DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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April 11, 2002

Regis B. Kelly, Ph.D.
Executive Vice Chancellor
University of California, San Francisco
513 Parnassus Avenue, Room S-101
San Francisco, California 94143-0407

RE: Human Research Subject Protections Under Federal Wide Assurance (FWA) FWA-00000068 and Multiple Project Assurance (MPA) M-1169

Research Project: Prospective, Randomized, Multicenter Trial of 12 ml/kg vs. 6 ml/kg Tidal Volume Positive Pressure Ventilation and Lisofylline vs. Placebo for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome
Principal Investigator: Michael A. Matthay, M.D.
UCSF Approval Number: H2811-12480-04A

Research Publication: Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome (N. Engl J Med 2000;342:1301-8)
HHS Project Number: N01-HR46063

Dear Dr. Kelly:

The Office for Human Research Protections (OHRP) has reviewed the University of California at San Francisco's (UCSF's) April 2, 2002 report that was submitted in response to OHRP's February 8, 2002 letter to UCSF regarding the 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:

(1) HHS regulations at 45 CFR 46.116 stipulate that, except as provided elsewhere under the HHS regulations, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. HHS regulations at 45 CFR 102(c) define a legally authorized representative as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

OHRP acknowledges the following regarding the above-referenced research:

(a) UCSF's report stated the following regarding a description of the applicable state and local laws that established an individual who consented on the behalf of a subject enrolled in the research as the legally authorized representative of such subject.

(i) "As to consent for participation in medical research, California Health and Safety Code Sections 24170-24179.5 address the issue of medical research generally. Although Section 24173 describes restrictions on who may give consent for research participation, Section 24178 indicates that section 24173 does not apply to 'any person who is conducting a medical experiment as an investigator within an institution which holds an assurance with the Department of Health, Education and Welfare pursuant to Part 46 of Title 45 of the Code of Federal Regulations and who obtains informed consent in the method and manner required by such regulations'...This creates a circular situation in which there is an exemption under state law which means we need to rely on 45 CFR 46; however, 45 46.102(c) refers back to 'applicable law."

(ii) "Since the two tidal volumes used as part of this study both constituted accepted medical treatment, California law related to surrogate consent for medical treatment seem applicable. Pursuant to California law, others may give substituted consent for treatment for a patient who lacks the capacity to give such consent, as follows: an adult designated pursuant to a power of attorney for health care (Probate Code section 4671), a conservator appointed to make health care decisions (Probate Code Sections 1880-1898, 2353-2357, and 3200), a public guardian (Probate Code Section 2920), and the closest available relative (Cobbs v. Grant (1972), 8 Cal. 3d 229, 224 and Barber v. Superior Court (1983) 147 Cal. App. 3d 1006)."

(b) OHRP acknowledges that UCSF interprets applicable California statutes and case law as authorizing the above classes of individuals to consent on behalf of a prospective subject to the subject's participation in the procedures involved in the research.

(2) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of Institutional Review Board (IRB) meetings be in sufficient detail to show, among other things, the vote on these actions, including the number of members voting for, against, and abstaining. In its February 8, 2002 letter, OHRP found that minutes of UCSF IRB meetings provided with UCSF's December 14, 2000 report failed to satisfy this requirement.

Corrective Action: OHRP acknowledges UCSF's plans to require that the minutes of IRB meetings document the vote on all IRB actions including the number of members voting for, against, and abstaining. OHRP finds this corrective action to be satisfactory and appropriate under the UCSF MPA.

(3) In its February 8, 2002 letter, OHRP found that the informed consent documents reviewed and approved by the UCSF IRB for the above-referenced research failed to adequately describe the reasonably foreseeable risks and discomforts of the research, in accordance with the requirements of HHS regulations at 45 CFR 46.116(a)(2). In specific, OHRP found that the informed consent documents failed to describe the following risks and potential discomforts associated with the non-traditional, 6 ml/kg tidal volume group that were described in the UCSF IRB-approved protocol: dyspnea, agitation, potential need for higher doses of sedatives and paralytics, volume overload, and hypernatremia.

Corrective Action: OHRP acknowledges that the research has been completed. OHRP also acknowledges that the current UCSF IRB procedures would require that all the risks and potential discomforts that the subject would be expected to undergo are described in the informed consent document. OHRP notes UCSF's plans to revise educational materials and guidelines to explicitly discuss this requirement. OHRP finds these corrective actions to be satisfactory and appropriate under the UCSF MPA.

(4) In its February 8, 2002 letter, OHRP found that the UCSF IRB approved informed consent documents for the above-referenced research failed to include an explanation of whom to contact for answers to pertinent questions about the research subjects' rights, as required by HHS regulations at 45 CFR 46.116(a)(7).

OHRP acknowledges that this requirement is referenced in the current UCSF procedures and standard consent form formats. OHRP notes that HHS regulations at 45 CFR 46.116(a)(7) require the identification of contact persons who would be knowledgeable to answer questions of subjects about the research, research subjects' rights, and research-related injuries. OHRP advises that these three areas must be explicitly stated and addressed in the consent process and documentation.

(5) HHS regulations at 45 CFR 46.117(a) require that informed consent be documented by use of a written consent form approved by the IRB and that is signed by the subject or the subject's legally authorized representative, unless the IRB waives this requirement in accordance with 45 CFR 46.117(c). In its February 8, 2002 letter, OHRP found regarding the above-referenced research that (a) witnessed telephone consent by the subject's legally authorized representative; and (b) consent by a nodding gesture of the subject that was documented and witnessed by a registered nurse failed to comply with the requirements for waiver of documentation of informed consent as required by 45 CFR 46.117(c). Furthermore, OHRP found that the investigator initiated a change in the research without approval of the UCSF IRB in contravention of the requirements of HHS regulations at 45 CFR 46.103(b)(4)(iii).

Corrective Action: OHRP acknowledges that the current UCSF IRB procedures discuss the Federal regulations regarding (a) the requirement for the investigator to obtain a consent form signed by the subject of the subject's legally authorized representative; (b) the requirements for IRB waiver of documentation of informed consent; and (c) the requirement for IRB review and approval of proposed changes in approved research. OHRP notes UCSF plans to emphasize these requirements in UCSF's overall human subjects protection education and training programs. OHRP finds these corrective actions to be satisfactory and appropriate under the UCSF MPA.

(6) HHS regulations at 45 CFR 46.116(d) require that the IRB make and document four criteria when waiving the requirements to obtain informed consent. In its February 8, 2002 letter, OHRP found no evidence in the IRB records that the UCSF IRB made and documented these four criteria when it approved the principal investigator's February 3, 1999 request for a waiver of the requirement to obtain informed consent for collection of data from the medical records of patients who were screened for participation in the above-referenced research but were not enrolled.

Corrective Action: OHRP acknowledges UCSF's plans to revise its policies and the initial research application form for investigators to ensure that the criteria for altering or waiving the requirements to obtain informed consent are fully considered by the IRB and documented in the

IRB meeting minutes. OHRP finds these corrective actions to be satisfactory and appropriate under the UCSF MPA.

(7) OHRP finds that UCSF has adequately addressed the additional concerns raised by OHRP in its February 8, 2002 letter.

As a result of the above determinations, 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,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. W. Sue Shafer, Assistant Vice Chancellor, Office of Research Administration, UCSF
Ms. Sharon K. Friend, Director, Research Subjects Protection Committees, UCSF
Dr. Reese T. Jones, IRB Chair, Committee A, UCSF
Dr. Susan Sniderman, IRB Chair, Committee 1, UCSF
Dr. John Mather, Director, Office of Research Compliance and Assurance, Veterans Health Administration
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