DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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June 21, 2006

Myron Rosenthal, Ph.D.
Senior Associate Dean and Director, Human Subjects Research Office
Faculty/Professional Affairs
University of Miami
Park Plaza East, Suite M
Miami, FL 33136

RE: Human Research Subject Protections Under Federalwide Assurance FWA-2247

Research Project: A 4-Year, Double Blind, Randomized, Placebo-Controlled Study of Atorvastatin as Preventative of CHD End Points in Patients with (Type II) Noninsulin-Dependent Diabetes Mellitus
Principal Investigator: Dr. Ronald Goldberg
Project Number: 981-71-27

Dear Dr. Rosenthal:

The Office for Human Research Protections (OHRP) has reviewed the University of Miami's (UM) April 28, 2006 report responding to determinations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

In its August 9, 2005 letter, OHRP made the following determination, among others:

> (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, and not less than once per year. OHRP found that the UM IRB failed to conduct continuing review of research at least once per year for numerous studies.
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> **Corrective Action:** OHRP acknowledges that, while the UM IRBs are being reconstructed, a commercial IRB is reviewing all UM human subjects research, except research that is reviewed in an expedited manner. OHRP acknowledges UM's statement that letters have been sent to all investigators informing them that they must stop all human subjects research activity in protocols that have expired, unless it is in the best

interests of the subjects to continue, and that notices are being sent to investigators warning them of the expiration date of their protocols before the protocols expire. Your April 28, 2006 report stated that you have completed surveying department chairs and individual investigators to assure completeness of your database.

Required Action: Please provide OHRP with an update on the status of the UM IRBs and if they are convening meetings; and, if not, when you expect them to begin convening meetings.

OHRP has the following additional concern:

(2) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364-60367. OHRP is concerned that continuing review may have been conducted in an expedited manner for protocols that are not eligible for expedited review. Please provide abstracts for the following protocols: #20030549, #20057357, #20057183, #20020065, #20000693, and #19990282.

By July 25, 2006, please provide responses to the required action and concern above.

At this time, OHRP offers the following guidance regarding the UM Written Policies and Procedures for the Protection of Human Subjects in Research:

(1) OHRP recommends that the written IRB procedures provide a step-by-step description with key operational details for each of the IRB procedures required by HHS regulations at 45 CFR 46.103(b)(4) and (5). In particular, important operational details for 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 should include the specific criteria used to make these determinations (e.g., such criteria could include some or all of the following: (i) randomly selected projects; (ii) complex projects involving unusual levels or types of risk to subjects; (iii) projects conducted by investigators who previously have failed to comply with the requirements of the HHS regulations or the requirements or determinations of the IRB; and (iv) projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources). OHRP also recommends that the written IRB procedures provide details on the procedures for ensuring prompt reporting to the department or agency head 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.

(2) Section 2.E "Does a Project Constitute Human Subject Research" includes the statement at the bottom of page 13 "The definition of research generally does not include ... program evaluation, quality assurance or improvement...or marketing studies." OHRP

notes that these activities often include research.

(3) Section 3.A "IRB Authority" includes the statement on page 18 that "Such actions [suspension or termination of research] shall be determined at a convened meeting of the IRB with a quorum present...." OHRP notes that Section 20.B&C allow certain institutional officials and/or the IRB chair to take such actions under certain circumstances. OHRP would agree that this is appropriate and recommends that the statement in Section 3.A be modified to reflect this.

(4) Section 9.C.3 and Section 10.C.3 refer to review in which approval is deferred for subsequent expedited review by the IRB chair or designee. OHRP notes that for research that is not eligible for expedited review, review and approval must be conducted at a convened meeting of the IRB. The IRB chair may not approve research that is not eligible for expedited review. OHRP notes that when the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the IRB 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.

(5) Section 14.2 "Minor Violations/Deviations" lists examples of violations that ostensibly do not impact subject safety, compromise the integrity of study data and/or affect a subject's willingness to participate in the study, and only need to be reported to the IRB at continuing review. Examples include: implementation of unapproved recruitment procedures, missing pages of executed consent form, inappropriate documentation of informed consent, consent form not given to the person signing the form, and study procedure conducted out of sequence. OHRP notes that some of these violations could impact subject safety, or affect a subject's willingness to participate in the study, and could represent serious or continuing noncompliance with the HHS regulations at 45 CFR part 46 and would need to be reported promptly to the IRB.

(6) Section 16 "Closing Studies and Final Reports" states on page 87 that "Studies may be voluntarily closed by the Principal Investigator when completed and ongoing IRB approval is no longer required, when all subject accrual is completed and/or all data (including study follow-up data) pertaining to human subjects has been collected and when no further human subjects interaction is planned for the purpose of research." OHRP recommends adding here "and no further analysis of identifiable private information is to be conducted."

(7) Section 17.B "Waiver or Modification of Informed Consent" on page 93 incorrectly characterizes HHS regulations at 45 CFR 46.117. The section erroneously indicates that there are three possible ways to waive documentation of informed consent. There are only two (the first and second in this section are not connected by an "or" but are part of the same requirement.)

OHRP appreciates the continued commitment of the University of Miami to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight

cc: Dr. Steven Ullman, Vice Provost for Faculty Affairs, UM
Dr. Leo Twiggs, Assistant Vice Provost, Human Subjects Research Office, UM
Ms. Kelly Insignares, Exec Dir for HSRO, UM
Ms. Judith Aguirre, Dir for Regul Affairs and Educ Initiatives, UM
Dr. Thomas Sick, chair, UM IRB #1
Dr. Stephen Sapp, IRB chair, UM Social and Behavioral Sci Committee
Ronald A. Gadde, chair, Western Institutional Review Board-IRB/Panels 1-8 & 11-12
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Sam Shekar, NIH
Dr. Bernard Schwetz, OHRP
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Ms. Janet Fant, OHRP
Ms. Patricia El-Hinnawy