DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 240-453-8238
FAX: 240-453-6909
E-mail: Karena.Cooper@hhs.gov

June 19, 2006

Philip Johnson, MD
Joseph Stokes, Jr. Research Institute
Chief Scientific Officer
Children's Hospital of Philadelphia
Abramson Research Center, First Floor
Philadelphia, PA 19104

RE: Human Research Subject Protections Under Federalwide Assurance FWA-459

Research Project: Phase I Safety Trial: A Study to Test the Safety of Recombinant Interleukin-2 (rIL-2) in HIV- Infected Children
Project Number: ACTG #299
Principal Investigator: Stuart Starr, M.D.

Dear Ms. Argon:

The Office for Human Research Protections (OHRP) has reviewed Children's Hospital of Philadelphia's (CHOP) March 31, 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 CHOP IRB documents for the above-referenced research revealed no evidence that the CHOP IRB considered and made the required findings when reviewing this research involving children.
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> **Corrective Action:** OHRP acknowledges the following statements made by CHOP in its March 31, 2006 response:

> In 2000, the IRB implemented a template for minutes, which is followed to document IRB deliberations...in instances where children are the subjects of the research, the IRB specifically discusses and determines the risk level and thereby, the section of Subpart D under which the research is approved. The minutes uniformly reflect that determination. Please note that the CHOP IRB is in the process of revising the template for minutes to conform to the NIH IRB Minutes template....
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> The IRB Face Sheet <IRB application, version date 3-16-2006> has been revised to capture information on Vulnerable Subjects. There are two items, which specifically address children as vulnerable subjects. There is also a subsection, which delineates which risk category under Subpart D, the proposed research would be approved.

OHRP finds that the above corrective actions adequately address the finding noted in (1) and are appropriate under the CHOP Assurance.

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 the above-referenced research, the CHOP 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 CHOP 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.

Corrective Actions: OHRP acknowledges CHOPS's response to OHRP's expression of concern about the issue above:

> The IRB minutes template is utilized to address this item for each protocol review and the IRB's consideration of this factor is contained in all current IRB minutes. Investigators are advised in their approval letter, for studies approved under 406 and 407, that, if wards are to be enrolled in the study, the IRB needs to be notified, so additional protections for the population may be put into place. The IRB also will independently raise the issue of protection of wards and require protection in accordance with Subpart D

> where it is apparent from the description of the protocol that wards will be involved in the study.

Required Action: Please explain how the CHOP IRB will ensure that it obtains sufficient information from the principal investigator *prior to* initial IRB review regarding the enrollment of wards of the state or foster children.

(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 CHOP 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.

Corrective Actions: CHOP indicated in its March 31, 2006 response the following:

> In its deliberations, the IRB considers the special requirements in connection with the informed consent process for wards. The process had not, however, been formally documented, but the IRB now documents these deliberations. We are in the process of developing an SOP regarding informed consent that will conform in all respects to the requirements of Subpart D governing protection of wards.

Required Action: Please send to OHRP a copy of the policy referenced above. In addition, please explain how the CHOP IRB will ensure that it obtains sufficient information from the principal investigator regarding the process of 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 CHOP 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.

Corrective Action: OHRP acknowledges the following statements made by CHOP in its March 31, 2006 response:

> The IRB is actively recruiting a child advocate whose qualifications satisfy Section 409 of Subpart D, to serve as a member of the IRB. Pending that recruitment, the IRB will appoint a qualified advocate for each protocol in which wards participate. Any advocate will be fully involved in the

deliberations of the IRB, and the conduct of the research, for the duration of the research in accordance with Section 409.

OHRP finds that the above corrective actions adequately address the finding noted immediately above in 2(c) and are appropriate under the CHOP Assurance.

CHOP indicated in its March 31, 2006 response that since 1996, there has been considerable change in IRB personnel, chairs, and committee membership and that the CHOP IRB is "cognizant of the special concerns with research involving vulnerable populations." There have also been a number of improvements to the systems the IRB currently has in place...IRB SOP 503....addresses wards of the state and foster children as research subjects..."

Required Action: Please describe to OHRP the procedures used to ensure that the IRB is "cognizant" of the special concerns with research involving vulnerable populations. In your response, it may be appropriate to describe education and training opportunities afforded to IRB staff, IRB members and investigators.

Please forward your response to the above findings 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: Lynn Bevan, Dir. Regulatory Affairs, Joseph Stokes Jr. RI, CHOP
Dr. Mark Schreiner, Chairperson, IRBs #1- #3
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
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP

Dr. Irene Stith-Coleman, OHRP
Dr. Kristina Borror, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Janet Fant, OHRP