DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

FOR US POSTAL SERVICE DELIVERY:
Office for Human Research Protections
6100 Executive Boulevard, Suite 3B01
National Institutes of Health (MSC 7507)
Rockville, Maryland 20892-7507

FOR HAND DELIVERY OR EXPRESS MAIL:
Office for Human Research Protections
6100 Executive Boulevard, Suite 3B01
Rockville, Maryland 20852

Telephone: 301-435-5649
FAX: 301-402-2071
E-mail: beitinsi@od.nih.gov

December 22, 2000

Jay Moskowitz, Ph.D.
Senior Associate Dean
The Bowman Gray School of Medicine
Wake Forest University
Medical Center Boulevard
Winston-Salem, NC 27157-1023

Len B. Preslar
President
North Carolina Baptist Hospitals, Inc.
Medical Center Boulevard
Winston-Salem, NC 27157

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

Research Activity: Investigator Request for Data on Combined Hemodialysis and Peritoneal Dialysis for Presentation at American Society of Nephrologists' Professional Meeting
Principal Investigators: John Burkart, M.D. and Patricia Clinard, M.S.

Dear Dr. Moskowitz and Mr. Preslar:

The Office for Human Research Protection (OHRP), formerly the Office for Protection from Research Risks (OPRR) has reviewed your November 15, 2000 report, as well as Mr. Lawrence D. Smith's December 7, 1999 follow-up letter, regarding the above referenced research activity.

OHRP acknowledges your report that the above referenced research was conducted (i) without prior review and approval by an institutional review board (IRB), as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.109; and (ii) without obtaining the legally effective informed consent of the subjects, as required by HHS regulations at 45 CFR 46.116.

Furthermore, OHRP acknowledges that your institutions have implemented the following corrective actions in response to the above noncompliance:

(1) Dr. Burkart and Ms. Clinard have been counseled, and both now understand, that the above research activity required IRB review and approval prior to the conduct of the research.

(2) Staff from the Wake Forest University School of Medicine (WFUSM) Office of Research sequestered all completed survey instruments for the above referenced research, and all identifying information has been obliterated from the survey instruments.

(3) A letter from the WFUSM Office of Research defining human subject research and the requirement for IRB review of such research was distributed to all full-time faculty and staff.

(4) Clinical investigators at WFUSM and IRB members are now required to participate in a mandatory certification program for clinical research.

(5) Additional multifaceted education programs related to human subject protections have been established for IRB members, IRB staff, and investigators.

OHRP has determined that these corrective actions adequately address the above cited noncompliance and are appropriate under your MPA. As a result, there should be no need for further involvement of OHRP in the above matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

At this time, OHRP provides the following additional guidance:

(1) OHRP notes that Dr. Moskowitz is both the Authorized Institutional Official for WFUSM on MPA M-1161 and a non-voting member of the IRB. Because of the real or apparent conflicts of interest that may result from this arrangement, a revised IRB membership roster should be submitted to OHRP's Division of Policy and Assurance that does not include Dr. Moskowitz as an IRB member (either voting on non-voting).

(2) Regarding the November 1999 Draft Policy of the Institutional Review Board, please note the following:

(a) For section V, page 23, section B.6, the definition of a quorum of the IRB should be modified to include the presence of at least one member whose primary concerns are in nonscientific areas, as required by HHS regulations at 45 CFR 46.108(b).

(b) Regarding section V, page 25, section C.13, OHRP notes the following:

> "Members must leave the meeting when a protocol in which they are to participate is discussed and voted upon. In such instances, that individual's vote may be counted in abstention."

Please note that HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the IRB's initial or continuing review of a project in which the member has a conflicting interest. As such, members with a conflicting interest who are excluded from the deliberations and vote on a research protocol may not be counted toward IRB quorum requirements for the review of that research.

(c) The written IRB policy should be expanded to include operational details for each of the following procedures, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

> (i) The procedures which the IRB will follow for conducting its continuing review of research
>
> (ii) The procedure which the IRB will follow for determining which projects require review more often than annually.
>
> (iii) The procedure which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review
>
> (iv) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, OHRP, and Department or Agency head of any unanticipated problems involving risks to subjects or others, any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB, any suspension or termination of IRB approval.

(d) Continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the

last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc95-01.htm). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

When conducting research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above referenced documentation.

You should confirm that your IRB is conforming to the above requirements.

(e) OHRP recommends that institutions adopt clear procedures under which the IRB determines whether proposed research is exempt from the human subjects regulations [see 45 CFR 46.101(b)]. Documentation should include the specific category justifying the exemption.

(f) OHRP recommends that documentation for initial and continuing reviews conducted utilizing expedited review procedures include the specific permissible categories (see 63 FR 60364) justifying the expedited review.

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

Sincerely,

Inese Z. Beitins, M.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Mr. Lawrence D. Smith, Associate Dean for Research, WFUSM
Dr. Ronald Smith, Chair, IRB, WFUSM
Mr. Gerald T. Finley, North Carolina Baptist Hospitals, Inc.
Dr. John Burkhart, WFUSM
Commissioner, FDA

Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. John Mather, Department of Veterans' Affairs
Dr. Gregory Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Katherine Duncan, OHRP
Mr. George Gasparis, OHRP
Dr. Clifford C. Scharke, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. Barry Bowman, OHRP