also acknowledges that the decision to continue the participation of already enrolled subjects in research activities was made by a non-IRB member that UM judged to be fully professionally qualified to render this judgment but who was not a current IRB member. OHRP notes that 45 CFR part 46 does not state who may decide whether it is in the best interest of already enrolled subjects to continue in research activities; however, OHRP recommends that IRB Chairs or designees who are IRB members render decisions on whether it is in the best interest of already enrolled subjects to continue in research activities after lapse of IRB approval.

In the May 24, 2007 response letter, UM further addressed the issue of failure to perform continuing review in a timely manner in UM's proposed corrective actions to make investigators aware of pending expiration of approval at 90, 60, and 30 days prior to lapse of IRB approval by letter. OHRP further notes the UM advice to investigators to submit the necessary documents for continuing review no later than 45 days prior to the expiration of IRB approval. OHRP also notes the draft suspension letter that will be used in the event a study must be suspended due to a lapse in IRB approval. Finally, OHRP notes UM's added policy of not approving new studies from the principal investigator (PI) of a study that has been suspended due to a lapse in IRB approval and that studies that have lapsed for more than 90 calendar days shall be administratively closed.

(2) 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 found that the UM IRB administrative staff lacked sufficient space to conduct IRB duties.

Corrective Action: OHRP acknowledges UM's commitment to add 2,270 total square feet of space directly across the hall from the UM Human Subject Research Office (HRSO).

OHRP makes the following additional determinations:

(3) In one instance, the UM IRB approved research contingent upon substantive modifications or clarifications that were directly relevant to the determinations that the IRB was required to make under HHS regulations at 45 CFR 46.111, without requiring additional review by the convened IRB. OHRP notes that when the convened IRB requests substantive information regarding the protocol or informed consent documents that is necessary for the IRB to make the determinations required under HHS regulations at 45 CFR 46.111, IRB approval of the proposed research must be deferred, pending subsequent review by the convened IRB of responsive material.

In specific, in protocol 20057249, "Neural and cognitive facets of reward responses in bipolar disorder," the UM IRB approved the protocol at its convened meeting on April 20, 2006 without additional review by the convened IRB even though the IRB requested clarification on the intended use of the audiotapes, how data would be handled to ensure subject confidentiality and privacy, the number of subjects that would be enrolled, and the compensation range that participants would expect from participation.

Corrective Actions: OHRP notes that UM acknowledges the above requested information should have been considered as substantive rather than "minor". OHRP notes that UM has modified the IRB policies to clarify the circumstances under which an IRB Chair or designee may review and sign-off on the PI's response to IRB-mandated conditions and the difference between substantive and non-substantive or minor clarifications and revisions based on whether or not the revisions or clarifications are relevant to determinations required under 45 CFR 46.111. OHRP finds that this corrective action adequately addresses this finding and is appropriate under the UM FWA.

(4) HHS regulations at 45 CFR 46.115(a) require that the institution prepare and maintain adequate documentation of IRB activities. OHRP could not reconstruct a complete history of all IRB actions related to the review and approval of protocols 20030496, 20030724, and 20030452.

Corrective Actions: OHRP acknowledges that UM has undertaken an extensive restructuring of the HRSO subsequent to the IRB review and approval of these protocols. OHRP also acknowledges UM's new methods for taking, reviewing, and approving minutes as well as organizing records. OHRP finds that these corrective actions adequately address this finding and are appropriate under the UM FWA.

(5) 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 following protocol change was implemented without IRB approval: A letter was distributed to UM physicians treating patients enrolled in protocol 20053304, which stated, "This patient is

part of a retrospective study for Avastin. Both blood pressure and consent are required".

Corrective Action: OHRP notes that UM has restructured its HRSO, qualified personnel are available to advise investigators about human subjects protections matters, UM's policies on amendments have been revised to define the responsibilities of the investigators on amendments and related issues, and the PI for protocol 20053304 has been advised about these responsibilities. OHRP finds that these corrective actions adequately address this finding and are appropriate under the UM FWA.

OHRP has the following additional request:

(6) OHRP acknowledges that UM is in the process of clarifying the written IRB procedures that describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(b) The procedures for ensuring prompt reporting to appropriate institutional officials, any department or agency head, and OHRP of: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

Please provide OHRP with UM's final revised IRB written procedures on these issues by August 30, 2007.

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

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
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