DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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November 19, 2003

Regis B. Kelly, Ph.D.
Executive Vice Chancellor
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Office of Executive Vice Chancellor
UCSF Box 0407
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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. Kelly:

The Office for Human Research Protections (OHRP) has reviewed the University of California, San Francisco (UCSF) August 30, 2002 report that was submitted in response to allegations of possible 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.

Based upon its review, OHRP makes the following determinations regarding the above-referenced research.

(1) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the Institutional Review Board (IRB) review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds that the following protocol changes were implemented without IRB approval:

(a) Addition of collection of a sample of blood once a day for 3 days.

(b) Changing ventilator settings to tidal volume of 10 ml/kg during the 10-20 minute collection of expired gases from the ventilator.

(c) Increase of enrollment ceiling.

(2) OHRP finds that the informed consent documents reviewed and approved by the 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).

(3) 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 finds 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 notes 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 (which had already been implemented as outlined in finding (1)) made the protocol no longer appropriate for expedited continuing review.

(4) 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 finds that the IRB failed to document the findings required by 45 CFR 46.116(d) to waive informed consent. In addition, OHRP finds that waiver of informed consent was not appropriate for this research, as it was not impracticable to carry out the research without the waiver. (OHRP notes that the investigator later proposed to obtain informed consent when amendments were proposed.)

Corrective Actions: OHRP acknowledges that the UCSF IRB has suspended enrollment in the above-referenced study, requested that Dr. Matthay review his other studies to ensure they involve neither unapproved changes nor inappropriate waivers of consent, and asked what additional steps Dr. Matthay will take to ensure that no such violations will occur in the future. The UCSF IRB will determine whether additional actions are needed, including whether it is appropriate to contact subjects to inform them about the conduct of the study and whether the IRB needs to re-review or audit Dr. Matthay's other studies. Given that, in another study, Dr. Matthay made changes in the study recruitment procedures without prior IRB approval, OHRP recommends that Dr. Matthay's other studies be audited by the IRB for compliance with HHS regulations at 45 CFR part 46.

OHRP also acknowledges that since this research was first reviewed and approved, the UCSF IRB has made numerous changes to its procedures including revising standard approval letters, Guidelines, and training materials to emphasize the need to seek IRB approval before modifying studies, and revising the format for the minutes and applications to improve the documentation of the reasons for granting waivers of informed consent. In addition, UCSF has implemented online human subject protections training, which is required for all principal investigators.

Required Action: By January 4, 2003, please provide OHRP with a satisfactory corrective action plan for addressing findings (2)-(4). In your response, please include the findings of the IRB's additional determinations in this matter. Please indicate whether or not the trial has been or will be restarted, and the IRB's determinations whether it is appropriate to contact subjects to inform them about the conduct of the study and whether the IRB needs to re-review or audit Dr. Matthay's other studies.

OHRP has the following additional guidance:

(5) Where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (b) approving research involving pregnant women, human fetuses, or neonates (see 45 CFR 46.204-207); (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP recommends that for

research approved by the convened IRB, all required findings be fully documented in the minutes of the IRB meeting, including *protocol-specific* information justifying each IRB finding.

For research reviewed under an expedited review procedure, these findings should be documented by the IRB Chairperson or other designated reviewer elsewhere in the IRB record.

OHRP appreciates the commitment of UCSF to the protection of human research subjects. Please do not hesitate to contact us 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
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