DEPARTMENT OF HEALTH & HUMAN SERVICES **PUBLIC HEALTH SERVICE**

Office for Human Research Protections
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April 17, 2002

Maria H. Sjogren, M.D., M.P.H.
Colonel, Medical Corps
Chief, Department of Clinical Investigation
Walter Reed Army Medical Center
6900 Georgia Avenue, N.W.
Washington, DC 20307-5001

RE: Human Research Subject Protections Under Federalwide Assurance FWA-477

Research Project: The Utility of Electron Beam Computed Tomography (EBCT) as a Screening Test for Coronary Artery Disease, and as an Intervention for Risk Factor Modification Among over 40 Active Duty Personnel
Principal Investigator: Allen J. Taylor, M.D.
Work Unit Number: 1215-98

Dear Dr. Sjogren:

The Office for Human Research Protections (OHRP) has reviewed the Walter Reed Army Medical Center (WRAMC) report dated March 31, 2000, submitted in response to OHRP's December 20, 2001 letter regarding the above-referenced research.

Based on its review, OHRP makes the following determinations:

(1) 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.

(a) OHRP finds that a research coordinator ran an advertisement using language that was not approved by the IRB. When brought to the attention of the investigator, the

advertisement was retracted and the coordinator "corrected the mistake" by the removal of one word ("mandatory"). However, the language of the advertisement was completely different from any advertisements that had been approved.

(b) The March 10, 2000 Record of Audit Review for this study stated that the investigator recruited some subjects by phone. This procedure was not in the protocol, and there is no evidence that the script for this recruitment was ever reviewed and approved by the IRB.

(c) The investigators hired a contractor, Systems Assessment & Research, Inc. (SAR) who provided technical support. There appears to be no evidence that the IRB reviewed and approved the conduct of some of the research by this particular organization.

(d) The IRB reviewed and approved the protocol 11-25-97. However, after that date the protocol was reviewed by several other bodies, including the Walter Reed Army Institute of Research (WRAIR) Scientific Committee Review, who required major changes to the protocol, including changing the study design from a two-arm randomized control trial to a two-by-two factorial design. OHRP notes that, while these changes may not have increased risk to the participants, they were major changes to the protocol. There appears to be no evidence that the changes were reviewed and approved by the convened IRB prior to the start of enrollment, although the final protocol was sent to the IRB May 15, 1998.

Corrective Action: OHRP acknowledges that the advertisement referenced in (2)(a) was retracted and a new advertisement was approved by the IRB and is in use. OHRP also acknowledges that the investigators have been told to cease phone calls to prospective subjects until the telephone script is submitted to the IRB and the committee approves it.

Required Action: By May 29, 2002, please provide further corrective actions to ensure that no WRAMC investigator implements changes to research protocols prior to review and approval by the IRB.

(2) In its December 20, 2001 letter, OHRP expressed concerned that the WRAMC may not have any members who are not otherwise affiliated with the institution, in contravention of HHS regulations at 45 CFR 46.107(d). In specific, the non-affiliated members noted on the IRB rosters for the last several years are from the Uniformed Services University for the Health Sciences, and the Walter Reed Army Institute of Research.

OHRP acknowledges WRAMC's statement that a Department of Defense Directive allows that non-affiliated member requirements may be met by the appointment of a member of an

institution or organizational unit not subject to immediate authority of the approving official, and that Army Regulations require that all IRB members be federal employees. However, OHRP notes that including "non-affiliated" members with close ties to the WRAMC may not be in keeping with the requirements of 45 CFR 46.107(e), even if those individuals are not subject to the immediate authority of the approving official. The requirement for IRB members to be federal employees may still be met by including members who are not affiliated with the WRAMC, the Army, or the Armed Services, such as employees of the Treasury Department, Department of the Interior, or Department of Health and Human Services, to name a few. Please respond.

(3) HHS regulations at 45 CFR 46.116 prohibit any exculpatory language in informed consent through which the subject is made to waive, or appear to waive, any of the subject's legal rights. OHRP finds that the following language in IRB-approved informed consent documents was exculpatory: "I voluntarily and freely donate any and all blood to the study sponsor...and hereby relinquish all right, title, and interest to said item."

Corrective Action: OHRP acknowledges that the institution now requires that the form for blood donation be devoid of exculpatory language, and the exculpatory language was deleted from the informed consent document for the above-referenced research. OHRP finds that this corrective action adequately addresses the finding and is appropriate under the WRAMC MPA.

OHRP has the following additional questions and concerns regarding the above-referenced research:

(4) Department of Health and Human Services (HHS) regulations at 45 CFR 46 116 state that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. The draft manuscript titled "Do Conventional Risk Factors Predict Sub-Clinical Coronary Artery Disease?: Results from the Prospective Army Coronary Calcium Project" stated "[t]hose personnel who did not consent to the study (n=75) were similar to participants with respect to age, gender, education, and cardiovascular risk factors (diabetes mellitus, total cholesterol, and smoking status.)" Did the investigators obtain identifiable private information about these non-consenting subjects? There appears to be no evidence that such "non-consenters" ever consented to have their personal medical information studied in this way, nor that the IRB found that waiver of informed consent was appropriate. OHRP acknowledges that the investigator has been asked to cease data collection until the WRAMC IRB reviews the issue and rules on it. Please provide OHRP with a copy of the IRB's deliberations and decision on this matter.

Please submit to OHRP your response to the above questions and concerns no later than May 29,

2002. If upon further review of the concerns and questions, WRAMC identifies instances of non-compliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

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 Compliance Oversight

cc: Dr. James W. Kikendall, WRAMC
Dr. Allen J. Taylor, WRAMC
Dr. Audrey S. Chang, WRAMC
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Mr. George Gasparis, OHRP
Mr. Barry Bowman, OHRP