Improving Patient and Parent Understanding of Safety Monitoring in CF Clinical Trials

Andrew Kern-Goldberger, PGY-2
PI: Dr. Lisa Saiman

1. Study Purpose and Rationale

Cystic fibrosis (CF) is an inherited disease that compromises function of the lungs and digestive system. The Cystic Fibrosis Foundation (CFF) has been instrumental in both facilitating and performing clinical trials to improve the health and quality of life for individuals with CF, of whom 28,676 are active in the CFF Patient Registry as of 2014.[1] These trials are supervised for safety at multiple levels of regulation – including by the U.S. Federal Drug Administration, the CFF Therapeutics Development Network, local Institutional Review Boards, and the CFF Data Safety Monitoring Board (DSMB). However, given the complexity of the illness, participants in CF clinical trials have adverse events at relatively high rates, even when enrolled in the placebo arms of studies.[2] The CFF DSMB – an independent committee including CF-specific physicians, bioethicists, statisticians, and patient representatives – was specifically established to provide an additional layer of protection for study participants. Clinical trials sanctioned by the CFF Therapeutics Development Network are assigned a study specific Data Monitoring Committee (DMC) that has the unique ability to monitor, modify or stop studies based on access to unblinded data.[3] In spite of the aforementioned safety measures, patients still cite their concerns over safety as a principal barrier to enrolling in a clinical trial. In a recent survey of 760 adults with CF and parents of affected children, 32% of respondents identified concern over possible negative side effects from an investigational agent as a reason not to participate in a CF clinical trial.[4]

The need to address and overcome these barriers is particularly pronounced among Hispanic patients with CF. Despite having the same CF mutations as non-Hispanic patients, Hispanic patients may have increased morbidity and mortality.[5] Hispanic patients are often under-represented in CF clinical trials; therefore, study findings may not be generalizable to Hispanic individuals with CF.

Consequently, the CFF DSMB has developed a pilot brochure, ***How Is Your Safety Protected in A Clinical Trial?***, to educate patients and their families about how their safety is protected in CF clinical trials. Our study team at Columbia University Medical Center (CUMC) is currently performing structured, audio-recorded interviews with adolescents and adults with CF and parents of children with CF cared for at CUMC to obtain qualitative feedback on how effectively the pilot brochure addresses concerns regarding patient safety monitoring in CF clinical trials. Once this feedback has been used to revise the brochure, the proposed study will be conducted in order to evaluate the impact of this brochure on CF patient and parent *knowledge* of patient safety monitoring during clinical trials, *attitudes* toward patient safety monitoring, and the potential influence of safety concerns on *practice*, i.e., participation in trials.

The specific aims of this study are as follows:

1. To develop and pilot test a knowledge, attitudes, and practices (KAP) survey assessing patient safety concerns as a barrier to participation in CF clinical trials.
2. To administer the KAP survey at three CF centers.
3. To assess the impact of the brochure on barriers to participation in CF clinical trials.

We hypothesize that CF patients and parents who receive the brochure will have increased knowledge about patient safety monitoring, fewer attitude barriers to participation, and higher rates of anticipated future clinical trial participation than those who do not receive the brochure. If our hypothesis is correct, this educational tool could be used in CF centers across the U.S. to improve participation in CF clinical trials.

2. Study Design and Statistical Procedures

In this prospective, interventional, randomized study, an anonymous and confidential survey will be administered at three CF centers serving diverse CF patient populations that include Hispanic patients. The KAP survey will be developed in consultation with experts in CF care and survey development. It will first be pilot tested at CUMC, first among 8-10 non-CF respondents with content expertise and then among 8-10 individuals with CF cared for at the pediatric center (Sue and John L. Weinberg CF Center) and the adult center (Gunnar Esiason Adult CF and Lung Program). Feedback ascertained from pilot testing will be used to revise the survey, as needed, prior to multicenter administration.

The KAP survey will then be administered to 150 respondents at 3 CF centers including the CUMC pediatric and adult centers; pediatric (Maria Fareri Children's Hospital) and adult centers at New York Medical College / Westchester Medical Center (Valhalla, NY); and pediatric (Ann and Robert H. Lurie Children's Hospital) and adult centers at Northwestern University (Chicago, IL). Respondents will be recruited from three categories: ~1/3 will be parents of children with CF <16 years, ~1/3 will be adolescents and young adults with CF 16-21 years and ~1/3 will be adults with CF $\geq$ 22 years. Respondents will be randomly assigned to receive or not to receive the brochure prior to completing the survey. Randomization will be stratified by study site and by the above respondent categories.

The survey will collect demographic characteristics (e.g., age, sex, ethnicity), clinical characteristics (e.g. previous hospitalizations, previous participation in clinical trials), and questions assessing knowledge, attitudes, and practice barriers (see "Study Questionnaires" below). These questions will utilize 4-point Likert scales (e.g., "strongly disagree" to "strongly agree") and forced-choice formats (e.g., true/false). Likert responses will be dichotomized.

Composite scores specific to questions addressing knowledge barriers, attitude barriers, and practice barriers – as well as an aggregate "KAP score" summing responses to questions across all three barrier types – will be computed. Multiple regression analysis will be performed to compare KAP scores between the "brochure" and "no brochure" groups as well as additional variables (e.g., site, pediatric vs. adult center, patient age, patient vs. parent, language of test administration, prior clinical trial participation, prior hospitalizations) that may be associated

with KAP barriers and future participation in clinical trials. Statistical significance will be set at $p \leq 0.05$.

3. Study Procedures

At Columbia University Medical Center, the study will be conducted at the Sue and John L. Weinberg Cystic Fibrosis Center and Gunnar Esiason Adult Cystic Fibrosis and Lung Program in conjunction with routine CF clinic visits. After written informed consent and/or assent is obtained from each respondent, the survey will then be administered to the patient and/or parent. Written study materials will be translated into Spanish and an interpreter will be available throughout research-related procedures. Paper surveys will be used; not all CF clinics have Internet access to administer online surveys. Incentive for participation will be provided in the form of a $25 gift card.

4. Study Drugs or Devices

N/A

5. Study Questionnaires

The KAP survey will use the paradigms pioneered by Cabana and others,[6,7] and previously used in the cystic fibrosis population.[8,9,10] In this model, KAP barriers are explored as barriers to a desired outcome, e.g., adherence to treatment guidelines; or in the current study, participation in future CF clinical trials. The domains explored include: *knowledge* barriers (lack of awareness or understanding); *attitude* barriers (lack of agreement, lack of self-efficacy [confidence], or lack of outcome expectancy [impression that patient outcomes will improve]); and *practice* barriers (lack of time, inconvenience, or lack of reimbursement).[7]

Representative survey questions include the following:

- In CF drug studies, my doctor knows which patients are getting the drug or placebo (inactive drug). *(**true**; forced-choice, knowledge measure)*
- I can withdraw (my child) immediately from a CF drug study if I (he/she) has side effects. *(**true**; forced-choice, knowledge measure)*
- I worry about my (my child's) safety when I (my child) participate(s) in a clinical trial. *(Likert scale, attitude measure)*
- I am confident that my (my child's) safety is being closely monitored during a CF drug study. *(Likert scale, attitude measure)*
- I plan to ask my CF care team about CF drug studies that I (my child) may qualify for. *(forced-choice, practice measure)*

6. Study Subjects

The inclusion criterion for this study is confirmed CF diagnosis. The only exclusion criterion is non-fluency in the English or Spanish language. Participants will include parents of children with CF <16 years, adolescents and young adults with CF 16-21 years, and adults with CF $\geq$ 22 years.

Fifty respondents per site reflects a realistic recruitment goal. By comparing KAP scores between 75 individuals each in the "brochure" vs. "no brochure" groups, the study is powered to detect a difference in KAP score of the magnitude (0.46 * SD).

7. Recruitment

Patients and/or parents will be informed of the study by their primary CF physician and then contacted by telephone by the one of the investigators. The study will be explained over the phone and for those in the "brochure" group, a copy of the brochure will either be mailed or emailed to the patient/parent as per their preference for their review prior to a scheduled clinic visit.

8. Confidentiality of Study Data

Surveys will be conducted in a private space within the CF Centers with only the participant (and child, if applicable) and members of the research team present. The results of this study will remain confidential and coded, and only used for research purposes by the designated research team. No identifiers will be maintained. Each subject will have a study number (01, 02 etc) and notation will be made if they are a pediatric patient, adult patient or parent. Study numbers will be assigned sequentially by the PI. Study materials, including surveys, will be destroyed following publication of the data. The research information that is shared with people outside of Columbia University Medical Center and New York-Presbyterian Hospital will not include the participant's (or child's, if applicable) name, address, telephone number or any other direct identifier unless disclosure of the information is required by law or the disclosure has been authorized by the participant.

9. Potential Risks

There are minimal risks associated with this study. There is a potential of loss of confidentiality but the study team plans to protect confidentiality of study data as described in the protocol. No identifying information will be collected. Study subjects might feel uncomfortable answering questions but they are free not to answer any question.

10. Potential Benefits

There are no anticipated direct benefits to patients or the families for participating in this study. Indirect benefits include improved knowledge of how safety is protected in CF clinical trial and the potential to contribute to improved education methods for people with CF.

11. Alternatives

There are no alternatives.

References:

[1] Cystic Fibrosis Foundation Patient Registry 2014 Annual Data Report. Bethesda, Maryland: Cystic Fibrosis Foundation; 2015.

[2] Sucharew H, Goss CH, Millard SP, and Ramsey BW. Respiratory adverse event profiles in cystic fibrosis placebo subjects in short- and long-term inhaled therapy trials. *Contemporary Clinical Trials* 2006 Dec;27(6):561-570.

[3] Goss CH, Mayer-Hamblett N, Kronmal RA, and Ramsey BW. The Cystic Fibrosis Therapeutics Development Network (CF TDN): A paradigm of a clinical trials network for genetic and orphan diseases. *Adv Drug Deliv Rev.* 2002 Dec 5;54(11):1505-28.

[4] Retsch-Bogart G. "Opening Doors to CF Clinical Research: Change Is Coming" (Plenary Session #2). Presented at the 2015 North American Cystic Fibrosis Conference, 9 Oct 2015, Phoenix, AZ.

[5] Watts KD, Seshadri R, Sullivan C, McColley SA. Increased prevalence of risk factors for morbidity and mortality in the US Hispanic CF population. *Pediatr Pulmonol* 2009;44:594–601.

[6] Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282(15):1458–1465

[7] Cabana MD, Ebel BE, Cooper-Patrick L, Powe NR, Rubin HR, Rand CS. Barriers pediatricians face when using asthma practice guidelines. *Arch Pediatr Adolesc Med* 2000;154(7):685–693.

[8] Garber E, Desai M, Zhou J, Alba L, Angst D, Cabana M, Saiman L. CF Infection Control Study Consortium. Barriers to adherence to cystic fibrosis infection control guidelines. *Pediatr Pulmonol* 2008;43(9):900–907.

[9] Miroballi Y, Garber E, Jia H, Zhou JJ, Alba L, Quittell LM, Angst D, Cabana M, Saiman L. Infection control knowledge, attitudes, and practices among cystic fibrosis patients and their families. *Pediatr Pulmonol* 2012;47(2):144–152.

[10] Zhou JJ, Patel SJ, Jia H, Weisenberg SA, Furuya EY, Kubin CJ, Alba L, Rhee K, Saiman L. Clinicians' knowledge, attitudes, and practices regarding infections with multidrug-resistant gram-negative bacilli in intensive care units. *Infect Control Hosp Epidemiol* 2013;34(3):274-283.