DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 301-402-5189
FAX: 301-402-2071
E-mail:kgottfried@osophs.dhhs.gov

February 6, 2003

Sharon Friend & Regis B. Kelly
Director, Research Subjects Protections Committees
Executive Vice Chancellor, Research
University of California San Francisco
513 Parnassus Avenue
Room S-101
San Francisco, CA 94143-0407

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1169 and Federalwide Assurance (FWA) 000068

Research Publication: Brian K. Alldredge, Pharm.D., et. al., A comparison of Lorazepam, Diazepam, and Placebo for the Treatment of Out-of Hospital Status Epilepticus. NEHM, 345(9): 631-637, 2001.

Dear Ms. Friend and Dr. Kelly:

The Office for Human Research Protections (OHRP) has reviewed the University of California at San Francisco's (UCSF) report dated February 20, 2002 regarding the above-referenced research. Based on its review of your report responding to the allegations in OHRP's October 25, 2001 letter, OHRP raises certain concerns listed below but does not make any definitive determinations of non-compliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects at 45 CFR part 46. As a result OHRP does not anticipate further involvement in this matter. Of course, should new information be identified which might alter this determination OHRP must be notified.

OHRP notes the following concerns:

(1) HHS regulations at 45 CFR 46.116(d) require that the Institutional Review Board (IRB) find and document the four specific criteria outlined below when approving a waiver or alteration of some or all of the required elements of informed consent.

(a) the research involves no more than minimal risk to the subjects;

(b) the waiver or alteration will not adversely affect the rights and welfare of the subjects;

(c) the research could not practicably be carried out without the waiver or alteration; and

(d) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

OHRP acknowledges the communications between Thomas Puglisi, Ph.D. and UCSF, particularly the letter dated April, 7, 1994 discussing not the waiver of a "signed" consent but the actual waiver of the informed consent process. At that time, Dr. Puglisi noted that the UCSF materials did not reflect documentation of any determination by the Committee related to each of the four criteria outlined in the regulation. UCSF's response, dated May 18, 1994 clarified that the minutes were in error, that the Committee reaffirmed its original decision for a waiver of informed consent, based on the assertion that the subjects were not exposed to any risks greater than those that subjects would normally encounter in a clinical context (and satisfaction of the other two criteria), and that an information sheet would be given to subjects.

At the outset of this research protocol, in 1991, the IRB made a determination to waive informed consent because the research involved no more than minimal risk to the subjects based on the fact that paramedics were not routinely administering benzodiazepines pre-hospital for Status Epilepticus (SE). However, some ambiguity exists relative to information that surfaced in 1993, and there does not appear to be Committee on Human Research documentation relative to this issue. According to the trial study plan dated September 22, 1993, a generally accepted method of therapy was adhered to by the paramedic first responders. The study plan recommended that

> "the current protocol for the treatment of Status Epilepticus (SE) in the adult patient population by the DPH paramedics of San Francisco EMS be placed on hold for the duration of this 4 year study. Current protocol and procedure calls for the administration of Valium for the treatment of SE. The treatment of SE in the adult population of SF would then follow the study protocol."

OHRP recognizes that the study was designed to analyze efficacy of different modalities of care, however there is no documented discussion by the IRB at this time regarding the deviation from the paramedics' treatment protocol and the proposed study design including a placebo arm, which potentially could have put patients/subjects at greater than minimal risk. OHRP reminds UCSF that the specifics of the criteria for waiver of informed consent, and all aspects of a study, must be re-reviewed prior to implementation of any change to the protocol.

(2) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB Chair or another IRB member designated by the Chair, continuing review must occur no more than one year after the date the protocol **was reviewed** by the convened IRB, **not on the anniversary of the date the IRB Chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.** OHRP notes several instances in which the IRB may have failed to conduct continuing review of research at least once per year. On several occasions the convened IRB reviewed the above-referenced protocol and granted contingent approval requiring investigator response. The response subsequently was reviewed in an expedited manner and approved. The continuing review date for the following year was then set to the *approval* date, not the *review* date of the protocol resulting in continuing review occurring at intervals less than once per year.

OHRP reminds UCSF that continuing review is to take place within a one-year period after the convened meeting at which approval occurred, see "How Is the Continuing Review Date Determined?" found on the website at: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/contrev2002.htm#HOW IS THE CONTINUING REVIEW DATE DETERMINED".

OHRP appreciates the continued commitment of your institution to the protection of human subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kate-Louise Gottfried, J.D., M.S.P.H.
Division of Compliance
Office for Human Research Protections

cc:
Dr. Reese T. Jones, Committee on Human Research
Dr. Susan H. Sniderman, Committee on Human Research
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Mr. George Gasparis, OHRP
Ms. Shirley Hicks, OHRP
Dr. Kamal Mittal, OHRP
Mr. Barry Bowman, OHRP
Dr. Kristina Borror, OHRP