DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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December 20, 2001

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Elliot G. Cohen
Senior Executive Officer
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Thomas P. Pishioneri
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Glenn D. Warden, M.D.
Chief of Staff
Shriners Burns Institute
3229 Burnet Avenue
Cincinnati, OH 45229

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1138

Research Project: A Dose Response Study of Inhaled Nitric Oxide in the Treatment of Adult Respiratory Distress Syndrome
Principal Investigator: Jay Johannigman, MD

UC Study Number: 94-10-19-2

Dear Dr. Harrison, Mr. Cohen, Mr. Pishioneri and Dr. Warden:
The Office for Human Research Protections (OHRP) has reviewed your report of January 26, 2001 regarding the above referenced research conducted at the University of Cincinnati (UC).

Based upon its review, OHRP makes the following determination regarding the above-referenced research project:

(1) HHS regulations at 45 CFR 46.116(a)(2) require that informed consent documents include a complete description of the procedures to be followed, and identification of any procedures which are experimental. OHRP finds that the institutional review board (IRB)-approved informed consent document failed to provide a complete description of the research procedures. In specific, OHRP finds that the informed consent document stated that "I will receive one of four concentrations of nitric oxide," whereas the protocol stated that "Treatment gas will be utilized at one of the four following concentrations....Each concentration will be employed for a continuous six hour period....At the end of each six hour period the concentration of inhaled nitric oxide will be changed in a random fashion to one of the remaining concentration...."

Required Action: Please confirm in writing by January 31, 2002 whether or not the above-referenced research protocol is closed to subject enrollment. If not, the investigator should revise the informed consent document to reflect the actual procedures performed in this study and provide OHRP with a copy of the revised informed consent document that has been reviewed and approved by the IRB.

(2) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116 stipulate that no investigator may involve a human 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 Ohio case law, rather than statute, indicates that authorized persons can make a treatment decision consistent with the *patient's* expressed wishes or with what the *patient* would have wanted. OHRP has the following concerns and questions:

(a) The case law referenced by UC that names family members as being able to consent for patients refers to termination of life support in the context of provision of health care. It is not clear how this applies to provision of experimental treatment in a

research context.

(b) HHS regulations clearly state that a legally authorized representative is an individual who is authorized to consent on the subject's behalf to **procedures involved in the research**. It is not clear how the case law cited (regarding termination of life support) applies to the procedures conducted in this particular research.

Please respond. In your response please clarify whether UC has obtained an opinion of the Ohio Attorney General or other legal authority on the applicability of such case law to consent for research?.

Please submit to OHRP your response to the above no later than January 31, 2002. If upon further review of the concerns and questions, UC identifies additional instances of non-compliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

OHRP has the following additional guidance:

(3) 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 recommends that the UC IRB take special care to ensure that informed consent documents do not include complex language that would not be understandable to all subjects (or their legally authorized representatives). OHRP notes that words such as "investigational," "catheter," and "adverse" may not be well understood by all subjects.

(4) OHRP acknowledges that the investigator received verbal permission from the UC IRB Chair to enroll a child in the above-referenced study. OHRP notes that HHS regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval (see 45 CFR 46.103(b), 46.116(f) and OPRR Reports 91-01). When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a research activity. When emergency care involves investigational drugs, devices, or biologics, U.S. Food and Drug Administration (FDA) requirements must be satisfied.

OHRP appreciates your institution's continued commitment to the protection of human research subjects. Do not hesitate to contact me if you have any questions regarding this matter.

Sincerely,

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

cc: Mr. Michael Walton, Medical Center Director, Chillicothe VAMC
Dr. Peter Frame, IRB Co-Chair, UC IRB-01/A
Dr. Frederick J. Samaha, MD, Chair, UC IRB-01/B
Dr. Margaret Miller, Chair, UC IRB-02XM
Ms. Carolyn West, UC IRB Administrator
Dr. Jay Johannigman, UC
Dr. John Mather, VA
Commissioner, FDA
Dr. David Lepay, FDA
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Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Jeffrey M. Cohen, OHRP
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