DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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February 17, 2006

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Senior Associate Dean for Clinical Affairs
Columbia University Medical Center
VP & Dean's Office, 630 W. 168th St.
New York, NY 10032

Laura L. Forese, M.D., M.P.H.
Vice President/Chief Medical Officer
New York Presbyterian Hospital
161 Fort Washington Avenue, HIP 1412
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. Shea 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; February 11, 2005; July 28, 2005; September 29, 2005; and December 8, 2005 responses to OHRP's March 16, 2004; December 16, 2004; May 23, 2005; and October 24, 2005 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.

In its May 23, 2005 letter, OHRP made the following determinations of noncompliance regarding the above-referenced research:

(1) OHRP found 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): OHRP found that CUMC IRB records for the above-referenced research demonstrated 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): OHRP found that CUMC IRB records for the above-referenced research demonstrated 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): OHRP found that CUMC IRB records for the above-referenced research demonstrated a failure of the IRB to obtain sufficient information regarding safeguards with respect to the enrollment of wards of the state or foster children.

Corrective Actions: NYPH/CUMC stated in its August 19, 2004 response to OHRP that CUMC had increased it resources and the number of IRBs since 2003; the IRB is migrating to a Web-based system; the IRB has implemented a pre-review system for all new protocols and modifications; and the IRB 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.

OHRP acknowledges that NYPH/CUMC stated in its July 28, 2005 letter: "Effective June 20, 2005, the IRB implemented new reviewer forms for all protocols, which systematically address a range of issues including many of the regulatory provisions raised in your letter."

OHRP notes that the "Columbia University Revised IRB Policies and Procedures" includes a list of information to be submitted to support the findings required by subpart D of 45 CFR 46:

- Description of procedures used to obtain assent or justification for not obtaining assent; when assent will be obtained, identification of the ages for which assent will be required and a description of the method to document that assent was provided
- Description of procedures for obtaining, and forms used to document, parental permission;
- Sufficient information to determine level of risk, investigator's initial assessment of risk level, and whether there is the prospect of direct benefit to the individual subject;
- Statement regarding the inclusion of wards, i.e., will wards be included, and if so, what procedures have been developed for identifying an advocate for each ward, if the research involves greater than minimal risk and no prospect of direct benefit to the individual subjects;
- Procedures for determining who is a legally authorized representative, when permission will be sought from someone other than the parent of a minor child.

OHRP also notes that the "Revised Research Involving Children Policy" includes a section entitled "Wards" that includes, in pertinent part, the following statements:

- "If wards are to be included in any research study, the investigator must provide the IRB with detailed information about the proposed informed consent process as well as identity and authority of the individuals who will provide consent."
- "In New York City, if wards are to be included in Section 406 or Section 407 Research, the Administration for Children's Services ('ACS') must be notified and agree to the inclusion of wards in the study. In addition, permission for the enrollment of each ward in the study must be obtained from the person designated by the ACS to give such permission."

(2) OHRP found that CUMC IRB documents for the above-referenced research revealed no evidence that the CUMC IRB considered and made the required findings in 45 CFR 46.404-409 when reviewing the above-referenced research involving children.

Corrective Actions: NYPH/CUMC stated in its August 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 February 11, 2005 response to OHRP that in recent months, it had enhanced the detail in its documentation of required findings, including subpart D. In its September 29, 2005 response, NYPR/CUMC stated that it is "consistently documenting the subpart D findings."

OHRP reviewed IRB minutes from April, May and June 2005 for three CUMC IRBs. OHRP notes that subpart D categories are consistently documented in the minutes reviewed. In many cases, a statement regarding the basis for the subpart D category determination is also included. There is occasional evidence of 46.408 determinations. For example, an entry in the June 15, 2005 minutes for CUMC IRB #1 for deferred final approval of a study renewal included the following statement: "Current Federal Regulations require both parents sign the consent form for studies that are greater than minimal risk without direct benefit to the participant unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. Please add a second parent/guardian signature line."

OHRP acknowledges that NYPH/CUMC stated in its July 28, 2005 letter: "The IRB has developed a separate form for research involving children that specifically addresses each of the Subpart D determinations. This Subpart D form is currently being used on a pilot basis and after the pilot phase will be implemented for all new protocols involving children.... It is expected that these reviewer forms will sharpen IRB members' and staff's focus on issues OHRP has raised in its letter." NYPH/CUMC also stated in its July 28, 2005 letter: "Columbia has completed a thorough review of its policy concerning research involving children and is implementing a revised policy.... We also have completed a review of the full set of IRB procedures to determine whether any procedures concerning research involving children should be changed...."

OHRP required in its May 23, 2005 letter that NYPH/CUMC provide 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, NYPH/CUMC was asked to provide information about initial IRB review, specific information about subpart D review, and information about the enrollment, if applicable, of wards of the state and/or foster children.

NYPH/CUMC indicated in its letter dated September 29, 2005 that "none of the studies were approved to enroll wards of the state or foster children, and none of the protocols

referred to any plan to enroll wards of the state or foster children." However, there was no indication whether any wards of the state or foster children were *actually* enrolled in any of the studies. From the list of 441 studies, OHRP identified seventeen studies that either were approved or may have been approved under 45 CFR 46.406.

In a letter dated October 24, 2005, NYPH/CUMC was asked to provide OHRP with a report indicating whether or not each of those seventeen studies enrolled any wards of the state or foster children. NYPH/CUMC's December 8, 2005 response indicated that no wards were enrolled in the seventeen studies.

OHRP finds that the corrective actions above adequately address OHRP's findings, questions, and concerns. 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. 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
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Dr. Bernard Schwetz, OHRP
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Ms. Patricia El-Hinnawy, OHRP
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