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Effects of clinical research participation on disease progression in cystic fibrosis

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EFFECTS OF CLINICAL RESEARCH PARTICIPATION ON DISEASE PROGRESSION IN CYSTIC FIBROSIS

by

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EFFECTS OF CLINICAL RESEARCH PARTICIPATION ON DISEASE PROGRESSION IN CYSTIC FIBROSIS

ROBERT FOWLER

ABSTRACT

CF is an autosomal recessive disorder caused by mutations in the CFTR gene. The life expectancy for patients with CF remains severely shortened, with the median predicted survival for patients currently estimated at 36.5 years. For patients with a life-limiting disease such as CF, the decision to participate in a clinical trial is often based on the desire to improve quality of life and/or increase the likelihood of long-term survival. Recent advances in CF care have increased the number of therapies available for CF patients which in turn has increased life expectancy and diminished disease progression.

The CFF has developed a patient registry and has worked with individual CFF-accredited care centers in the US to approach all patients followed at these CF centers to participate in an observational prospective cohort study. Using data from 504 patients followed at Boston Children’s Hospital and submitted to the data registry maintained by the CFF, we examined disease progression, as measured by the decline in pulmonary function tests between 2007 and 2012 and compared multiple subsets of CF patients: those who participated in interventional studies, those who participated in observational studies only, and those who did not participate in any research studies. Results suggest a lower amount of lung function decline for adults who participate in interventional trials; however, the opposite pattern is true for children, with a higher amount of lung function decline seen for children who participate in interventional trials.
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INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CF is one of the most common inherited diseases affecting approximately 28,000 patients in the United States and approximately 36,000 patients across the world.¹ CF is the most common fatal genetic disease in persons of European descent² (and estimated survival in the US is reported as 36.5 years.³ The mutations in CFTR cause reduced chloride transport, as well as associated water transport abnormalities because of increased viscosity of the secretions and exocrine gland dysfunction across the epithelium in the lungs, pancreas, liver, and intestines.

CF primarily affects the lungs but also affects multiple other organs including the paranasal sinuses, intestines, and liver. Reduced chloride transport across the cell membranes results in a build-up of tenacious mucus in the lungs of CF patients, as well as pancreatic enzyme insufficiency, hepatic and biliary abnormalities, intestinal obstruction, and reduced fertility due to absence of the vas deferens in males and delayed puberty/menarche in females. This abnormal mucus leads to increased cycles of infection and inflammation of the airways leading to progressive and irreversible lung damage, predominantly bronchiectasis. CF patients usually require intensive, lifelong therapy including oral and inhaled medications, antibiotic treatment, and digestive enzyme capsules. The life expectancy for patients with CF is severely shortened. Most therapies focus on slowing the rate of disease progression and treating symptoms.
CF is diagnosed based on the evaluation of sodium chloride secretion, or sequencing of the CFTR gene to confirm the presence of two known CF causing mutations. A sweat chloride of greater than 60 mEq/L is determined to be a positive sweat test, although a positive sweat test is not sufficient by itself to diagnose CF in the absence of CF disease manifestations such as sinusitis or pancreatic insufficiency. Sequencing of the CFTR gene is now available commercially and is part of the standard screening panel in all 50 states.

There are approximately 1800 known CFTR mutations that cause clinical phenotypes of CF. The mutations are grouped according to their molecular and functional effects on the CFTR gene. Different mutations can lead to reduced amounts of functional CFTR that reaches the cell surface through a) impaired cellular processing, b) reduced protein synthesis, or c) faulty delivery of proteins. CFTR gene mutations associated with minimal CFTR function include: defects in CFTR synthesis, defects in processing of CFTR and delivery to the cell surface, defects in the channel’s ability to open/close, and defects in channel conductance.

The most prevalent CF causing mutation is F508del, commonly referred to as deltaF508 or ΔF508. The mutation is an in-frame deletion in the CFTR gene resulting in a loss of phenylalanine at position 508. In the USA, almost 87% of patients with clinical CF have at least 1 copy of the F508del-CFTR mutation, and about 47% have 2 copies. This mutation impairs the CFTR protein in multiple ways. The mutation can interfere with its ability to reach and stay on the cell surface, by impairing the protein folding and thus allowing the protein to be trafficked to the correct location on the cell
surface. The few proteins that do make it to the cell surface do not have the ability to open and close to allow chloride to pass through.\textsuperscript{13,14} These deficits result in severely decreased chloride secretion.

Because of the many mutations that may cause CF, and because of the variety of ways in which these mutations may cause dysfunction, disease severity is quite variable in CF. Pulmonary symptoms occur in greater than 90\% of patients. The degree of pulmonary involvement is associated with decreased longevity.\textsuperscript{14} As early as 4 weeks of age, patients with CF begin to develop mucus plugging, neutrophilic invasion, and inflammation of airways.\textsuperscript{15,16} High levels of the neutrophils in the airways and sputum contribute to persistent inflammation and airway obstruction,\textsuperscript{17} and ultimately bronchiectasis.

As a result of the layers of viscous mucus in the airways of CF patients and their coexistent inflammation, the lungs are an excellent environment for bacteria to grow. Many patients will develop chronic bacterial colonization/infection of the airways. The most common bacteria found in sputum cultures from patients with CF are \textit{Pseudomonas aeruginosa} (PA), \textit{Haemophilus influenzae}, \textit{Staphylococcus aureus}, \textit{Burkholderia cepacia}, and nontuberculous mycobacteria. Constant colonization and infection lead to pulmonary dysfunction and irreversible lung damage.

Ultimately for CF patients, increased infection and inflammation in the lung leads to loss of lung capacity and eventually to respiratory failure and death. The median age of survival is projected to be \textasciitilde35 years of age if all genotypes are considered\textsuperscript{11,18}, but survival is generally shorter in patients with severe phenotypes.\textsuperscript{19} Since 1990, the median
age of survival has almost doubled, in large part due to advances in CF care brought about by research organized and supported by the CFF. The CFF has become the paradigm for other orphan diseases in how they organize and implement clinical trials, and also create collaborations with pharmaceutical companies to continue to fund new research into CF.

**Therapies for CF**

The therapeutic regimen for CF is aimed at slowing the progression of lung disease and loss of lung function by improving mucus clearance from the lung, treating bacterial infections and pulmonary exacerbations, and by supporting nutritional status through the use of pancreatic enzyme replacement therapy. The first FDA approved therapy specifically for CF was dornase alfa (Pulmozyme®), a mucolytic enzyme that hydrolyzes deoxyribonucleic acid (DNA), which is abundant from neutrophilic inflammation in CF airways. Pulmozyme helps to hydrate the surface of the airway leading to less viscous secretions. Less viscous secretions allow the patient to move and clear mucus. Currently, two inhaled antibiotics are approved for treatment of *Pseudomonas aeruginosa* in CF; tobramycin inhalation solution (TOBI®) and aztreonam lysinate for inhalation (Cayston®). CF patients are also often treated with courses of intravenous antibiotics in response to increased symptoms, also called pulmonary exacerbations.

Recently a new medication has received regulatory approval for CF. Ivacaftor (Kalydeco™; 150-mg tablets) was developed by Vertex Pharmaceuticals as a CFTR potentiator. Ivacaftor was approved in the United States, the European Union, and
Canada in 2012 for the treatment of CF in patients 6 years of age and older who have a G551D mutation in the CFTR gene. The drug is an oral tablet that targets the underlying CFTR defect by increasing the channel gating activity of CFTR protein located at the cell surface. This restoration of chloride secretion allows for proper airway hydration resulting in a reduction on the cycle of inflammation, infection, and irreversible lung damage.\(^{26}\)

Ivacaftor is the first CFTR modulator to show an improvement in CFTR function and clinical benefit in patients with CF. Results from Phase 3 studies showed that ivacaftor is effective in the treatment of patients with CF who have the G551D-CFTR mutation, as evidenced by sustained improvements in CFTR channel function (measured by reduction in sweat chloride concentration) and corresponding substantial, durable improvements in lung function, pulmonary exacerbations, respiratory symptoms, and weight gain.\(^{26}\) The G551D mutation is present in only about 4% of the CF population.\(^{55}\)

**Modifiers of Disease Progression**

**Bacterial Colonization - Pseudomonas Aeruginosa**

Acquisition of specific pathogens, namely Pseudomonas Aeruginosa (PA) and Burkholderia species can significantly alter the clinical course of the patient with CF.\(^{26,27,28}\) PA is the most common and most significant bacteria associated with chronic airway colonization and infection in CF.\(^{14}\) Chronic PA infection is a significant predictor of mortality,\(^{29}\) has been associated with higher rates of pulmonary function decline,\(^{30}\) and children with PA-positive respiratory cultures during the first year of a study had a 2.6-fold increase in mortality over the subsequent 8 years of follow-up relative to children
who had PA-negative cultures.\textsuperscript{31} In the US, approximately 72\% of CF patients 18 years or older are colonized with PA; with approximately 53\% of the total CF population colonized with PA.\textsuperscript{32} Once colonization occurs, bacterial eradication is quite difficult, if not impossible. Colonization with PA can have dramatic effects on clinical outcome and disease progression. Chronically infected patients experience frequent infections and significant loss of lung function, which is due in large part to the inflammatory response to chronic bacterial infection.\textsuperscript{33} Li \textit{et. al.} showed that early detection and eradication of PA is critical and there appears to be a window of opportunity for possible eradication. They also showed that mucoid PA, a phenotype of PA, plays a much greater role in CF lung disease progression than non-mucoid PA.\textsuperscript{34}

\textbf{Burkholderia species}

PA is the most common and extensively researched bacterial pathogen associated with CF pulmonary disease, however other organisms are often associated with more rapid decline in pulmonary status and lung function. The Burkholderia species are recognized as causing significant change in the clinical course of patients with CF. In 2007 approximately 3\% of CF patients were infected with Burkholderia. The prevalence of infection with Burkholderia was also 3\% in 2012\textsuperscript{11} but there is a wide variety of types and range of prevalence across centers and regions. At Boston Children’s Hospital, the overall prevalence is approximately 10\%. This increase in prevalence is primarily due to an outbreak of a specific type of Burkholderia species now called Burkholderia dolosa.

In 1992, a patient infected with a type of burkholderia transferred to BCH. In 2001, as genotyping improved, cultures previously characterized as Burkholderia
multivorans revealed an increasing incidence of a newly described genomovar, genomovar VI, *burkholderia dolosa*. Thirty-six patients ultimately became colonized with this bacteria, and only 18 are still living.\(^5\)

Certain strains of *Burkholderia* are more virulent than other strains and are associated with ~ 40% loss of FEV1 per year or a 2-year mortality rate of > 50%; these strains are considered the most serious because of their association with rapid progression to severe necrotizing pneumonia and death.\(^{35,36,37}\)\(^\text{The most common *Burkholderia* species that infect CF patients are *Burkholderia multivorans* and *Burkholderia cenocepacia*;\(^{38,39,40}\) however, all species are associated with a marked clinical decline.}

*Burkholderia* species are inherently resistant to most antibiotics and are known to acquire resistance quickly when exposed to antibiotics. Despite advances in the care of patients with CF, there is no standard therapy for treating *Burkholderia* infection. Patients typically receive a combination of systemic, oral, or inhaled antibiotics frequently or even continuously for control of their symptoms. Since patients with *Burkholderia* infection frequently have rapid loss of lung function, they are often considered for lung transplantation. However, *Burkholderia* infection is associated with worse outcomes, and many transplant centers exclude or limit transplantation in these patients.\(^{41}\)

**Nontuberculous mycobacteria (NTM)**

Infections with NTM are also associated with a more rapid decline in lung function.\(^{42}\) Recovery of NTM from CF respiratory secretions is relatively common, with an overall prevalence of 13% reported in a large prospective study.\(^{43}\) More recent studies have suggested that the NTM prevalence in CF may be increasing.\(^{44,45}\) It is hypothesized
that screening is becoming better and more routine, but also that the early treatment of PA is leading to colonization with other bacteria, including NTM. At Children’s Hospital Boston the overall prevalence is approximately 6-10%.

**Clinical Trial Participation**

In the last two decades there has been a dramatic shift in research toward evidence based medicine. Evidence based medicine places strong emphasis on the results of randomized clinical trials when determining individual patient treatment. This shift has seen a significant increase in the number of randomized, including placebo-controlled, clinical trials. The placebo-control group in a randomized clinical trial may receive no benefit from their participation, while it is hoped that the active drug group will receive the benefit of a new therapy that is as effective as or more effective than what is currently available.

The most common reasons patients report for participating in clinical trials are in descending order: potential medical benefit, trust in physician/advice of physician, potential benefit to others, and study compensation/reduction in medical costs. Patients who decide not to participate in clinical research most often report they do not want to be randomized into a treatment arm, do not view the risk/benefit ratio as favorable, do not have the time to commit to the study, do not wish to be a “guinea pig, “or have a distrust in drug research or their physician/medical facility in general. Previous research has shown that there are certain demographic factors that are more often associated with participation in clinical trials including; males, older, lower socio-economic status,
patients who have a higher level of trust in their physicians, and those who have a lower level of education.\textsuperscript{23, 51, 52}

For patients with a life-threatening illness or disease, the decision to participate in a clinical trial is often based on the desire to improve quality of life and/or increase the likelihood of long-term survival. However, a clinical trial is by definition experimental. The researchers are testing to determine if the new treatment has any effect on health outcomes.

Previous research has shown improved outcomes for patients who participate in randomized clinical trial (RCT) regardless of treatment assignment.\textsuperscript{49} Davis et al showed that patients with non-small cell lung cancer who participated in a RCT had significantly better survival rates than that of subjects not participating. Four of the five trials in a meta-analysis of cancer survival found that patients in trials survived significantly longer than patients not in trials.\textsuperscript{50}

Also, physicians who are actively involved in clinical research may be more aware of the results of trials and would be more likely to prescribe newer treatments. This suggests that receiving care at a facility where clinical research is conducted may be beneficial. Other research has shown that there is a psychological benefit in terms of better mood, more positive outlook, and decreased prevalence of mood symptoms when participating in clinical trials.\textsuperscript{51, 52}

**Primary Aim**

This study examined the amount of disease progression as measured by loss of lung function, as defined by the forced expiratory volume in 1 second (FEV1) of CF.
patients who participated in clinical research (both in observational/clinical trials vs. clinical trials only) and compares these groups against patients who did not participate in research of any kind. In this study participation in clinical trials is defined as enrollment in a clinical trial involving an investigational drug. Comparisons were made between the FEV1 of patients in these three groups in an attempt to measure the effect of trial participation. It was expected that patients who participated in clinical trials would have lower amounts of disease progression than those subjects who did not to participate in interventional research. In the previous 5 years, BCH has conducted approximately 45 interventional trials.

**Hypothesis 1**

It was hypothesized that participation in clinical trials would benefit subjects in multiple ways. First, subjects were provided access to new investigational drugs that could improve their health. Subjects participating in trials do not know whether they received the investigational drug or whether the drug was beneficial. However two recent medicines have recently received approval from the FDA for patients with CF. Many of the patients in the interventional group may have received one of these medications in the many trials undertaken at BCH.

Second, participation in clinical trials may lead to better adherence with the complicated CF medication regimen. The pulmonary team including doctors, nurses, and research coordinators evaluate the subjects more often compared to patients who do not participate in clinical trials. Study investigators and staff often provide education at study visits with regards to a participants’ medication regimen (especially during the trial). This
increased interaction may lead to better adherence with medications during a clinical trial. During participation in a clinical trial research coordinators and nurses asked about each medication the patient was taking at each visit to ensure subjects remained on a consistent regimen that allowed the trial to investigate the effect of the investigational drug.

Third it was hypothesized that clinical trial participation would improve the subjects overall mood and demeanor and might also increase their overall knowledge of their disease. These changes might therefore lead to improved lung function Because of infection control precautions in CF, the patient often does not speak to or interact with anyone other than their family regarding their disease. Through trial participation the patient/subject interacted with the research team on a frequent basis and had a chance to speak to someone who perhaps could understand their disease and could offer insight into disease specifics, difficulties, and problem-solving. The research team was very knowledgeable about CF and could often answer questions and provided information on clinical research in CF, which especially with the recent success of CF clinical trials may offer the patients hope and increased optimism for the future.

**Hypothesis 2:**

Lower amounts of disease progression were not expected in subjects who participated in observational studies when compared to subjects who did not participate in interventional research. There was little and no direct medical benefit to subjects who participated in observational studies, and thus differences in amount of disease progression were not expected.
METHODS

This was a retrospective cohort study of CF patients ages 6 years and older followed at BCH. Since 1985, the CFF has asked all patients followed at CF centers nationwide to participate in a research study allowing the centers to enter medical information into a database. The CFF database includes more than 115 CF Care Centers across the United States, and approximately 30,000 patients. The purpose of the CF registry is to compile and maintain long-term epidemiological data for researchers and clinicians regarding medication use, clinical patterns outcomes, and mortality and morbidity rates. The BCH registry contains entries for approximately 550 patients dating back approximately 20 years. This study examined data from the previous six years.

Data was collected at all clinic visits, admissions, and surgical procedures for all patients enrolled. The data collected included demographics (age, sex, marital status, education level), diagnostic information (sweat test values, form of diagnosis, age of diagnosis, CF genotype, CF clinical symptoms), morbidity data, pulmonary function test results, exacerbation history, microbiology results, and hospitalization dates.

Using the CFF database, a query was generated for all spirometry data between the years 2007 and 2012. The query returned data on 504 individual patients with 15,326 spirometry results.

Patient selection

Cystic fibrosis patients who were ages 6 years and older, and for whom data were available were included in this study. The number of subjects followed at BCH was 556. Of note, 52 of the 556 patients followed at BCH were not included in this analysis.
because they did not provide consent to participate in the CF registry study. The reasons for not participating included religious reasons, the inability to consent (language or developmental delay), the inability to contact (most often because of infrequent clinical visits), and general refusal to provide data to a registry. This patient population was generally healthier than patients who have provided consent and have far fewer clinical visits. Subjects who did not perform at least two spirometry measures in 4 of the 6 years in this group, were not included in the overall analysis as disease progression could not accurately be measured. This excluded 115 additional subjects.

**Disease Progression**

Disease progression was quantified using results of pulmonary function tests (PFTs); specifically the forced expiratory volume in one second (FEV₁), a standard measure of lung function. FEV₁ is expressed as a percentage of a predicted value based on age, gender, race, and height. FEV₁ is the most frequently used measure of disease status in CF and other obstructive lung diseases as well as the primary outcome measure in numerous CF clinical trials. The measure is highly correlated with quality of life and mortality in CF. The average FEV₁ was calculated for each year for each patient for calendar years 2007-2012. The amount of disease progression is the absolute difference between the average FEV₁ from 2007 (or 2008 if no records are available for a specific patient in that year) and the average FEV₁ from 2012 (or 2011 if no records are available for a specific patient in that year).

**Participant Groups**
The interventional group included all subjects who participated in a clinical trial involving an investigational drug between 2007 and 2012 (other than expanded access programs). Patients participating in expanded access (compassionate use) programs have not been counted as participating in a clinical trial because although they have received an investigational drug; the drug was shown to have some benefit for this group and this group is also usually much sicker than the average patient. The observational group included all subjects who participated in observational research studies only (excluding subjects who participated in clinical trials) including surveys, sample collection, and any other non-interventional clinical trial. Of note, all patients who participated in clinical trials between 2007 and 2012 also participated in an observational trial. The third group included patients who had not participated in any research trials of any kind other than the CF registry.

RESULTS

The average FEV1 percent predicted was calculated for each year for each patient. 115 patients who did not have at least two spirometry measures performed in at least 4 of the years examined were not included in the analysis. The average FEV by year is shown in Table 1.0.

The average FEV₁ for the interventional group in 2007 was 82.9, standard deviation 22.78. The observational group average FEV₁ in 2007 was 83.5%, standard deviation 23.76, the non-participant group was 86.9%, standard deviation 19.60. Baseline lung function on average in 2007 was no different across the 3 groups. The average FEV₁
for the interventional group in 2012 was 74.4. The observational group average FEV1 in 2012 was 78.4%, the non-participant group was 79.6%. The differences between each of the three groups were not statistically significant.

The average age of the sample was 24.4 years, standard deviation 11.49. This was a slightly older sample than the entire CF population at Children’s Hospital Boston whose average age is 21.6 years. The likely explanation for that is that patients 6 years and younger do not generally perform spirometry and were not included in the analysis.

The average ages of the interventional, observational, and the non-participants groups were 25.9, 24.4, and 24.2 years, respectively. In 2007 the average FEV1 for all adults was 77.66%, standard deviation 22.85, while for children it was 97.36%, standard deviation 15.62. Similarly, in 2012 the average FEV1 for the adults was 68.75%, standard deviation 24.45 and for children it was 93.25%, standard deviation 17.75. For adults in the interventional group the average FEV1 in 2007 was 76.8%, standard deviation 21.60 and for children in the interventional group in 2007 the average was 99.36%, standard deviation 17.47. In 2012 the average FEV1 for adults was 68.5%, standard deviation 20.52 and for children it was 88.1%, standard deviation 17.86.

Of the 389 patients (see Table 1) included in the analysis, sixty-four patients had participated in interventional research trials between the years 2007-2012: 207 patients had participated in observational trials only, and 118 patients did not participate in any research studies (other than participation in the CFF registry). The average amount decline of lung function for subjects in the interventional group was 9.58%, standard deviation 10.12, between 2007 and 2012 compared to 8.27%, standard deviation 13.61, in
the observational group, and 8.33%, standard deviation 12.59, in the non-participant group. When controlling for number of years of data for each patient, the interventional group declined at a rate of 1.64% per year from 2007 to 2012 compared to 1.49% per year to all other patients. The observational group declined on average 1.89% per year and the non-interventional group declined 1.44% per year.

There was no statistically significant difference between the amount of decline in the interventional group compared with observational group (t268) = 0.70, p = 0.47 or the non-interventional group (t181) = 0.68, p = 0.49. There was also no statistically significant difference in the rate of decline of the interventional group compared with observational group (t268) = 0.76, p = 0.45 or the non-interventional group (t181) = 0.61, p = 0.54. Ten of the 64 subjects who participated in clinical trials (15.63%, compared to 12.05% ((47 of 389)) of the group in this analysis) were colonized with the specific organisms associated with a rapid decline. Of note, the sixty-four patients who participated in intervention trials performed on average 52 pulmonary function tests between 2007 and 2012, compared to 37 pulmonary function tests for all other patients.

The effect of clinical trial participation for adults and children was examined separately (or in a stratified analysis) (See Figure 2.0). Adults in the interventional group experienced an average lung function decline of 8.86%, standard deviation 10.71 from 2007 to 2012 standard deviation 14.40, compared to 10.24%, for adults in the observational group and 10.30% (standard deviation 11.50), for adults in the non-interventional group. Adults in interventional group declined at a rate of 1.52% per year compared to 1.86% per year to all other adults. Adults in the observational group decline
at a rate of 1.91% per year and adults in the non-interventional group decline at a rate of 1.78% per year.

There was no significant difference in the amount of decline for adults in the interventional group compared with all other adults \((t_{241}) = 0.68, p = 0.50\), or with each group specifically; observational \((t_{163}) = 0.58, p = 0.56\), and non-interventional \((t_{121}) = 0.68, p = 0.49\). There was not a statistically significant difference in the rate of decline for adults in the interventional group compared to the observational and the non-participant groups.

The rate of disease progression between the three groups was different for children compared to adults. For children who participated in interventional trials, the average loss of lung function between 2007 and 2012 was 11.41%, standard deviation 8.54, compared to 5.28%, standard deviation 12.84, for all other children. The difference in quantity of decline for children in the interventional group compared to all other children was statistically significant \((t_{144}) = 2.06, p = 0.04\). Children in the observational group declined on average 5.40% and children in the non-interventional group declined on average 4.47%. Both of these results when compared to the interventional group were statistically significant \((t_{104}) = 1.97, p = 0.05\) and \((t_{57}) = 2.00, p = 0.05\), respectively. Children in interventional group declined at a rate of 1.92% per year compared to 0.93% per year to all other children. Children in the observational group declined at a rate of 0.98% per year and children in the non-interventional group decline at a rate of 0.80% per year.

**DISCUSSION**
Using data from 504 patients submitted to a data registry maintained by the Cystic Fibrosis Foundation, we examined disease progression, as measured by amount of decline in pulmonary function tests between 2007 and 2012 and compared multiple subsets of CF patients: those who participated in interventional studies, those who participated in observational studies only, and those who did not participate in research. There was no difference in the amount of decline in lung function between adults who participated in intervention trials and adults who did not. In contrast, children who participated in intervention trials had a significantly larger amount of decline of lung function than children in the observational and non-participant groups. This may be a result of several factors, including the possibility that the families of children who participate in research may looking for new and better treatments because they see the child’s health declining. Also, many inclusion criteria for studies do not allow children or adults with a certain level of FEV1; for example above 90%. Children who participate in research are often included because their lung function has already declined at a faster rate from that of other patients.

Many patients choose to participate in clinical trials as a way to improve their quality of life in terms of better symptom control or increased monitoring of care. Research has shown that additional medical monitoring, the opportunity for a “second opinion” and the reassurances received were more important benefits than the physical improvement. A recent study found that even those patients who do not medically benefit from a trial often found joining the clinical trial a meaningful experience in terms of benefiting future research. The experience of interacting with the research staff partly
influenced the final impression of the trial participation experience. Adults may also benefit from the trial more than children specifically through the interaction with the research staff. Often the attention of the research staff is divided when working with children between the patient and the family and or family members who are present during the visit. Adults often receive more attention from the research staff and this increased attention may be of benefit in itself to the patient.

This difference may also be explained by the effect of improved adherence to chronic therapies by individuals enrolled in research trials. The medication regimen for the younger patients is often supervised and overseen by the parents and generally compliance with medications is often higher in the younger age groups. Adults may improve their medication adherence during a clinical trial more than children who already have high levels of adherence. Also, the research staff may direct much of their attention and teaching to the parents regarding CF care, research, and problem solving leaving less benefit to a distracted child.

Clinical trials may also be more beneficial for adults because trial participation for adults may be for a longer period of time. Many of the CF interventional trials with children are for shorter periods of time than the trials with adults. BCH primarily participates in Phase 2 and 3 studies with Phase 3 studies being the longest of the trials. Many of the Phase 3 studies will often start with subjects at least 12 years of age; excluding many of our pediatric participants. The Phase 2 studies in CF that do include ages 6 and up are first very short trials with few participants because of safety. Also, adult participants are eligible for more trials and have participated in a greater number of
trials than children at BCH in this time period. Adults participated on average in 1.60 trials and children participated in 1.26 trials. Future research is needed to parse out the effect of clinical trial participation in CF; especially the different pattern seen in adults and children.

Further research is needed to understand the relationship between disease progression in CF and participation in clinical research. This study did not control for other possible disease progression modifiers such as education, adherence to medication regimen, colonization with harmful bacteria, or genetics. Future studies

If it were true that children who participate in clinical research have larger amounts of disease progression, families would need to strongly consider the decision to enroll a child in a clinical trial. More research would be needed to understand what the possible mechanism of action for this larger increase compared to the adult population. Sponsors and investigators would need to strongly examine trial design when enrolling children into trials. This researcher does not believe that clinical trial participation is harmful or results in worse disease outcomes; for children or adults. The result may most easily be explained by differences in the groups that participate in trials versus those who do not. We also know that in CF, the greatest amount of disease progression often occurs during the teenage/adolescent years. The difference we are seeing in terms of disease progression in adults versus children is not an affect of clinical trial participation, but simply an effect of the disease itself in the adolescent years.

Children and adults who participate in research are participating because they often hope to receive some medical benefit from the trial. Patients and families are more
likely to participate if they recognize that they or their child is sick and that current medications and therapies are not effective. Patients who feel sick and have constant symptom burden are more likely to seek additional ways to improve their condition and participation in clinical trials offers that. Patients and families of CF patients who experience low symptom burden and overall better health are less likely to view research as a way to improve their lives.

We hope that the investigational drugs being tested are of benefit themselves to the research subjects. But we also know that for those patients who receive placebo during a randomized trial, there may be benefit to them. Increased monitoring, increased interaction with medical and research staff, and the opportunity for a second opinion are potentials benefits of participation in a clinical trial. Research has shown that subjects who received placebo during a clinical trial of anti-thrombin therapy in premature infants had better outcomes than those infants who were eligible to participate in the trial but did not participate⁵⁹. That is, there was a benefit to simply participating in the clinical trial itself on health outcomes in this population.

**Limitations**

There are several difficulties with this overall approach. First, patients who participate in clinical trials are often more adherent to their medications; both during the trial because of increased monitoring, and outside of the trial. Patients who participate in research may do so to please the physician and would follow their physician’s orders regarding medication use. Also, a different way to examine the effect of clinical trial participation on disease progression would be to examine the FEV1 change each year for
each patient and then to code each year that a patient participated in a trial versus the years that patients did not participate in trials. This method would allow the researcher to examine the effect of trial participation both within and across subjects.

Also, the participants of interest in this study (the subjects in the interventional group) chose to participate in clinical trials. It is possible that these patients are sicker and declining more rapidly and may be more likely to want access to investigational drugs than patients whose clinical courses are much more stable. Lastly, the data analyzed in this study was only for a short period of time (2007 to 2012) at only one hospital. This time period was chosen because of the limited data available to the researcher and unfortunately a database is only as good as data entered. The overall number of subjects analyzed is small and additional work is needed to understand if these results hold true at other CF centers across the country.

Conclusions

Patients that participated in clinical trials at BCH between the years of 2007 and 2012 did not have a significantly different amount of disease progression than subjects who did not participate in interventional trials (including patients who that participated in observational trials only and patients that did not participate in any research). There was a different pattern of disease progression when comparing adults and children. Children who participated in interventional trials had a larger amount of disease progression than children who did not while adults had a smaller amount of disease progression; although this did not meet clinical significance.
### Table 1.0

Demographics of All Subjects

*Or first year of data collection if not 2007

**Or last year of data collection if not 2012

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Patients</th>
<th>Average Age (range 12 - 58)</th>
<th>Number of Subjects</th>
<th>Gender</th>
<th>Average FEV1 in 2007*</th>
<th>Standard Deviation in 2007</th>
<th>Average FEV1 in 2012**</th>
<th>Standard Deviation in 2012</th>
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</thead>
<tbody>
<tr>
<td>Intervenational Group</td>
<td>64</td>
<td>25.9</td>
<td>64</td>
<td>Males: 29 Females: 35</td>
<td>83.0</td>
<td>22.78</td>
<td>74.4</td>
<td>21.62</td>
</tr>
<tr>
<td>Group</td>
<td>N</td>
<td>Mean Age</td>
<td>Range</td>
<td>Males</td>
<td>Females</td>
<td>80-84</td>
<td>75-79</td>
<td>70-74</td>
</tr>
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</tr>
<tr>
<td>Observational Group</td>
<td>207</td>
<td>24.4</td>
<td>10-71</td>
<td>102</td>
<td>105</td>
<td>23.76</td>
<td>78.4</td>
<td>26.15</td>
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<tr>
<td>Non Participant Group</td>
<td>118</td>
<td>24.2</td>
<td>9-73</td>
<td>63</td>
<td>55</td>
<td>19.6</td>
<td>79.6</td>
<td>22.63</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>Average FEV1 in 2007</td>
<td>Average FEV1 in 2012</td>
<td>Rate of Decline per Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Adults</td>
<td>Children</td>
<td>Adults</td>
<td>Children</td>
<td>Adults</td>
<td>Children</td>
<td>Adults</td>
<td>Children</td>
</tr>
<tr>
<td>Interventional</td>
<td>45</td>
<td>19</td>
<td>76.8 (+/− 21.6)</td>
<td>96.5 (+/− 17.9)</td>
<td>68.1 (+/− 20.5)</td>
<td>88.36 (+/− 17.5)</td>
<td>1.52</td>
<td>1.92</td>
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<tr>
<td>Observational</td>
<td>120</td>
<td>87</td>
<td>74.1 (+/− 21.6)</td>
<td>66.2</td>
<td>94.5</td>
<td>98.2</td>
<td>1.91</td>
<td>0.98</td>
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<tr>
<td>Non Participant</td>
<td>78</td>
<td>40</td>
<td>84.0</td>
<td>72.7</td>
<td>92.8</td>
<td>94.0</td>
<td>1.78</td>
<td>0.80</td>
</tr>
</tbody>
</table>

**Figure 1.0**
FEV 1 Percent Predicted between 2007 and 2012
Figure 2.0: Rate of FEV1 Decline for Subjects by Group
REFERENCES


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EDUCATION

Boston University School of Medicine - Boston, MA
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Bradley University- Peoria, IL - Graduation: May 2004
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WORK EXPERIENCE

Clinical Research Coordinator II, Pulmonary Department, Children’s Hospital Boston
September 2008 – Present
– Responsible for obtaining and maintaining IRB approval; corresponding with regulatory agencies and sponsor regarding study status; adverse event reporting, query resolution; study budgets; maintaining regulatory documentation including correspondence, FDA form 1572, medical licenses, CV’s, and study site qualifications; performing chart reviews to assess eligibility; recruitment; coordination of study visits including scheduling and communicating with study physicians; data collection and entry; resolving queries; corresponding with study sponsor including scheduling and meeting with site monitor regarding site initiation, monitoring, and study close-out.

Research Technician/Clinical Research Coordinator, Department of Neurology, University of Chicago Hospitals - July 2005 – August 2008
- Coordinated all activities of research subjects, reviewed regulatory documents, maintained master subject lists, corresponded with the Institutional Review Board for approval of protocols, developed protocol, consent, and source documents, obtained informed consent, resolved queries and corresponded with pharmaceutical sponsors, performed neuropsychological and mental status examinations, performed behavioral, EEG, and fMRI experiments, generated reports and maintained records related to
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PUBLICATIONS
