DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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August 28, 2006

Richard Homan, M.D.
Dean
Drexel University College of Medicine
(Philadelphia Health and Education Corporation)
245 N. 15th Street
Mail Stop 444, Suite 2105
Philadelphia, PA 19102-1192

Calvin Bland
President and CEO
St. Christopher's Hospital for Children
Erie Avenue at Front Street
Philadelphia, PA 19134

RE: Human Research Subject Protections Under Multiple Project Assurance M-1532A, Cooperative Assurance T-4530, and Federalwide Assurance FWA-5917

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: Harold W. Lischner, M.D.

Dear Dr. Homan and Mr. Bland:

The Office for Human Research Protections (OHRP) has reviewed Drexel University College of Medicine's (DUCM) August 8, 2006 response to OHRP's June 19, 2006 letter to St. Christopher's Hospital for Children (SCHC) 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.

OHRP notes that responsibility for the SCHC institutional review board (IRB) was assumed by DUCM in 2003 under FWA-5917.

(1) OHRP made the following finding of noncompliance in its June 19, 2006 letter:
OHRP noted that there is no documentation that the investigator requested nor received a determination from the IRB that it would not be in the best interests of the six subjects on the study to stop the study pending continuing re-review by the IRB. There is also no documentation in the February 24, 2999 IRB minutes that there was any discussion or explanation for the 3-month lapse in IRB approval. The study is listed in the "Pending New" section of the minutes and there is no mention of the fact that this study had been previously approved since 1997 prior to the 3-month lapse in approval.

OHRP asked DUCM to develop a corrective action for the finding above. DUCM was asked to address whether research with the six enrolled subjects was halted during the 3-month lapse in IRB approval and whether or not there was interaction or intervention or analysis of private, identifiable information with any previously enrolled human subjects during the lapse. If, during the lapse, subjects were taken off the HIV drugs being investigated in the study, DUCM was asked to describe what provisions were made to ensure the safety of those subjects.

DUCM indicated in its August 9, 2006 response that five previously enrolled subjects continued to receive research interventions during the almost 4-month lapse. Subjects were not taken off the study drugs, clinic visits were held, laboratory tests were performed and individual subject data was collected.

Corrective Actions: DUCM stated that it has adopted a separate continuing review policy on ongoing, lapsed, and expired protocols that includes specified actions to be taken by the IRB for investigators who are in non-compliance with the policy. DUCM indicated that each DUCM IRB will be trained about the application of this policy.

OHRP notes that the policy contains the following statements:

> Research activities include but are not limited to recruitment and enrollment of subjects, collection of specimens, research on previously collected specimens, review of medical records or other health information, and the performance of research tests/procedures, treatment or follow-up on previously enrolled subjects. If treatment and/or follow-up of previously enrolled subjects is necessary for subject safety and welfare after the expiration date, the Principal Investigator must obtain IRB approval before continuing treatment and/or follow-up. The IRB will consider these requests on a case-by-case basis...
>
> If the Principal Investigator is in communication with the IRB, the required continuing review documents are forthcoming, and the Principal Investigator demonstrates that participants in the research project would suffer hardship or threats to their well-being if medical care and/or treatment were to be discontinued, the IRB chair or chair's designee may permit the appropriate medical care and/or treatment to continue for a reasonable

> period of time not to exceed 30 days beyond the expiration date of IRB approval. The IRB chair or chair's designee must then place the extension of treatment on the agenda of the next convened meeting of the IRB for its action. New participants may not be enrolled in research during such an extension of approval for necessary treatment of enrolled subjects.

OHRP has determined that the corrective actions above adequately address OHRP's finding and are appropriate under the DUCM FWA.

(2) In its February 17, 2006 letter, OHRP asked DUCM to provide evidence that the IRB makes the findings required under HHS regulations at 45 CFR part 46, subpart D, in the approvals for all research involving children. DUCM stated in its March 2006 response, "It is our policy now that each protocol as it is being reviewed is discussed for level of risk and the risk level is clearly marked on the reviewer's checklist and minutes of the meeting." In its June 19, 2006 letter, OHRP asked DUCM to provide a copy of the above-referenced policy.

OHRP would like to make the following comments and suggestions regarding Policy Section 9.3, entitled "Protections for Children Involved as Subjects in Research."

> (a) OHRP notes that the definition of minimal risk listed in DUCM policy 9.3.2, subsection F, is the definition of minimal risk used in 45 CFR 46.303(d), subpart C, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects:
>
> "*Minimal risk* is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons."
>
> OHRP suggests that it would be more appropriate to use the definition found in Subpart A, at 45 CFR 46.102(i):
>
> > *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
>
> (b) Subsection B of Section 9.3.3, Additional IRB Responsibilities begins as follows:
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> > If the IRB finds that the research poses more than minimal risk to the child subject, the IRB must then determine whether the proposed intervention or procedure holds out the prospect of direct benefit for the individual child, or whether a proposed monitoring procedure is likely to contribute to the individual child's well-being.

Subsection B(1) then states:

> If the IRB determines there is minimal risk, the research may be approved only if the IRB also establishes that:
>
> 1. The risk is justified by the anticipated benefit to the subjects;
> 2. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
> 3. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians...

OHRP notes that the first paragraph and the three conditions under subsection 1 above are derived from 45 CFR 46.405. However, the first sentence of the subsection seems to be missing the phrase "more than" before "minimal risk."

Subsection B(2) states:

> If the IRB determines there is more than minimal risk, the research may be approved only if the IRB also establishes that: 1. The risk represents a minor increase over minimal risk, 2. The intervention or procedure presents experiences that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; 3. The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition; and 4. Adequate provisions are made for soliciting assent of the children...

OHRP notes that subsection B(2) is derived from 46.406. Therefore, it is confusing to include this subsection in section B, which begins with the text from 46.405 which is inapplicable to 46.406.

(c) OHRP notes that requirements in 45 CFR 46.409 are triggered only when research is approved under 46.406 or 46.407. Section G of the DUCM Guidelines begins with the following statement: "The IRB may approve the use of children who are wards of the state or any other agency, institution, or entity, in research covered by section 9.3.3(B)(2) and 9.3.3 of these Guidelines, only if the IRB...." and then lists the conditions found in 46.409.

Section G references both section 9.3.3(B)(2), which contains the requirements of 46.406 and to section 9.3.3, which is the section entitled "Additional IRB Responsibilities" that contains the requirements of 45 CFR 46 subpart D. It is not clear in Section G whether DUCM is creating a more stringent policy than the regulations mandate by requiring that the conditions of 46.409 apply to the approval of all research involving child wards of the state.

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. Sreekant Murthy, Ph.D., Vice Provost for Research Compliance, DUCM
Dr. Victor Lidz, Chairperson, IRB #1, DUCM
Dr. Patricia Shewokis, IRB #3, DUCM
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