DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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November 14, 2002

Vincent J. Cristofalo, Ph.D.
President
Lankenau Medical Research Center
100 Lancaster Ave.
Wynnewood, PA 19096

RE: Human Subject Research Protections Under Multiple Project Assurance (MPA) M-1554 and Federalwide Assurance FWA-1169

Research Project: Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)
Project Number: F/N-R95-918
Principal Investigator: James Burke, M.D.

Dear Dr. Cristofalo:

The Office for Human Research Protections (OHRP) has reviewed the Main Line Hospitals (MLH) October 11, 2002 report regarding the above-referenced research that was submitted in response to OHRP's August 5, 2002 letter to MLH.

Based upon its review of your report, OHRP makes the following determinations regarding the above-referenced research:

(1) OHRP finds that certain unanticipated problems involving risks to subjects or others were not promptly reported to appropriate institutional officials, the institutional review board (IRB), OHRP, or the head of the sponsoring Federal department or agency as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(a) and 46.103(b)(5).

Corrective Actions: OHRP acknowledges that MLH has approved a revised Adverse Event Reporting Policy that provides clear definitions of serious adverse events, unanticipated events, and on-site and off-site events. OHRP also acknowledges MLH's statement that this policy

provides for a standardized reporting of adverse events via the introduction of the new Adverse Event Report Form.

Required Action: OHRP is concerned that the Adverse Event Policy and Report Form does not define unanticipated problems involving risks to subjects or others and focuses only on "unexpected reactions to biologicals, drugs, or medical devices." OHRP notes that unanticipated problems involving risks to subjects or others that are unrelated to drugs, biologics and devices (for example, loss of privacy or confidentiality, or suicide attempt after participating in a survey on a sensitive topic) may occur in clinical research. By November 19, 2002, please provide a corrective action plan to address this concern.

(2) OHRP finds that the informed consent documents reviewed and approved by the MLH IRB for this study failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts to the subject. The informed consent document does not describe the Step 2 and 3 study drugs or their risks, although the informed consent document stated "should you need different or stronger drugs to lower your blood pressure than you receive at first, your doctor will explain to you any side effects that these medications have." OHRP acknowledges MLH's statement that Dr. Duzy stated that prior to the administration of hydralazine, he discussed the risks and side effects of this and other medications options with the subject. Dr Duzy stated that, during this discussion, they ruled out the use of some of these other medications due to the subject's concerns about certain side effects. However, subject SS apparently was not told about the risk of hydralazine-induced lupus.

Corrective Action: OHRP acknowledges that the MLH IRBs are developing a continuing education program specifically for MLH IRB members. As part of this program, the IRB members would be reminded periodically of the elements of informed consent and their responsibility for updating information about risks and side effects in informed consent documents as part of the continuing review process. OHRP finds that these corrective actions adequately address OHRP's finding and are appropriate under the MLH FWA.

(3) OHRP finds that when reviewing the above-referenced protocol application, the IRB appeared to lack sufficient information to make the determinations required for approval of research under the HHS regulations at 45 CFR 46.111. For example, the IRB did not receive an August 21, 1997 memo to ALLHAT investigators, informing the investigators of major changes to the ALLHAT manual of operations. This memo indicated, among other things, numerous clarifications for eligibility criteria, details on adverse event reporting, clarification of dosing information, and the addition of an informed consent for "step down" of subject's current medications. OHRP can find no evidence that the IRB reviewed and approved the changes described in the August 21, 1997 memo.

Required Action: By December 19, 2002, please provide OHRP with a corrective action to address this finding.

(4) In its August 5, 2002 letter, OHRP expressed concern that the informed consent documents reviewed and approved by the MLH IRB for this study may have failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a)(3): A description of any benefits to the subject or others that may *reasonably* be expected from the research. The ALLHAT Patient Brochure, reviewed and approved by the IRB on June 26, 1995 stated "Why Get Involved [with ALLHAT]?.....if you agree to help us, we promise to make every effort to safeguard your welfare and provide the best possible care for your high blood pressure and high cholesterol." It is not clear how randomizing subjects can represent the best possible care.

OHRP acknowledges MLH's statement that the MLH IRB interpreted this statement to mean that subjects would be tested and followed more closely than those not in the study. OHRP would like again to emphasize that informed consent documents should not overstate the benefits to subjects. This is particularly important to avoid the "therapeutic misconception" that the research is medical treatment.

Please submit to OHRP your response to the above required actions no later than December 19, 2002.

OHRP appreciates the commitment of your institution to the protection of human subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

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

cc Dr. Gerald Litwack, Thomas Jefferson University
Dr. Albert A. Keshgegian, Chair, Lankenau Hospital IRB #1
Dr. James Burke, Lankenau Hospital
Dr. Wendy Baldwin, Deputy Director for Extramural Research, NIH
Dr. Claude Lenfant, Director, NHLBI
Dr. Jeffrey A. Cutler, Program Director, NHLBI
Dr. Curt D. Furberg, ALLHAT Steering Committee Chair
Dr. Greg Koski, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Mr. George Gasparis, OHRP
Dr. Hal Blatt, OHRP
Mr. Barry Bowman, OHRP
Commissioner, FDA

Dr. David Lepay, FDA