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Floyd D. Loop, M.D.
Executive Vice President and Chairman, Board of Governors
The Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, OH 44195

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1388

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: A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Trial of Lisofylline in Patients with Acute Lung Injury and Adult Respiratory Distress Syndrome
Principal Investigator: Herbert Wiedemann, M.D.
HHS Project Number: N01-HR46063

Dear Dr. Loop:

The Office for Human Research Protections (OHRP) has reviewed the Cleveland Clinic Foundation's (CCF) September 27, 2000 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 August 3, 2000.

Based upon its review, OHRP makes the following determination regarding CCF'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) 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.

(a) CCF's report indicated that 53 subjects enrolled in the study at CCF 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, some of whom were assigned power of attorney for the subject).

(b) CCF's report stated the following regarding the basis for family members having been legally authorized representatives for the subjects enrolled in the research:

(i) "Ohio statues and case law clearly support treatment of ventilator-dependent patients participating in clinical trials involving non-emergent, non-life sustaining treatment with the family's consent."

(ii) "In Estate of Leach v. Shapiro (1984), 13 Ohio App. 3d 393, the court confirmed that family member may appropriately consent, as surrogates, to medical treatment for another ..."

(iii) "Ohio's Uniform Rights of the Terminally Ill statutes, codified at O.R.C. §2133.01 *et seq.* probably do not specifically apply to this clinical trial situation, because the patients may not have written advance health care directives and are not necessarily terminally ill. However, O.R.C. § 2133.08 contains a hierarchy of which family members may make decisions in the absence of a written advance directive, as surrogates."

(iv) "In O.R.C. § 2133.08(B)m the 'hierarchy' is as follows: (1) guardian, if appointed (though not required); (2) spouse; (3) adult children; (4) parents; (5) adult sibling (in that order); and (6) other nearest available relatives."

(c) CCF interprets applicable Ohio 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 CCF 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: agitation, potential need for higher doses of sedatives and paralytics, volume overload, and hypernatremia. Additionally, the investigators brochure for lisofylline stated the following:

> "Adverse events expected in these populations include all degrees of the following: death, allergic reactions including anaphylaxis, neutropenia including severe and absolute, thrombocytopenia and resultant bleeding, anemia requiring transfusion, mucositis including stomatitis and pharyngitis, serious infections including septic shock, multi-organ dysfunction, venocclusive disease, cerebral hemorrhage resulting in death, seizures, cardiac dysfunction (congestive heart failure) and cardiac dysrhythmia, pneumonia including noninfectious pneumonia and pulmonary fibrosis, nausea, vomiting including hematemesis, diarrhea including hematochezia, and anorexia."

Based on the subject population in the above-referenced research, OHRP is concerned that it may have been appropriate to include a number of the conditions listed above in the informed consent document. Please respond.

Based on 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 CCF 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. Please respond in detail.

(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 statement 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 CCF:

> (a) "Presently, doctors use varying volumes of oxygen-enriched air to inflate your lungs."
>
> (b) "Both methods of inflating your lungs are safe and 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 CCF at the time the research was initially reviewed by the IRB; (b) whether the CCF IRB was aware of these statistics when it initially approved the research; and (c) which members of the CCF IRB who participated in the initial review of the protocol had expertise in the areas of critical care medicine and ventilatory support.

(5) OHRP is aware that some sites for this multicenter trial approved a waiver of informed consent for collection of data from the medical records of patients who were screened for enrollment in the clinical trial, but were not enrolled. Please clarify whether the CCF IRB approved 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.

Please submit CCF's response to the above questions and concerns so that OHRP receives it no later than March 14, 2002. If upon further review of the questions and concerns CCF 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. Alan Lichtin, IRB Chair, CCF
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