DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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February 1, 2002

Ralph Snyderman, M.D.
President
Duke University Health System, Inc.
DUMC Box 3701
Durham, North Carolina 27710

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA)M-1106
Research Publication: Ventilation with Lower Tidal Volumes as Compare with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome (N Eng J Med 2000;342:1301-8)
HHS Project Number: N01-HR46056
IRB Project Number: 186-96-2
Principal Investigator: William Fulkerson, M.D.

Dear Dr. Snyderman:

The Office for Human Research Protections (OHRP) has reviewed Duke University Health System's (DUHS) September 28, 2000 report regarding the above-referenced research. These reports were submitted in response to OHRP's August 3, 2000 letter to DUHS 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 DUHS's oversight of 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) Seventy-four subjects enrolled in the study at DUHS 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, nephew, uncle, cousin).

(b) Applicable North Carolina 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 patient's spouse.

(ii) Parents of the patient.

(iii) The appointed guardian of the patient.

(iv) The nearest relative.

(v) Other person authorized to give consent, defined as an individual to whom the patient has given a "Health Care Power of Attorney".

(c) DUHS interprets applicable North Carolina 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 DUHS 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.

(3) OHRP finds that the informed consent documents reviewed and approved by the DUHS IRB failed to adequately disclose appropriate alternative procedures or courses of treatment that might be advantageous to the subject, in accordance with the requirements of HHS

regulations at 45 CFR 46.116(a)(4).

Corrective Action: OHRP acknowledges that the research has been completed. Furthermore, OHRP acknowledges that DUHS has implemented appropriate corrective actions under its MPA to ensure that informed consent documents approved by the IRB include all elements required by HHS regulations at 45 CFR 46.116(a).

(4) OHRP notes that on March 11, 1999, the DUHS IRB approved a modification of the informed consent procedure to permit witnessed telephone consent by the subject's legally authorized representative, to be followed obtaining a signed informed consent document from the legally authorized representative at a later time after enrollment of the subject. Under HHS regulations 45 CFR 46.117(a), informed consent shall be documented by use of a *written* consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. An IRB may waive the requirement for the investigator to obtain a signed consent in accordance with 45 CFR 46.117(c) if it finds either that (a) the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality, or (b) the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. OHRP finds that the IRB-approved procedure permitting telephone consent by the subject's legally authorized representative did not satisfy the requirements for waiver of documentation of informed consent as required by 45 CFR 46.117(c).

Required Action: OHRP acknowledges that the research has been completed. By March 8, 2002, DUMC must submit to OHRP a detailed corrective action plan to address finding (4) above for any ongoing or planned research activities.

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

(5) 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 DUHS IRB failed to 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.

(6) 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 acknowledges the following statement in correspondence dated February 19, 1996 from the principal investigator to the IRB chairman:

> "You have raised the question of which ventilator protocol represents 'standard therapy'. These strategies represent opposing philosophies, but both are used in current practice by different clinicians."

However, 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 they implied that both tidal volumes were used with equal frequency in clinical practice at DUHS**:**

"One [purpose of the study] is to compare two ways of inflating your lungs while on the machine. Doctors currently use both methods to breathe for patients, but it is not known if one method is better."

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

Please submit DUHS'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 DUHS 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 DUHS to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Leslie K. Ball, M.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. John Falletta, Chair, IRB-01, DUHS
Ms. Charlotte Coley, IRB Administrator, DUHS
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