DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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November 17, 2003

George F. Kalf, Ph.D., CIP
Professor of Biochemistry/Molecular Pharmacology
Associate Dean for Scientific Affairs
Director, Division of Human Subjects Protection
Office of Scientific Affairs
Thomas Jefferson University
1015 Chestnut Street, Suite 1100
Philadelphia, PA 19107

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 2109 and Multiple Project Assurance (MPA) M-1115

Research Project: Prospective, Randomized, Multi-Center Trial of 12 ml/kg vs. 6 ml/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome (ARMA Trial)
Principal Investigator: Jonathan Gottlieb, M.D.

Research Project: Prospective, Randomized, Multi-Center Trial of Pulmonary Artery Catheter (PAC) vs. Central Venous Catheter (CVC) for Management of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) and Prospective, Randomized, Multi-Center Trial of 'Fluid Conservative' vs. 'Fluid Liberal' Management of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) (FACTT Trial)
Principal Investigator: Jonathan Gottlieb, M.D.

Dear Dr. Kalf:

The Office for Human Research Protections (OHRP) has reviewed Thomas Jefferson University's (TJU) September 8 and October 29, 2003 reports responding to determinations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects involving the above-referenced research.

Based upon its review, OHRP finds that TJU has implemented the required actions stipulated by OHRP's July 25, 2003 letter. In particular, OHRP acknowledges the following:

(1) The TJU Institutional Review Board (IRB) received the additional supplemental information and the revised model informed consent document for the FACTT trial, and have subsequently re-reviewed and approved the research.

(2) TJU has provided OHRP with a copy of the final version of the IRB-approved informed consent document.

(3) TJU has implemented a variety of procedures including a checklist "Element of IRB Review: Questionnaire for Reviewers" to help ensure that the TJU IRBs receive sufficient information to make all determinations required under HHS regulations at 45 CFR 46.111 and that the TJU IRBs approve an informed consent process that satisfies all requirements of HHS regulations at 45 CFR 46.116.

OHRP finds that the above corrective actions adequately address OHRP's findings and are appropriate under the TJU FWA. As a result, OHRP anticipates no need for further involvement with TJU related to this matter.

AT this time, OHRP offers the following additional comments and guidance:

(4) OHRP recommends that instructions to investigators or protocol application forms solicit the information necessary to make the required determinations under HHS regulations at 45 CFR 46.111 and 46.116.

(5) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. The informed consent document approved by the IRB for this study appeared to include some complex language that may not be understandable to all subjects. For example, the second paragraph on page 2, beginning with the words, "Be aware that your relationship with the research physician...." and the HIPAA authorization language appear to be somewhat complex.

(6) The document "Research in the Intensive Care Unit" stated "Before a clinical trial gets underway, the treatment must show that it has potential benefit. It must also meet rigorous government and scientific requirements for safety, and have acceptable side effects." The document also states "The [hospital's Ethics] Committee also reviews any existing studies using the new treatment to ensure that side effects are acceptable and the study is safe." These statements may imply that all clinical research has potential benefit, acceptable side effects, and is safe. This is not always the case. OHRP recommends that the document be revised to indicate this. OHRP also notes that this and similar language may imply that participation in a clinical trial is the same as treatment.

OHRP appreciates the commitment of TJU to the protection of human subjects. Do not hesitate

to contact us should you have any questions.

Sincerely,

Kristina Borror, Ph.D.
Director
Division of Compliance Oversight

Michael A. Carome, M.D.
Associate Director for Regulatory Affairs
Office for Human Research Protections

cc: Dr. David G. Brock, Chairperson, IRB #1, TJU
Dr. Stephen P. Weinstein, Chairperson, IRB #2, TJU
Dr. Gregory Mokrynski, Chairperson, IRB #3, TJU
Dr. Jonathan Gottlieb, Principal Investigator, ARMA and FACTT Trials, TJU
Dr. B. Taylor Thompson, ARDS Network Coordinating Center Principal Investigator, Massachusetts General Hospital
Dr. Arthur Wheeler, FACTT Trial Committee Chair, Vanderbilt University
Dr. Gordon R. Bernard, Chairman, ARDS Steering Committee, Vanderbilt University
Dr. Herbert P. Wiedemann, FACTT Trial Committee Chair, Cleveland Clinic Foundation
Dr. James Kiley, Director, Division of Lung Diseases, NHLBI
Dr. Lana Skirboll, Director, Office of Science Policy, NIH
Dr. David Lepay, Director, Good Clinical Practices Program, FDA
Ms. Melinda Hill, OHRP
Ms. Patricia El-Hinnawy, OHRP