

## I. Brief Summary of Rationale for Protocol

The investigators seek to understand the cause and/or effect relationship between the mutation in the gene for CFTR and the production of a dysfunctional chloride ion transport protein (i.e., the genetic basis for cystic fibrosis (CF)), hypothesized abnormalities in airway surface liquid (ASL) (i.e., mucin peptides and mucus biochemistry), and chronic infection and inflammation. This understanding requires the sampling of ASL from infants with cystic fibrosis prior to and after the onset of infection and inflammation, using bronchoalveolar lavage (BAL) during bronchoscopy. There are no appropriate cell culture or animal models in which to answer this question.

Infants diagnosed with cystic fibrosis in the neonatal period will be enrolled. These include infants with meconium ileus, infants who are diagnosed early in life through genetic testing, and siblings of known CF patients who are diagnosed prior to or just after birth. The proposed sample size is 8-10 infants in order to obtain at least 4 to 5 infants without infection prior to the first bronchoscopy. The BAL will be performed three times in the first year of life, starting at less than 6 weeks of age, at 6 months and then at 12 months of age. Appropriate controls will be selected from age-matched infants without CF undergoing clinically-indicated bronchoscopy and BAL.

## II. Procedures included in the Protocol (along with a discussion of risks)

### A. Flexible Fiberoptic Bronchoscopy (with bronchoalveolar lavage (BAL))

The procedure described in the research protocol includes being NPO for 4 hours, placement of an intravenous line, and the use of 2% lidocaine for local analgesia.

The following modifications to the procedure as described in the protocol should be made in order to minimize the risks of pediatric bronchoscopy.

1. The protocol description lists “clinically indicated bronchoscopy” as an inclusion criteria, suggesting that the BAL will only be performed if it offers the infant the prospect of direct (clinical) benefit. However, the procedural description on the same page states that the bronchoscopy will be performed in a similar fashion to clinically-indicated bronchoscopy (suggesting that the bronchoscopy to be performed in this study is not clinically indicated). From the IRB discussion, it is clear that the bronchoscopy will not be limited to those performed for clinical indications. *This should be stated clearly in the protocol.*

2. The proposal does not address when the investigators would stop the bronchoscopy, such as in response to apnea, oxygen desaturation, bradycardia, and so forth. Since one or more of the bronchoscopy procedures may not offer the prospect of direct benefit (i.e., not be clinically indicated), the procedure should be stopped sooner than would be usual when performing a clinically indicated procedure of direct benefit to the infant. *The investigators need to clearly specify the criteria for withdrawal of an infant from the study during a “research only” bronchoscopy.*

3. *The maximum dose of lidocaine should be specified on a per kilogram basis (i.e., less than 7 milligram per kilogram), independent of the concentration to be used.*

4. There are no inclusion or exclusion criteria listed for the second and third bronchoscopy procedures. For example, if the infant will undergo a clinically indicated procedure, can the BAL be performed at that time? Also, if the infant is in the midst of an acute respiratory infection, and a BAL is not clinically indicated, should the BAL be deferred based on an increased risk? The investigator indicates in his response to the OHRP inquiry that infants with signs of active infection or respiratory symptoms will be excluded. *These contraindications to bronchoscopy and BAL need to be clearly defined.* In addition, it is left ambiguous whether this exclusion also applies to subsequent bronchoscopy to be performed in an infant already enrolled in the study. *The BAL should be combined with any clinically indicated procedures, and the research-only BAL should not be performed during an acute illness that increases the risks of BAL.*

5. The investigators provided data about the complication rates from the UNCH bronchoscopy suite from November 1998 to the present. During these four years, there were 2,171 procedures with 432 of these procedures being in infants less than 12 months of age. This information alone indicates that the investigators are experienced in these procedures, averaging one bronchoscopy every three or four days in the study’s target age population. The incidence of adverse events is quite low (less than 1 %), with only a few considered potentially serious. In experienced hands, these isolated adverse events can be readily handled to prevent any serious morbidity or mortality from the procedure.

6. The bronchoscopy and BAL will only be performed by one of three experienced pediatric pulmonologists, as listed on the protocol. Trainees will not be involved in these procedures. *This should be explicitly mentioned in both the protocol and the permission document.*

7. The grant proposal includes a number of other sites for which data concerning the safety of pediatric bronchoscopy have not been provided. In conversation with the investigator, it was clarified that *these sites will not be performing pediatric bronchoscopy as part of this protocol.* This clarification is important, for the data that supports the risk classification of pediatric bronchoscopy should be site-specific.

8. *The language contained in the letter from the Data Monitoring Committee of the CF Foundation that death is “virtually unheard of” from bronchoscopy requires clarification.* The chances of death are extremely remote, and usually reflect a failure to stop the procedure in the face of difficulties and/or complications. For example, the death of a healthy adult after a research-only bronchoscopy was due to a lidocaine overdose. The protocol used in that case lacked information about the proper dosing of lidocaine, and the investigators failed to withdraw the subject when difficulties arose in performing the bronchoscopy.

#### B. Procedural Sedation

The procedural sedation described in the research protocol includes premedication with chloral hydrate, followed by intravenous fentanyl and midazolam.

The following modifications to the procedure as described in the protocol should be made in order to minimize the risks of procedural sedation.

1. The presence of an anesthesiologist is not mentioned in the protocol. The guidelines for sedation and analgesia provided with the review materials is for non-anesthesiologists. *Provided that the end-point of the procedural sedation, and the medications to be used, are clearly specified in the protocol, the presence of an anesthesiologist may not be necessary to minimize risks.* The guidelines for sedation and analgesia only mention the use of ketamine, which is not appropriate for use with this protocol. Rather, the research protocol indicates that fentanyl and midazolam will be used for the procedural sedation. *A maximum dose of both agents should be specified* (such as up to 5 micrograms per kilogram of fentanyl, and 0.2 milligrams per kilogram of midazolam), *along with the dosing frequency and rate of administration* (such as administering fentanyl in 1 microgram per kilogram increments over no less than 2 minutes). *In addition, the endpoint of the procedural sedation should be specified as moderate or “conscious” sedation.* This level of sedation does not impair protective airway reflexes, nor require assisted ventilation. The procedure should be terminated (and the subject given reversal medications) if a deeper level of sedation is inadvertently achieved.

2. The policy for administration of procedural sedation indicates that infants fed formula should be NPO for six hours, rather than four (which applies only to breast fed infants). *The protocol should be changed to be consistent with UNC policy.*

This reviewer considers the fiberoptic bronchoscopy and the associated procedural sedation to present greater than minimal risk. The data presented by the investigators suggest that the bronchoscopy procedure (along with the procedural sedation) can be safely performed at UNCH. The UNC IRB determined that bronchoscopy presents more than a minor increase over minimal risk. However, no data nor specific adverse events were cited in support of the IRB claim that the “risk of bronchoscopy in an asymptomatic infant was of sufficient magnitude to be beyond that described as a minor increase over minimal risk” The probability of any adverse event is extremely low, yet there are a few isolated adverse events (i.e., laryngospasm, pneumothorax) which are of a potential magnitude that this reviewer does not consider the bronchoscopy procedure to present only a minor increase over minimal risk. It should be emphasized, however, that these events are rare, and can be handled by experienced clinicians without any serious morbidity or mortality. This reviewer considers the approach to procedural sedation outlined above to present a minor increase over minimal risk in the hands of experienced pediatric clinicians.

### III. Comments on Permission Process (Undue Influence and Coercion)

*The permission form should be re-worded to clearly indicate that the bronchoscopy and BAL will not benefit the infant.* Although Table 4 suggests that clinical decisions would be based on the results of the BAL, there is little data to support the actions taken under each scenario. In the absence of data, it is difficult to argue that the culture results may be directly beneficial to the infant in the absence of another indication for treating a pulmonary infection.

Although the amount of money seems proportional to the time and effort required for participation in the protocol, and a portion is appropriately directed to the infant, one could argue that the possibility for undue influence on the parent to enroll his or her infant should

be altogether eliminated. *The parents should be compensated for expenses only*, as an infant of this age would require adult attendance even if not enrolled in the study.

*As opposed to what is stated in the protocol, the study should be presented to a parent by an investigator who is not the infant’s primary pulmonologist.* Especially in a setting such as UNCH where bronchoscopy is a fairly routine clinical event, every attempt should be made to avoid the misconception that the bronchoscopy procedures included in this protocol are for the direct benefit of the infant.

*The descriptions of the procedures and risks in the permission form are not complete.* For example, there is no mention of the NPO period, the risks of the 2% lidocaine, nor the specific risks of the medications used for the procedural sedation (such as chest wall rigidity with fentanyl infusion).

#### IV. Additional Concerns

Why are three as opposed to two bronchoscopy procedures necessary? The scientific purpose of the protocol is to ascertain the pathophysiologic role of changes in mucin and mucous. The investigators, when questioned, indicated that if the second bronchoscopy was delayed until after chronic infection was established, it would be difficult to determine if the changes were primary or secondary to the infection. *The investigators should address the scientific necessity of the three bronchoscopy procedures in the protocol.*

*An independent Data and Safety Monitoring Committee (DSMC) should be established to review any of the adverse events that occur during the course of the research.* If an adverse event occurs, no further research bronchoscopy procedures should be performed until the AE is reviewed by the DSMC and the research allowed to continue. This reviewer considers the occurrence of any irreversible morbidity or mortality as a reason for the study to be stopped immediately. No child should ever be placed at risk of irreversible morbidity or mortality during research that does not offer the prospect of direct benefit.

One issue to be considered is whether the storage of specimens for unspecified research should be considered optional. As the bronchoscopy and BAL does not offer the prospect of direct benefit, the storage of specimens as part of the research may not be considered coercive (i.e., failure to agree to specimen storage will jeopardize the infant’s health care). There is no direct benefit within the research that would be denied if a parent did not participate in this research protocol. However, it is still appropriate to offer the choices of withdrawing the specimen from the tissue bank at some point in the future, and specifying that consent should be obtained for any future studies. The materials reviewed indicate that this issue will be handled in accord with the policies of the UNC IRB: however, no information nor documents were provided on this point. *This deficiency needs to be corrected.*

*The study should only be performed if there is compensation available for any physical injury that may occur as a result of participation in the research.* Contrary to the letter dated February 7, 2003, the UNC IRB is precisely in a position to alter institutional and/or state policy on an ad hoc basis, especially when considering approval under §46.407. Compensation for research injury is one of the essential “sound ethical principles” that must be met for any research to be considered under §46.407. The waiving of professional fees is

insufficient, as this is a small part of the total expense of caring for any research-related injury.

V. Should these studies be performed in older subjects prior to infants?

Given the fact that infants with CF become colonized and/or infected early in life, the scientific questions asked by this protocol can *only* be answered through performing a bronchoscopy during the first months of life. One can ask, however, whether it is more appropriate to study infants who present with either meconium ileus, respiratory symptoms or failure to thrive, rather than the “apparently well” infant diagnosed with cystic fibrosis through screening techniques. If, for example, infants with meconium ileus underwent a bronchoscopy at the time of surgical intervention, what would be the impact on the risks of the research, on the ability to answer the scientific question, and on the feasibility (i.e., recruitment of an appropriate sample size) of the research? In addition, do we believe parents of an infant newly diagnosed with CF will have the capacity to provide research consent under the duress of emergent neonatal surgery? Is it ethically less (or more) challenging to enroll infants with CF under these circumstance?

The grant application (signed 7-18-97) has limited applicability to the protocol outlined in the materials. In the grant application, bronchoscopy and BAL appears limited either to children with cystic who are less than 3 years of age undergoing a clinically indicated bronchoscopy or infants born with meconium ileus who would undergo bronchoscopy and BAL while undergoing surgical repair of the bowel obstruction. It is not clear why the investigators expanded on this subject population to include asymptomatic infants diagnosed with CF. There are two possible reasons. First, the need to perform follow-up BAL raises the issue of a non-therapeutic bronchoscopy anyway. Second, there may be insufficient infants born with meconium ileus at UNCH in order to achieve an appropriate sample size in a reasonable time period. *Performing the first bronchoscopy at the time of an initial surgical procedure minimizes the risks of the BAL, and should be done whenever possible. Parents should be able to provide informed and voluntary permission in spite of the duress of an urgent surgical procedure. Permission should be obtained from someone other than the clinicians caring for the infant.* This reviewer, however, would not limit enrollment to infants with meconium ileus, given the safety record of the investigators in performing pediatric fiberoptic bronchoscopy.

VI. Application of the Criteria for IRB Approval

A. Apply the general criteria of 45 CFR 46.111.

Provided that changes in the protocol are made in accord with the italicized recommendations (above), the risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk. This reviewer considers these changes in the research protocol to simply document the precautions and approaches that the investigators are likely already using in their clinical practice, given their excellent safety record. When the bronchoscopy can be performed safely (i.e., clinically indicated), it is appropriate to use procedures already being performed on the subjects for diagnostic or treatment purposes (§46.111(a)(1)). The selection of subjects is equitable, taking into account the purposes of the research and the setting in which the research will be conducted (§46.111(a)(3)). The risks to

subjects are reasonable in relation to the importance of the knowledge that may reasonably be expected to result, as there are no direct benefits to the subjects. (§46.111(a)(2)). Nevertheless, when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as infants, ... additional safeguards have been included in the study to protect the rights and welfare of these subjects (§46.111(b)), requiring us to apply the additional protections found in 45 CFR 46, Subpart D.

B. Assess the risk presented by each intervention or procedure in the proposed research.

As discussed above, the bronchoscopy and procedural sedation present more than minimal risk, and thus cannot be considered under §46.404/50.51. The bronchoscopy and procedural sedation present greater than minimal risk (§46.405/50.52 or §46.406/50.53), and thus require us to evaluate the possibility of direct benefit to the infant. This reviewer agrees with the UNC IRB that the evidence for a prospect of direct benefit is insufficient to consider the bronchoscopy under §46.406/50.53. Although the procedural sedation, taken alone, presents no more than a minor increase over minimal risk (§46.406(a)/50.53(a)); the sedation is only a means to an end and does not result in any knowledge to ameliorate the infant’s disorder or condition (§46.406(c)/50.53(c)). The fiberoptic bronchoscopy presents more than a minor increase over minimal risk, and thus requires consideration under §46.407/50.54.

Although not stated in the regulations, one could argue that a procedure not offering the prospect of direct benefit yet presenting greater than a minor increase over minimal risk should nevertheless meet the other criteria listed under §46.406/50.53. The bronchoscopy is an essential part of this research protocol, and would likely yield generalizable knowledge about cystic fibrosis which is of vital importance for the understanding or amelioration of cystic fibrosis (§46.406(c)/50.53(c)). Premature death from CF occurs as a result of chronic bacterial lower airways infection, leading to bronchiectasis and eventual respiratory failure. This research could serve as the basis for developing new therapeutic agents to improve lysis and hydration of mucus. In addition, the research presents experiences that are reasonably commensurate with those inherent in the infant’s actual or expected medical situation (§46.406(b)/50.53(b)). Apparently, the majority of infants diagnosed with CF at UNCH undergo a clinically-indicated bronchoscopy by nine months of age. Finally, based on the review and discussion of the protocol, this reviewer believes that the research does present a “reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.” (§46.407(a); 50.54(a)).

C. For all categories, consider the requirements for parental permission (§46.408;50.55).

With the italicized modifications outlined above, this reviewer determines that informed consent (that is, parental permission) will be sought (and appropriately documented) from each subject's legally authorized representative, in accordance with, and to the extent required by §46.116 and §46.117. (§46.111(a)(4,5))

D. When appropriate, there are adequate provisions for monitoring the data collected to ensure the safety of subjects. (§46.111(a)(6))

- E. When appropriate, there are adequate provisions to protect subject privacy and to maintain data confidentiality. (§46.111(a)(7))

With the italicized changes outlined above, this reviewer determines that these two criteria for IRB approval are met.

Final Recommendation:

This reviewer finds that the research under consideration does not satisfy the conditions of §46.404, §46.405, or §46.406. However, after the recommended modifications, 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) ...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 §46.408.”

Consistent with sound ethical principles guiding pediatric research, and assuming that the modifications recommended above are in fact made, the exposure of infants with cystic fibrosis to the risks of pediatric fiberoptic bronchoscopy in the proposed research is scientifically appropriate and necessary, and can be performed safely. It should be emphasized that this determination is limited to the UNCH site based on the documented experience of the investigators. The protocol should not be performed by less experienced personnel. The infant subjects will be chosen to minimize the likelihood of individual harm and maximize the likelihood of gaining knowledge that furthers the understanding, prevention, or alleviation of a serious problem specifically affecting the health or welfare of other infants with cystic fibrosis. The risks of the research to the infants are balanced by the importance of the knowledge gained. After some modifications, the research optimizes a parent’s capacity to give permission, and to understand the anticipated experience and risks of the research.