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

[May 14, 2004]

TO: Cristina V. Beato, M.D.
Acting Assistant Secretary for Health

FROM: Director, Office for Human Research Protections

SUBJECT: Recommendation for Approval of HHS Support for Research Involving Children–ACTION

ISSUE

Recommendation by the Office for Human Research Protections (OHRP) that the Department of Health and Human Services (HHS) approves, with conditions, supporting the proposed research protocol entitled "Characterization of Mucus and Mucins in Bronchoalveolar Lavage Fluids from Infants with Cystic Fibrosis," involving the enrollment of infants with a clinical diagnosis of cystic fibrosis (CF) within the first six weeks after birth. In making this recommendation, OHRP has reviewed the proposed research, considered the opinions of experts, and reviewed the one comment received after providing an opportunity for public review and comment via a *Federal Register* Notice, in accordance with HHS regulations at 45 CFR 46.407.

DISCUSSION

Background: All studies conducted or supported by HHS that are not otherwise exempt and that propose to involve children as research subjects require institutional review board (IRB) review in accordance with the provisions of HHS regulations at 45 CFR part 46, subpart D. Pursuant to HHS regulations at 45 CFR 46.407, if an IRB reviewing a protocol to be conducted or supported by HHS does not believe that the proposed research involving children as subjects meets the requirements of HHS regulations at 45 CFR 46.404 (research not involving greater than minimal risk), 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects), or 46.406 (research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition), and was suitable for review under the procedure provided in 45 CFR 46.407 (research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children), the research may proceed only if the following conditions are met: (a) the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and (b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and

comment, determines either: (1) that the research in fact satisfies the conditions of 45 CFR 46.404, 46.405, or 46.406, or (2) that the following conditions are met: (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) the research will be conducted in accordance with sound ethical principles; and (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.

In July 2002, 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. After reviewing the proposed research, the UNC IRB determined that it could not approve this sub-study under HHS regulations at 45 CFR 46.404, 46.405, or 46.406, but found the research presented a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children and was suitable for review under 45 CFR 46.407.

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." Dr. Terry Noah, the principal investigator (PI) of the adapted sub-study, proposes a longitudinal study of the changes in bronchoalveolar lavage fluid (BALF) of infants diagnosed with CF in the neonatal period. The proposed study would enroll infants with a clinical diagnosis of CF in the neonatal period and would obtain BALF from these infants via flexible fiberoptic bronchoscopy at 3 time points: (1) After diagnosis, within the first six weeks after birth; (2) at six months of age; and, (3) at 12 months of age. The goals of the proposed study are to: (a) Quantify mucin in BALF and compare quantities before infection versus after infection onset in CF; (b) correlate mucin quantity with measures of infection (quantitative bacteriology) and inflammation (cell numbers, neutrophil products, and inflammatory cytokines); and (c) isolate mucus plugs and characterize their histology before and after infection, in order to more accurately describe early relationships among mucus obstruction, infection, and inflammation. (See Tab A - Research Protocol)

Review by HHS Panel of Experts: In May 2003, OHRP assembled a panel of six experts in accordance with the provisions of HHS regulations at 45 CFR 46.407, and each provided his/her recommendation to the Secretary (See Tab B - Tabular Summary of Expert Recommendations). The experts possessed expertise in pediatric pulmonology (including CF), ethics, pediatrics, public health, law, and regulation. The panel also included a parent of a child with cystic fibrosis. All of the experts found that the research was approvable under 45 CFR 46.407.

Two of the panelists believed that, insofar as all of the subjects will have been diagnosed with CF, the research was approvable under 45 CFR 46.406 ("research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition").

All experts, as individually expressed in their reports, indicated that the research was approvable under 45 CFR 46.407, presenting a reasonable opportunity to understand a serious problem (i.e., CF) affecting the health and welfare of children. In general, the experts found that the research was not likely to directly benefit the individual subjects.

While all experts, as individually expressed, found that the protocol could be approved under 45 CFR 46.407, several experts stipulated that the protocol should be approved only after specific modifications were made to the protocol and parental permission document, and the UNC provided additional consideration to certain issues. The recommended revisions to the protocol and permission document, and the areas for further consideration included:

(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 bronchoalveolar lavage (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 have been without feeding ("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 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, a statement that future use of these samples will require a separate IRB review of the proposed use, and statement regarding whether subject eligibility will be affected by decision to refuse sample storage;

(10) 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);

(11) 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;

(12) fuller description in the protocol of the scientific necessity of three bronchoscopy procedures--first, around the time of neonatal diagnosis; again at six 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;

(13) removal from the parental permission document of the statement, "If such complications arise, the researchers will assist you in obtaining appropriate medical treatment, but any costs associated with the treatment will be billed to you and/or your insurance company," and, instead, inclusion of a statement in the protocol and parental permission document that compensation will be provided to cover the costs of any temporary or lasting complication that arises due to the study procedures;

(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);

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

(17) 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;

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

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

(20) 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, the statement that the BAL procedure findings might assist in determining treatment options for a subject should be removed);

(21) 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;

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

(23) consider 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 right to withdraw at any time) or how the intervention will be experienced by the child; and,

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

Public Review and Comment: 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, parental permission documents, IRB deliberations on the proposed protocol, IRB response to questions from the panel assembled

under 45 CFR 46.407, and the individual reports and recommendations from each expert. 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.

NHLBI Special Emphasis Panel: During the review under 46.407 of the proposed research, OHRP considered the report of the Special Emphasis Panel, the peer-review committee convened in Feb/March 1998 to review the original grant application. The Special Emphasis Panel report found no human subjects concerns with the protocol and adequate human subjects protections in place.

OHRP FINDINGS AND RECOMMENDATION:

OHRP has reviewed the research protocol, considered the recommendations provided by the experts, reviewed the report of NHLBI's Special Emphasis Panel, and reviewed the comment received from the public.

In order to approve research under HHS regulations at 45 CFR 46.404 (research not involving greater than minimal risk), the IRB must find that, among other things, the research presents no greater than minimal risk to the subjects. OHRP finds that the proposed research is not approvable under 45 CFR 46.404 because the research involves procedures that present greater than minimal risk to the subjects.

In order to approve research under HHS regulations at 45 CFR 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects), the IRB must find that, among other things, (a) the risk is justified by the anticipated benefit to the subjects; and (b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternatives. OHRP finds that the proposed research is not approvable under 45 CFR 46.405 because (a) the proposed protocol involves children who are unlikely to directly benefit from participation in the research; and (b) if there is any prospect for direct benefit for the individual subject, the risk is not justified by the anticipated benefit, and the relation of any anticipated benefit to the risk is not as favorable as that presented by available alternative approaches.

In order to approve research under HHS regulations at 45 CFR 46.406 (research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition), the IRB must find that, among other things, the risk to subjects represents a minor increase over minimal risk. OHRP finds that this research is not approvable under 45 CFR 45.406 because the risk of the research represents more than a minor increase over minimal risk.

Contingent upon IRB and investigator execution of the stipulated revisions to the protocol and parental permission document outlined below, OHRP finds that the research may be approved under 45 CFR 46.407 (research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children), and recommends that HHS support the proposed research protocol.

OHRP bases its recommendation on the reports of experts who have reviewed this research protocol under 45 CFR 46.407, the comments of the Special Emphasis Panel (which reviewed the initial grant application), the public comment received, and the requirements of 45 CFR 46, subparts A and D.

OHRP has determined that the research protocol reaches the threshold required for approval under the provisions set forth in HHS regulations at 45 CFR 46.407, 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, as set forth in 45 CFR 46.408.

OHRP finds that the research is approvable under 45 CFR 46.407 because it presents a reasonable opportunity to understand, prevent or alleviate a serious problem (i.e., CF) affecting the health or welfare of children. OHRP believes that the proposed research under grant P50 HL 60280 addresses a fundamentally important topic, namely the early pathophysiology of CF, a common, serious genetic disorder that results in life-threatening infections, and, in nearly all cases, death by early adulthood as a result of progressive obstructive lung disease. Infants with CF are born with histopathologically normal lungs, but over the first weeks or months of life begin to develop chronic bacterial infections, inflammation, and obstruction of the conducting airways. A precise knowledge of the order of early pathogenetic events may focus efforts toward early therapy interrupting the primary processes leading to established infection and inflammation in the lungs of CF patients. Furthermore, there are no appropriate in vitro or animal models in which important questions about CF pathophysiology and management can be tested and answered. As a result, understanding the fundamental pathophysiology of CF and developing strategies to alleviate its complications can only be accomplished by conducting studies in humans during the earliest stages of the disease. OHRP believes that the following specific aims of the proposed research provide a reasonable opportunity to understand the early pathophysiology of CF: (a) quantify mucin in BALF and compare quantities before infection versus after infection onset in CF; (b) correlate mucin quantity with measures of infection (quantitative bacteriology) and inflammation (cell numbers, neutrophil products, and inflammatory cytokines); and (c) isolate mucus plugs and characterize their histology before and after infection, in order to more accurately describe early relationships among mucus obstruction, infection, and inflammation in infants with a diagnosis of CF. According to the PI and experts assembled by OHRP, there is at present almost no information characterizing mucus or mucins in CF infants prior to the onset of infection and inflammation.

In determining whether the research would be conducted in accordance with sound ethical principles, OHRP has considered the relevant requirements set forth in 45 CFR 46, subpart A. Under HHS regulations at 45 CFR 46.111(a)(1)(i), the IRB must ensure that risks to subjects are minimized by using procedures which are consistent with sound research design and do not unnecessarily expose subjects to risk; and, HHS regulations at 45 CFR 46.111(a)(2) require the IRB to determine that risks are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of knowledge that may reasonably be expected to result therefrom. HHS regulations at 45 CFR 46.111(a)(3) require an IRB to determine that the selection of research subjects be equitable and that the research setting be particularly cognizant of the special problems of vulnerable research populations, including children. OHRP concludes that the investigator and IRB have taken the appropriate steps to ensure that the study population will be adequately protected.

Regarding whether adequate provisions have been made for soliciting the assent of the study subjects and parental permission, in accordance with 45 CFR 46.408, OHRP finds that the protocol, with the stipulated revisions, would include adequate provisions for soliciting parental permission, and that given the age of the subjects, assent cannot be solicited.

As stated, OHRP finds that the research can be approved under 45 CFR 46.407, with stipulated revisions to the protocol and parental permission document. OHRP has adopted all but one of the experts' recommended modifications as required changes. OHRP refers to the investigators and the reviewing IRB for action the required revisions and recommendations identified below.

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 six 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").

Separately, OHRP notes that four of the six expert panelists called for either IRB consideration of compensation or required compensation for subjects who are injured as a result of participation in the research; OHRP has not included that issue in its list of required actions.

RECOMMENDATIONS

1. Determine that HHS should support the proposed research protocol, involving the enrollment of infant subjects within the first six weeks after birth, with stipulated revisions to the protocol and parental permission document.

2. Make this decision available to the public via appropriate methods, such as placement on the OHRP web site.

DECISION

1. Determine that HHS should support of the proposed research protocol, involving the enrollment of infant subjects within the first six weeks after birth, with stipulated revisions to the protocol and parental permission document.

Approved /s/ Cristina V. Beato, M.D. Disapproved _____ Date May18, 2004

2. Make this decision available to the public via appropriate methods, such as placement on the OHRP web site.

Approved /s/ Cristina V. Beato, M.D. Disapproved _____ Date May 18, 2004

/s/ Melody Lin for

Bernard A. Schwetz, D.V.M., Ph.D.

2 Attachments:
Tab A - Research Protocol; Permission Document
Tab B - Tabular Summary of Experts' Recommendations