DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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June 19, 2006

A. Eugene Washington, M.D.
Executive Vice Chancellor
University of California, San Francisco
P.O. Box 0407
San Francisco, CA 94143-0407

RE: Human Research Subject Protections Under Federalwide Assurance FWA-68

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: Diane W. Wara

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: Diane W. Wara

Research Project: Phase I Safety Trial: A Study to Test the Safety of Recombinant Interleukin-2 (rIL-2) in HIV- Infected Children
Project Number: ACTG #299
Principal Investigator: Diane W. Wara

Research Project: Phase I/II Trial: Subcutaneous IL-2 with Highly Active Antiretroviral Therapy in HIV-Infected Children with Immunosuppression
Project Number: ACTG #402
Principal Investigator: Diane W. Wara

Dear Dr. Washington:

The Office for Human Research Protections (OHRP) has reviewed the University of California, San Francisco's (UCSF) March 15, 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.

Based upon its review, OHRP makes the following determinations:

(1) Regarding the request by the UCSF IRB for clarification on the risks and benefits of ACTG #402, OHRP notes that your March 15, 2006 report includes a response from the investigator dated April 17, 2000 which states the following:

(a) "Trials of rIL-2 have been conducted in HIV-infected adults with the goal of boosting the immune system (2,3,7,8). Thus far, the data suggests that rIL-2 can significantly augment CD4 counts."

(b) "Because children have a greater potential than adults do to have a functional thymus by virtue of their younger age (9), it is anticipated that the greater and more complete immune restorative responses to rIL-2 will occur with sustained CD4 counts and a diverse T cell receptor repertoire such that it translates into true immunocompetence." [Emphasis in original]

(c) "Also, it is important to remember that we are not aiming for an increase in CD4 T cell numbers - rather our goal is to achieve functional immune reconstitution."

(d) "Finally, the adult data indicates that a course of IL-2 may achieve long lasting immunologic benefit such that patients can go for long periods of months to years with sustained CD4 T cell counts which are promptly boosted by a single injection if IL-2 if they fall below a threshold level."

Your report goes on to state the following:

(e) "The IRB chair [name] reviewed this response on April 19, 2000 and signed off on the study, which indicates he considered that the committee's concerns had been satisfied."

(f) "With clarification of the potential of direct benefit, the requirements at 45 CFR 46.405 were deemed satisfied."

OHRP finds that the IRB approved ACTG 402 contingent upon substantive modifications or clarifications that were directly relevant to the determinations required of the IRB under HHS regulations at 45 CFR 46.111 without requiring additional review by the convened IRB. OHRP notes that when the convened IRB requests substantive clarifications or

modifications regarding the protocol or informed consent documents that are directly relevant to the determinations required of the IRB under HHS regulations at 45 CFR 46.111, IRB approval of the proposed research must be deferred, pending subsequent review by the convened IRB of responsive material.

Corrective Action: OHRP notes that UCSF has revised its procedures to ensure that determinations required of the IRB are made by the convened IRB and documented appropriately. UCSF has also included a checklist, distributed to all IRB members, indicating that if substantive clarifications are requested by the IRB, the investigator's response must be returned to the convened IRB.

(2) As requested in OHRP's February 17, 2006 letter, UCSF has provided copies of its most recent written procedures, as well as copies of IRB minutes which illustrate the implementation of these recent changes.

OHRP finds that these corrective actions taken by UCSF adequately address the above determination and address the concerns noted in OHRP's February 17, 2006 letter. As a result of the above 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,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Sharon K. Friend, Director, Committee on Human Research, UCSF
Dr. Victor I. Reus, Chairperson, Parnassus Committee IRB #1, UCSF
Dr. Susan H. Sniderman, Chairperson, San Francisco Gen Hosp Committee IRB #2, UCSF
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