DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 301-435-8072
FAX: 301-402-2071
email: kborror@osophs.dhhs.gov

December 4, 2002

Steven G. Ullmann, Ph.D.
Vice Provost for Faculty Affairs,
University Admin
University of Miami
P.O. Box 248033
Coral Gables, FL 33124-4628

Norman Altman, VMD
Vice Provost for Research
University of Miami
1600 N.W. 10th Avenue (R-64)
Miami, FL 33101

RE: Human Subject Research Protections Under Multiple Project Assurance (MPA) M-1196 and Federalwide Assurance FWA-2247

Research Project: Selenium Therapy to Slow HIV Progression in IDU's
Principal Investigator: Marianna Baum, Ph.D.
HHS Project Number: R01 DA113278
MU Protocol Number: 97/084

Research Project: Neuroprotection with Selenium Therapy in HIV-positive IDU's (Selenium Therapy Trial Cognition Study)
Principal Investigator: Gail Shor-Posner, Ph.D.
HHS Project Number: R01 DA12797
MU Protocol Number: 98/700

Dear Drs. Ullmann and Altman:

The Office for Human Research Protections (OHRP) has reviewed your October 8, 2002 and November 26, 2002 correspondence regarding the above-referenced research conducted at the University of Miami (UM) that was submitted in response to OHRP's August 5, 2002 letter.

Based on its review, OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii) require that the Institutional Review Board (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 additional protocol changes were implemented without UM IRB approval:

(a) In your July 31, 2000 letter to OHRP, UM expressed concern that the investigator was not conducting adequate data and safety monitoring as called for in the protocol, which stated that study personnel would visit the subjects once per month to deliver the study pills and conduct a brief interview regarding the acceptability of the supplements as well as side effects. The protocol listed monthly assessments for excessive self-administration as the major safety feature of the intervention, and stated that "[p]articipants will be vigorously monitored for signs of sensitivity and toxicity." However, the research team apparently did not learn about several subject deaths until many months after the subjects died. In addition, a December 18, 2000 audit of the study by an outside auditor found that a significant percentage of subjects were not being seen in adherence with the timelines in the approved protocol. OHRP finds that subjects were not being visited monthly, as stipulated by the IRB-approved protocol.

(b) Protocol # 97/084 stated that subjects would be paid $25 for each clinic assessment and $10 for all other visits. However, a December 18, 2000 audit of the study by an outside auditor found that study staff indicated they were paying $15 for study visits at 3-month intervals. The audit and OHRP's review of the IRB records revealed no documentation of UM IRB review and approval of this change in subject compensation.

(c) Protocol # 97/084 stated that blood would be drawn from subjects every 6 months. However, a December 18, 2000 audit of the study by an outside auditor found that blood was being drawn every 3 months. The audit and OHRP's review of the IRB records revealed no documentation of UM IRB review and approval of this change in study procedures.

(d) For protocol # 97/084 the IRB approved use of bioimpedence to measure body fat in February of 2000. However, a December 18, 2000 audit of the subject records by an outside auditor indicated that bioimpedence measurements were conducted for the study as early as September of 1998.

Corrective Action: OHRP acknowledges that the UM IRB has implemented numerous changes since this protocol was active. The changes include the following: (i) a mandatory, comprehensive

education and training program in the protection of human subjects for all key personnel; (ii) weekly seminars to discuss specific topics; (iii) institution of the requirement that IRB members complete both intensive initial and ongoing education; and (iv) establishment of an Office of Research Compliance to perform random and for-cause scientific audits and reviews of human subjects protocols.

(2) OHRP finds that the informed consent documents reviewed and approved by the IRB for protocol #97/084 failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116 (a):

(a) Section 46.116(a)(1): a complete description of the procedures to be followed, and identification of any procedures which are experimental. In particular, OHRP notes the following:

(i) The protocol for #97/084 included a physical exam, urine drug tests, and monthly questionnaires; these were not described in the informed consent document.

(ii) The protocols for these studies included a one month placebo run-in, "to minimize non-compliance." The informed consent documents did not state that all subjects would be receiving placebo for a short time at some point in the study, but stated "participants will be randomly assigned to receive either the nutritional supplementation, or placebo."

(b) Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts to the subject.

(i) The informed consent document for protocol #97/084 did not describe the risks of selenium overdose.

(ii) A March 16, 2000 memo from Dr. Baum to the IRB responded to a request by the IRB for changes to the informed consent document, including mention of the risks involved if there is a breach of confidentiality of the sensitive information being solicited from the subjects. The investigator stated that "[n]o breach of confidentiality of this sensitive information is expected because no names will be used-coded study numbers will be used to identify all records as indicated in the revised consent form." However, because the information is coded, it is still possible that there could have been a breach of confidentiality. The IRB did not press this further and the change was not made to the informed consent document.

Corrective Actions: OHRP acknowledges that, in addition to the corrective actions noted in item (1) above, UM has made a significant investment in the Human Subjects Research Office including the addition of two medical IRBs, an increase in the meeting schedule of the Social and Behavioral IRB, and the addition of three IRB administrators and seven support staff. In addition, the UM

IRB has established a web page for human subjects research, a "Protocol Review Check-Off List" used for review of new protocols, and the IRB Administrators now conducts pre-review of protocols submitted for review and, along with the primary reviewer, complete a "Reviewer Checklist for New Protocols."

(3) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. OHRP finds that the informed consent document approved by the IRB for these studies appeared to include complex language that would not be understandable to all subjects. For example, the informed consent document for protocol #97/084 included phrases such as nutritional supplementation, immune disturbances, venipuncture, attributable; and the informed consent document for protocol #98/700 included phrases such as cognitive impairment, and psychological distress.

Corrective Actions: OHRP acknowledges that the UM IRB now stresses the importance of full and proper presentation of the study in the informed consent document, and that the language be in layperson terms that is understandable to the subject. Responsibility for reviewing the informed consent document language is also addressed in the "Reviewer Checklist" and the "IRB Administrator Checklist."

(4) In accordance with HHS regulations at 45 CFR 46.103(b) and 46.109(a), the IRB must review and approve all non-exempt human subject research covered by an assurance. The grant applications for both protocols #97/084 and #98/700 referred to a pilot study in which small numbers of HIV-positive drug users were given either selenium or placebo to determine the efficacy of selenium in slowing disease progression and slowing mental decline. UM stated in its October 8, 2002 report to OHRP that the UM IRB had no record of the pilot study in question being reviewed and approved by the UM IRB during the period for which the grant was active, although the principal investigator certified to the funding agency in the pilot study grant application that the project had received IRB review and approval. As a result, OHRP finds no evidence that the pilot study was reviewed and approved by the UM IRB.

Corrective Action: OHRP acknowledges that UM will make changes to the protocol application form that requests the IRB approval number for any preliminary data included as part of the new application submission. In addition, UM will instruct IRB members to review materials submitted (e.g. grant proposals) to ensure that any preliminary data presented includes reference to the approval IRB protocol number and date under which the preliminary data was obtained.

OHRP finds that the corrective actions listed above adequately address OHRP's findings and are appropriate under the UM FWA. As a result, OHRP is closing the case and there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

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,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Human Subject Protections

cc: Ms. Maria J. Arnold, UM
Dr. Arturo Brito, UM IRB A Chair
Dr. Stephen Cohn, UM IRB B Chair
Dr. Stephen P. Richman, UM IRB C Chair
Dr. Stephen Sapp, UM Social and Behavioral IRB Chair
Dr. Gail Shor-Posner, UM
Dr. Wendy Baldwin, NIH
Dr. Glen R. Hanson, NIDA
Dr. Laura Rosenthal, NIDA
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Jeff Cohen, OHRP
Mr. George Gasparis, OHRP
Ms. Jan Walden, OHRP
Mr. Barry Bowman, OHRP