DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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June 19, 2006

James Hendricks, Ph.D.
Vice President for Research
Children's Hospital and Regional Medical Center
Hospital Administration CH-01
4800 Sand Point Way NE
P.O. Box 5371
Seattle, WA 98105-0371

RE: Human Research Subject Protections Under Multiple Project Assurance M-1214 and FederalWide Assurance FWA-2443

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: Lisa M. Frenkel, M.D.

Dear Dr. Hendricks:

The Office for Human Research Protections (OHRP) has reviewed the Children's Hospital and Regional Medical Center's (CHRMC) March 29, 2006 response to OHRP's February 17, 2006 letter regarding indications of 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, 2006 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 acknowledged CHRMC's statement in its July 14, 2005 response that "Children's IRB approved this project under category 45 CFR 46.405....The IRB application file and the minutes for this study do not document that the IRB approved the research under category 45 CFR 46.405." OHRP's review of CHRMC IRB documents for the above-referenced research revealed no other evidence that the CHRMC IRB considered and made the required findings when reviewing this research involving children.

Corrective Action: OHRP acknowledges that the CHRMC IRB has, since April 2002, documented the category of approval under 45 CFR 46.404-407 for all new research studies and the letter to the investigator makes him or her aware of the applicable category of approval. In addition, in October 2005, the CHRMC IRB initiated a process of formally considering and documenting the approval category under 45 CFR 46.404-407 for all open studies approved prior to April 2002; CHRMC anticipates the process will be completed no later than October 2006.

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

(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 CHRMC 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 CHRMC 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(a)(4): Informed consent will be sought from each prospective subject or the subjects's legally authorized representative, in accordance with 45 CFR 46.116. In particular, OHRP finds that CHRMC IRB records demonstrate a failure of the IRB to obtain sufficient information regarding the process for obtaining permission of parents or guardians for wards of the state or foster children.

(c) 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 CHRMC IRB records 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 Action: OHRP acknowledges that the CHRMC IRB application has been modified to include foster children or wards of the state as possible research participants and the IRB determination/contingency letter has been modified to include a statement that foster children and wards of the state are not eligible for enrollment in the study if the application failed to identify these special populations. The CHRMC IRB application also now directs investigators planning to enroll foster children or wards of the state to review relevant regulatory requirements and to document the steps taken to obtain proper consent. In addition, the CHRMC IRB consent/assent form template has been modified to include

the statement "If the child to be involved in this research study is a foster child or a ward of the state please notify the researcher or their staff who is obtaining your consent." The researcher's consent/assent form checklist also includes a notation to confirm whether the adult providing written permission has the legal authority to give permission if the child is a foster child or a ward of the state. The CHRMC Human Subjects Protection Program training curriculum has also been revised to include more information about the rights of foster children and wards of the state as well as the responsibilities of investigators to such participants.

OHRP finds that the corrective actions taken adequately address the findings and are appropriate under the CHRMC 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,

Kristina C. Borror, Ph.D.
Director, Division of Compliance Oversight

cc: Elizabeth Trias, HPA, Children's Hospital & Regional Med. Ctr.
Dr. Douglas Diekema, IRB Chairperson
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Sam Shekar, NIH
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