DEPARTMENT OF HEALTH & HUMAN SERVICES

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February 4, 2002

Richard M. Cagen
Administrator
LDS Hospital
Eighth Avenue and C Street
Salt Lake City, UT 84143

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1089

Research Project: **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: Alan H. Morris, M.D.
IRB Number: **IRB# 617**
HHS Project Number: N01-HR46063

Dear Mr. Cagen:

The Office for Human Research Protections (OHRP) has reviewed the LDS Hospital's September 27, 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 August 3, 2000.

Based upon its review, OHRP makes the following determination regarding the LDS Hospital'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) 50 subjects enrolled in the study at LDS Hospital were unable to provide legally effective informed consent, and consent for these subjects instead was obtained and documented from another individual (spouse, parent, adult child).

(b) Applicable Utah law indicates that the following classes of persons are authorized to provide informed consent to health care:

(i) Any parent, whether an adult or a minor, for his minor child.

(ii) Any married person for a spouse.

(iii) Any person temporarily standing in loco parentis, whether formally serving or not, for the minor under his care and any guardian for his ward.

(iv) Any person 18 years of age or over for his or her parent who is unable by reason of age, physical or mental condition, to provide such consent.

(v) Any patient 18 years of age or over.

(vi) Any female, regardless of age or marital status, when given in connection with her pregnancy or childbirth.

(vii) In the absence of a parent, any adult for his minor brother or sister.

(viii) In the absence of a parent, a grandparent for his minor grandchild.

(c) LDS Hospital interprets applicable Utah 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 LDS Hospital 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: dyspnea, agitation, potential need for higher doses of sedatives and paralytics, volume overload, and hypernatremia.

Required Action: OHRP acknowledges that this research has been completed. By March 8, 2002, LDS hospital must submit a corrective action plan for ensuring that all IRB-approved informed consent documents include a description of all reasonably foreseeable risks and discomforts to the subject.

OHRP has the following additional concerns, questions and guidance 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 LDS Hospital 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 LDS Hospital:

> "Since either large of small amounts of air are good medical practice, and since either could be used for your care, we are comparing them by randomly assigning patients to larger or smaller amounts of air and examining the results of treatment."

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 LDS Hospital at the time the research was initially reviewed by the IRB; (b) whether the LDS Hospital IRB was aware of these statistics when it initially approved the research; and (c) which members of the Hospital 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 LDS Hospital 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., "Subsequently, any changes in the volume will be determined by the pressures in your airways and the acidity of your blood;" "... inhibit several types of inflammatory cells ..." "... high oxygen concentration ..."). Please respond.

(6) HHS regulations at 45 CFR 46.116 require that an investigator will seek consent only under circumstances that provide the prospective subject or representative sufficient opportunity whether or not to participate and which minimize the possibility of coercion or undue influence. OHRP is concerned that the following statements in the IRB-approved informed consent document for the above-referenced research may have overstated the potential benefit of the research and posed an undue influence to the prospective subjects or their legally authorized representatives:

> (a) "The computer protocols which will be used to standardize care in both treatment

groups have been extensively tested and been associated with a four-fold increase in survival for patients with severe lung disease."

(b) "The alternative to participating in this trial would be similar therapy provided by physicians independent of the clinical trial. This therapy may, however, not be controlled using a computer protocol."

(c) "A special protocol, or set of rules, has been developed that has received approval from doctors at all of the participating hospitals as well as by an independent review group organized by the National Institutes of Health."

Please respond.

(7) OHRP notes that the minutes of the LDS Hospital IRB meetings on August 8, 1996 and September 11, 1997 at which the research was approved for continuing review appear to provide little in the way of discussion of the protocol. Minutes of IRB meetings after these dates appear to provide a greater amount of detail relating to continuing review. OHRP wishes to remind LDS Hospital that continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

(8) HHS regulations at 45 CFR 46.115(a)(2) require that the minutes of IRB meetings document the vote on all IRB actions including the number of members voting for, against, and abstaining. Recording the vote as "unanimous" is not sufficient. In order to document the continued existence of a quorum, OHRP strongly recommends that votes be recorded in the minutes using the following format: Total = 15; Vote: For-14, Opposed-0, Abstained-1 (NAME).

(9) Where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which alters or waives the requirements for informed consent [see 45

CFR 46.116(d)]; (b) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP strongly recommends that all required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

Please submit your 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 LDS Hospital 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: Mr. David Grauer, LDS Hospital
Dr. A. Jennifer Fishbach, IRB Chair, LDS Hospital
Dr. Alan Morris, LDS Hospital
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
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Dr. Michael A. Carome, OHRP
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Mr. George Gasparis, OHRP
Ms. Jan Walden, OHRP
Mr. Barry Bowman, OHRP