

Report as Member of Expert Panel to Consider Research Involving Children under 45 CFR46.407

Date of Meeting May 5, 2003

Date of Report May 16, 2003

Expert panel member: George B. Mallory Jr. MD

Research Protocol: "Characterization of mucus and mucin in bronchoalveolar lavage fluids from infants with cystic fibrosis", University of North Carolina at Chapel Hill, Terry Noah, MD, Principal Investigator (PI)

I will provide my recommendations in what I hope will be logical flow based on materials provided to us as panel members by our Chairman, Dr. Nelson.

I believe that this protocol is an appropriate one to be considered under the provisions of the 407 regulations because I believe that the elective flexible bronchoscopy used in the research three times in the first year of life in 8 to 10 CF infants is a procedure with risks "greater than a minor increase over minimal risk.

I will further discuss the research project point by point as follows:

1. its research design presents a reasonable opportunity to further the understanding of an important aspect of cystic fibrosis-related lung disease, which, in turn, could lead to measures which would ameliorate the disease process.

Comment: All subjects will, by inclusion criteria, have a clear diagnosis of CF and will be at least a few weeks of age. It is likely that half or more of the infants will have minimal, if any infection and the first bronchoalveolar lavage fluid (BALF) specimen will have minimal inflammation or infection. The PI confirmed to us that approximately 75% of CF infants in their care center undergo elective bronchoscopy because of suspicion of lower respiratory tract illness in the first year of life. Thus, at least ¾ of the subjects will likely have at least one of the three planned protocol procedures at a time of illness, which would fulfill the research design for a post-inflammatory sample.

Although the portion of the research protocol that was available to us did not contain the methodologies for mucus analysis, the UNC center is the leading CF research center in the world related to airway secretions in CF. In short, with the specimens obtained per protocol, there is a high likelihood (REASONABLE OPPORTUNITY) of cutting edge knowledge with respect to mucus constituents in early infancy which have never been described to date.

To a person like me with deep clinical experience in the field, it is clear that lung disease in CF is A VERY SERIOUS PROBLEM. Lung disease is the cause of mortality in over 90% of people with CF and there is growing information that lung disease begins to be established in many patients in the first year of life. Mucus plugging is an understudied aspect of the early lung disease.

2. the research design is in keeping with high ethical standards;

Comment:

a) My only reservation about the research design from the ethical perspective is the identity of the physician presenting the research protocol and obtaining consent from the parents. At and shortly after the diagnosis of CF in infants, the parents are usually in a state of grief and dependence. The parents would have good reason to regard the treating CF physician with great hopes for potential treatments and cures. It would be ethically more appropriate, in my opinion, for the PI, if he is not the treating physician, to present and obtain the consent. If the treating physician is the PI, then the Co-PI should take on that responsibility. Because of the outstanding technical abilities and track record of the physicians at UNC in infant flexible bronchoscopy, the risks are, in my opinion, just barely over the minor increase over minimal risk, which should trigger a 407 panel. I do believe that the risk of untoward outcome to any of the infants is extremely low.

b) On another aspect of the ethical issues involved here, it is extremely unlikely that mucus analysis from an older cohort of CF subjects would provide the same kind of basic insights into mucus before and after the first infectious illnesses. From this vantage point, infants with CF are the only appropriate target population. The identification of the control group is quite straightforward and there are no risks to them as they will, by definition, already be undergoing intravenous sedation and flexible bronchoscopy.

*c) The protocol and facilities at the research center minimizes the risk to the infants (covered above) and because BALF is so commonly used in 75% of CF infants in this center to obtain clinically applicable information, there is a reasonable chance of obtaining information that will be a direct benefit to **some** of the infants involved.*

d) The risk of this procedure in the investigators' hands is just beyond the minor increase above minimal risk, in my opinion. Given that risk, the high likelihood of general information which will be of use to the general CF population, especially children developing early stages of lung disease, and the lesser but still reasonable chance of direct benefit to the individual subjects, the research meets ethical standards.

3. there is no possibility of obtaining assent from infant subjects for obvious reasons.

Comment: *Clearly, infants cannot give assent to anything other than a feeding!*

Respectfully submitted _____