DEPARTMENT OF HEALTH & HUMAN SERVICES

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November 4, 2004

Timothy F. Hawkins
Vice President, Clinical Services
Baptist Hospital of Miami, Inc.
8900 North 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) June 20, 2004 response to OHRP's April 23, 2004 letter.

In its letter of April 23, 2004, OHRP made the following determinations of noncompliance and raised the following concerns:

(1) OHRP found that protocol changes were implemented prior to institutional review board (IRB) approval, in contravention of Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii). 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 Action: OHRP acknowledged in its April 23, 2004 letter 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. In its April 23, 2004 letter, OHRP required BHM to provide a satisfactory corrective action plan to ensure that all BHM investigators enroll only eligible subjects in their protocols.

BHM's June 20, 2004 letter described a corrective action plan that includes mandatory education for investigators and increased monitoring through an auditing process that involves on-site evaluations and the use of a detailed auditing checklist. OHRP finds that the above corrective actions adequately address the above finding.

(2) OHRP found that Dr. Daghistani did not document legally effective informed consent prior to commencing research interventions and interactions for some subjects, in contravention of HHS regulations at 45 CFR 46.116 and 45 CFR 46.117(c). In particular, the report from the January 23, 2003 COG audit cited two instances in which the informed consent document was signed after the subject began "treatment" on the protocol.

Corrective Action: BHM stated in its June 20, 2004 letter that all subjects who signed informed consent documents that were deficient in content or in signature were contacted and reconsented with newly revised, IRB-approved consent forms. In addition, Dr. Daghistani and his staff have developed standardized practices and a checklist to use when enrolling subjects, to help ensure that study eligibility criteria are met and informed consent documents are signed appropriately. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the BHM FWA.

(3) OHRP found that BHM did 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.

Corrective Action: OHRP notes that BHM Policy No. 831.00 was revised to include information about the IRB submission process for all studies.

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

Corrective Action: OHRP notes that Policy No. 834.02 is a new policy on continuing review procedures. This policy appears to address the finding above adequately.

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

Corrective Action: OHRP notes that the procedure for determining which projects require review more often than annually is included in the new continuing review policy, Policy No. 834.02, at section B, "Frequency of Continuing Review." OHRP notes that this determination should also be made at the time of the initial review of a study, and suggests that it would be appropriate to include information about it in the policy entitled "IRB Review of Protocols," Policy No. 831.00.

(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.

Corrective Action: OHRP notes that a procedure for determining which projects require verification from sources other than the investigators is included in the new continuing review policy, Policy No. 834.02, at section C, "Criteria for Determination of which projects need verification...." OHRP notes that this determination should also be made at the time of the initial review of a study, and suggests that it would be appropriate to include this information in the policy entitled "IRB Review of Protocols," Policy No. 831.00.

(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.

Corrective Action: BHM's new Policy No. 834.00, "Proposed Changes to Approved Research," includes a section entitled "Request to Modify the Protocol." BHM Policy No. 832.02, "Amendments," contains a sentence stipulating that no changes in a protocol or informed consent can be made without IRB approval. However, neither policy contains a description of the steps that are taken to ensure that investigators do not implement any protocol changes without prior IRB review and approval. OHRP suggests that this issue might be addressed through training programs and materials for investigators, specific directives included in approval letters to investigators, and random audits of

research records.

(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.

Corrective Action: OHRP notes that the following sentence was added to the most recent version of Policy No. 831.00 but cautions that this sentence, in isolation, does not satisfactorily address any of the requirements in 45 CFR 46.103(b)(4) or (5): "Study will be conducted under HHS regulatory guidelines and ICH/GCP principles." OHRP notes the following deficiencies in the IRB written procedures regarding reporting requirements:

(i) OHRP was unable to find any reference in the BHM procedures to the reporting requirements referenced in 45 CFR 46.103(b)(5)(i), which states that an institution must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head (OHRP) of any unanticipated problems involving risks to subjects or others. OHRP notes that neither BHM Policy No. 832.00, "Reports of Adverse Reactions and Unexpected Events," nor the section entitled "Adverse Experience Reports" in BHM Policy No. 834.00 references reporting requirements to OHRP.

(ii) OHRP was also unable to find any reference in the procedures to the reporting requirements referenced in 45 CFR 46.103(b)(5)(ii) for any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB. OHRP notes that this reporting requirement is distinct from the one contained in 45 CFR 46.103(b)(5)(iii), which refers to reporting of suspensions or terminations of IRB approval.

(iii) OHRP notes the addition of OHRP and the funding department or agency to the sentence that lists the parties to whom suspensions and terminations will be reported. However, the paragraph begins with a reference to FDA regulations at 21 CFR 56.113 and contains no reference to 45 CFR 46.103(b)(5)(iii).

Required Action: By December 15, 2004, please provide OHRP with revised

procedures that specifically address the deficiencies noted above. In your response, please reference the enumerated items in this letter and the specific revisions per policy number and title.

OHRP expressed the following additional questions and concerns in its April 23, 2004 letter regarding the research protocols referenced above and the BHM system for protecting human subjects:

(4) OHRP expressed concern that there is no evidence in the IRB minutes, the IRB application, or the reviewer checklists that the IRB considered the requirements of HHS regulations at 45 CFR 46.401-409 (Subpart D) in their review of pediatric research.

Corrective Action: OHRP acknowledges BHM's statement that the reviewer worksheet has been updated to address the additional protections for children involved in research, and that Subpart D is referenced in the IRB application. However, OHRP is concerned that the following statement does not reflect a complete understanding of the required findings contained in 45 CFR 46.404-407: "We acknowledge that in the past the minutes may have not adequately documented our actual deliberations of the risk of the child." OHRP notes that the findings in Subpart D require more than an assessment of risk to the child. OHRP recommends that for research approved by the convened IRB, all required findings be fully documented in the minutes of the IRB meeting, including protocol-specific information justifying each IRB finding. Please respond.

(5) OHRP expressed concern that there is lack of concordance among the requirements for the assent of children required in BHM policy number 833.06; the required assent statement dictated by the IRB in the March 24, 1998 minutes; and the assent statement language that was included in the consent form approved on May 15, 1998 for COG study #3961.

Corrective Action: OHRP acknowledges BHM's statement that age-appropriate assents meeting the criteria established in BHM policy 833.06 are currently being prepared, reviewed, and approved for all BHM COG studies. OHRP notes that assents for all studies reviewed by BHM should also conform to the requirements of 45 CFR 46.408(a).

(6) OHRP was concerned that the April 15, 2003 NCI/COG re-audit of Dr. Daghistani's studies reported the use of expired consents for COG study #9905. BHM was asked to explain whether or not the consent document found to be expired in the NCI/COG audit was the correct IRB-approved version of the consent document to be used with subjects in April and September 2002.

Corrective Action: OHRP acknowledges BHM's statement that the above-referenced consent form, found to be expired in the NCI/COG audit, did in fact contain the most current IRB-approved information.

(7) OHRP expressed concern that Dr. Daghistani is conducting research without

experienced research staff and that as a result, risks to subjects may not be minimized. OHRP noted that according to a recent list (dated 2/26/2004) of Dr. Daghistani's pediatric oncology studies, it appears that he has at least 28 active studies. BHM was asked to indicate the steps it has taken to ensure that Dr. Daghistani has sufficient resources to conduct his studies in a manner that minimizes risks to subjects.

Corrective Action: OHRP acknowledges BHM's statement that a senior oncology research nurse has been assigned to evaluate Dr. Daghistani's research program and to provide supervision and mentoring for the site staff. In addition, BHM has provided Dr. Daghistani with an experienced research coordinator to assist him with his research program, and has provided funding for Spanish translations of his consent forms.

(8) OHRP noted in its June 20, 2004 letter that although the procedures for continuing review by the BHM IRB appear to have improved over the past two years, OHRP was concerned that continuing review of research by the BHM IRB still may not be substantive and meaningful.

Corrective Action: BHM indicated that it revised its continuing review policy in 2002. The new continuing review policy, Policy No. 834.02, appears to be satisfactory under BHM's assurance.

(9) OHRP notes that the version of the IRB roster dated 2/26/2004 lists a nonvoting member. Please be advised that all IRB members are voting members.

Corrective Action: BHM indicated that it has changed its "nomenclature to 'administrative representatives' to better describe those who regularly attend the meeting in an administrative or ex officio capacity but do not participate in the voting process."

OHRP has the following additional concerns, based on its review of the February and March 2004 BHM IRB minutes attached to the June 20, 2004 letter:

(10) [Redacted]

OHRP would like to provide the following guidance regarding expedited review:

> OHRP recommends that documentation for initial and continuing reviews conducted under an expedited review procedure include: (a) the specific permissible categories (see 63 FR 60364-60367 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/expedited98.htm) justifying the expedited review; and (b) documentation of the review and action taken by the IRB chairperson or designated reviewer, and any findings required under the HHS regulations. OHRP also recommends that institutions adopt policies describing the types of minor changes in previously approved research that can be approved by expedited review in accordance with HHS regulations at 45 CFR 46.110(b)(2).

Please submit your responses to the above findings, questions, and concerns so that OHRP receives them no later than December 15, 2004.

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
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