DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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August 15, 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 Dr. Johnson:

The Office for Human Research Protections (OHRP) has reviewed Children's Hospital of Philadelphia's (CHOP) July 28, 2006 response to OHRP's June 19, 2006 letter regarding determinations 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 June 19, 2006 letter, OHRP made the following additional determinations regarding the above-referenced research:

> OHRP found 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:
>
> > (1) 45 CFR 46.111(a)(3). OHRP found that CHOP IRB records for the above-referenced research demonstrated a failure of the IRB to obtain sufficient information regarding the selection of wards of the state and foster children as research subjects.

OHRP asked CHOP to 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.

Corrective Actions: OHRP notes that the revised CHOP IRB application solicits specific information from the investigator regarding children and wards as research subjects. If the investigator indicates that the study should be approved under either HHS regulations at 45 CFR 46.406 or 45 CFR 46.407 and indicates that wards of the state could potentially participate in the research, the investigator is instructed to complete another section of the application entitled "Wards as Research Subjects."

CHOP stated the following in its July 28, 2006 response:

> The designated reviewer(s) reviews these determinations as part of the protocol review process. If there is insufficient information to make these determinations, the investigator is instructed to provide additional detail. The reviewer(s) completes the Protocol Review Form, indicating their recommended findings with respect to:
> - Additional safeguards that adequately protect vulnerable subjects,
> - Subpart D Risk Category,
> - Adequate provisions for soliciting assent and permission,
> - If wards are included, that the criteria of §46.409 are met.

CHOP also stated the following:

> Going forward, for any research considered under §46.406 or §46.407, the IRB will determine whether wards of the state could potentially participate in the research. If so, the IRB will determine whether the criteria of §46.409 have been met. That determination will be documented in the minutes, and in the letter of approval sent to the principal investigator.

(2) 45 CFR 46.111(a)(4). OHRP found that CHOP IRB records for the above-referenced research demonstrated 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.

CHOP indicated in its March 31, 2006 letter to OHRP that it was in the process of developing an SOP regarding informed consent that would conform in all respects to the requirements of Subpart D governing protection of wards.

In its June 19, 2006 letter, OHRP requested that CHOP send OHRP a copy of the above-mentioned policy. In addition, CHOP was asked to 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.

Corrective Actions: OHRP notes that the revised CHOP IRB application contains a section entitled "Description of Consent/Parental Permission Procedures." In its July 28, 2006 response, CHOP states the following about the revised CHOP Standard Operating Procedure (SOP) entitled "Assent and Parental Permission":

> The SOP states that it is the investigator's responsibility to provide the IRB with either a detailed description of how permission and assent will be obtained, or to request consideration of a waiver of permission and/or assent.
>
> If children who are wards are to be included in the research, this SOP also assigns to the investigator the responsibility to provide the IRB with detailed information about the proposed permission/assent process, as well as the identity and authority of the individuals who will provide permission for the ward subjects. Investigators are informed that a foster parent is not legally authorized to provide permission for a foster child.

(3) 45 CFR 46.111(b). OHRP found that CHOP IRB records for the above-referenced research demonstrated 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.

In its June 19, 2006 letter, OHRP asked CHOP to describe to OHRP the procedures used to ensure that the IRB is "cognizant" of the special concerns with research involving vulnerable populations.

Corrective Action: CHOP's July 28, 2006 response includes the following statement:

> We have begun to implement a new training program for IRB administrative staff, IRB members, and investigators and their staff, to further increase their awareness and understanding of the regulations and CHOP policies and procedures governing the participation of vulnerable subjects, and particularly, children in research, with a special emphasis on the special protections afforded to wards and foster children as research subjects...The training is conducted both in person and by distribution of SOPs and forms, with explanation.

CHOP also stated that beginning in September 2006, all researchers will be required to complete online IRB training to begin or continue research. Those researchers involved in studies with children as participants must complete an online training module on research with children.

OHRP has determined that the corrective actions above adequately address OHRP's findings. As a result, there should be no need for further involvement of OHRP in this matter. Of course,

OHRP must be notified should new information be identified which might alter this determination.

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, CHOP IRBs #1- #3
Dr. Stuart Starr, CHOP
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Sam Shekar, NIH
Dr. Anthony Fauci, NIH
Dr. Edmund C. Tramont, NIH
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Dr. Robinsue Frohboese, OCR
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Dr. Irene Stith-Coleman, OHRP
Dr. Kristina Borror, OHRP
Ms. Patricia El-Hinnawy, OHRP
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