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: 301-402-5567
FAX: 301-402-2071
E-mail: mcarome@osophs.dhhs.gov

February 4, 2002

Alvin W. Kwiram, Ph.D.
Vice-Provost for Research
Office of the Provost
Box 351237
University of Washington
312 Gerberding Hall
Seattle, Washington 98195

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1183

Research Project: Prospective, Randomized, Multicenter Trial of 12 ml/kg vs. 6 ml/kg Tidal Volume Positive Pressure Ventilation and Ketoconazole vs. Placebo for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome
IRB Project #: 96-0892
Principal Investigator: Dr. Leonard D. Hudson
HHS Project Number: N01-HR46055

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. Kwiram:

The Office for Human Research Protections (OHRP) has reviewed the University of Washington's (UW's) December 1, 2000 report regarding the above-referenced research. This report was submitted in response to OHRP's August 3, 2000 letter to UW presenting allegations of noncompliance with the Department of Health and Human Services (HHS) regulations for the protection of human

subjects (45 CFR Part 46).

Based upon its review, OHRP makes the following determinations regarding the above-referenced research:

(1) 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.

OHRP acknowledges the following regarding the above-referenced research:

(a) Seventy-one subjects enrolled in the study at UW were unable to provide legally effective informed consent, and consent for 55 of these subjects instead was obtained and documented from another individual (spouse, parent, adult sibling, adult child).

(b) Applicable Washington state law indicates that the following classes of persons are authorized to provide informed consent to health care on behalf of a patient who is not competent to consent:

(i) The appointed guardian of the patient, if any.

(ii) The individual, if any, to whom the patient has given durable power of attorney that encompasses the authority to make health care decisions.

(iii) The patient's spouse.

(iv) Children of the patient who are at least 18 years of age.

(v) Parents of the patient.

(vi) Adult brothers and sisters of the patient.

(c) WU interprets applicable Washington state law as authorizing the above classes of individuals to consent on behalf of a subject to the subject's participation in the procedures involved in the research.

(2) OHRP acknowledges your report that for 16 of the 71 subjects who enrolled in the study at

UW and were unable to provide legally effective informed consent, the requirement to obtain informed consent from either the subject or the subject's legally authorized representative was waived under HHS regulations at 45 CFR 46.116(d).

OHRP finds that the research failed to satisfy all criteria required under HHS regulations at 45 CFR 46.116(d) for waiver of informed consent. In particular, OHRP finds that:

(a) The risks of the research described in the Institutional Review Board- (IRB-) approved protocol (e.g., risks and potential discomforts associated with the non-traditional, 6 ml/kg tidal volume group included agitation, potential need for higher doses of sedatives, volume overload, and hypernatremia) exceeded the limits of minimal risk, and thus failed to satisfy the requirements of HHS regulations at 45 CFR 46.116(d)(1).

(b) The research could practicably be carried out without the waiver, and thus failed to satisfy the requirements of HHS regulations at 45 CFR 46.116(d)(3). Indeed, more than 800 subjects were enrolled in the research without a waiver of informed consent. A slower rate of enrollment at UW was not sufficient justification for determining that the research could not practicably be carried out without the waiver.

(3) OHRP finds that the informed consent documents reviewed and approved by the WU 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: agitation, potential need for higher doses of sedatives and paralytics, volume overload, and hypernatremia.

Required Action: By March 15, 2002, UW must submit to OHRP a satisfactory corrective action plan to address findings (2) and (3) above.

OHRP has the following additional comments, questions and concerns regarding 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 likely to have been vulnerable to coercion or undue influence; and (b) the UW IRB failed ensure that

there were additional safeguards included 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.

(5) OHRP is concerned that when the UW IRB initially reviewed the research on March 6, 1996, it approved the research contingent upon substantive modifications or clarifications that were directly relevant to the determinations required under HHS regulations at 45 CFR 46.111 without requiring additional review by the convened IRB. For example, the IRB requested the following substantive clarifications from the investigator:

> (a) "Do you anticipate that eligible subjects will be able to give consent, or do you think their illness will prevent them from being able to do so? Is this an emergency situation? . . . Is it likely that next of kin will be available for subjects who are not competent to provide informed consent?"
>
> (b) We note that in this study subjects will be randomized to either a 12 mL/kg or 6 mL/kg ventilator strategy group. What if a subject assigned to the lower tidal volume group cannot tolerate this level and needs to go to the higher tidal volumes? Would such a person be dropped from the study?"

Please respond.

OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions that are directly relevant to the IRB determinations required under HHS regulations at 45 CFR 46.111, IRB approval of the proposed research should be **deferred**, pending subsequent review by the convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

(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 were misleading because they implied that both tidal volumes were used with equal frequency in clinical practice at UW:

> "Presently doctors use varying volumes of oxygen-enriched air to inflate the lungs. It is unknown whether it is better to use a large or small volume of oxygen-enriched air to inflate lungs of patients with lung injury."
>
> "Both ways of inflating a patient's lungs are considered acceptable methods and are commonly used to 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 UW at the time the research was initially reviewed by the IRB; (b) whether the UW IRB was aware of these statistics when it initially approved the research; and (c) which members of the UW IRB who participated in the initial review of the protocol had expertise in the areas of critical care medicine and ventilatory support.

(7) HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, research be reviewed at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in a nonscientific area. OHRP is concerned that the April 14, 1999 meeting of the UW IRB did not include a nonscientist member. In particular, OHRP notes the following:

> (a) Eight IRB members were listed as present, each of whom had either an M.D., Ph.D., or Pharm.D. degree.
>
> (b) No nonscientist member is listed as being in attendance. One guest was identified as being present and a nonscientist, but this individual does not appear to be an IRB member based upon the minutes of the UW IRB meeting and the IRB membership rosters dated February 16, 1999 that were submitted to OHRP.

Please respond. Please note that any actions taken at an IRB meeting lacking an appropriate

quorum must be considered invalid. OHRP emphasizes that when no nonscientist member is present during the course of the meeting, the IRB may not take further actions or votes until a nonscientist member returns.

Please submit UW's response to the above questions and concerns so that OHRP receives it no later than March 15, 2002. If upon further review of the questions and concerns UW 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 UW 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: Ms. Helen McGough, Manager, Human Subjects Division, UW
Dr. Zane A. Brown, Chairperson, Institutional Review Board-01, UW
Dr. Alan J. Wilensky, Chairperson, Institutional Review Board-02, UW
Dr. Patricia Kuszler, Chairperson, Institutional Review Board-03, UW
Dr. Sharon Durfy, Chairperson, Institutional Review Board-04, UW
Dr. Leonard D. Hudson, UW
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. George Gasparis, OHRP
Dr. Kamal Mittal, OHRP
Mr. Barry Bowman, OHRP