DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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June 19, 2006

Daniel H. Winship
Chief
Cook County Bureau of Health Services
1900 West Polk Street
Suite 220
Chicago, IL 60612

RE: Human Research Subject Protections Under Multiple Project Assurance M-1150 and Federalwide Assurance FWA-1802

Research Project: Phase I/II Study: Ritonavir Therapy in HIV-I Infected Infants and Children
Project Number: ACTG #345
Principal Investigator: Kenneth Boyer, M.D.

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: Kenneth Boyer, M.D.

Dear Mr. Winship:

The Office for Human Research Protections (OHRP) has reviewed the Cook County Bureau of Health Services' (CCBHS) March 29, 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, 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 Institutional Review Board (IRB) for approval of research involving children. OHRP's review of CCBHS IRB documents for the above-referenced research revealed no evidence

that the IRB considered and made the required findings when reviewing this research involving children.

Corrective Action: CCBHS stated the following in its March 29, 2006 response to OHRP:

> "...the CCBHS IRB has a standing policy...that no minor is to be enrolled in any study that is neither minimal risk nor for the potential benefit of the minor unless a justification is documented in the minutes that the study is for the potential benefit of the group as a whole."
>
> "In 2001, we undertook steps to have our minutes more fully reflect our discussion and we implemented a new database in 2004. Our procedure for approving research involving minors now requires the explicit recording in the minutes as to which criterion is met - 45CFR46.404 or 45CFR46.405. In 1997, the minutes would not yet have reflected a positive assessment that the study met these criteria but any study not meeting the criteria would have documentation and justification recorded in the minutes....In addition, we will add to this corrective action plan the creation of new IRB submission forms that explicitly ask the principal investigator to address these issues."

Required Action: Please submit to OHRP a copy of the CCBHS procedure and a copy of the newly created IRB submission forms referenced above.

OHRP makes the following additional determinations:

(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 CCBHS 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 CCBHS IRB records for the above-referenced research demonstrate a failure of the IRB to obtain sufficient information regarding the selection of wards of the state and foster children as research subjects.

OHRP acknowledges the following statement made by CCBHS in its March 29, 2006 response:

> "The mission of the County hospital facility is to provide quality health care to the residents of Cook County regardless of their

> inability to pay...Wards of the state are brought to the CORE Center for its excellent care. Since equal care for all is such a fundamental mission value of our activities, we did not consider it necessary to restate this in the minutes concerning this particular research activity. If there is any language concerning this area that you would like us to routinely include please let us know."

OHRP reminds CCBHS that under its Assurance the IRB has an independent responsibility to review research appropriately under HHS regulations at 45 CFR 46.111, regardless of the institution's mission statement for clinical care.

OHRP further reminds CCBHS that IRB minutes are intended in part to reflect activities and discussions that actually occur during IRB minutes. It is not appropriate to insert template language in the minutes unless that language reflects actual consideration of a specific regulatory issue that occurred during the IRB meeting.

Required Action: Please provide OHRP with a corrective action plan to address the above finding. In your plan, please describe the manner in which the CCBHS IRB ensures that it receives sufficient information to make the determinations at 45 CFR 46.111(a)(3) for all research that it reviews.

(b) 45 CFR 46.111(a)(4): Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with 45 CFR 46.116. In particular, OHRP finds that CCBHS IRB records for the above-referenced research 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.

OHRP acknowledges CCBHS's entire response to OHRP's expression of concern about the issue above:

> "Because the protocol was approved for the vulnerable population of children under 45 CFR 46.405 for the potential benefit of the subjects themselves the authorized signature would be the guardian from the Department of Children and Family Services. This signature was appropriated recorded on the form. Additionally, though not required, the consent was signed by the child's aunt who intended to and later did adopt the child. The girl's mother was also present at the time of the consent"

OHRP notes that CCBHS's response does not acknowledge the responsibility of the IRB to prospectively obtain information from the principal investigator regarding the possible inclusion of wards of the state in research studies. In addition, it does not indicate whether in fact the IRB discussed at initial IRB

review the inclusion of wards of the state in the above-referenced research and discussed the manner in which the investigator would obtain permission from parents or guardians

Required Action: Please provide OHRP with a corrective action plan to address the above finding. In your plan, please describe the manner in which the CCBHS IRB ensures that it receives sufficient information to make the determinations at 45 CFR 46.111(a)(4) for all research that it reviews.

(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 CCBHS IRB records for the above-referenced research 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.

OHRP acknowledges the following statement made by CCBHS in its March 29, 2006 response:

> "45CFR46.111(b) <sic> asks that additional safeguards be put in place when a subject may be vulnerable to coercion. In this study, the vulnerable subject was an infant. Since infants are not asked to assent to the research, coercion is not a meaningful issue. The guardian was certainly not a particularly vulnerable consenter. The child's aunt had the additional protection of the support of the child's mother, and the staff member from DCFS. Additionally, the guardian of the child was reconsented for participation throughout her participation. As we reported earlier, the Department of Children and Family Services also reviewed (and approved) the protocol."

OHRP notes that CCBHS's response does not acknowledge the responsibility of the IRB to prospectively obtain information from the principal investigator regarding additional safeguards to be included when potential subjects are likely to include persons who may be vulnerable to coercion or undue influence; in this case, the IRB did not obtain such information.

Required Action: Please provide OHRP with a corrective action plan to address the above finding. In your plan, please describe the manner in which the CCBHS IRB ensures that it receives sufficient information to make the determinations at 45 CFR 46.111(b) for all research that it reviews.

Please forward your response to the above finding and concerns so that OHRP receives it no later than July 31, 2006.

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,

Karena Cooper, J.D., M.S.W.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Lynda Brodsky, Director, Research Affairs, Cook County Bureau of Health Services
Dr. Peter Orris, Chairperson, John H. Stoger Hosp Cook Co IRB #1
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Sam Shekar, NIH
Dr. Anthony Fauci, NIH
Dr. Edmund C. Tramont, NIH
Ms. Donna Marchigiani, NIH
Dr. Robinsue Frohboese, OCR
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
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Ms. Janet Fant, OHRP