DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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January 6, 2004

Regis B. Kelly, Ph.D.
Executive Vice Chancellor
University of California, San Francisco
Office of Executive Vice Chancellor
UCSF Box 0407
San Francisco, CA 94143-0407

RE: Human Research Subject Protections Under Federalwide Assurances FWA-68 and -315

Research Project: Prospective, Randomized, Multi-Center Trial of 12 ml/kg vs. 6 ml/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome (ARMA Trial)
Principal Investigators: Dr. Michael Matthay, Dr. John Luce, and Dr. Michael Peterson

Research Project: Prospective, Randomized, Multi-Center Trial of Pulmonary Artery Catheter (PAC) vs. Central Venous Catheter (CVC) for Management of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) and Prospective, Randomized, Multi-Center Trial of 'Fluid Conservative' vs. 'Fluid Liberal' Management of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) (FACTT Trial)
Principal Investigators: Dr. Michael Matthay, Dr. John Luce, and Dr. Michael Peterson

Dear Dr. Kelly:

The Office for Human Research Protections (OHRP) has reviewed the University of California, San Francisco (UCSF) [and the San Francisco General Hospital's (SFGH)] August 27 and November 25, 2003 reports that were 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.

Based upon its review, OHRP finds that the UCSF has implemented the required actions stipulated by OHRP's July 25, 2003 letter. In particular, OHRP acknowledges the following:

(1) The UCSF Institutional Review Board (IRB) received the additional supplemental information and the revised model informed consent document for the FACTT trial, and has subsequently re-reviewed and approved the research.

(2) UCSF has provided OHRP with a copy of the final version of the IRB-approved informed consent document.

(3) UCSF has implemented a variety of procedures including listing the criteria for IRB approval of research in the UCSF Committee on Human Research Revised (CHR) Application to help ensure that the UCSF IRBs receive sufficient information to make all determinations required under HHS regulations at 45 CFR 46.111. The UCSF IRBs also list the required elements of informed consent in the UCSF Standard Consent Form Format #1 and includes an informed consent checklist to help ensure that the UCSF IRBs approve an informed consent process that satisfies all requirements of HHS regulations at 45 CFR 46.116. In addition, the UCSF IRB has added mandatory investigator training, revised the recording of minutes of IRB meetings, revised the application for continuing review and guidance for investigators, and initiated audits by the Quality Improvement Unit.

OHRP recommends that all of the criteria for IRB approval under HHS regulations at 45 CFR 46.111 be included in the UCSF CHR Guidance on Research Topics and Issues to help ensure that the UCSF IRBs receive sufficient information to make all determinations required under HHS regulations at 45 CFR 46.111. In addition, OHRP notes that the following elements required under HHS regulations at 45 CFR 46.116 appear to be inadequately addressed in the UCSF Standard Consent Form Format #1: a statement that the study involves research; an explanation of whom to contact for answers to pertinent questions about research subjects' rights (should include someone other than the investigator); and a statement that 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. While the UCSF Standard Consent Form Format #1 includes the statement "You have the right to decline to participate or to withdraw at any point in this study without jeopardy to [your medical care/employment/student status—only the appropriate category or categories should be indicated]," OHRP notes that there could be other penalties or losses of benefits other than a subject's medical care, employment, or student status.

OHRP finds that the above corrective actions adequately address OHRP's findings and are

appropriate under the UCSF and SFGH FWAs. As a result, OHRP anticipates no need for further involvement with UCSF and SFGH related to this matter.

OHRP appreciates the commitment of UCSF and SFGH 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

Michael A. Carome, M.D.
Associate Director for Regulatory Affairs
Office for Human Research Protections

cc: Dr. Reese Jones, Chair, IRB #1, UCSF
Dr. Susan Sniderman, Chair, IRB #2,UCSF
Dr. Michael Matthay, Dr. John Luce, and Dr. Michael Peterson, Principal Investigators, ARMA and FACTT trials, UCSF and SFGH
Dr. B. Taylor Thompson, ARDS Network Coordinating Center Principal Investigator, Massachusetts General Hospital
Dr. Arthur Wheeler, FACTT Trial Committee Chair, Vanderbilt University
Dr. Gordon R. Bernard, Chairman, ARDS Steering Committee, Vanderbilt University
Dr. Herbert P. Wiedemann, FACTT Trial Committee Chair, Cleveland Clinic Foundation
Dr. James Kiley, Director, Division of Lung Diseases, NHLBI
Dr. Lana Skirboll, Director, Office of Science Policy, NIH
Dr. David Lepay, Director, Good Clinical Practices Program, FDA
Ms. Melinda Hill, OHRP
Ms. Patricia El-Hinnawy, OHRP