DEPARTMENT OF HEALTH & HUMAN SERVICES

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February 4, 2002

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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1011

Research Publication: Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Respiratory Distress Syndrome. (N Engl J Med 2000; 342:1301-8)

Project Title: Prospective, Randomized, Multicenter Trial of 12 ml/kg vs 6 ml/kg Tidal Volume Positive Pressure Ventilation and Ketoconazole vs Placebo fro the Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome

Principal Investigator: Roy Brower, M.D.

IRB Number: RPN 95-12-15-02
HHS Project Number: N01-HR46063

Dear Dr. Dang, Dr. Klag, and Mr. Peterson:

The Office for Human Research Protections (OHRP) has reviewed the Johns Hopkins School of Medicine's (JHU) October 30, 2000 report responding to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46) involving the above-referenced research that were presented in OHRP's letter of September 21, 2000.

Based upon its review, OHRP make 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) 46 subjects enrolled in the study at Johns Hopkins University (JHU) 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, legal guardian, aunt).

(b) Applicable Maryland 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 patient's spouse.

(iii) Adult children of the patient.

(iv) Parents of the patient.

(v) Adult brothers and sisters of the patient.

(vi) A friend or other relative of the patient.

(c) JHU interprets applicable Maryland 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 finds that the informed consent documents reviewed and approved by the JHU 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: agitation, potential need for higher doses of sedatives and paralytics, volume overload, and hypernatremia.

Of particular note, in a October 30, 1996 protocol amendment submitted to the JHU IRB, the principal investigator reported that in the first 100 subjects enrolled into the study, some patients randomized to the 6 ml/kg tidal volume group became "very dyspneic and agitated." Nevertheless, the JHU IRB failed to require modification of the informed consent document to describe risks associated with such circumstances.

Corrective Action: OHRP acknowledges that the research has been completed. Furthermore, OHRP acknowledges that JHU has implemented appropriate corrective actions under its MPA as part of its response to OHRP's letter of July 19, 2001 to ensure that informed consent documents approved by the IRB include an appropriate description of reasonably foreseeable risks and discomforts.

Based upon its review, OHRP has the following additional questions and concerns regarding the above-referenced research:

(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 JHU IRB failed ensure that there were additional safeguards include 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.

An October 23, 2000 letter from the IRB chair stated, "The file shows that we carefully considered the informed consent procedures several times during the course of the trial. Please see correspondence dated 3/11/97, 5/6/98, and 9/19/99." OHRP notes that these correspondence are requests from the investigator to designate individuals to consent prospective subjects (OHRP also notes that the 9/19/99 correspondence was not provided with your report). OHRP finds little evidence in the documents provided in your report that the IRB considered the issues listed in the above paragraph, including the correspondence noted by the IRB chair. Please respond in detail. With your response please provide minutes of the IRB meetings where the above-referenced research was discussed.

(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 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 JHU:

> "Both ways of inflating the lungs are acceptable methods that are commonly used in 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 JHU at the time the research was initially reviewed by the IRB; (b) whether the JHU IRB was aware of these statistics when it initially approved the research; and (c) which members of the JHU IRB who participated in the initial review of the protocol had expertise in the areas of critical care medicine and ventilatory support.

(5) HHS regulations at 45 CFR 46.116 require that the information provided in the informed consent documents be in language understandable to the subject. OHRP is concerned that the

informed consent document approved by the JHU IRB for this study appeared to include complex language that would not have been understandable to all subjects or their legally authorized representatives. In particular, OHRP is concerned that some of the sentences and terminology were too complex (e.g., "... you will continue to receive extra oxygen and pressure from the ventilator ...;" "Occasionally there are mild increases in the levels of enzymes produced by the liver that are without symptoms (5%)."). Please respond.

Please submit JHU's 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 JHU 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 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,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Martha Hill, Interim Dean, School of Nursing, JHU
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