DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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June 26, 2002

Lee E. Limbird, Ph.D.
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William A. Mountcastle
Director
Veterans Affairs Medical Center
Room 00 VAMC
1310 24th Avenue, South
Nashville, Tennessee 37212-2637

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1363

Research Protocol: Prospective, Randomized, Multicenter Trial of 12ml/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;342:1302-8)

Dear Dr. Limbird and Mr. Mountcastle:

The Office for Human Research Protections (OHRP) has reviewed Vanderbilt University's (VU's) March 7, 2002 report responding to OHRP's February 4, 2002 letter regarding the above- referenced research.

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

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(a)(2) require investigators to provide research subjects with a description of any reasonably foreseeable risks or discomforts to the research. In its February 4, 2002 letter to VU, OHRP found that the informed consent documents for the above research reviewed and approved by the VU IRB failed to adequately describe all reasonably foreseeable risks and discomforts of receiving non-traditional, 6 ml/kg tidal volume mechanical ventilation, and required VU to take corrective action.

Corrective Action: OHRP finds that VU has adequately addressed the above OHRP finding in its March 7, 2002 corrective action plan. Specifically, OHRP notes that the VU IRB adopted several policies effective September 15, 2000, including a policy providing guidance to ensure that research subjects are provided with an adequate description of the reasonably foreseeable risks and discomforts of research. OHRP acknowledges VU's concern that the HHS regulations protecting human research subjects do not expressly state whether risks of standard care treatments are included within the requirements of 45 CFR 46.116(a)(2). OHRP notes that the regulatory requirement to inform subjects of *any reasonably foreseeable risks or discomforts* includes the risks of standard care treatments that are part of the research protocol.

(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. VU's September 26, 2000 report indicated that 78 subjects enrolled in the above-referenced research at VU 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, uncle, or cousin). OHRP expressed several concerns regarding the legal basis for such individuals serving as legally authorized representatives for the subjects under Tennessee law.

Based upon its review of VU's September 26, 2000 and March 7, 2002 reports, OHRP finds that:

(a) VU has not cited to OHRP any Tennessee statute or other applicable law which permits a family member or other close relative not appointed under a durable power of attorney for health care (Tenn. Code Ann. section 34-6-201 *et seq.)* to consent to medical procedures involved in research.

(b) Tennessee law apparently does not authorize surrogate consent for medical procedures or for research in the absence of judicial intervention or the appointment of a durable power of attorney for health care under Tenn. Code Ann. section 34-6-201 *et. seq*.

(c) VU has not indicated that any of the 78 subjects for whom surrogate consent was obtained in the above-referenced research had, under applicable Tennessee law, either a durable power of attorney for health care or a judicially authorized guardian for medical treatment and/or research decisions. As a result, OHRP finds that VU failed to demonstrate that legally effective informed consent was obtained in accordance with 45 CFR 46.116 and 46.102(c) for these 78 subjects.

Required Corrective Action: OHRP acknowledges that the above-described research has been completed. OHRP requests that VU submit a response that adequately addresses this finding.

(3) OHRP finds that VU has adequately addressed the additional concerns raised in OHRP's February 4, 2002 letter.

Please submit VU's response to the above request so that OHRP receives it no later than August 2, 2002. 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,

Carol J. Weil, J.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Mark Magnuson, Assistant Vice Chancellor for Research, VU
Dr. Margaret Rush, Chairperson, IRB-01, VU
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Dr. Arthur Wheeler, VU
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