DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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May 23, 2005

Harvey R. Colten, M.D.
Vice President and Senior Associate Dean
for the Faculties of Health Sciences and Medicine
Columbia University Medical Center
722 West 168th Street, 4th Floor
New York, NY 10032

Laura L. Forese, M.D., M.P.H.
Vice President/Chief Medical Officer
New York Presbyterian Hospital
525 E. 68th Street, M-106
New York, NY 10032

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1356 and Federalwide Assurances FWA-2635 and FWA-2636

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: Anne Gershon, M.D.

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: (Jane Pitt, M.D., succeeded by) Anne Gershon, M.D.

Research Project: Phase I/II Trial: The Safety and Immunogenicity of Live-Attenuated Varicella Vaccine (Varivax) in HIV-Infected Children
Project Number: ACTG #265
Principal Investigator: Anne Gershon, M.D.

Research Project: Phase I/II Study: Ritonavir Therapy in HIV-I Infected Infants and Children
Project Number: ACTG #345
Co-Principal Investigators: Stephen Nicholas, M.D. and Anne Gershon, M.D.

Dear Dr. Colten and Dr. Forese:

The Office for Human Research Protections (OHRP) has reviewed the New York Presbyterian Hospital (NYPH)/Columbia University Medical Center's (CUMC) August 19, 2004 and February 11, 2005 responses to OHRP's March 16, 2004 and December 16, 2004 letters regarding allegations 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.

Based upon its review, OHRP makes the following determinations of noncompliance regarding the above-referenced research:

(1) HHS regulations at 45 CFR 46.111(a) 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 CUMC IRB failed to obtain sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111.

(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. OHRP finds that CUMC 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 subjects's legally authorized representative, in accordance with 45 CFR 46.116. In particular, OHRP finds that CUMC 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 HHS regulations to protect the rights and welfare of these subjects. In particular, OHRP finds that CUMC 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: OHRP acknowledges that NYPH/CUMC stated in its Aug. 19, 2004 response to OHRP that CUMC had increased it resources and the number of IRBs since 2003; was migrating to a Web-based system; implemented a pre-review system for all new protocols and modifications; and was pilot-testing a comprehensive reviewer's form. The response also stated that CUMC had initiated education and training programs for IRB staff, chairpersons and members, as well as for investigators, and was applying for accreditation from AAHRPP.

Required Action: By June 30, 2005, NYPH/CUMC must provide a satisfactory corrective action plan to specifically address the above findings. In addition, please provide with your response updated information about the planned corrective actions stated above.

(2) 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 CUMC IRB documents for the above-referenced research revealed no evidence that the CUMC IRB considered and made the required findings when reviewing this research involving children.

Corrective Action: OHRP acknowledges that NYPH/CUMC stated in its Aug. 19, 2004 response to OHRP that the CUMC IRB is "in the process of planning steps specifically to improve protections for children, and particularly foster children." The response stated that:

- CUMC will appoint a task force to develop a training program on the participation of children in research, and will require researchers and IRB members and staff to complete it;
- CUMC will conduct a review of IRB procedures; and
- CUMC will make research involving children a topic for education and training at an upcoming annual IRB retreat.

NYPH/CUMC stated in its Feb. 11, 2005 response to OHRP that in recent months, it had enhanced the detail in its documentation of required findings, including Subpart D.

Required Action: By June 30, 2005, please develop a corrective action to address the above finding. In your response, please provide updated information about the planned corrective actions stated above.

In addition, please send to OHRP the following materials:

(a) A list of all active studies involving children as subjects approved by any of the three CUMC IRBs and the IRB on the University campus. For each study, please provide the following information:

(i) The date of initial IRB approval and the Subpart D category (45 CFR 46.404, 405, 406, or 407) under which each study was approved.

(ii) A description of how the IRB ensured that the requirements of HHS regulations at 45 CFR 46.408 were fulfilled for each of the studies.

(iii) An indication of whether the study enrolled, or was approved to enroll, wards of the state and/or foster children.

(iv) For those studies that were approved under 45 CFR 46.406 or 407 and involved wards of the state, a description of how the IRB fulfilled the requirements under HHS regulations at 45 CFR 46.409.

(b) NYPH/CUMC's current IRB policies and procedures.

(c) Minutes of all CUMC IRB meetings for the past three months.

(3) HHS regulations at 45 CFR 46.409(a) state that children who are wards of the State or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is: (1) related to their status as wards; or (2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. HHS regulations at 45 CFR 46.409(b) state that, for research involving wards that is approved under 45 CFR 46.409(a), the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or *in loco parentis.*

It was alleged by the complainant that the above-referenced research did not meet the criteria in 45 CFR 46.409(a)(1) and (2), and that no advocates were appointed for wards enrolled in the research.

OHRP acknowledges that NYPH/CUMC stated in its August 19, 2004 and Feb. 11, 2005 responses to OHRP, "All of the research in the four above-referenced protocols involved the prospect of direct benefit for each subject for whom there was greater than minimal risk." NYPH/CUMC further stated that because "all of the research fell under either 45 CFR 46.404 or 46.405, the requirements in 45 CFR 46.409, which applies only to research approved under 45 CFR 46.406 or 46.407, does not apply to any of the research at issue."

OHRP does not make a determination at this time as to whether the above-referenced research was "approvable" under either 45 CFR 46.404 or 45 CFR 46.405, and therefore does not make a determination as to the applicability of 45 CFR 46.409.

(4) HHS regulations at 45 CFR 46.111(a)(1) require the IRB to determine that risks to subjects are minimized by using procedures which are consistent with sound research design and which do not necessarily expose subjects to risk. It was alleged by the complainant that prior to confirmatory diagnostic HIV testing, infants were enrolled in the above-referenced research to treat HIV infection; and as a result, risks to the subjects were not minimized. Based upon information provided in NYPH/CUMC's reports, OHRP finds that this allegation is not substantiated.

OHRP would like to express the following additional questions and concerns:

(1) [Redacted]

(2) [Redacted]

(3) [Redacted]

(4) [Redacted]

Please forward your responses to the above required actions, questions, and concerns so that OHRP receives them no later than June 30, 2005.

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. Steven Corwin, NY Presbyterian
Mr. George Gasparis, Executive Director, HSPP, NY Presbyterian
Dr. Andrew S. Wit, Chairperson, Columbia U Hlth Sci IRB #1
Dr. Elaine H. Laarson, Chairperson, Columbia U Hlth Sci IRB #2
Dr. Andrew R. Davidson, Chairperson, Columbia U Hlth Sci IRB #3
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Lana Skirboll, NIH
Dr. Anthony Fauci, NIH
Dr. Edmund C. Tramont, NIH

Ms. Donna Marchigiani, NIH
Dr. Robinsue Frohboese, OCR
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