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: 301-435-0062
FAX: 301-402-2071

June 10, 2002

Dr. Gerald Litwack
Vice Dean for Research
Jefferson Medical College
Thomas Jefferson University
233 South 10th Street
Suite 350 B.L.S.B.
Philadelphia, PA 19107-5541

RE: Human Research Protections Under Multiple Project Assurance (MPA) M-115

Research Protocol: A Multi-Center, Phase II/III, Randomized, Double-Blind, Placebo-Controlled Trial of Lisofylline and Controlled Ventilation in Patients with Acute Lung Injury and Acute Respiratory Distress Syndrome
IRB Protocol #: 96.0563
Principal Investigator: Jonathan E. Gottlieb, M.D.
HHS Project Number: N01-HR46058

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;342:1302-8)

Dear Dr. Litwack:

The Office for Human Research Protections (OHRP) has reviewed Thomas Jefferson University's (TJU's) April 24, 2002 report regarding the above-referenced research, submitted in response to OHRP's January 30, 2002 letter. Based upon its review, OHRP makes the following determinations concerning TJU's oversight of this research:

(1) Department of Health and Human Services (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. In its January 30, 2002 letter, OHRP noted that 38 subjects enrolled in the above-referenced research at TJU were unable to provide legally effective informed consent and consent for these subjects instead was obtained from another individual (spouse, parent, adult sibling, adult child, aunt, legal guardian, legal power of attorney, or "impartial third party"). OHRP expressed several concerns regarding the legal basis for such individuals serving as legally authorized representatives for the subjects under applicable state law. Based upon its review of TJU's April 24, 2002 report, OHRP acknowledges the following:

(a) Pennsylvania law authorizes a "legally responsible person" to consent to a subject's participation in medical research procedures.

(b) Pennsylvania law does not define who constitutes a "legally responsible person" for this purpose.

(c) TJU interprets applicable Pennsylvania law as authorizing close family members of a subject, as well as an individual appointed a subject's durable power of attorney, to consent on behalf of the subject to the subject's participation in the procedures involved in medical research.

OHRP finds that TJU's response adequately addresses OHRP's concerns regarding the issue of legally authorized representatives.

(2) In its April 24, 2002 letter, paragraph 2(c), TJU reported that for subject 0720002 in the above-referenced research, informed consent was obtained from a social worker employed by TJU Hospital. OHRP finds that for subject 0720002, informed consent was not obtained in accordance with the requirements of HHS regulations at 45 CFR 46.102(c) and 45 CFR 46.116.

Corrective Action: OHRP acknowledges that TJU's current policy does not authorize social workers to serve as legally authorized representatives for research in accordance with 45 CFR 46.102(c) and 45 CFR 46.116.

(3) OHRP finds that TJU has adequately addressed the additional concerns raised in OHRP's January 30, 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.

At this time, OHRP provides the following additional guidance in response to TJU's April 24, 2002

letter:

> (4) HHS regulations at 45 CFR 46.116(d)(3) for waiving the requirements for obtaining informed consent require that the IRB find and document that the research could not *practicably* be carried out without the waiver. Please note that mere inconvenience in contacting individuals is not a justification for concluding that obtaining informed consent is impracticable.

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

Sincerely,

Carol J. Weil, J.D.
Division of Compliance Oversight

cc: Dr. Neal Nathanson, U Penn
Dr. Joseph Sherwin, Director of Regulatory Affairs, U Penn
Dr. David G. Brock, Chairperson, IRB-01, TJU
Dr. Stephen P. Weinstein, Chairperson, IRB-02, TJU
Dr. Gregory Mokrynski, Chairperson, IRB 03XB, TJU
Dr. George Kalf, TJU
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Mr. George Gasparis, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. Hal Blatt, OHRP
Mr. Barry Bowman, OHRP
Commissioner, FDA
Dr. David Lepay, FDA