DEPARTMENT OF HEALTH & HUMAN SERVICES

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January 30, 2002

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

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1025

Research Protocol: 12 ml/kg vs. 6 ml/kg Tidal 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) October 4, 2000 report and Thomas Jefferson University's (TJU's) October 26, 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 U Penn's oversight of the

above-referenced research:

(1) HHS regulations at 45 CFR 46.108(b) stipulate that except when an expedited review procedure is used, the Institutional Review Board (IRB) shall review research at a convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas.

OHRP finds that:

(a) The above-referenced research was not eligible for expedited review because the research involved more than minimal risk and involved research activities which were not included on the published list of research activities eligible for an expedited review procedure.

(b) The U Penn IRB reviewed and approved the research under an expedited review procedure in March 1997, March 1998, and March 1999.

Corrective Action: OHRP acknowledges that U Penn has implemented appropriate corrective actions under its MPA to ensure that the convened IRB reviews and approves all research undergoing continuing review, except when the research is eligible for expedited review under the provisions of HHS regulations at 45 CFR 46.110.

(2) HHS-regulations at 45 CFR 46.115(a)(2) require that minutes of 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. OHRP finds that minutes of IRB meetings provided with U Penn's report failed to satisfy this requirement.

Corrective Action: OHRP acknowledges that U Penn has implemented appropriate corrective actions under its MPA to ensure that minutes of IRB meetings include all information required by HHS regulations at 45 CFR 45.115(a)(2).

(3) 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 finds no evidence in the IRB records that the U Penn IRB made and documented these four criteria when it approved the principal investigator's December 18, 1998 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.

Required Action: By March 8, 2002, U Penn must submit to OHRP a satisfactory corrective action plan to ensure the U Penn IRBs make and document the four criteria required by HHS

regulations at 45 CFR 46.116(d) 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 requirements to obtain informed consent.

Recommended Action: Where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (b) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP strongly recommends that all required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

(4) OHRP finds that the informed consent documents reviewed and approved by the U Penn 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 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." Nevertheless, the U Penn IRB failed to require modification of the informed consent document to describe these risks.

Corrective Action: OHRP acknowledges that the research has been completed. Furthermore, OHRP acknowledges that U Penn 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:

(5) 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.

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."

(a) It is unclear from U Penn's statements whether the surrogate consent procedure allowed under State of Pennsylvania laws applies only to emergency medical care or all healthcare-related decisions. Please clarify in detail.

(b) If the surrogate consent procedure allowed under State of Pennsylvania laws applies only to emergency medical care, it is unclear why next-of-kin could have acted as legally authorized representatives for the subjects enrolled in the above-research since at least some of the procedures in the research appear not to have been within the scope of emergency medical care. In particular, OHRP notes that the administration of Ketoconazole, Lisofylline, or their respective placebos do not appear to have been emergency medical procedures. Please respond.

(c) U Penn's report stated that the spouse, parent or adult child as next-of-kin is empowered to make decisions related to health care delivery. Please clarify the basis under State of Pennsylvania law for an aunt to serve as the legally authorized

representative for subject 0710008.

(d) Please clarify why "the reputation and sensitivity of the principal investigator" would have been relevant to the determination regarding which individuals could have been legally authorized representatives for the prospective subjects in the research.

(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 clarify whether U Penn 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.

(6) TJU's report indicated that all 38 subjects enrolled in the study at TJU were unable to provide legally effective informed consent and consent 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.[']"

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

(7) 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 likely to have been vulnerable to coercion or undue influence; and (b) the U Penn 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 in the IRB records regarding the procedures for 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.

(8) 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. 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.

(9) 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 were misleading because they implied that both tidal volumes were used with equal frequency in clinical practice at U Penn:

> "Presently doctors use different size breaths of oxygen-rich air to inflate the patient's lungs. It is unknown whether it is better to use large (12 ml/kg) or small (6 ml/kg)."
>
> "Both ways of inflating the lungs are acceptable methods that are commonly used to treat patients with [acute lung injury (ALI)] and [acute respiratory distress syndrome

(ARDS)]."

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 U Penn at the time the research was initially reviewed by the IRB; (b) whether the U Penn IRB was aware of these statistics when it initially approved the research; and (c) which members of the U Penn IRB who participated in the initial review of the protocol had expertise in the areas of critical care medicine and ventilatory support.

(10) 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 U Penn 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., "It has been shown to inactivate several types of inflammatory cells (white blood cells) the body activates during severe illness, including the type of lung injury the patient now has;" "Afterwards, changes in the breath size will be decided by the pressures in the airways and by the acidity of the blood;" "The genes contained in the frozen patient samples may have significant scientific value in increasing our understanding of ARDS. . . . These samples may also be useful in the study of genes of other disease which may involve inflammatory processes not necessarily related to ARDS;" and the discussion of risks). Please respond.

Please submit U Penn'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 U Penn 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. Joseph Sherwin, Director of Regulatory Affairs, U Penn
Dr. Nicholas Kefalides, IRB Executive Chair, U Penn

Dr. Paul N. Lanken, U Penn
Dr. Gerald Litwack, Associate Dean for Scientific Affairs, TJU
Dr. John Mather, Department of Veterans Affairs
Commissioner, FDA
Dr. David Lepay, FDA
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