DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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June 19, 2006

Richard Homen, MD
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. Homen and Mr. Bland:

The Office for Human Research Protections (OHRP) has reviewed Drexel University College of Medicine's (DUCM) March 28, 2006 response to OHRP's February 17, 2006 letter to St. Christopher's Hospital for Children (SCHC) 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 notes that responsibility for the SCHC IRB was assumed by DUCM in 2003 under FWA-5917.

OHRP makes the following determinations regarding the above-referenced research:

(1) 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 the SCHC IRB failed to obtain sufficient information to make the following determinations required for approval of research under HHS regulations at 45 CFR 46.111 when reviewing the above-referenced research.

(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 SCHC IRB records 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 SCHC IRB records 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 SCHC IRB records 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: DUMC stated in its March 28, 2006 response, "You are correct <sic> when the IRB approved this study the subject of wards of state was probably not discussed as it was not documented in the minutes. However, it is our impression that the study was approved for everyone who was eligible to participate...For this one ward of the state, appropriate measures were taken to obtain permission from a legally authorized person to include this subject participant in the study. For inclusion of wards of the state in any study, the IRB and the Department of Immunology has specific policies in place and they were followed."

OHRP notes that the St. Christopher's Pediatric Associates and St. Christopher's Hospital for Children Section of Immunology "Policies and Procedures for Consent and Documentation of Custody for Children in Substitute Care," Section C, "Research Consent" discusses *who* may provide consent for children in substitute care situations. The policy does not address the *process* of informed consent and therefore on its own does not address 46.111(a)(4). OHRP also notes that there is no documentation that this policy existed or that the IRB was aware of or discussed this policy at the time the above-

referenced research was initially approved in 1997 or reapproved in 1999 after a 3-month lapse in approval.

DUCM presented the following corrective actions in its March 28, 2006 response:

> The IRB will be using the new checklist which alerts the reviewers to take into consideration the issues related to equitable selection of subjects and inclusion of wards of state in all of the studies to be reviewed by the IRB. Investigators will be guided in the IRB submission forms to provide sufficient information on subject category and safeguards in place for including population and wards of the state without undue influence or coercion. The checklist, the policy on equitable selection and the new Draft IRB application form which requires investigators to provide research participant recruitment process and justification for equitable selection of participants are attached."

DUCM stated, "The IRB training involved presentation of educational material to all of the IRBs and discussion by the committee for the need to pay sufficient attention towards <sic> the 'Equitable Selection of Participants.'" DUCM also stated, "Minutes of the meeting will record discussions ensuing <sic> equitable selection of subjects."

DUCM's response to OHRP's concerns regarding 45 CFR 46.111(a)(3) and (4) and 46.111(b) focus on the issue of equitable selection of subjects. OHRP suggests that issues characterized as related to the "recruitment process" in the new policy on equitable selection also relate to the process of informed consent. For example, the policy states: "The investigator must address all areas to be considered for approval by DUCOM IRB: a. Consent (On-going consent): The subject my <sic>be informed through a dynamic continuous process of Informed Consent, b. Coercion...." OHRP notes that the IRB Reviewer Checklist (no version date) does not have a specific section on the process of informed consent, but also notes that the new IRB application does solicit such information. For example, the principal investigator is asked to answer the following questions:

- Describe what you will be saying to the subjects to introduce the research.
- In relation to actual data gathering, when will you be discussing consent and obtain documentation?
- Will the Principal Investigator be securing all of the informed consent?
- What questions will be at ask <sic> to assess the subjects' understanding of the risks and benefits of participation?

OHRP notes that the revised copy of the IRB Reviewer Checklist (no version date) contains the following notation in the section entitled "Studies involving minor and children": "Note: If subject population involves wards, a child advocate must be appointed or approved by the IRB." There is no corresponding statement in the Sectional 9.3.3 of the IRB policy entitled "Additional IRB Responsibilities". OHRP suggests that

the policy be revised to clearly state whether advocates will only be appointed for studies approved under 46.406 and 46.407, as required by the regulations, or whether advocates will be appointed for all studies that involve wards.

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

(2) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk, and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. OHRP finds that the DUCM IRB failed to conduct continuing review of the above-referenced research at least annually.

OHRP previously expressed concerns about this matter in its February 17, 2006 letter. OHRP requested that DUCM provide a chronology of the various approval dates for this study. OHRP also requested that DUCM send the minutes for the 1998 renewal.

DUCM stated in its March 28, 2006 response that the study expired on November 11, 1998 when the principal investigator failed to respond to two notices from the Office of Research regarding continuing review. DUCM stated "There are no minutes that we can submit to you documenting the renewal of the study in 1998." DUCM stated "The initial and final continuing review notices specifically stated that the subject study will expire on November 11, 1998 and in the event of expiration no further research involving human subjects may be conducted. Per federal regulations and our university policy this protocol expired for all intents and purposes."

DUCM's March 2006 letter contains an excerpt from the DUCM IRB standard operating procedure for continuing review that includes the following statement: "If an investigator has failed to provide continuing review information to the IRB or the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of IRB approval." DUCM stated that "We believe the above procedure was used for approval of the study."

DUCM indicated that the IRB reviewed a new version of the study on February 24, 1999, along with information on six subjects enrolled in 1998 during the approval period. The principal investigator, in a memo to the IRB

Chair dated Feb. 12, 1999, stated "There will be no new enrollments to this protocol and have been none since June 1998." OHRP notes that the investigator made no indication of whether research as per the protocol continued during the 3-month lapse in IRB approval.

OHRP notes 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 Feb. 24, 2999 IRB minutes that there was any discussion or explanation for the 3-month (November 11, 1998 - Feb. 24, 1999) 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.

Required Actions: Please develop a corrective action for the finding above. In your response, please address whether research with the six enrolled subjects was halted during the 3-month lapse in IRB approval. Please indicate whether or not there was interaction or intervention 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, please

describe what provisions were made to ensure the safety of those subjects. Please also indicate whether or not there was any analysis of private, identifiable information of previously enrolled human subjects during the 3-month lapse.

Based upon its review, OHRP would like to express the following additional concerns:

(3) [redacted]

[Redacted]

[Redacted]

Please send your response to the above finding and concern 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: Dr. Sreekant Murthy, Ph.D., Vice Provost for Research Compliance, DUCM
Dr. Victor Lidz, Chairperson, IRB #1, DUCM
Dr. Patricia Shewokis, IRB #3, DUCM
Dr. Carol Anderson, IRB #4, DUCM
Dr. Adamadia Deforest, HPA, St. Christopher's Hosp. for Children
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Sam Shekar, NIH
Dr. Anthony Fauci, NIH
Dr. Edmund C. Tramont, NIH
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