DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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June 19, 2006

Steve Anderman
Senior Vice President/Chief Operating Officer
Bronx-Lebanon Hospital Center
1650 Grand Concourse
Bronx, NY 10457

RE: Human Research Subject Protections Under Multiple Project Assurance M-1518 and Federalwide Assurance FWA-1632

Research Project: Phase I Trial: Safety and Effectiveness of Four Anti-HIV Drug Combinations in HIV-Infected Children and Teens
Project Number: ACTG #377
Principal Investigator: Andrew Wiznia, M.D.

Dear Dr. Anderman,

The Office for Human Research Protections (OHRP) has reviewed the Bronx-Lebanon Hospital Center's (BLHC) March 17, 2006 response to OHRP's February 17, 2006 letter regarding indications of possible noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) involving the above-referenced research.

In its February 17 letter, OHRP made the following determination regarding the above-referenced research:

> (1) HHS regulations at 45 CFR 46.404-409 require specific findings on the part of the IRB for approval of research involving children. OHRP's review of BLHC IRB documents for the above-referenced research revealed no evidence that the BLHC IRB considered and made the required findings when reviewing this research involving children.
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> OHRP acknowledged that BLHC stated in its September 8, 2005 response that the above-referenced research trial was approved by the BLHC IRB under HHS regulations at 45 CFR 46.405. However, OHRP has found no evidence in the materials reviewed to support this statement.

Based upon its review of your March 17, 2006 response, OHRP makes the following additional determination:

(2) HHS regulations at 45 CFR 46.111 state that, in order to approve research covered by the regulations, the IRB shall determine that certain requirements are satisfied. OHRP finds that when reviewing this research, the BLHC IRB failed to obtain sufficient information to make the following determinations required for approval of research under HHS regulations at 45 CFR 46.111.

(a) 45 CFR 46.111(a)(3): Selection of subjects is equitable. In making this determination, IRBs should be particularly cognizant of the special problems of research involving vulnerable populations. In particular, OHRP finds that BLHC IRB records appear to demonstrate a failure of the IRB to obtain sufficient information regarding the selection of wards of the state and foster children as research subjects.

(b) 45 CFR 46.111(b): When some or all of the subjects (e.g., children) are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects. In particular, OHRP finds that BLHC IRB records appear to demonstrate a failure of the IRB to obtain sufficient information regarding such safeguards with respect to the enrollment of wards of the state or foster children.

Corrective Actions: OHRP acknowledges the efforts by your institution to improve human subjects protections which address these findings. A revised IRB application checklist for pediatric studies has been developed which includes category of risk and potential benefits, with vote required by IRB for concurrence; and an anticipated subject population section, where the principal investigator will list possible sources of research subjects, including wards of the state. This checklist also asks whether an advocate has been appointed for children who are wards, and asks for contact information. IRB minutes will reflect discussion of equitable selection of research subjects, and will document the category under HHS regulations at 45 CFR 46.404-407 when research involving children is approved. The pediatric informed consent used for children 13 through 17 years of age will be revised to include the question "Is this child a ward of the state?" prior to the signature lines. A ward of the state 13 through 17 years of age may not sign the informed consent until an advocate has been appointed. The Investigator will ensure that the advocate has signed the required IRB Advocate Statement which outlines the advocates's responsibility. All IRB approval letters to Pediatric Investigators will include a caution statement informing the investigator that an advocate must be appointed prior to signing the informed consent, and that the advocate is required for the duration of the study. The IRB will require re-education regarding regulations affecting wards of the state and foster children.

In parallel to the protections described above, OHRP recommends that the pediatric assent form used for children ages 7-12 also be revised to include the question "Is this child a ward of the

state?" prior to the signature lines for the parent(s) or guardian, and that an advocate be appointed prior to the signing of this assent.

OHRP finds that these corrective actions adequately address the stated findings and are appropriate under the BLMC assurance. 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,

Julia Gorey, J.D.
Division of Compliance Oversight

cc: Dr. Murli Purswani, FAAP, Chief, Division of Pediatric Infectious Diseases
Dr. Stephen Schultz, HPA and IRB #1 Chairperson, Bronx-Lebanon Hosp. Ctr.
Dr. Sam Shekar, NIH
Dr. Anthony Fauci, NIH
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