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Rationale and design of a randomized trial of home electronic symptom and lung function monitoring to detect cystic fibrosis pulmonary exacerbations: The early intervention in cystic fibrosis exacerbation (eICE) trial ☆

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ABSTRACT

Background: Acute pulmonary exacerbations are central events in the lives of individuals with cystic fibrosis (CF). Pulmonary exacerbations lead to impaired lung function, worse quality of life, and shorter survival. We hypothesized that aggressive early treatment of acute pulmonary exacerbation may improve clinical outcomes.
Purpose: Describe the rationale of an ongoing trial designed to determine the efficacy of home monitoring of both lung function measurements and symptoms for early detection and subsequent early treatment of acute CF pulmonary exacerbations.
Study design: A randomized, non-blinded, multi-center trial in 320 individuals with CF aged 14 years and older. The study compares usual care to a twice a week assessment of home spirometry and CF respiratory symptoms using an electronic device with data transmission to the research personnel to identify and trigger early treatment of CF pulmonary exacerbation. Participants will be enrolled in the study for 12 months. The primary endpoint is change in FEV_1 (L) from baseline to 12 months determined by a linear mixed effects model incorporating all quarterly FEV_1 measurements. Secondary endpoints include time to first acute protocol-defined pulmonary exacerbation, number of acute pulmonary exacerbations, number of hospitalization days for acute pulmonary exacerbation, time from the end of acute pulmonary exacerbation to onset of subsequent pulmonary exacerbation, change in health related quality of life, change in treatment burden, change in CF respiratory symptoms, and adherence to the study protocol.

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; AE, adverse event; BCDM, Biostatistics and Clinical Data Management; CF, cystic fibrosis; CFRSD, Cystic Fibrosis Respiratory Symptom Diary; CFQ-R, Cystic Fibrosis Questionnaire-Revised; DSMB, Data Safety Monitoring Board; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; HRQOL, Health related quality of life; MOS-SSS, Medical Outcomes Study Social Support Survey; PI, Principal Investigator; SAE, serious adverse event; TAQ-CF, Treatment Adherence Questionnaire-CF; TDNCC, Therapeutics Development Network Coordinating Center.

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Conclusions: This study is a first step in establishing alternative approaches to the care of CF pulmonary exacerbations. We hypothesize that early treatment of pulmonary exacerbations has the potential to slow lung function decline, reduce respiratory symptoms and improve the quality of life for individuals with CF.

1. Introduction

Cystic fibrosis (CF) is the most common life-shortening inherited disease in Caucasians and affects approximately 30,000 individuals in the U.S. It is an autosomal recessive genetic disease caused by mutations of a chloride channel, the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). CF is a systemic disease, which has profound effects on the respiratory and digestive systems. Individuals with CF have abnormally viscous mucus in their airways and develop chronic pulmonary infections. Most with CF suffer from pancreatic insufficiency and do not absorb nutrients normally [1,2]. Despite extensive advances in our understanding of the basic science of CF, the large majority of individuals with CF die from respiratory failure after repeated events termed acute pulmonary exacerbations. Exacerbations are common and present clinically with increased cough, increased sputum production, dyspnea, decreased energy level and appetite, weight loss, and decreases in spirometry [3]. These episodes are likely related to a complex relationship between host defense and airway microorganisms that impact sputum production and airflow obstruction. Pulmonary exacerbations have been associated with decreased survival [4–7], diminished future lung function [8], CF related diabetes [9], sleep disturbances and worse health related quality of life [10,11]. The mainstay of exacerbation treatment is antibiotic therapy (intravenous, oral, or inhaled), airway clearance, mucolytics, and sometimes corticosteroids as an immune-modulator [12]. Pulmonary function tests, and the forced expiratory volume in 1 s (FEV_1) in particular, are the best clinical method for objectively evaluating lung health in CF [13]. Changes in FEV_1 can be used, in part, to define exacerbations, and to monitor response to treatment. Currently, unlike patients with asthma, individuals with CF do not routinely monitor their lung function at home, nor do they objectively track respiratory symptoms. Consequently, CF pulmonary exacerbations can be diagnosed weeks after onset when their symptoms progress to a point at which they seek medical care [14]. Use of home monitoring of lung function and symptoms may allow for earlier detection of pulmonary exacerbations, which would allow earlier treatment. This study will test the hypothesis that earlier treatment of CF exacerbations will result in better clinical outcomes.

Investigators reported on their experiences with home monitoring in CF in the late 1980's and early 1990's [15,16]. For a two-year period, 111 CF individuals maintained daily diaries recording vital capacity, weight, respiratory rate, pulse, and symptoms. The daily participation rate was approximately 80%. Subsequently, these investigators carried out a non-concurrent cohort study on 50 individuals with CF [16]. Twenty-five participants were selected randomly from the group that had used home monitoring and were matched to 25 participants that had not performed home monitoring. The groups were matched on age and gender and followed for four years. FEV_1 declined from 73.1% predicted to 70.1% predicted in the home monitoring group (N.S.) and declined from 72.3% predicted to 60.8% ($p < 0.001$) in the control group. Later extensions of this early work demonstrated the ability of patients to transmit the results of their home spirometry to the CF clinic via computer modem [17]. Our group has completed several pilot studies demonstrating that home spirometry and symptom measurement with a single electronic device is feasible [18–20]. We also completed a randomized pilot study showing that home monitoring can detect more exacerbations than standard care [21]. The current trial is the first large, randomized trial to assess the efficacy of home symptom and lung function monitoring on change in FEV_1. Enrollment began in October 2011 and completion is expected in the spring of 2014 (Fig. 1). The study objectives are listed in Table 1.

2. Methods

2.1. General overview

This is a randomized, non-blinded, multi-center trial in individuals with CF. The study compares a usual care arm to an early intervention arm. The intervention arm uses small electronic devices capable of electronic data transmission, to perform home spirometry and assessment of patient reported respiratory symptoms. We are using computerized remote data collection to identify and trigger the treatment of pulmonary exacerbation in adolescents and adults with CF (Fig. 2). Additionally, subjects are seen for study visits every three months. Those in the usual care arm attend clinic every 3 months, as is the current standard of care and is combined with a study visit, and they are asked to contact their CF care center for acute visits. Individuals participate in the study for 12 months with five planned study visits and additional acute pulmonary exacerbation visits. For both arms, treatment of a pulmonary exacerbation is determined by the patient's clinician but is encouraged to follow treatment guidelines from the CF Foundation [12]. Recruitment and enrollment is occurring over a 36-month period. Due to the nature of the study intervention, it is not possible for participants to be blinded. Additionally, given that clinical decisions may need to be made based on the results of home monitoring, the investigators and research teams cannot be blinded either.

2.2. Study population

Individuals with CF who are 14 years of age or older are recruited from the thirteen participating centers. Those who meet all of the inclusion criteria and none of the exclusion criteria are eligible for participation in this study. The participating sites are listed in the Appendix A. Participants need to be in stable condition at enrollment, with no evidence of a pulmonary exacerbation in the preceding two