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: 301-435-0668
FAX: 301-402-2071
E-mail: pmcneilly@osophs.dhhs.gov

December 27, 2002

Richard H. Dean, M.D.
President and Chief Executive Officer
Wake Forest University School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1161 and Federalwide Assurance (FWA) 00001435

Research Project: Human T Lymphocyte Function in Systemic Lupus Erythematosus (SLE) and Control Populations
Principal Investigator: Dr. Gary M. Kammer

Dear Dr. Dean:

The Office for Human Research Protections (OHRP) has reviewed the Wake Forest University School of Medicine's (WF) October 30, 2002 and November 6, 2002 reports submitted in response to OHRP's August 23, 2002 letter regarding the above-referenced research.

OHRP makes the following determinations regarding the above referenced-research:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116 state that, except as provided elsewhere in the regulations, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. OHRP notes that WF's October 30, 2002 report stated the following:

(a) "The principal investigator confirms that signed consent forms have not been obtained routinely from healthy volunteer students, fellows and laboratory personnel who participated as part of the control population for this study."

(b) "A list provided by the principal investigator of dates of blood draws from these individuals contains 92 entries representing 67 unique individuals. A review of informed consent documents found that only 12 of the individuals provided written signed informed consent."

(c) "... the Committee finds that informed consent was not obtained from all healthy controls; however, the Committee finds no evidence that blood was drawn prior to obtaining informed consent from patient cases or patient controls."

OHRP finds that the investigator initiated human subject research without obtaining the legally effective informed consent of healthy controls enrolled in the above-referenced research.

(2) HHS regulations at 45 CFR 46.117(a) require that informed consent be documented by the use of a written consent form approved by the IRB and that is signed by the subject, or the subject's legally authorized representative, unless the IRB waives this requirement in accordance with 45 CFR 46.117(c). OHRP finds that informed consent was not documented by a written consent form signed by the subject(s) for this research and that the IRB did not waive this requirement.

Corrective Action: OHRP acknowledges the following corrective actions taken by WF related to findings (1) and (2) above:

(a) The laboratory will institute procedures requiring that signed informed consent forms be obtained for all blood specimens collected.

(b) The research nurse will monitor, on a monthly basis, that informed consent is obtained from all healthy controls.

(c) The principal investigator, study nurse and all other research team members will be required to complete additional education on the ethical principles and regulatory requirements for the protection of human subjects.

(d) The principal investigator will contact all healthy controls and provide them with a written description of the lapse in obtaining informed consent and provide them with the option of having their sample destroyed or retained for analysis.

(e) A memo will be sent from the Dean to all faculty members reminding them of the requirement to obtain informed consent from all healthy controls prior to obtaining specimens.

(3) HHS regulations at 45 CFR 46.117(a) require that a copy of the informed consent document be given to the person signing the form. In particular, OHRP notes that WF's October 30, 2002 report stated "The principal investigator acknowledges that subjects were not routinely provided copies of the informed consent document." OHRP finds that the principal investigator for the above-referenced research failed to meet this requirement.

Corrective Action: OHRP acknowledges that WF's October 30, 2002 report stated that the investigator and study nurse are now aware that subjects must be given a copy of the informed consent document and will now make this a standard procedure. In addition, the need to provide a copy of the informed consent document to subjects will be emphasized in WF educational programs.

(4) HHS regulations at 45 CFR 46.111(a)(3) require that selection of subjects is equitable. OHRP notes that WF's October 30, 2002 and November 6, 2002 reports state "Although the data do not support the overuse of subjects of Asian or Pacific Islander descent as healthy controls, the Committee was unable to resolve the differences in the data submitted as part of the January 2002 continuing review indicating 217 subjects were enrolled and the data provided by the principal investigator indicating 196 subjects enrolled."

OHRP finds that the principal investigator failed to provide the IRB with sufficient information to make the determination that the selection of subjects is equitable, which is required for continuing approval of the above-referenced research under HHS regulations at 45 CFR 46.111(a)(3).

Corrective Action: Information related to discrepancies in reporting of the number of subjects enrolled in the above-referenced research has been forwarded to the WF Research Integrity Officer for inclusion into an inquiry into allegations of research misconduct.

OHRP recommends that WF consider reminding all investigators of the importance of maintaining accurate research records and providing a complete and accurate summary of research to the IRB at the time of continuing review.

(5) 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. OHRP notes that your October 30, 2002 report states:

> (a) "The principal investigator acknowledges that on two occasions he obtained blood specimens from the external jugular vein of a lupus patient."
>
> (b) "The principal investigator acknowledges that the use of the external jugular vein was contrary to the IRB approved protocol and consent."

OHRP finds the investigator used the external jugular vein to draw blood prior to obtaining IRB review and approval for this change.

Corrective Action: No further blood specimens will be obtained using the external jugular vein. The investigators have been informed that they are to adhere to the IRB-approved protocol. As noted above, the investigators are to undergo additional education on the ethical principles and regulatory requirements for the protection of human subjects.

OHRP recommends that WF consider reminding all investigators of the regulatory requirements to report changes in a research activity to the IRB as required by HHS regulations at 45 CFR 46.103(b)(4)(iii).

(6) In its August 23, 2002 letter, OHRP described an allegation that the investigator failed to provide adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, as required by HHS regulations at 45 CFR 46.111(a)(7). OHRP finds that this allegation could not be substantiated.

(7) In its August 23, 2002 letter, OHRP described an allegation that the principal investigator failed to seek consent under circumstances that provide the prospective subject or the subject's legally authorized representative sufficient opportunity to consider whether or not to participate in the research, as required by HHS regulations at 45 CFR 46.116. OHRP finds that this allegation could not be substantiated.

(8) In its August 23, 2002 letter, OHRP described an allegation that the development of low blood pressure in one subject may represent an unanticipated problem involving risks to subjects or others and therefore require reporting to the WF IRB, appropriate institutional officials, the Department or Agency head, and OHRP, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5)(i). OHRP finds that this allegation could not be substantiated.

OHRP finds that the corrective actions noted above adequately address the findings of noncompliance and are appropriate under the WF MPA and FWA. As a result of this determination, there should be no need for further involvement of OHRP in this matter.

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,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Wesley Byerly, Director, Institutional Review Board, WF
Dr. Ronald Smith, IRB Chair, WF
Dr. Gary Kammer, WF
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Melody H. Lin, OHRP
Mr. George Gasparis, OHRP
Dr. Jeffrey Cohen, OHRP
Ms. Jan Walden, OHRP
Mr. Barry Bowman, OHRP