DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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William A. Mountcastle
Director
Veterans Affairs Medical Center
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1310 24th Avenue, South
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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1363

Research Protocol: 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 Protocol #: 7942
Principal Investigator: Dr. Arthur Wheeler
HHS Project Number: N01-HR46054

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. Limbird and Mr. Mountcastle:

The Office for Human Research Protections (OHRP) has reviewed Vanderbilt University's (VU's) September 26, 2000 report regarding the above-referenced research. This report was submitted in

response to OHRP's August 3, 2000 letter to VU and the Nashville Veterans Affairs Medical Center (VAMC) 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) OHRP finds that the informed consent documents reviewed and approved by the VU Institutional Review Board (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.
>
> **Required Action:** OHRP acknowledges that this research has been completed. By March 8, 2002, VU must submit to OHRP a satisfactory corrective action plan to ensure that informed consent documents approved by the IRB adequately describe all 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.
>
> VU's report indicated that 79 enrolled in the study at VU 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, uncle, or cousin).
>
> VU's report stated the following regarding the basis for family members having been legally authorized representatives for the subjects enrolled in the research:

"When a patient previously identified an individual to act on his or her behalf such as a guardian, conservator, or attorney-in fact under Durable Power of Attorney for Healthcare (DPOA), that individual was deemed to be the appropriate decision maker and surrogate consent was obtained if the patient was unable to consent. In Tennessee, the standard of care for identifying a decision-maker when a patient is unable to consent is to turn to the patient's appropriate next of kin. In the absence of a DPOA, guardian or conservator, physicians routinely rely on this practice. The authority for family members (and others) as surrogates is found in numerous Tennessee statutes and regulations. When read in the context of medical-decision making, it is clear the State of Tennessee views certain family members and others as appropriate decision makers. In this study, the surrogate, as required by the IRB (see consent form), was identified by the Investigator to be an individual who was actively involved in the life of and appeared to be acting in the best interest of the subject."

(a) VU's report cited the following Tennessee state laws as supporting the above interpretation: Tennessee Right to Natural Death Act (living wills); Durable Power of Attorney for Health Care statute; Consent for Autopsy statute; Uniform Anatomical Gift Act statute; Specific Anatomical Donation statutes for Eye Enucleation and Pituitary Gland.

It appears from VU's report that few, if any, of the persons who consented on behalf of the subjects enrolled in the research at VU were designated as health care decision makers under a subject's living will or held a DPOA for the subjects. Furthermore, the other statutes cited appear to apply to consent for autopsy and consent for organ donation for a deceased individual. Given that the research did not involve autopsy procedures or organ donation, these laws do not appear to allow family members or other individuals to consent on behalf of another individual to the procedures in the above-referenced research. Please respond in detail.

(b) Please clarify whether VU has obtained an opinion of the Tennessee Attorney General or other legal authority on the applicability of such laws to consent for participation in research procedures.

(3) 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 VU 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.

(4) 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 statement 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 VU:

> "The ventilator settings used to treat your disease vary widely. It is unknown whether it is better to use large or small volumes of oxygen enriched air to inflate your lungs. In this project your breathing machine will be managed using one of two very well defined ventilator management methods."

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

(5) OHRP is concerned that the IRB-approved informed consent document failed to adequately describe the alternative procedures or courses of treatment that may have been advantageous to the subjects, as required by HHS regulations at 45 CFR 46.116(a)(4). Please respond.

(6) OHRP is aware that in 1998 other institutions involved in the conduct of the research

approved 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. Please clarify (a) whether the VU approved a similar waiver; and (b) if so, whether the IRB made and documented the required findings under HHS regulations at 45 CFR 46.116(d).

Please submit VU 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 VU 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 VU 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. Mark Magnuson, Assistant Vice Chancellor for Research, VU
Dr. Margaret Rush, Chairperson, IRB-01, VU
Dr. William Cooper, Chairperson, IRB-02, VU
Dr. Arthur Wheeler, VU
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