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. Neal Nathanson
Vice Provost for Research
215 College Hall
University of Pennsylvania
Philadelphia, PA 19104-6381

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

Research Protocol: 21 ml/kg vs. 6 ml/kg Tiday Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome
IRB Protocol #: 338801
Principal Investigator: Dr. Paul N. Lanken
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;342:1301-8)

Dear Dr. Nathanson:

The Office for Human Research Protections (OHRP) has reviewed the University of Pennsylvania's (U Penn's) April 19, 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 U Penn's oversight of this research:

(1) In its January 30, 2002 letter OHRP found no evidence in institutional review board (IRB) records that the U Penn IRB made and documented the four required findings for waiver of informed consent under Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(d). OHRP requested that U Penn submit a corrective action plan to ensure that the U Penn IRBs make and document the required regulatory criteria whenever the IRBs (i) approve a consent procedure which does not include, or which alters, some or all of the required elements of informed consent; or (ii) waive the re1quirements to o tain informed consent.

Corrective Action: OHRP acknowledges that U Penn Policy #702, which documents the IRB process for handling requests to waive any or all elements of informed consent, requires review and documentation of the four requirements set forth under 45 CFR 46.116(d). OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the U Penn MPA.

(2) 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 32 subjects enrolled in the above-referenced research at U Penn 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, or aunt). 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 U Penn's April 19, 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) U Penn interprets applicable Pennsylvania law as authorizing close family members of a subject to consent on behalf of the subject to the subject's participation in the procedures involved in medical research.

(d) U Penn is drafting a written policy designating a hierarchy of family members who may serve as legally authorized representatives for adult subjects who are incapacitated.

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

(3) OHRP finds that U Penn 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.

OHRP appreciates the commitment of U Penn 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. Gerald Litwack, Associate Dean for Scientific Affairs, TJU
Dr. John Mather, Department of Veterans Affairs
Dr. Joseph Sherwin, Director of Regulatory Affairs, U Penn
Dr. Nicholas Kefalides, IRB Executive Chair, U Penn
Dr. Paul Kanken, U Penn
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