DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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October 7, 2002

Lee E. Limbird, Ph.D.
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Vanderbilt University
D-3300 Medical Center North
Nashville, Tennessee 37232-2104

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 your July 18, 2002 letter and has determined that the corrective action summarized below appropriately addresses the issues raised:

HHS regulations for the protection of human research subjects 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 46.102(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.

In the above-referenced research at VU, 78 enrolled subjects lacked capacity to provide legally effective informed consent, and consent for these subjects was obtained from another individual (spouse, parent, adult sibling, adult child, uncle, or cousin). None of these surrogates was appointed under the Tennessee durable power of attorney for health care statute (Tenn. Code Ann. section 34-6-201 *et seq*.) or by judicial appointment (34-3-101 *et seq.)* In its June 26, 2002 letter, OHRP found 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. None of the additional information provided to OHRP in VU's July 18, 2002 response and subsequent communications alters this finding.

Corrective Action: OHRP acknowledges that VU is actively pursuing a revision of Tennessee health care regulations which would constitute applicable law authorizing surrogate consent on behalf of prospective human subjects to the subjects' participation in medical procedures involved in research. The revised regulations have been reviewed by the Tennessee Department of Health Board for Licensing Health Care Facilities and are slated for adoption by the State of Tennessee. It is OHRP's understanding that VU will not conduct or sponsor human subject research in which informed consent is obtained from surrogates other than those appointed under Tennessee law (i.e., Tenn. Code Ann. section 34-6-201 *et seq.* or 34-3-101 *et seq.)* until the revised regulations are effective or VU can supply other evidence of the existence of applicable law, such as a Tennessee Attorney General opinion.

Presuming full implementation of the corrective action described, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

OHRP appreciates the continued commitment of your institution 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
Dr. William Cooper, Chairperson, IRB-02, VU
Ms. Julia Morris, VU
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Mr. George Gasparis, OHRP
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Ms. Janice Walden, OHRP
Commissioner, FDA
Dr. David Lepay, FDA
Dr. John Mather, Director, Office of Research Compliance and Assurance, Veterans Health Administration