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Panel Review of Research Involving Children under Subpart D: "Characteristics of Mucus and Mucins in Broncheolar Lavage Fluids from Infants with Cystic Fibrosis"

Consultative Review—Attn: Dr. Bernard Schwetz, Dr. Irene Stith-Coleman & Dr. Leslie Ball, Office for Human Research Protections, Department of Health and Human Services

General Remarks:

The first questions to address in research involving children are "Why children" and "Why children now?" The answers to these queries establish the importance of the scientific question(s) at hand, and should also speak to (1) the competence of the investigators and (2) the integrity of their methodology. Inherent in these questions is also an assessment of the potential risks of the study to individual subjects relative to any possible individual subject benefits, as well as to the importance of the general knowledge gained. The study under review appears to be a timely opportunity to ascertain the early pathogenesis of lung disease in children born with Cystic Fibrosis (CF), a disease that is fatal in 85 to 90% of affected individuals by the fourth decade of their lives. The investigators at the Cystic Fibrosis/Pulmonary Research and Treatment Center at the University of North Carolina, Chapel Hill are leaders in the field of Cystic Fibrosis research. As clinical investigators, they can be counted among the worlds' experts in their scientific approach and in the procedures involved in the proposed study (bronchoscopy and pulmonary lavage). Their expertise is an important contingent factor in evaluating the current study; it may be approvable, for example, with these particular investigators at this particular institution but not at other institutions or with other investigators.

The investigators propose to study three research questions:

1. Quantify mucin in bronchiolar lavage fluid (BALF) and compare quantities before infection vs. after infection onset in infants with cystic fibrosis; and compare Cystic Fibrosis (CF) vs. non-CF;
2. Correlate mucin quantity with measures of infection (quantitative bacteriology) and inflammations (cell numbers, neutrophil products, inflammatory cytokines); and
3. 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.

Research in the infant is proposed since early studies by these and other investigators "suggest a short 'window' of infection and inflammation free lungs occurs in the weeks after birth in children with CF." Cystic Fibrosis is a genetic disorder involving a mutation in the gene for CFTR (a protein that transports chloride ions out of epithelial cells). The literature shows that children with CF are born with histopathologically normal lungs; however, these infants soon develop chronic bacterial infections resulting in inflammation and obstruction of the airways. The mechanism by which the CFTR defect results in these changes is not understood. The investigators hope to determine whether the absence of normal CFTR function results in a drying of airway surface liquid (ASL) due to hyperabsorption of sodium and water secondary to the lack of chloride efflux. The resultant drying impairs mucociliary clearance of inhaled bacteria and leads to chronic infection. Abnormalities of mucus biochemistry and expression of mucin peptides in CF are suggested from sputum studies and cell culture models. The question remains, however, whether CFTR dysfunction causes these abnormalities, or whether they are secondary to chronic infection and inflammation. A completely analogous animal model in which the order of pathogenic events can be established (thus leading to early therapy) does not exist.

Subjects in the proposed study would include infants diagnosed with CF who are <12 months of age (often presenting with meconium ileus). Subject recruitment would begin at age 2 months or less. Controls would include infants < 12 months of age who do not have CF but who are undergoing bronchoscopy and BALF for clinical indications. The proposed investigation is a longitudinal study of BALF changes over the first year of life in infants with CF. The subjects will be tested at three time points: (1) post diagnosis, within the first 6 weeks after birth; (2) at 6 months of age, and (3) at 12 months of age. Subjects will undergo flexible fiberoptic bronchoscopy per standard protocol at the UNC Children's Hospital. BALF will then be processed for bacterial, viral, and fungal cultures and cell counts. Remaining BALF will be stored for possible future use in other studies.

45 CFR § 46.404 Research not involving greater than minimal risk.

The study is not approvable under this category as the risks of bronchoscopy are greater than minimal risk.

§ 46. 102 (i) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

The Report from NHRPAC: Clarifying Specific Portion of 45 CFR 46 Subpart D that Governs Children's Research (2002) addresses the interpretation of minimal risk under the Common Rule. The report is under review by DHHS, and has not been adopted as guidance by OHRP/DHHS. However, this reviewer (an author of the report) finds it useful in considering and evaluating risk in children's research. The report states:

"We interpret the definition of minimal risk to be that level of risk associated with the daily activities of a normal, healthy, average child. Risks include all harms, discomforts, indignities, embarrassments, and potential breaches of privacy and confidentiality associated with the research. Conceptually, the minimal risk standard defines a permissible level of risk in research as the socially allowable risks which parents generally permit their children to be exposed to in non-research situations. Healthy children, ranging from newborns to teens, experience differing levels of risk in their daily lives. Indexing the definition of minimal risk to the socially allowable risks to which normal, average children are exposed routinely should take into account the differing risks experience by children of different ages…The interpretation of whether the level of risk is minimal should be one of 'equivalence of risk.' A test or procedure which entails minimal risk is one for which the probability and magnitude of harm associated with the test or procedure is equivalent to and no greater than the risk of events ordinarily encountered in the daily life of a normal healthy, average child, or the socially allowable risks parents permit their normal, healthy, average children to be exposed to in their ordinary lives."

45 CFR § 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

This reviewer agrees with the reviewing IRB that the research does not present the prospect of direct benefit to subjects. Contingent issues include the risks of the bronchoscopy procedure (including the intravenous line, the sedation, the use of the bronchoscope, and the lavage, bradycardia, oxygen desaturation, pulmonary infection, atelectasis or pneumothorax), the number of bronchoscopies required as part of the research, the indications for bronchoscopy in asymptomatic infants,the risk of antibiotic resistance in early treatment, and breaches in confidentiality or privacy. Generally, bronchoscopy in infants with meconium ileus occurs within twenty-four hours post diagnosis; this protocal allows for bronchoscopies up to two-to-three months post diagnosis.

45 CFR § 46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to

yield generalizable knowledge about the subject's disorder or condition.

45 CFR § 46.406 requires for approval that (a) the risk represents a minor increase over minimal risk, and (b) the intervention or procedure presents experiences to children that area reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations. The proposed research might be approvable under this category if the subject population were limited to children born with meconium ileus or CF diagnosis. Given the proposed use of asymptomatic and non-CF infants, it is not approvable under this category. Taking into account this study population, and the potential risks enumerated above, the research presents more than a minor increase over minimal risk.

45 CFR § 46.407 Research not otherwise approvable which represents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

This reviewer finds the study, "Characteristics of Mucus and Mucins in Broncheolar Lavage Fluids from Infants with Cystic Fibrosis" approvable under 45 CFR § 46.407, as explicated below.

1. **The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;**

The study question is important as there are no *in vivo* data to support ion transport in bacterial infection. The consensus among experts in the field seems to support the facts that:

   a. The research question is highly important in that it will help define the early pathogenesis of lung disease in infants with CF;
   b. The data cannot be obtained from studies with animals, adults or older children;
   c. The study design is reasonable, and the investigators are exceedingly competent;
   d. The time has come to move from *in vitro* to an *in vivo* model of research.

2. **The research will be conducted in accordance with sound ethical principles;**

• Distributive Justice: Fair distribution of potential risks and benefits among potential study populations is a justice issue that inheres in any

study. The potential for abuse or exploitation increases when subjects cannot make their own assessments of the relative risks and benefits of the proposed research, or when those assessment-making capabilities are not fully developed. Such potential subjects are, in effect, vulnerable to abuse by others. Thus, the standard practice, when feasible, of performing animal studies prior to human studies (although one could argue the biological or philosophical underpinnings of this approach), of studying adults prior to children, older children prior to younger children, and those with full decisional capacity prior to those with impaired or no decisional capacity. The study population at hand, children < 12 months of age, is, by definition, a vulnerable population.

Subject selection is equitable given the epidemiology of Cystic Fibrosis. Gender distribution is equal; Caucasians will outnumber African-Americans and Hispanics 20:1. No subjects or classes are being systematically selected because of easy availability, compromised position, or manipulability. The potential subjects have been selected for reasons directly related to the problem being studied or, as controls, include children who will already undergo the procedure for clinical, not research, indications.

• Compensatory Justice: The consent document states that, in the event of research-related injury, investigators 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." Although compensation for research injury is not required by regulation, virtually all federal human research advisory committees have recognized it as a moral duty owed by the sponsors of the research. The study sponsors (National Institutes of Health), investigators, and research institutions should consider mechanisms for compensation for research injury. [Institute of Medicine report, Responsible Research: A Systems Approach to Protecting Research Participants (2002): Recommendation 6.8: Compensate any research participant who is injured as a direct result of participating in research, without regard to fault. "Because the contributions of science benefit society as a whole, it seems indisputable that society is obligated to assure that the few who are harmed in government-sponsored scientific research are appropriately compensated for study-related injuries...the same argument applies to privately funded research." pg. 188. See also: Advisory Committee on Human Radiation Experiments, 1995; Department of Health, Education and Welfare, 1977, National Bioethics Advisory Commission, 2001 a,b; President's Commission, 1982).

• Amelioration of Risk:

In the absence of direct benefit, risks to the subjects should be balanced by the importance of the knowledge gained to further the understanding, prevention, or alleviation of a serious problem specifically affecting the health or welfare of other children. Given the age of the participants and the seriousness of their disease, this reviewer recommends the constitution of an independent Data and Safety Monitoring board to advise the investigators on an assessment of whether the study is adequately powered, on data accrual, on stopping rules and on adverse event assessment. [Institute of Medicine report Responsible Research: A Systems Approach to Protecting Research Participants (2002); Recommendation 5.6: Ensure an independent Data and Safety Monitoring Board/Data Monitoring Committee is assigned to high-risk studies or those involving participants with life-threatening illnesses]. Although the Cystic Fibrosis Foundation DSMB has reviewed and supported this study, there are currently no plans for it to serve as its DSMB.

The Report from NHRPAC: Clarifying Specific Portion of 45 CFR 46 Subpart D that Governs Children's Research (2002) also addresses amelioration of risk under the Common Rule. The report is under review by DHHS, and has not been adopted as guidance by OHRP/DHHS. However, this reviewer (an author of the report) finds it useful in considering and evaluating risk in children's research. The report states:

"…the experience of the investigator and research team as well as the setting of the research may influence the level of risk experienced by the subjects. In some settings an IRB might consider certain risks as a minor increase over minimal while the same risks in another setting would be more than a minor increase over minimal."

As stated above in the General Comments section, the members of this investigative team is are leaders in the field of Cystic Fibrosis research. They are experts in their scientific approach and in the procedures involved in the proposed study (bronchoscopy and pulmonary lavage). The study, which was originally proposed at three sites, has been amended to take place only at the Cystic Fibrosis/Pulmonary Research and Treatment Center at the University of North Carolina, Chapel Hill. The bronchoscopy and lavage should be performed only by members of the investigating team, and the sedation only by their consulting anesthesiologist.

3. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.

The age range of the prospective subjects (< 12 months) precludes assent procedures. Permission of the parents is required. All consent and any educational materials should be available to non-English speaking

parents in their languages, and translators should be available during the consent process, and at each visit required under the protocol.

Written Consent Document:
• The document should explicate what “medicine” will be given for sedation prior to bronchoscopy. It should also state that sedation will be administered by an anesthesiologist.
• It is possible that parents of asymptomatic children may interpret bronchoscopy as a benefit; the lack of individual subject benefit in this context should be clarified.
• Use of the term “inducement” in the recruitment section of the protocol is inappropriate. Subjects may appropriately be compensated for their participation in the study. Their parents may be compensated for their time and travel expenses. Parents should not, however, receive money directly for their child’s participation in the study. Compensation for the child should not be prorated for completion of the study, as this may be coercive.
• Re: Storage of BAL fluid for future research; the investigators should consider a separate consent document for this. It should specify that the parents or the child may be contacted in the future for permission to use the specimen in research unless the data are anonymized.
• Some of the language in the document needs to be simplified; for example, the phrase “pulmonary exacerbation” is not targeted to the 8th grade reading level.
• The section addressing the subject’s privacy should state how and where the data will be stored, and who will have access to them.
• The written consent document (and the protocol) should explicate a dissemination plan for communicating general study results that includes subjects (parents).

Other:

• The protocol does not, and should, specify the target level of sedation during the bronchoscopy.
• The reviewer commends the investigators, especially Dr. Noah, for his thoughtful and collegial responses to inquiries by the local IRB, and by the 407 Review Panel.

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