DEPARTMENT OF HEALTH & HUMAN SERVICES **Office of the Secretary**
Office of Public Health and Science

Office for Human Research Protections
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April 23, 2004

Timothy F. Hawkins
Vice President, Clinical Services
Baptist Hospital of Miami, Inc.
8900 N. Kendall Drive
Miami, FL 33176

RE: Human Research Subject Protections Under Federalwide Assurance FWA-1752

Research Projects: Children's Oncology Group Research

Project Numbers: NCI Code Number FL078
Children's Oncology Group (COG) protocols:
3961, 9494, 9673, 9720, 9904, 9905, 9754, 9440

Principal Investigator: Doured Daghistani, M.D.

Dear Mr. Hawkins:

The Office for Human Research Protections (OHRP) has reviewed the Baptist Hospital of Miami's (BHM) April 14, 2003 response to OHRP's February 13, 2003 letter. OHRP apologizes for its delay in responding to your report.

Based upon its review, OHRP makes the following determinations regarding the above-referenced protocols:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii) require that the institutional review board (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 finds that protocol changes were implemented without IRB approval. In particular, it was noted in the report for the National Cancer Institute (NCI) Clinical Trials Monitoring Branch COG audit conducted on January 23, 2003 that Dr. Daghistani enrolled ineligible subjects in COG research protocols at BHM.

Corrective actions: OHRP acknowledges that the BHM IRB has implemented a number of changes to its procedures, including the development of the IRB Guidelines for Investigators booklet for 2002 and 2003; development of an audit system; and mandatory training for IRB members, IRB staff, and research staff.

Required action: By May 28, 2004, please provide a satisfactory corrective action plan to ensure that all BHM investigators enroll only eligible subjects in their protocols.

(2) 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. HHS regulations at 45 CFR 46.117(a) require that, except as provided under 45 CFR 46.117(c), informed consent shall be documented by use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. The written consent form should be signed by the subject or the subject's legally authorized representative before any research interactions or interventions with the subject are initiated.

The report from the January 23, 2003 COG audit cited the following two instances in which the informed consent document was signed after the subject began "treatment" on the protocol:

> (a) Patient #718508 in COG study #A3961 signed the consent form after the subject started receiving protocol "treatment." The report states that "treatment" started on March 26, 2002 and that the consent was signed on March 28, 2002.
>
> (b) Patient #708808 in COG study #9404 started "treatment" on May 10,

2001 and signed the consent form on May 11, 2001.

OHRP finds that the investigator did not document the legally effective informed consent prior to commencing research interventions and interactions for some subjects.

Required action: By May 28, 2004, please provide OHRP with a satisfactory corrective action plan to address the above finding.

(3) OHRP finds that, prior to 2002, the BHM IRB lacked sufficient information when reviewing protocol applications to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, the IRB appeared to review only minimal information regarding (a) subject recruitment and enrollment procedures; (b) the equitable selection of subjects; (c) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (d) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable.

Corrective actions: OHRP acknowledges that a new IRB application, entitled "Application for Study Approval by Full Board Review" was implemented in March 2002. OHRP finds that this corrective action adequately addresses the finding above and is appropriate under the BHM FWA.

(4) OHRP finds that BHM does not have written IRB procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow for conducting its initial review of research.

(b) The procedures which the IRB will follow for conducting its continuing review of research.

(c) The procedures which the IRB will follow for determining which projects require review more often than annually.

(d) The procedures 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.

(e) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(f) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any department or agency head, and OHRP of: (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. OHRP notes that while BHM written procedures include reporting to FDA and sponsors, they do not include reporting to OHRP.

Required action: By May 28, 2004, please provide OHRP with revised procedures which address the deficiencies noted in the above finding. Please see OHRP guidance located on the OHRP website at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/irbgd702.htm.

OHRP has the following additional questions and concerns regarding the research protocols referenced above and the BHM system for protecting human subjects:

(5) [Redacted]

(6) [Redacted]

(7) [Redacted]

[Redacted]

(8) [Redacted]

(9) [Redacted]

(10) [Redacted]

(11) [Redacted]

(12) [Redacted]

Please submit your responses to the above findings, questions, and concerns so that OHRP receives them no later than May 28, 2004. If during your review you identify additional areas of noncompliance with the HHS regulations for the protection of human subjects, please provide corrective action plans that have been or will be implemented to address the noncompliance.

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

Sincerely,

Karena Cooper, J.D., M.S.W.
Compliance Oversight Coordinator
Office for Human Research Protections

cc: Dr. Harold S. Goldstein, IRB Chair, BHM
Ms. Kelly A. Cohn, Clinical Research Manager, BHM
Dr. Doured Daghistani, Principal Investigator, BHM
Dr. Lana Skirboll, Director, Office of Science Policy, NIH
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