DEPARTMENT OF HEALTH & HUMAN SERVICES

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February 11, 2002

Dr. Fazwaz T. Ulaby
Vice President for Research
University of Michigan Ann Arbor
4080 Fleming Building
503 Thompson Street
Ann Arbor, MI 48109-1340

RE: Human Research Protections Under Multiple Project Assurance (MPA) M-1184

Multistudy Research Project: 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)

UM Approved Protocols:

(1) Prospective, Randomized, Multicenter Trial of 12ml/kg vs. 6 ml/kg Tiday Volume Positive Pressure Ventilation and Ketoconazole vs. Placebo for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome (IRB No. 1996-152)(Galen Toews, P.I.)

(2) Ketoconazole and Respiratory Management in Acute Lung Injury and Adult Respiratory Distress Syndrome (KARMA) (IRB No. 1996-152, Version 2) (Galen Toews, P.I.)

(3) A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Trial of Lisofylline in Patients with Acute Lung Injury and Adult Respiratory Distress Syndrome (IRB No. 1998-081) (Galen Toews, P.I.)

Dear Dr. Ulaby:

The Office for Human Research Protections (OHRP) has reviewed the University of Michigan's

(UM's) February 5, 2001 report regarding the above-referenced research. This report was submitted in response to OHRP's August 3, 2000 letter to UM 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 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 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.

OHRP acknowledges that UM's report states the following regarding the above-referenced research:

(a) 68 of 71 subjects enrolled in the above studies at UM were unable to provide legally effective informed consent, and consent for these subjects instead was obtained and documented from an immediate relative (parent, adult sibling, or adult child).

(b) Section 400.66h of the Michigan Social Welfare Act 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 "nearest relative" of the patient;
(ii) The legally appointed guardian of the patient; or
(iii) The person standing *in loco parentis* on behalf of the patient.

(c) UM interprets Section 400.66h of the Michigan Social Welfare Act as authorizing the consent of a parent, sibling, or child of a subject to the subject's participation in the procedures involved in the research, in accordance with 45 CFR 46.116 and 45 CFR 46.102(c).

(2) HHS regulations at 45 CFR 46.116(d) require that the Institutional Review Board (IRB) make and document the following four criteria when waiving the requirements to obtain informed consent: (a) the research involves no more than minimal risk, (b) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (c) the research could not practicably be carried out without the waiver or alteration; and (4) when appropriate, subjects are provided with additional pertinent information after their participation. OHRP acknowledges UM's finding

in its report that the UM IRB failed to document these four criteria when it approved an amendment requesting a waiver of the requirement to obtain informed consent for collection of data from the medical records of patients who were screened for participation but were not enrolled.

Corrective Action: OHRP acknowledges that UM has implemented an appropriate corrective action plan under its MPA to ensure that the IRB satisfies the regulatory requirements for waiver of informed consent. Specifically, UM requires inclusion of a check-off list for the findings required under HHS regulations at 45 CFR 46.116(d) in the IRB records.

(3) OHRP finds that the informed consent documents reviewed and approved by the UM 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.

Of particular note, in an October 24, 1996 protocol amendment submitted to the UM IRB, it was 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 UM IRB failed to require modification of the informed consent document to describe these risks.

Required Corrective Action: OHRP acknowledges that the above-described research has been completed. OHRP requests that UM submit a corrective action plan to ensure that informed consent documents approved by the UM IRB include a description of *any reasonably foreseeable risks or discomforts to the subject*, as required under HHS regulations at 45 CFR 46.116(a)(2).

(4) HHS regulations at 45 CFR 46.117(a) require that informed consent be documented in a written, IRB-approved informed consent form. UM's report states that for 11 of the 71 subjects who participated in the above research, consent was obtained via a witnessed telephone conversation with patient representatives in accordance with a procedure established for obtaining consent for clinical care in the UM Health System. UM's report further states that "[s]ignature on a formal consent document is secured after the fact." OHRP acknowledges UM's statement that this telephonic consent procedure does not meet the regulatory requirements of 45 CFR 46.117.

Corrective Action: OHRP acknowledges that UM has taken steps to implement a corrective action plan to address the deficiencies in its current procedure for obtaining telephonic consent for research from patient representatives. Specifically, UM is setting new standards for telephonic consent for research that will be consistent with 45 CFR 46.117, and developing

guidance and application forms for investigators seeking IRB approval of requests for telephonic consent. OHRP requests that UM provide to OHRP a copy of the new standards and guidance on obtaining informed consent for human subject research via telephone conversations with legally authorized representatives.

(5) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require that institutions have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any supporting Department or Agency head, and OHRP of (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. OHRP finds that UM's reporting policies do not address the above regulatory requirements.

Required Corrective Action: UM must develop a corrective action plan to amend its reporting policies so that they implement the requirements for ensuring prompt reporting of unanticipated problems involving risks to subjects or others, serious or continuing noncompliance with the requirements of HHS regulations or the IRB, and any suspension or termination of IRB approval. The reporting policies should provide operational details, including a description of which office(s) or institutional official(s) is/are responsible for each reporting requirement.

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

(6) 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 notes that the UM IRB meeting minutes for April 11, 1996 indicate that the subjects involved in this research are not a vulnerable population. OHRP is concerned that (a) both the subjects of the research, because of their impaired consciousness, 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 UM IRB failed to ensure that there were additional safeguards included in the study to protect the subjects' rights and welfare. 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.

(7) 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 (August 27, 1998 version) were misleading because they implied that both tidal volumes were used with equal frequency in clinical practice at UM:

> "Presently, doctors use varying volumes of oxygen-enriched air to inflate your lungs. It is unknown whether it is better to use large volumes or small volumes of oxygen-enriched air to inflate the lungs of patients with a lung injury like yours."
>
> "Both ways of inflating your lungs are acceptable methods and are commonly used in medical practice."
>
> "The large and small inflation volumes used by the breathing machine are both standard treatments for acute lung injury patients such as yourself."
>
> "Of the procedure[s] listed above only the administration of lisofylline for acute lung injury is experimental. The large and small volumes used to inflate your lungs are both standards of care."

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

(8) 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 documents approved by the UM IRB for this study appear 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., "This drug [lisofylline] has been shown to inhibit the effects of several types of inflammatory cells that your body produces during severe illnesses, including the type of lung injury that you have;" "We will make changes in the amount of air being delivered to your

lung based on the pressure required to inflate your lungs and the status of your blood acidity, as defined by the study protocol." Please respond.

(9) As referenced in (2) above, HHS regulations for waiving informed consent require, at 45 CFR 46.116(d)(3), that the IRB find and document that the research could not practicably be carried out without a waiver of consent. In its report, UM stated that the IRB waived informed consent for the collection of prospective data from the medical records of individuals who were screened but did not participate in the research. OHRP questions the basis for the IRB's finding that the research could not practicably be carried out without a waiver of consent. Please respond.

Please submit UM's response to the above questions and concerns so that OHRP receives it no later than March 11, 2002. If upon further review of the questions and concerns in this letter, UM 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 UM 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.
Division of Compliance Oversight

cc: Dr. Galen Toews, UM
Dr. Judity Novack, Assistant Vice President for Research, UM
Dr. David Smith, Chair, IRB-01, UM
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