DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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June 19, 2006

Frank Tiedemann
President / CEO
Children's Hospital & Research Center at Oakland
747 Fifty-second Street
Oakland, CA 94609

RE: Human Research Subject Protections Under Federalwide Assurance FWA-94

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 ≥1 Month Old with Asymptomatic HIV Infection
Project Number: ACTG #218
Principal Investigator: Ann Petru, M.D.

Research Project: Phase I Study: A Double-Blind Placebo-Controlled Trial of the Safety and Immunogenicity of a Seven Valent Pneumococcal Conjugate Vaccine in Presumed-HIV-Infected Infants
Project Number: ACTG #292
Principal Investigator: Ann Petru, M.D.

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: Ann Petru, M.D.

Dear Mr. Tiedemann:

The Office for Human Research Protections (OHRP) has reviewed the Children's Hospital & Research Center at Oakland's (CHRCO) March 27, 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 letter, OHRP made the following determinations 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 CHRCO IRB documents for the above-referenced research revealed little evidence that the CHRCO IRB considered and made the required findings when reviewing this research involving children.
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> OHRP noted that one ward was involved in ACTG #218, and that this subject was not recruited at your institution; however, OHRP was unable to find any reference to the specific findings required under HHS regulations at 45 CFR 46.404-409 in IRB minutes for this study. ACTG #292 and #377 included wards and were determined by the IRB to fall under HHS regulations at 45 CFR 46.405.
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> OHRP acknowledged the December 1989 CHRCO Advocacy Policy, a document that specifies the responsibilities of the advocate required in research involving children who are wards of the state in accordance with HHS regulations at 45 CFR 46.409.

Based upon its review of your March 27, 2006 response, OHRP now 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 this research, the CHRCO IRB failed to obtain sufficient information to make the following determinations required for approval of research under HHS regulations at 45 CFR 46.111.
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> > (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 CHRCO IRB records appear to demonstrate a failure of the IRB to obtain sufficient information regarding the selection of wards of the state and foster children as research subjects.
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> > (b) 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 CHRCO IRB records appear to 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.
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> **Corrective Actions:** OHRP acknowledges the efforts by your institution to improve human subjects protections which address these concerns. A revised IRB application asks

whether the investigator plans to enroll wards of the state and if so, to explain the rationale for such enrollment; the application also requires a discussion of the informed consent process including how and by whom it will be determined that the subject or the legally authorized representative did or did not understand the information provided. The application further solicits explicit risk and benefit statements. The IRB checklist requires a determination regarding the category of research under the HHS regulations at 45 CFR 46.404-407 and prompts discussion of category criteria, including that adequate provision for soliciting assent of the children and permission of their parents or guardians has been made; the checklist also specifically cites 45 CFR 46.409 and requests information on the appointment of an advocate for wards. The institutional policies and procedures also address the appointment of the advocate. The institution further points to the March 2004 OHRP Quality Assurance site visit and an expanded administrative staff, including the hiring of a IRB administrator, as actions improving the quality of human subjects protections at CHRCO.

OHRP finds that these corrective actions adequately address the stated findings and are appropriate under the CHRCO assurance. As a result of this determination, there should be no need for further involvement of OHRP in this matter.

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,

Julia Gorey, J.D.
Division of Compliance Oversight

cc: Mordechai D. Pelta, IRB Administrator, Children's Hosp & Research Ctr at Oakland
Dr. John R. Waterson, Chairperson, Children's Hosp Oakland IRB #1
Dr. Sam Shekar, NIH
Dr. Anthony Fauci, NIH
Dr. Edmund C. Tramont, NIH
Ms. Donna Marchigiani, NIH
Dr. Robinsue Frohboese, OCR
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Kristina Borror, OHRP
Ms. Shirley Hicks, OHRP

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