DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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January 30, 2002

Gerald Litwack, Ph.D.
Associate Dean for Scientific Affairs
Thomas Jefferson University
1020 Locust Street, M-5
Philadelphia, PA 19107-6799

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1115

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;342:1301-8)

Dear Dr. Litwack:

The Office for Human Research Protections (OHRP) has reviewed Thomas Jefferson University's (TJU's) October 26, 2000 report and the University of Pennsylvania's (U Penn's) October 4, 2000 report regarding the above-referenced research. These reports were submitted in response to OHRP's August 3, 2000 letter to U Penn presenting allegations of noncompliance with the Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46). OHRP acknowledges that TJU was a subcontractor with U Penn on the above-referenced research.

Based upon its review, OHRP makes the following determinations regarding TJU's oversight of the above-referenced research:

(1) OHRP finds that the informed consent documents reviewed and approved by the TJU IRB 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 finds 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 IRB-approved protocol: dyspnea, agitation, potential need for higher doses of sedatives and paralytics, volume overload, and hypernatremia. Of particular note, in a November 7, 1996 protocol amendment submitted to the U Penn IRB, the U Penn principal investigator reported that in the first 100 subjects enrolled into the study, some patients randomized to the 6 ml/kg tidal volume group became "very dyspneic and agitated."

Corrective Action: OHRP acknowledges that the research has been completed. Furthermore, OHRP acknowledges that TJU has implemented appropriate corrective actions under its MPA to ensure that informed consent documents approved by the IRB include an appropriate description of reasonably foreseeable risks and discomforts.

Based upon its review, OHRP has the following additional questions and concerns regarding the above- referenced research:

(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) defined 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.

TJU's report indicated that all 38 subjects enrolled in the study at TJU were unable to provide legally effective informed consent and consent for these subjects instead was obtained and documented from another individual (spouse, parent, adult sibling, adult child, aunt, legal guardian, legal power of attorney, or "impartial third party").

TJU's report stated the following regarding the basis for family members having been legally authorized representatives for the subjects enrolled in the research:

> "The Office of the University Counsel has provided my office with a legal opinion concerning Pennsylvania law on substituted consent[.] Our policy is enclosed.

'Pennsylvania law provides neither direct authorization for nor any prohibition for the use of close family members to permit clinical research. While judicial and legislative policies on substituted consent are contradictory, Pennsylvania's highest court has strongly expressed a policy favoring family control over medical decisions involving the life and death of patients in a vegetative state. The spirit of this decision applies forcefully in the research context. Our subject surrogates are making medical and research decisions that may benefit the individual subject and others.'

"'Despite the absence of direct support in most states, a majority of Institutional Review Boards, including ours, allow family members to substitute their permission for research purposes. Our determination is that consent by family members provides on-par protection for vulnerable research subjects.[']"

(a) Please explain in detail the above-referenced contradiction between judicial and legislative policies on substituted consent.

(b) TJU's report stated that Pennsylvania's highest court has strongly expressed a policy favoring family control over medical decisions involving the life and death of patients in a vegetative state. It is unclear why this is relevant to the determinations related to legally authorized representatives for subjects enrolled in the above-research since is appears the subject population was not in a vegetative state. Please respond in detail.

(c) TJU reported that for subject 0720007 informed consent was obtained from an "impartial third party." Please clarify in detail (i) who this impartial third party was; and (ii) the legal basis for this person having been the legally authorized representative for this subject.

(d) TJU reported that for subject 0723038 informed consent was obtained from an individual with legal power of attorney. Please clarify in detail (i) who this individual was; and (ii) whether the power of attorney was applicable to health care decisions.

(e) Please provide OHRP with copies of all relevant local and state laws related to surrogate consent procedures and next-of-kin decision making for health care delivery that were in effect when the research was conducted. Please ensure that your response includes copies of the above-referenced judicial and legislative policies on substituted consent, and all decisions and written opinions of Pennsylvania's highest court that expressed a policy favoring family control over medical decisions involving the life and death of patients in a vegetative state. Please clarify whether TJU has obtained an opinion of the Pennsylvania Attorney General or other legal authority on the applicability of such laws to consent for participation in research procedures.

(3) U Penn's report indicated that all 32 subjects enrolled in the study at U Penn were unable to provide legally effective informed consent and consent for these subjects instead was obtained and documented from another individual (spouse, parent, adult sibling, adult child, or aunt).
U Penn's report stated the following regarding the basis for family members having been legally authorized representatives for the subjects enrolled in the research:

> "The University of Pennsylvania has had a policy of accepting the State of Pennsylvania's surrogate consent procedure for emergency medical care as providing a framework for determining legal authorized representation for entry into research studies. The IRB considers these protocols carefully and is especially careful of considering the reputation and sensitivity of the principal investigator. . . .
>
> "The laws of the Commonwealth of Pennsylvania are silent on the role of spouse or next-of-kin as appropriate legally authorized representative to participate in the research although they are spelled out for treatment or emergency medical care. Thus, the spouse, parent or adult child as next-of-kin is empowered to make decisions related to health care delivery[;] the standards followed were modeled after and consistent with emergency consent procedure for the State of Pennsylvania."

Please clarify whether TJU and U Penn relied upon different state laws for making determinations regarding legally authorized representatives for the above-referenced research.

(4) HHS regulations at 45 CFR 46.111(b) stipulate that in order to approve research, the IRB shall determine that when some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of the subjects. OHRP is concerned that (a) both the subjects of the research, because of their impaired mental state, and the subjects' family members, because of the psychological stress of having a critically ill family member being treated in an intensive care unit, appear to have likely been vulnerable to coercion or undue influence; and (b) the TJU IRB failed ensure that there were additional safeguards include in the study to protect the rights and welfare of these vulnerable subjects. In particular, OHRP notes a lack of important details regarding the recruitment and enrollment of subjects, and finds no evidence in the IRB-approved protocol or other relevant IRB records that additional safeguards were included during the subject recruitment and enrollment process. Please respond in detail.

(5) OHRP notes that on October 28, 1996, the U Penn IRB approved a request from the principal investigator to provide a $50 gift certificate as a financial incentive to individuals

referring potential subjects to the investigators. Please clarify whether the TJU IRB approved a similar incentive. If so, OHRP is concerned that providing such a financial incentive for prospective subject referrals may have enhanced the probability of coercion or undue influence on a vulnerable subject population. Please respond.

(6) HHS regulations at 45 CFR 46.116(a)(1) require that when seeking informed consent, each subject be provided with, among other things, a description of the procedures to be followed, and identification of any procedures which are experimental.

OHRP notes the following statement in the above-referenced publication (N. England J Med 2000;342:1301-8):

> "Traditional approaches to mechanical ventilation use tidal volumes of 10 to 15 ml per kilogram of body weight."

OHRP is concerned that the IRB-approved informed consent document failed to describe the 12 ml/kg tidal volume as being the traditional volume used for ventilatory support and the 6 ml/kg as being experimental or non-traditional. Furthermore, OHRP is concerned that the following statements in the IRB-approved informed consent document was misleading because it implied that both tidal volumes were used with equal frequency in clinical practice at TJU:

> "Presently doctors use varying volumes of oxygen-enriched air to inflate lungs. It is unknown whether it is better to use a large or small volume of oxygen-enriched air to inflate the lungs of patients with a lung injury."
>
> "Both ways of inflating my lungs are acceptable methods that are commonly used in medical practice."

Please respond. In your response, please clarify (a) the relative frequency with which 12 ml/kg and 6 ml/kg tidal volumes were used in clinical practice at TJU at the time the research was initially reviewed by the IRB; (b) whether the TJU IRB was aware of these statistics when it initially approved the research; and (c) which members of the TJU IRB who participated in the initial and continuing review of the protocol had expertise in critical care medicine and ventilatory support.

(7) HHS regulations at 45 CFR 46.116 require that the information provided in the informed consent documents be in language understandable to the subject. OHRP is concerned that the informed consent document approved by the TJU IRB for this study appeared to include complex language that would not have been understandable to all subjects or their legally authorized representatives. In particular, OHRP is concerned that some of the sentences and terminology were too complex. (e.g., "This drug has been shown to inhibit several types of

inflammatory cells that the body produces during severe illness, including the type of lung injury I have;" "Subsequently, any changes in volume will be determined by the pressures in my airways and the acidity in my blood;" and the discussion of risks). Please respond.

(8) 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. OHRP notes that in December 1998 the U Penn IRB approved an amendment to the protocol that included a 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 but were not enrolled in the research. Please clarify whether the TJU IRB approved a similar amendment to the research. If so, provide the required documentation of the TJU IRB's findings required under HHS regulations at 45 CFR 46.116(d).

Please submit TJU's response to the above questions and concerns so that OHRP receives it no later than March 8, 2002. If upon further review of the questions and concerns TJU identifies additional instances of noncompliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

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,

Michael A. Carome, M.D.
Director, 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. Jonathan E. Gottlieb, TJU
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Mr. George Gasparis, OHRP

Dr. Jeffrey Cohen, OHRP
Mr. Hal Blatt, OHRP
Mr. Barry Bowman, OHRP