DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

[June 4, 2004]

Dr. Stephen A. Bernard
Chairman, Committee on the Protection of
the Rights of Human Subjects
School of Medicine
University of North Carolina at Chapel Hill
CB# 7097, Medical School Bldg. 52
Chapel Hill, North Carolina 27599-7097

Subject: Secretary's Determination under Department of Health and Human Services Regulations at 45 CFR 46.407 on the Research Protocol Entitled "Characterization of Mucus and Mucins in Bronchoalveolar Lavage Fluids from Infants with Cystic Fibrosis;" Principal Investigator Dr. Terry L. Noah

Dear Dr. Bernard:

This letter is written on behalf of the Acting Assistant Secretary for Health (ASH), Department of Health and Human Services (HHS). In July 2002, the Office for Human Research Protections (OHRP) received a request from the University of North Carolina, Chapel Hill (UNC) Office of Human Research Studies and Dr. Terry Noah, to review the above-cited protocol, pursuant to requirements of HHS regulations for the protection of human subjects at 45 CFR 46.407 (i.e., research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children). The proposed research protocol would be funded by the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), under grant number P50 HL 60280 (SCOR in Pathogenesis of Cystic Fibrosis), principal investigator, Dr. Richard Boucher, and has been adapted from a sub-study contained within this grant, entitled, "Project IV: Airway Surface Liquid Composition of Humans In Vivo."

In accordance with the requirements of 45 CFR 46.407, HHS solicited opinions regarding the proposed study from experts in relevant disciplines in May 2003. On June 13, 2003, a *Federal Register* Notice was published soliciting public review and comment, pursuant to the requirements of 45 CFR 46.407, for a period of 45 days. Documents related to the protocol were made available on the OHRP website, including the grant proposal, IRB protocol application, assent/permission documents, IRB deliberations on the proposed protocol, and IRB response to questions from the panel assembled under 45 CFR 46.407. One comment was received in response to the *Federal Register* Notice. The comment supported the conduct of the research if certain modifications were made to the protocol and parental permission document.

Following consideration of the research protocol, recommendations by the experts, the public comment, and the report of the NHLBI Special Emphasis Panel, the ASH found that the research may be approved under 45 CFR 46.407, and recommended that HHS support the proposed research protocol, contingent upon specific modifications to the proposed research protocol as outlined below. The proposed research protocol, if so modified, would be in conformance with 45 CFR part 46, subpart A, as well as 45 CFR part 46, subpart D, sections 46.407 and 46.408, which require that the research (i) present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) be conducted in accordance with sound ethical principles; and (iii) have adequate provisions for soliciting the assent of children and the permission of their parents or guardians. For your reference, the ASH's decision memorandum is enclosed with this correspondence.

The required modifications are as follows:

(1) clarification in the protocol and parental permission document regarding the presence of an anesthesiologist and regarding who will be present during the procedure and actually performing the procedure (by name and experience; i.e., one of three experienced pediatric pulmonologists, not a trainee);

(2) removal from protocol of the words "clinically indicated bronchoscopy" in the inclusion criteria, so that there is no suggestion that the BAL will be performed in such a way that it offers the infant the prospect of direct benefit.

(3) delineation, in both the protocol and parental permission document, of maximum amounts of sedative agents to be used, explicit description of the sedative drugs to be used and targeted level of sedation, and corresponding discussion of aborting the procedure if the appropriate level of sedation (e.g., moderate or "conscious" sedation) cannot be achieved or is exceeded;

(4) change in protocol for administration of procedural sedation to be consistent with UNC policy (i.e., infants fed formula should be NPO for six hours, rather than four (which applies only to breast fed infants));

(5) restriction in the protocol of a maximum amount of topical lidocaine to be used (7 mg/kg), to decrease the risk of lidocaine toxicity;

(6) formulation of intraprocedural stopping rules for inclusion in the protocol and parental permission document, with regard to: (a) oxygen saturation (e.g., saturation below 90% with supplemental oxygen); (b) apnea; (c) bradycardia; (d) hypotension (with sedative agents); (e) laryngospasm; (f) bleeding, and clarification that procedure may be stopped sooner than would be the case in a clinically-indicated bronchoscopy;

(7) clarification in the protocol of contraindications to bronchoscopy and BAL;

(8) provision in the protocol of a time window in which a clinically indicated bronchoscopy can substitute for a protocol bronchoscopy, and encouragement to do so whenever scientifically appropriate;

(9) inclusion in the protocol of a provision for the involvement of a research subject advocate in the enrollment process, to screen for the possibility of vulnerable parents who do not adequately appreciate the voluntariness of trial enrollment (including the right to withdraw at any time) or how the intervention will be experienced by the child;

(10) inclusion in the parental permission document of a separate check box for permission regarding future use of samples, as well as delineation of a mechanism by which samples can be removed from this repository, and statement regarding whether subject eligibility will be affected by decision to refuse sample storage;

(11) provision in the protocol for periodic review by an independent safety monitoring committee comprised of experts in CF and bronchoscopy, with a directive regarding stopping rules that would terminate the study depending on the nature and frequency of complications or adverse events (e.g., review by the CF Foundation DSMB would be suitable);

(12) removal, from both the protocol and the parental permission document, of the word "inducement" and the $50 compensation add-on for completion of the study, insofar as this may be a coercive inducement to undergo the final bronchoscopy, and, clarification that the compensation will be provided even if a bronchoscopy is stopped for safety reasons, or, alternatively, compensation for expenses only;

(13) fuller description in the protocol of the scientific necessity of three bronchoscopy procedures--first, around the time of neonatal diagnosis; again at 6 months; and a third time at 12 months--to indicate that this number was established because three is necessary to obtain the maximal amount of useful data and that limiting the protocol to fewer, e.g., two bronchoscopies at nine month intervals, would decrease the likelihood of being able to distinguish between, for example, a recent versus more remote acquisition of infection;

(14) rewording of the parental permission document to indicate that while the purpose of the study is to try and evaluate the CF airway before children develop infection, in some cases the children may, in fact, already be infected prior to the first bronchoscopy;

(15) fuller description in parental permission document of procedures and risks attendant to, for example, the NPO period, the risks of the 2% lidocaine, and the specific risks of the medications used for the procedural sedation (e.g., chest wall rigidity with fentanyl infusion), using language that will be understandable to the parents of expected subjects;

(16) provision of information in the parental permission document regarding how identity will be protected in the videotape as well as provision of a separate check box to allow videotaping;

(17) discussion in the protocol and parental permission document of what will be done in the event that the heart rate slows;

(18) provision of statement in the parental permission document that indicates that the fever associated with bronchoscopy should disappear within 24 hours;

(19) removal of any statement in the parental permission document that suggests that the study provides the possibility of direct benefit to the infant subject (for example, any statement that the BAL procedure findings might assist in determining treatment options for a subject should be removed);

(20) provision to the IRB by the PI of an assurance that the PI will initiate and obtain permission only from the parents of potential subjects for whom he does not provide treatment; and, correspondingly, where the PI is the treating physician of a potential subject, he will make arrangements so that a co-PI takes on the responsibility of presenting and obtaining permission in those situations;

(21) provision in the parental permission document and protocol of a plan for communicating general study results to the subjects' parents;

(22) simplification of language throughout the parental permission document wherever possible (e.g., "pulmonary exacerbation"would not be understood by many people); and,

(23) provision of proper contact phone numbers in the parental permission document (draft provided OHRP included a typographical error: area code "191" instead of the proper "919").

The stipulations described above must be incorporated into the research protocol, permission form, and other documents as appropriate, approved by the reviewing IRB, and confirmed by OHRP, prior to HHS funding of the research protocol and the enrollment of human subjects. Once the requested stipulations have been incorporated into the protocol and related documents and approved by the IRB, the IRB should then forward the approved protocol to OHRP. Upon confirmation that the requested changes have been made, OHRP will send a letter to the IRB and principal investigator indicating that enrollment may begin.

Please do not hesitate to contact us with any questions. Thank you for your continuing commitment to the protection of human subjects.

Sincerely,

/s/ Bernard A. Schwetz

Bernard A. Schwetz, D.V.M., Ph.D.
Director
Office for Human Research Protections

Enclosure

cc: Dr. Terry L. Noah, UNC
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