

May 19, 2003

Bernard Schwetz
Acting Director
Office for Human Research Protections
Department of Health and Human Services
The Tower Building
1101 Wooten Parkway, Suite 200
Rockville, MD 20852

RE: Subpart D Panel Review, “Characterization of Mucus and Mucins in Bronchoalveolar Lavage Fluids from Infants with Cystic Fibrosis”

Dear Doctor Schwetz:

Thank you for the opportunity to review this important protocol. Having thoroughly considered the information provided, I conclude that this trial, involving repeat bronchoscopies of infants with cystic fibrosis, is not approvable under 45 C.F.R. § 46.404, 46.405, or 46.406 (also 21 C.F.R. § 50.51, 50.52, or 50.53). I believe the research is approvable under 45 C.F.R. § 46.407 (and the corresponding 21 C.F.R. § 50.54), but additional safeguards are required to ensure the voluntariness of the parents in their consent to enrolling their very young children in this research. The following discussion addresses why this protocol should not be characterized as one that offers the prospect of direct benefit to the trial participants, and expresses concern over the investigators’ suggestion that this research should be labeled beneficial. Nevertheless, I believe the protocol is well designed to answer a crucial research question that could have significant ramifications in the prophylaxis and treatment of cystic fibrosis. The trial should be permitted to go forward, with some modification.

I. The protocol is not approvable under 45 C.F.R. § 46.404, 46.405, or 46.406 (also 21 C.F.R. § 50.51, 50.52, or 50.53)

This protocol was appropriately referred to the OHRP for review under § 46.407, per the judgment of the institutional review board (IRB). Given the intervention involved to accomplish the lavage, including the risk of both sedation and bronchoscopy, this protocol is clearly greater than minimal risk. Even if it were the case that this procedure was the standard of care for infants with cystic fibrosis (a debatable point), it would still pose a greater than minimal risk as it is not one that would normally be encountered in the course of a child’s daily life. As such, the protocol is not approvable under § 46.404.

Given a finding of more than minimal risk, a protocol may also be approved if it offers “the prospect of direct benefit to the individual subjects.” § 46.405 The investigators here suggest that participation in this protocol offers the prospect of direct benefit to the patient because preclinical diagnosis of airway inflammation and pathogen infection might provide the opportunity for early intervention, generally in the form of intravenous antibiotic treatment. The incremental difference that enrolling in this trial would make in prompt diagnosis of respiratory infection is not such a significant benefit to outweigh the risks of three bronchoscopy procedures in the first year of life. Moreover, there is a real question in clinical management of cystic fibrosis as to whether such early, presymptomatic treatment of cystic fibrosis is likely to improve the quality of life in these patients. Data supports the assertion that the longer chronic infection (e.g. with *pseudomonas aeruginosa*) can be staved off, the better patients do clinically over time.

But it is not clear that preclinical treatment with antibiotics will have similar therapeutic benefit. Like the IRB, I would express concern about the possibility of resistant strains of infection developing in patients who are persistently treated with intravenous antibiotics so early in life. In staving off the early effects of this chronic, degenerative disease, clinicians may be inadvertently limiting treatment options for patients twenty, thirty or forty years down the line. I think the possibility of this eventuality should be taken seriously. As such, I believe that the suggested direct benefit of participation is invalid as it pertains to this protocol. Consequently, this research should not be approved under § 46.405.

At the IRB level, this protocol comes closest to being approvable under § 46.406, “Research involving greater than minimal risk and no prospect of direct benefit to the individual subjects, but likely to yield generalizable knowledge about the subject’s disorder or condition.” This protocol clearly targets an important research question that can only be answered by inclusion of newborns with cystic fibrosis. The results of this research will no doubt provide information that will direct the development of treatments to ameliorate the severity of this disease in future, and possibly present, patients. However, in approving research under this prong it is necessary to conclude that this research poses “no more than a minor increase over minimal risk.” Because I conclude that the increase over minimal risk is more than minor, I do not believe the research is approvable here.

Many medical interventions required in early treatment of cystic fibrosis already pose a greater than minimal risk. While it may not yet be the standard of care to perform a baseline bronchoscopy upon a diagnosis of cystic fibrosis (usually within the first year of life) in the absence of a clinical exacerbation, there is a trend towards incorporating this intervention into routine initial assessments. A single bronchoscopy alone might meet the test of minor increase over minimal risk, especially at a CF Center with as excellent a safety record as UNC. But repeat bronchoscopies, a series of three, would rarely be clinically indicated and as such, I could not call subjecting these very young patients to multiple interventions only a minor increase over minimal risk. Thus, the research should not be approved under § 46.406.

II. The protocol can be approved under 45 C.F.R. § 46.407 (and 21 C.F.R. § 50.54), with modifications.

Cystic fibrosis is a serious condition that drastically reduces the life expectancy of the affected population. It is indeed vital to understand the early biochemical mechanisms that spur the inevitable lung disease to take hold and progress. Answering a question as basic as whether infection or inflammation represent the initial manifestation of disease shortly after birth is essential to development of the most effective next generation of therapies. The UNC group has been particularly active in developing clinical data to answer this and like research questions and this study is the logical next step in their investigations. Reviewing the scientific information, I found it persuasive that this research could only be conducted in infants with cystic fibrosis who are diagnosed shortly after birth, either because of a prenatal diagnosis, neonatal testing or a diagnosis of meconium ileus. Moreover, the structure of the protocol, conducting bronchoalveolar lavage at three points during the first year of life to pinpoint the onset of inflammation, infection and other symptomology, seems appropriate, given that the same information could not be learned on the basis of one or even two bronchoscopies. Nor could upper airway samples provide the evidence of biofilms that the investigators seek. As such, the

research does present “a reasonable opportunity to understand, prevent or alleviate a serious health problem” affecting the cohort of children with CF.

In assessing whether this protocol will be conducted according to sound ethical principles, I think it is especially challenging to approve a protocol that poses more than a minimal risk in an affected population that is uniformly unable to assent to participation. I do not find the argument that these infants will not recollect their research experience, and any trauma associated with the bronchoscopies, a mitigating factor in this concern. It seems to me that parents and pediatric patients with chronic disease do have distinct interests, especially in the case of a genetic disease where family members may feel some burden of responsibility for the child having the condition. Adult CF patients would reasonably refuse participation in a protocol such as this based on its considerable discomfort; parents seeking optimal therapy for their newborn child may be less sensitive to this consideration.

The patients under eligibility here and their parents are especially vulnerable. While I would not usually characterize a patient suffering from a chronic, degenerative condition as necessarily vulnerable, in this case, where patients are being recruited shortly after a devastating diagnosis, they are. Parents arriving with newborns at CF Centers may feel particularly bewildered in appreciating a distinction between research and therapy, especially where the clinician managing their child’s care is responsible for introducing the protocol and securing consent for enrollment. Parents of these children, even moreso than most patients seeking treatment for chronic conditions, will be wanting to please the clinicians responsible for their child’s care. Furthermore, they are newly initiated into a patient population vigorously invested in the results of clinical research, and somewhat inclined to view research participation as a duty, when offered.

Given the somewhat precarious position of the parents, I am especially concerned that the clinicians at UNC, among the most sophisticated in the treatment of CF, will inadequately distinguish participating in this protocol from the standard of care. It would be easy for the clinicians to say that this intervention is far less risky than a bowel resection that a protocol candidate may have already undergone, or to say that the patient will likely have to undergo a bronchoscopy sometime in the first year of life anyway. These are not appropriate qualifiers in seeking consent for a *research* protocol. Likewise, though UNC has adopted the posture of aggressively treating early infection in CF patients, insinuating a likelihood of benefit for these patients, as discussed earlier, would be disingenuous.

In order for this protocol to meet the ethical standards appropriate for conducting a protocol pursuant to approval under § 46.407, there must be some change in the informed consent document and process. Any mention of direct benefit to the patient must be purged from the consent document. An investigator who is not the clinician assigned to the potential enrollee should be invited to initially present the protocol to the parents, making it evident that the research intervention is distinct from standard therapy. Finally, the investigators should give serious consideration to involving a research participant advocate in the enrollment process for this protocol, to screen for the possibility of vulnerable parents who do not adequately appreciate the voluntariness of trial enrollment or how the intervention will be experienced by the child. The option not to participate and the ability to withdraw from the protocol at any time should be emphasized. **If these concerns can be mitigated, I conclude that this important research should be approved under § 46.407.**

Other issues:

- The component of the consent that provides for storage of the biofilm samples is currently inadequate as to specifying the scope of use of samples, the duration of their storage, and apprising the patients/parents of their right to withdraw the samples from research in the future. See National Bioethics Advisory Commission, *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*, at <http://www.georgetown.edu/research/nrcbl/nbac/hbm.pdf>.
- In general, I am not concerned about the compensation mechanism being employed in this protocol. I believe the level of compensation to the parents, for the demands of bringing their child to UNC for participation, is appropriate. Furthermore, I believe compensation in general, and that directed at the child participant, has the effect of emphasizing the investigatory nature of trial enrollment. The amount is not coercive, however it is always inappropriate to provide bonus money for completion of the trial and that element should be eliminated from this scheme.
- In terms of the performance of the bronchoalveolar lavage, I have mentioned that the data on the experience of the UNC group is excellent. As such, I do not believe it is essential to have a separate anesthesiologist included in the research procedures. However, I think those conducting the bronchoscopies should err on the side of withdrawing from the procedure when adverse effects are demonstrated. How the investigators will deal with a patient who has an adverse event in the course of bronchoscopy may be important to lay out in the consent form, e.g. will this necessitate withdrawal?
- Finally, especially where the research is being approved under the ethical requirements of § 46.407 review, there should be a mechanism for compensation of research injury in place. It is not adequate to say that the donation of physician time could address this concern, given the institutional costs of prolonged medical management, if required. It is also not adequate to say that UNC is limited by law in providing adequate compensation. A mechanism must be established.

In closing, I want to thank these innovative researchers for their tenacity and insight in pursuing the early mechanisms of this very difficult disease. As someone who has had familiarity with the treatment of CF for three decades, I found the discussions surrounding this protocol inspiring and illuminating. However, I wish to flag an issue of clinical management that came to concern me during the discussion, which is the persistent medicalization of the lives of children with cystic fibrosis. It is possible that some patients will not benefit socially or personally from aggressive presymptomatic treatment early in life. Patients may come to conceive of themselves as more sick than able in this environment, thus self-limiting in their aspirations. Severity of disease differs widely in this diagnosis and may impact the appropriateness of this concern, but I urge clinicians to be vigilant in monitoring the extent to which aggressive care hinders some degree of normalcy in patient lives. While I admire the conviction to extend life in this population, living full lives may be preferable to living longer lives for some of these patients. Thank you again for inviting my opinion on this protocol.

Sincerely,

Rosemary B. Quigley, JD, MPH
Baylor College of Medicine