DEPARTMENT OF HEALTH & HUMAN SERVICES

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October 24, 2002

Mr. Daniel K. Nelson
Director, Office of Human Research Studies
Associate Professor of Social Medicine and Pediatrics
University of North Carolina- Chapel Hill
Chapel Hill, NC, 27599-7097

Subject: UNC Chapel Hill Request for HHS Review under 45 CFR 46.407
Re: P50 HL 60280 - Dr. R. Boucher (Grant PI) - Dr. T. Noah (Project PI)

Dear Mr. Nelson:

In a letter to Dr. Irene Stith-Coleman of OHRP, dated July 19, 2002, Dr. Terry Noah requested that a study entitled "Characterization of mucus and mucins in bronchoalveolar lavage fluids from infants with cystic fibrosis" be forwarded to the Secretary for review under 46.407. This study is a part of the P50 HL60280 SCOR grant entitled "Pathogenesis of Cystic Fibrosis" with Dr. R. Boucher as the principal investigator.

Included in the submitted materials were:

- the original protocol submitted to the IRB (11-16-01);
- the parental permission form;
- the IRB disapproval memorandum (02-05-02);
- Dr. Noah's response to the IRB (04-16-02);
- a review of the protocol by the Cystic Fibrosis Foundation's data safety monitoring board (07-01-02).

E-mail exchanges between OHRP and yourself clarified that the IRB, in fact, was requesting consideration of the protocol under 45 CFR 46.407. As a result, the OHRP 407 Checklist was forwarded on 10-11-02.

On reviewing the subsequently forwarded materials, the following missing items were noted:

- a copy of the award application and
- minutes of the IRB meetings in which deliberations regarding this study took place.

In order for HHS experts on any forthcoming panel to understand the IRB's rationale for deciding that this protocol

should be forwarded for review under 46.407, it is important to include pertinent discussion regarding the scientific value of the proposed study for furthering the understanding, prevention and alleviation of a serious problem affecting the health and welfare of children. In particular, it would be helpful to know the rationale upon which the IRB reached a conclusion that "the research is important and may alter the treatment paradigm for this group of children" and that "the IRB supports the research as a reasonable opportunity to further the understanding of pulmonary disease in cystic fibrosis...".

In addition, the IRB indicated that: (1) bronchoscopy was not indicated in asymptomatic children; (2) exclusion of children with respiratory symptoms would reduce the likelihood of detection of hidden infections; and (3) if pathogens were found and antibiotics started in asymptomatic children, early treatment could lead to resistance to antibiotics. Given these findings, it also would be helpful to know the ethical analysis of the risk/benefit ratio that resulted in an IRB determination favorable to participation of these infants in this protocol? Were other study options considered and, if found less favorable, did the IRB determine that risks to participants in this protocol were minimized to the extent possible?

Furthermore, it would assist expert reviewers to ensure that the following points are sufficiently addressed:

- section 4 of the submitted protocol states that the longitudinal bronchoscopic studies will be performed in the "bronchoscopy laboratory and PACU as per standard clinical protocol"; an explanation of the safety features provided and whether the standard clinical protocol is suitable for infants less than one year of age would be appropriate;
- section 7 and the parental permission form lists the risks of bronchoscopy; however, from these documents, it is not clear whether the percent incidences of all the potential complications pertain to infants under the age of one or represent those for the general population or if these risks and their incidence remain the same with repeated bronchoscopies performed within a relatively short period of time.
- section 9 and the parental permission form list "inducements for participation" as $350 for the child's participation and $200 for the parental participation, prorated according to completed sections of the protocol (in the parental permission form this section is called "Will you or your child be paid for participating?"); did the IRB consider this section to be coercive and that for some segments of the population the proposed sum could lead to perceived family benefit at the risk of the participating infant?
- page 5 of the parental permission form includes the statement that "your child might develop medical complications from participating in this study" and "the researchers will assist you in obtaining appropriate medical treatment"; considering that complications from bronchoscopy could include:
    - life-threatening conditions such as collapse of the lung, breathing difficulties, and transient slowing of the heart which may require immediate emergency treatments without waiting for appropriate consultations and insurance approvals and
    - secondary symptoms such as fever or worsening of breathing or cough which may also require professional attention for diagnosis and treatment both in the acute and long-term states,

  did the IRB consider it appropriate that immediate medical care would not be provided for research-related complications and that the parents would not receive financial assistance for medical and other complication-induced costs?
- in the submitted Checklist, under 408(d), it is stated that "A consent form is provided for parents. This form will be amended to obtain signatures of both parents per 46.408(b)" which is presumed to refer to parental permission for infants to participate in the proposed study; however, a copy of the amended permission document that provides for signatures of both parents has not been forwarded.

In summary, before OHRP makes a determination about convening a panel of experts, it's essential that you forward the following:

- award application and any IRB-approved summary (if any);
- minutes of the IRB deliberations; and
- final IRB-approved parental permission and parental consent forms.

Thank for your assistance in this matter. OHRP appreciates the efforts of yourself and your institution in protecting the rights and welfare of human research subjects, including the safety of infants in the proposed research. Please let me know if I can be of further assistance.

Sincerely,

Clifford C. Scharke, D.M.D., M.P.H.
Senior Advisor for Special Projects

cc: Irene Stith-Coleman, Ph.D., OHRP
Inese Beitins, M.D., OHRP