DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1100 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 301-435-8072
FAX: 301-402-2071
E-mail:kborror@osophs.dhhs.gov

February 26, 2004

A. Eugene Washington, M.D., M.Sc.
Executive Vice Chancellor
University of California, San Francisco
513 Parnassus Avenue, S-101
San Francisco, CA 94143-0407

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

Research Project: Ventilation Abnormalities in Patients with Acute Respiratory Distress Syndrome
Principal Investigators: Dr. Michael Matthay, Dr. Thomas Nuckton
Project Number: 97014524

Dear Dr. Washington:

The Office for Human Research Protections (OHRP) has reviewed the University of California, San Francisco's (UCSF) February 20, 2004 report that was submitted in response to determinations of noncompliance with the Department of Health and Human Services (HHS) regulations for protection of human subjects (45 CFR part 46) involving the above-referenced research.

OHRP has determined that the corrective actions summarized below appropriately address the issues raised:

(1) OHRP found that the informed consent documents reviewed and approved by the Institutional Review Board (IRB) for this research failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(2): A description of any reasonably foreseeable risks or discomforts to the subject shall be provided to the subject or the subject's legally authorized representative. The informed consent document failed to include the

risk of changing the tidal volume of the subject during collection of expired gases from the ventilator. The informed consent document states, "My routine care will not be changed," which is not accurate.

(b) Section 46.116(a)(8): A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. The informed consent document for this research (as well as the UCSF IRB model informed consent document) states, "I have the right to decline to participate or withdraw at any point in this study without jeopardy to my medical care." There could be other penalties or loss of benefits other than jeopardizing medical care (or employment/student status, as the model informed consent document includes).

Corrective Actions: OHRP acknowledges that the study has been changed so that collection of expired gases from the ventilator is no longer done and the tidal volume of the subject is therefore not changed. In addition, the statement "My routine care will not be changed" has been deleted from the informed consent document. UCSF is revising the language in its sample consent form to more accurately reflect the requirements of HHS regulations at 45 CFR 46.116(a)(8). OHRP finds that these corrective actions are adequate to address the above findings and are appropriate under the UCSF FWA.

(2) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364-60367. OHRP found that for the November 2001 review of this research, the IRB inappropriately applied expedited review to research that involved minimal risk but does not appear in the categories of research published in the Federal Register. OHRP noted that when the research was first approved, the protocol, as written, qualified for expedited review. However, the changes proposed in the fifth continuing review application made the protocol no longer appropriate for expedited continuing review.

Corrective Actions: OHRP acknowledges that the UCSF IRBs are revising the instructions and guidance for continuing review and modification of studies to clarify that researchers and IRB members should evaluate proposed new procedures against the categories for expedited review to ensure that protocols that were initially appropriate for review in an expedited manner continue to be appropriate for such review. UCSF notes that the above-referenced research is now subject to review by the convened IRB. OHRP finds that these corrective actions are adequate to address the above findings and are appropriate under the UCSF FWA.

(3) HHS regulations at 45 CFR 46.116(d) require that the IRB find and document four specific criteria when approving waiver or alteration of some or all of the required elements of informed consent. OHRP found that the IRB failed to document the findings required by 45 CFR 46.116(d) to waive informed consent. In addition, OHRP found that waiver of informed consent was not appropriate for this research, as it was not impracticable to carry out the research without the waiver.

Corrective Actions: OHRP acknowledges that the above-referenced study no longer involves any waivers of informed consent. In addition, the UCSF IRBs have revised the applications for IRB review to require that investigators specifically address the criteria for waiving informed consent. In addition, the UCSF IRBs document the findings required for waivers of informed consent in minutes of the IRBs' meetings.

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,

Kristina Borror, Ph.D.
Director
Division of Compliance Oversight

cc: Dr. Reese Jones, Chair, IRB #1, UCSF
Dr. Susan Sniderman, Chair, IRB #2, UCSF
Dr. Michael Matthay and Dr. Thomas Nuckton, Principal Investigators, UCSF
Commissioner, FDA
Dr. David Lepay, Director, Good Clinical Practices Program, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Jan Walden, OHRP
Ms. Shirley Hicks, OHRP
Ms. Melinda Hill, OHRP
Ms. Patricia El-Hinnawy, OHRP