DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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January 31, 2002

Dr. John R. Sladek, Jr.
Vice Chancellor for Research
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School of Medicine, Room 1660
Chancellor's Office
University of Colorado
Health Sciences Center
4200 East 9th Avenue
Denver, CO 80262

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1494

Research Project: Prospective, Randomized, Multicenter Trial of 12 ml.kg vs 6 ml/kg Tidal Volume Positive Pressure Ventilation and Ketoconozole vs Placebo for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome
Journal Article: Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome, The Acute Respiratory Distress Syndrome Network, New England Journal of Medicine. 2000; 342(18): 1301-08.
Principal Investigator: Edward Abraham, M.D.
UC Study Number: 96-06

Dear Dr. Sladek:

The Office for Human Research Protections (OHRP) has reviewed the University of Colorado Health Sciences Center's (CU's) report dated November 15, 2001 regarding the above-referenced research. This report was submitted in response to OHRP's August 3, 2000 letter to CU 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 CU's oversight of the above-referenced research:

(1) HHS regulations at 45 CFR 46.116(d) require that the Institutional Review Board (IRB) make and document four criteria when waiving the requirements to obtain informed consent. OHRP finds no evidence in the IRB records that the CU IRB made and documented these four criteria when it approved the principal investigator's November 6, 1998 request for 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.

Required Action: By March 8, 2002, CU must submit to OHRP a satisfactory corrective action plan to ensure the CU IRBs make and document the four criteria required by HHS regulations at 45 CFR 46.116(d) whenever the IRBs (i) approve a consent procedure which does not include, or which alters, some or all of the required elements of informed consent; or (ii) waive the requirements to obtain informed consent.

Recommended Action: 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.

(2) OHRP finds that the informed consent documents reviewed and approved by the CU IRB failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116 (a):

> (a) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts. 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.
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> (b) Section 46.116(a)(8): A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. The informed consent document simply stated "Your participation in this study is voluntary. You may withdraw from the study at any time."

Required Action: By March 8, 2002, please provide OHRP with appropriate corrective actions to ensure that informed consent documents approved by the IRB include all the elements required under HHS regulations at 45 CFR 46.116(a).

OHRP has the following additional concerns and questions regarding CU's oversight of the above-referenced research:

(3) 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.

CU's report indicated that most of the 114 subjects enrolled in the study at CU were unable to provide legally effective informed consent and consent for these subjects instead was obtained and documented from another individual (spouse, parent, sibling, adult child, step-son, niece, immediate family, family member, or legal proxy).

A September 25, 2000 memo from Esther Henry, Research Associate, to Steve Zweck-Bronner, Associate University Counsel, outlines Colorado State law on proxy decision-makers for medical treatment. According to this memo, with which the Associate University Counsel concurred, Colorado State law provides that if a guardian, person with durable power of attorney (DPA), or someone who has legal authority to consent on a patient's behalf exists, then such a person may consent for those who lack decisional capacity. If such a person does not exist, a proxy may be used. The memo outlines the process for choosing a proxy as locating "as many interested persons as practicable" and having all those persons "...reach a consensus as to one decision maker (this should be someone who has a close relationship with the patient and is currently advised of the patient's wishes)...." CU interprets applicable Colorado law regarding decision-makers for medical treatment as extending to authorizing individuals to consent on behalf of a subject to the subject's participation in the procedures involved in the research. OHRP has the following concerns and questions:

> (a) For each of the subjects enrolled at CU for this trial, please indicate whether the person who consented for subject (if the subject did not consent themselves) was a legal guardian or held DPA or otherwise had legal authority to consent on a patient's behalf for medical treatment under Colorado State law. If not, please outline the process that UCHSC used to locate all interested persons and arrive at a consensus appointment of a proxy decision maker.
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> (b) Please clarify whether CU has obtained an opinion of the Colorado Attorney General or other legal authority on the applicability of such laws to consent for **participation in research procedures** (as opposed to consent for medical treatment).

(4) 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 CU 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.

(5) 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 CU:

> "Presently doctors use varying volumes of oxygen-rich air to inflate the patient's lungs. It is unknown whether it is better to use large [12 ml/kg] or small [6 ml/kg] volume with a lung injury like yours."
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> "The large and small volumes used by the breathing machine are both standard treatments."
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> "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 CU at the time the research was initially reviewed by the IRB; (b) whether the CU IRB was aware of these statistics when it initially approved the research; and (c) which members of the CU IRB who participated in the initial review of the protocol had expertise in the areas of critical care medicine and ventilatory support.

(6) 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 CU 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., "Depending on the results of the randomization procedure, either 12 ml/kg or 6 ml/kg of oxygen-enriched air will initially be delivered to your lungs;" "Subsequently, any changes in the volume will be determined by the pressures in your airways and by the acidity of the blood;" and the discussion of risks). Please respond.

(7) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require that unanticipated problems involving risks to subjects or others be reported to OHRP. On October 7, 1998 an adverse event involving a sub-arachnoid hemorrhage was reported. It appears that this was unanticipated, as it was not mentioned in the informed consent document, and was deemed to be possibly related to the administration of the study drug. OHRP is

concerned that this was never reported to OHRP and that the informed consent document was not changed to reflect this new risk. Please respond.

Please submit CU'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 CU 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,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. James H. Shore, CU
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