DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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July 1, 2002

Aram V. Chobanian, M.D.
Medical Campus Provost
Boston University Medical Center
715 Albany Street
Boston, MA 02118-2526

**RE: Human Research Subject Protections Under Federalwide Assurance FWA– 301**

**Research Project:** An Evaluation of the Thalidomide Fetal Exposure Prevention Program
**Principal Investigator:** Allen Mitchell, M.D.
**BUMC Project Number:** E4403

Dear Dr. Chobanian:

The Office for Human Research Protections (OHRP) has reviewed your report of May 31, 2002 regarding the above-reference research conducted at the Boston University Medical Center (BUMC).

Based upon its review of your January 19, 2000 report, OHRP made the following determinations in its April 10, 2002 letter regarding the above-referenced research project.

(1) Insofar as the "System for Thalidomide Education and Prescribing Safety" (STEPS) program involved research, OHRP found that:

(a) The procedures for enrolling subjects failed to minimize the possibility of coercion or undue influence as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.116.

(b) The informed consent documents reviewed and approved by the BUMC Institutional Review Board (IRB) for this research failed to include the following element required by HHS regulations at Section 46.116(a)(8): A statement that

participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

**Corrective Action:** OHRP acknowledges that BUMC has defined which data elements are necessary for STEPS and which are collected for voluntary research. The FDA-mandated components of the STEPS program now are being conducted by the company which is marketing thalidomide, and the Slone Epidemiology Unit (SEU) at BUMC is now conducting a totally voluntary survey which will collect additional information to help assess the effectiveness of STEPS. Participants in the STEPS program are given the option of participating or not participating in the SEU survey. OHRP also acknowledges BUMC's statements that in the event another survey should be proposed for the purpose of enabling the government to monitor a public safety program, and the government should make participation in the survey mandatory for all members of the public involved in a certain high-risk activity, BUMC would seek guidance from the government agency and from OHRP as to whether or not the survey could be performed as a mandatory governmental monitoring activity rather than as voluntary research. BUMC also has developed an informed consent template and guidelines which make it clear that participation in research must be voluntary and that participants clearly understand that they are free to end their participation at any time without penalty or loss of benefits. OHRP notes that those aspects of the survey that were not research did not require review and approval by the IRB, and could have been conducted as non-research activities by SEU. OHRP finds that these corrective actions are adequate to address the above findings and are appropriate under the BUMC FWA.

OHRP has the following additional concerns and questions.

(2) In its April 10, 2002 letter to BUMC, OHRP expressed concern that the informed consent document that was used for the research may have failed to adequately address the following additional elements required by HHS regulations at 45 CFR 46.116(a)

(a) Section 46.116(a)(1):

(i) An explanation of the purposes of the research;

(ii) The expected duration of the subject's participation; and

(iii) A complete description of the procedures to be followed, and identification of any procedures which are experimental.

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

(c) Section 46.116(a)(3): A description of any benefits to the subject or others that may reasonably be expected from the research.
(d) Section 46.116(a)(7): An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights.

OHRP acknowledges that the BUMC IRB has required that the informed consent document include the length of time that subjects would be participating, IRB contact information, and the consequences of a subject's decision to withdraw from the research. OHRP remains concerned that the informed consent document was not modified to adequately address the other required elements: explanation of the purposes of the research; a complete description of the procedures to be followed, and identification of any procedures which are experimental; a description of the reasonably foreseeable risks and discomforts; and a description of any benefits to the subject or others that may reasonably be expected from the research. Please provide OHRP with the new protocol for the voluntary survey and the revised informed consent documents approved by the BUMC IRB.

(3) OHRP remains concerned that the institution does not appear to have written IRB policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5): the procedures for ensuring prompt reporting to appropriate institutional officials, OHRP and the Department or Agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval. Although the BUMC IRB policies and procedures do state that unanticipated problems and serious or continuing noncompliance needs to be reported to "appropriate institutional officials," the policies still do not state which officials or how this is done. Furthermore, the policies still do not describe procedures for reporting to OHRP.

Please respond.

Please submit to OHRP your response to the above determinations, questions and concerns no later than August 5, 2002. If upon further review of this matter you identify additional instances of non-compliance with the HHS regulations for protection of human subjects, please describe the corrective actions that have been or will be taken to address the noncompliance.

OHRP appreciates your institution's continued commitment to the protection of human research subjects. Do not hesitate to contact me if you have any questions regarding this matter.

Sincerely,

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

cc: Dr. Jonathan Woodson, IRB Chair IRB#1, BUMC
Dr. Louis Vachon, IRB Chair IRB#2, BUMC
Dr. Richard Saitz, IRB Chair IRB#3, BUMC
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Dr. David Lepay, FDA
Dr. Michael A. Carome, OHRP
Dr. Melody H. Lin, OHRP
Mr. George Gasparis, OHRP
Ms. Yvonne Higgins, OHRP
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