DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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June 19, 2006

Mary Ellen Sheridan, Ph.D.
Associate Vice President for Research
University of Chicago
970 E. 58th Street
Chicago, IL 60637

RE: Human Research Subject Protections Under Multiple Project Assurance M-1264 and Federalwide Assurance FWA-5565

Research Project: Phase I Safety Trial: A Placebo-Controlled, Phase I Clinical Trial to Evaluate the Safety and Immunogenicity of Recombinant Envelope Proteins of HIV-1 gp160 and gp120 in Children ≥1Month Old with Asymptomatic HIV Infection
Project Number: ACTG #218
Principal Investigator: Daniel Johnson, M.D.

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

Research Project: Pram 2 – A Phase I/II Randomized Multicenter Protocol Comparing Four Antiretroviral Regimens Containing Combinations of Protease Inhibitors, NRTIs and NNRTI
Project Number: ACTG #377
Principal Investigator: Daniel Johnson, M.D.

Dear Dr. Sheridan:

The Office for Human Research Protections (OHRP) has reviewed the University of Chicago's (UC) 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.

OHRP made the following determination regarding the above-referenced research in its February 17, 2006 letter:

> (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 UC institutional review board (IRB) documents for the above-referenced research revealed no evidence that the UC IRB considered and made the required findings when reviewing this research involving children.
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> **Corrective Action:** OHRP acknowledges the following statement in UC's March 29, 2006 letter:
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> > In 2002, the IRB implemented a new submission form (IRB Supplemental Form C) which outlines the requirements of 45 CFR 46 Subpart D. The IRB further refined the form in 2005. The Principal Investigator's assessment of the protocol on Supplemental Form C helps to guide the IRB Committees in determining whether the research may be approved under category 404, 405, or 406, or whether 407 consideration is merited. Supplemental Form C also requires the PI to address whether the requirements for permission by parents or guardians are adequately addressed, in accordance with Subpart D, including whether permission of one or two parents is required and if so, how the permission of one or two parents must be documented. Supplemental Form C guides the PI and IRB Committee in evaluation whether assent by the child is required. Finally, Supplemental Form C addresses the issues pertinent to wards of the state.
> >
> > The current reviewer analysis sheets for both the review of new protocol and continuing reviews include the requirements of 45 CFR 46 Subpart D in order to guide the IRB Committees and the IRB members in ensuring that all appropriate findings are discussed by the IRB and documented in the minutes.
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> Based on its review, OHRP notes the following:
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> - IRB Policies and Procedures Manual, revised Jan. 31. 2006, Roman Numeral III, "Preparing the Protocol," Section C, "Protocol Application Contents," Subsection 2(t) contains the following statement: "Note that depending on the risk level, additional protections may be required for children who are wards of the state."
> - Roman Numeral V, "Informed Consent," Section A, "Informed Consent Categories," Subsection 1(a), "Child Assent/Parental Consent" states: "For studies greater than minimal risk enrolling wards of the state, a witness is required to the consent procedure. Foster parents may not sign the consent form for a ward of the state to participate in research, either as parent/guardian or witness."
> - Roman Numeral VI, "Special Populations," Section A, "Children," contains a subsection entitled "Wards of the state" that contains the basic regulatory provisions of 45 CFR 46.409.

- The IRB Protocol Submission Form, section entitled "Description of Human Subject Population, question 6A, "Vulnerable populations to be targeted in the research," contains a checkbox for wards of the state.

- IRB Supplemental Form C, "Research Involving Children," revised March 2006, contains a separate section entitled "Wards of the State", which includes the following additions, as compared to the June 2005 version:
    - How will the consent of the legal guardian(s) of the ward(s) of the state be obtained? How will the investigator ensure that the appropriate person grants permission for each ward to participate in the research?
    - Please describe your plan to appoint an advocate for potential subjects who are wards of the State *participating in research that is greater then minimal risk with no prospect of direct benefit [45CFR46.406]. [text in italics added in revised version]*

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 UC IRB failed to obtain sufficient information to make the following determinations required for approval of research under HHS regulations at 45 CFR 46.111. OHRP notes that although the consent forms for all three studies referenced above refer to the subject as "your child/ward," there is no evidence in any of the IRB materials reviewed by OHRP that the IRB obtained sufficient information to make the following determinations:

(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 UC 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.

(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 UC 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.

(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 UC 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 Actions: Regarding 45 CFR 46.111(a)(3), OHRP acknowledges the following statement in UC's March 29, 2006 response:

> "As required by 45 CFR 46.111(a)(3), the IRB took into account that children were to be enrolled into this study, but based on the minutes, the IRB acknowledges that its review would have benefitted from additional information regarding the selection of wards of the state and foster children. The IRB Protocol Submission Form was revised in March 2006 to explicitly collect information regarding the selection of wards of the state and foster children. The reviewer analysis sheet has also been modified to prompt the Committee to discuss whether the selection of subjects is equitable."

Regarding 45 CFR 46.111(a)(4), OHRP acknowledges the following statement in UC's March 29, 2006 response: "...the IRB acknowledges that the minutes do not demonstrate that the IRB specifically discussed the process for obtaining permission of parents or guardians for wards of the state or foster children. Therefore Supplemental Form C now specifically asks investigators to describe the process for obtaining permission form the parents or guardians of wards of the state or foster children."

Regarding 45 CFR 46.111(b), OHRP acknowledges the following statement in UC's March 29, 2006 response:

> "The IRB minutes indicate that the Committee discussed the risks and benefits to children in these studies. The IRB acknowledges that, based on the minutes, the Committee's review would have benefitted from a discussion of whether additional safeguards were needed to protect the rights and welfare of wards of the state or foster children. Therefore, the reviewer analysis sheet has been revised to clearly identify wards of the state as a vulnerable population in order to prompt the Committee to discuss whether any additional safeguards are needed to protect this population. Additionally, Supplemental Form C has been revised to specifically ask investigators to describe what additional safeguards are in place to protect the rights and welfare of wards of the state or foster children."

OHRP had 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: Dr. Jonathan Moss, Chairperson, IRBs #1A, and #4-01, Cmte. C, Univ. of Chicago
Dr. Tina L. Rzepnicki, Chairperson, IRB #2, Univ. of Chicago
Dr. Bennett Bertenthal, Chairperson, IRB #3, Univ. of Chicago
Commissioner, FDA
Dr. David Lepay, FDA
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