Clinical Research Protocol

Multicenter study of patient-reported gastrointestinal symptoms in people with Cystic Fibrosis (GALAXY)

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PI or Sponsor Signature (A. Jay Freeman, MD, MSc) — Date: 11-20-2018

PI or Sponsor Signature (Baharak Moshiree, MD) — Date: 11-20-2018

PI or Sponsor Signature (Meghana Sathe, MD) — Date: 11-20-2018

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing the Sponsor-Investigator with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: GALAXY-OB-18

Protocol Title: Multicenter study of patient-reported gastrointestinal symptoms in people with Cystic Fibrosis (GALAXY)

Protocol Date: 19 NOV 2018

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Investigator Signature *Date*

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Print Name and Title

Site #: _____

Site Name: _____

Address: _____

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LIST OF ABBREVIATIONS AND ACRONYMS

CFR	Code of Federal Regulations
CFTR	cystic fibrosis transmembrane conductance regulator
CF	cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFFPR	Cystic Fibrosis Foundation Patient Registry
C.I.	confidence interval
CRF	case report form
CSBM	complete bowel movements
DIOS	distal intestinal obstruction syndrome
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
NPD	Nasal potential difference
PAC-SYM	Patient Assessment of Constipation-Symptoms
PAGI-SYM	Patient Assessment of Gastrointestinal-Symptoms
PAC-QOL	Patient Assessment of Constipation Quality of Life
PAGI-QOL	Patient Assessment of Gastrointestinal-Symptoms Quality of Life
PEG	polyethylene glycol
PI	Principal Investigator
PRO	patient reported outcome
PROMIS	FDA patient-reported outcomes measures
PROs	patient reported outcome surveys
QOL	Quality of Life
SIBO	small intestinal bacterial overgrowth
TDNCC	Therapeutics Development Network Coordinating Center

PROTOCOL SYNOPSIS

TITLE	Multicenter study of patient-reported gastrointestinal symptoms in people with Cystic Fibrosis (GALAXY)
SPONSOR-INVESTIGATOR	A. Jay Freeman, MD, MSc (Emory University/Children's Healthcare of Atlanta) Baharak Moshiree, MD (University of North Carolina Charlotte, Atrium Health) Meghana Sathe, MD (University of Texas Southwestern/Children's Health)
FUNDING ORGANIZATION	Cystic Fibrosis Foundation (CFF)
NUMBER OF SITES	Approximately 26
RATIONALE	There are currently no large, multicenter prospective clinical trials examining management of constipation or other gastrointestinal (GI) symptoms in people with cystic fibrosis (CF). Current recommendations in the CF literature are largely based on expert consensus and opinions. Yet, constipation and other GI symptoms are crucial factors in quality of life (QOL) and maintenance of optimal nutritional state in people with CF. This study will use GI-symptomatology questionnaires to understand the multiple overlapping GI symptoms in people with CF. This would be followed by studies to improve GI outcomes through establishing evidence-based algorithms, starting with constipation. In the future, we would also like to evaluate the impact of CF modulators on common GI symptoms and evaluate how this might impact the development of symptom-specific algorithms.
STUDY DESIGN	This is a prospective, multicenter, observational study designed to collect gastrointestinal related data in patients with CF. Eligible subjects will be consented and enrolled in the study at the Enrollment Visit. At the visit, the subject or parent/guardian will complete the patient reported outcome surveys (PROs) using their mobile device (e.g., smartphone or tablet). The PROs will consist of four questionnaires: Patient Assessment of Constipation-Symptoms (PAC-SYM), Patient Assessment of Gastrointestinal-Symptoms (PAGI-SYM), Patient Assessment of Constipation Quality of Life (PAC-QOL) and the disease-specific questionnaire. The disease-specific questionnaire will include the Bristol Stool Scale and will collect information on presence of fecal incontinence, stool quality and stool frequency. At the Enrollment Visit, weight and height will be collected in addition to medical history and concomitant medication information. The subject or parent/guardian will complete the PROs outside-the-clinic setting per the Schedule of Events using their mobile device.

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 29 days. The total duration of the study is expected to be approximately 13 months: 12 months for subject recruitment and 1 month for the final subject enrolled to complete the study.
PRIMARY OBJECTIVE	Assess the feasibility of electronic PROs conducted outside-the-clinic.
SECONDARY OBJECTIVES	▪ Estimate the prevalence and variability of GI symptoms occurring in pediatric and adult patients with CF ▪ Describe current management of GI symptoms in patients with CF ▪ Gather information to guide and inform on the design of future algorithm-based approaches to treating GI symptoms in people with CF
NUMBER OF SUBJECTS	Up to 400
SUBJECT SELECTION CRITERIA: **Inclusion Criteria**	1. All genders ≥ 2 years of age at time of consent 2. Documentation of a Cystic Fibrosis (CF) diagnosis as evidenced by one or more clinical features consistent with the CF phenotype and one or more of the following criteria: ▪ Sweat chloride equal to or greater than 60 mEq/liter by quantitative pilocarpine iontophoresis test (QPIT) ▪ Two well-characterized mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene ▪ Abnormal nasal potential difference (change in NPD in response to a low chloride solution and isoproteronol of less than -5 mV) 3. Enrolled in the Cystic Fibrosis Foundation Patient Registry (subjects may enroll in the Registry at Enrollment Visit if not previously enrolled) 4. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative 5. Willing to complete questionnaires on mobile device 6. Able to use the Medidata Patient Cloud mobile application for completing the questionnaires
SUBJECT SELECTION CRITERIA: **Exclusion Criteria**	1. Presence of a condition or abnormality that, in the opinion of the Investigator, would complicate interpretation of study outcome data or interfere with achieving the study objectives 2. Presence of a pulmonary exacerbation at the Enrollment Visit 3. Hospitalization for distal intestinal obstruction syndrome (DIOS) within the 28 days prior to the Enrollment Visit 4. Current gastrointestinal (GI) or abdominal/pelvic malignancy 5. Abdominal or pelvic surgery within the 28 days prior to the

	Enrollment Visit 6. At the time of the Enrollment Visit, planned abdominal or pelvic surgery or bowel cleanout in the 28 days after the Enrollment Visit 7. Initiation of new CFTR modulator therapy within the 4 weeks prior to the Enrollment Visit 8. Intent to initiate new CFTR modulator therapy within 28 days of the Enrollment Visit
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Not applicable
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Not applicable
CONCOMMITANT MEDICATIONS	**Allowed:** Standard therapy for CF is allowed. **Prohibited:** There are no prohibited medications.
PRIMARY ENDPOINT	Percentage of scheduled outside-the-clinic assessments with at least one of the four PROs fully completed.
SECONDARY ENDPOINTS	**Assess the feasibility of electronic PRO surveys conducted outside-the-clinic setting:** 1. At each scheduled outside-the-clinic assessment, number (%) of subjects with at least one PRO fully completed 2. For each PRO, number (%) of subjects with fully completed questionnaires at each scheduled outside-the-clinic assessment and overall 3. Number (%) of completed PROs by subject, site, and other demographic and clinical features **Estimate the prevalence and variability of GI symptoms:** ▪ Evaluate prevalence of protocol-defined constipation: 4. Number (%) of enrolled subjects with any occurrence of constipation during 1 month of follow-up (the period prevalence) ▪ Evaluate <u>frequency</u> and <u>severity</u> of each GI symptom at scheduled assessments and overall: 5. Number (%) of subjects with presence of GI symptom 6. Distribution of severity scores of GI symptom 7. Mean severity score of GI symptom 8. Distribution of stool frequency and type by Bristol Stool Scale 9. Change in distribution of GI symptoms and stool frequency/type from enrollment visit overall and by whether

	subjects were receiving treatment ▪ Evaluate PRO scores overall and by sub-scale at scheduled assessments: 10. Mean PRO score 11. Within and across subject variability of PRO scores 12. Mean PRO scores (also mean differences and 95% confidence interval) comparing subjects with constipation to those without constipation ▪ Evaluate alternative CF specific definitions of constipation: 13. Examine alternative definitions of constipation that are CF specific based on correlation with PRO questionnaires and maximizing the area under the receiver operating characteristic curve (ROC curve) for PAC-SYM scores 14. Number (%) reporting constipation based on patient self-assessment. Examine concordance of self-reported constipation against protocol/alternate definitions using Cohen's kappa coefficient **Describe current management of GI symptoms:** ▪ Evaluate treatment for GI symptoms and constipation at time of enrollment visit: 15. Number (%) of all subjects receiving treatment 16. Number (%) of all subjects initiating treatment 17. Number (%) of all subjects receiving treatment by Medication class/type 18. Among subjects with GI symptoms and constipation, number (%) receiving treatment ▪ Evaluate symptom scores due to treatment: 19. Mean PRO scores (also mean differences and 95% confidence interval) comparing subjects receiving treatment for GI symptoms to those not receiving treatment 20. Among subjects receiving treatment for constipation, mean absolute change in PRO scores over time overall and by medication type/class
PLANNED INTERIM REVIEW	When 100 subjects have enrolled, an interim review will be conducted by an External Advisory Committee to determine whether the study should continue or stop. The Advisory Committee decision to continue to enroll or stop will be made in consideration of several factors including but not limited to: overall rate of enrollment, adequate representation of sub-populations, missing PRO data, and prevalence of constipation as well as estimates of PRO variability. The two stage enrollment strategy will allow for enriching enrollment based on either under-enrolled sub-populations or on the observed variability of GI symptoms for demographics-related factors such as

	age-group (pediatric/adult), modulator use or pancreatic status. In addition to the interim review, the TDNCC will continuously monitor enrollment and provide the Advisory Committee quarterly reports of enrollment demographics.
STATISTICS **Primary Analysis Plan**	The analysis population consists of all eligible subjects who enroll into the study. Results will be based primarily on descriptive statistics of questionnaire results. The primary endpoint is the percentage of scheduled outside-the-clinic assessments with at least one PRO fully completed out of the four questionnaires administered (the PAC-SYM, PAGI-SYM, PAC-QOL and the disease-specific questionnaire). The denominator for the percentage is the expected number of outside-the-clinic assessments (# of enrolled subjects x 3 outside-the-clinic assessments/subject). Missing PRO data will be extensively summarized including a comparison of the representativeness of the enrolled subjects against the larger CF community. Constipation is defined as <3 bowel movements in the past week and/or Bristol Stool type 1 or 2. The secondary endpoint upon which the sample size is based is the number (%) of enrolled subjects with any occurrence of constipation during 1 month of follow-up. For all percentages, the 95% Confidence Interval (95% C.I.) will be calculated using the Wilson method. Summary statistics of stool frequency and type will be tabulated over time to evaluate overall disease fluctuation. Individual item responses will be summarized by the number and percentage having symptoms or receiving treatment. Questionnaire scores, overall as well as by subdomain, will be based on mean scores (and 95% C.I.s) with any group comparison made via the t-test. For subjects either receiving treatment or with constipation, mean absolute change in scores from the enrollment visit will be reported including the standard deviation and 95% C.I of the change. For select endpoints, stratification by whether the site did or did not receive DIGEST Awards (CFF grant to a gastroenterologist to focus on the comprehensive GI care of patients with CF) will be considered. Additional stratification variables include: age, CF genotype, and pancreatic status. To evaluate change in PRO scores, a covariate adjusted repeated measures model of PRO scores will be fit in addition to select graphical figures showing PRO scores at scheduled assessments. No adjustment for multiplicity testing will be made. The details of all planned analyses will be outlined in the Statistical Analysis Plan (SAP).
Rationale for Number of Subjects	Sample size estimates for this study are based on two criteria: 1. To assess feasibility and ensure representativeness of the

	enrolled CF subjects 2. To estimate prevalence of GI symptoms (specifically constipation) The sample size estimate for this study is based on a period prevalence of constipation (the proportion of subjects with occurrence of symptom over a 1 month interval of time) in the 20% - 30% range (25% average). Approximately 400 subjects will be needed to estimate a 25% prevalence of constipation with a 95% C.I. half-width of 4.5% (95% C.I. = 20.5%, 29.5%) and assuming a 12% missing data rate. With 400 subjects, this study will allow estimation of variability (between and within subject) in 160 pediatric subjects and 240 adult subjects (alternatively 40 pediatric and 60 adults for 100 subjects).

1 BACKGROUND

Cystic Fibrosis (CF) is an autosomal recessive disease caused by mutations in the CF transmembrane regulator (CFTR) gene. CFTR encodes a chloride channel that regulates fluidity within the ducts of the body including the lung, stomach, intestine, liver, pancreas, sweat glands, and reproductive organs. In the lung, mutations in CFTR result in thick secretions that impair movement of cilia and clearance of infection. In the gastrointestinal (GI) tract, mutations similarly affect fluidity of secretions, as well as pH. Recent studies have shown that CFTR is also located in the neurons that innervate the GI tract(1). Together these mechanisms contribute to suboptimal fluidity, inflammation and dysmotility resulting in a number of gastrointestinal manifestations of CF.

GI symptoms are highly prevalent in people with CF, adding to the burden of a complex multisystem disease. Tabori et al. showed a frequency of abdominal complaints ranging from 20-80% in persons with CF(2). Questionnaires directed at abdominal complaints have been used in pediatric and adult CF clinics and demonstrate a high frequency of abdominal complaints, many of them severe (Bozic and Freedman, unpublished data) (3, 4). Concerns expressed by people with CF include poor weight gain, pancreatic insufficiency, poor appetite, abdominal pain, constipation, nausea/bloating and reflux. These symptoms frequently overlap, with many individual patients experiencing more than one, and they greatly impact the day-to-day quality of life (QOL) of persons with CF.

In addition, the impact of CFTR modulators on GI symptoms is not yet well understood. This is due to the variance in location and functional consequence of CFTR within the GI tract, including the pancreas, cholangiocytes, and intestinal epithelium.

The aim of the current project is to describe the burden of GI symptoms and their relationship to morbidity in people with CF utilizing existing patient-reported outcome (PRO) measures. Based on these results, we will focus on a series of studies to improve GI outcomes through establishing evidence-based algorithms. In the future, we would also like to evaluate the impact of CF modulators on common GI symptoms and evaluate how this might impact the development of symptom-specific algorithms.

1.1 Overview of Non-Clinical Studies

Exploration of GI disease in animal models of CF has focused on impaired bicarbonate and chloride secretion related to CFTR dysfunction in order to help explain the clinical manifestations of the disease. In these models the GI tract demonstrates physiological sequelae of impaired CFTR function similar to that seen in the lungs. This includes, but is not limited to, altered fluid pH(1, 3), thickened mucus secretions(2, 4), increased inflammation(5), impaired motility(5, 6) and dysbiosis(7, 8).

CFTR is present throughout the GI tract from the esophagus to the rectum(9). As the biologic and physiological processes of the intestine and its associated GI organs change, so do the manifestations of impaired CFTR activity. However, CF animal models have demonstrated that these manifestations do not exist in isolation, with CF therapies often having benefits to the GI tract beyond their primary target, the lung. As an example, successful treatment of dysbiosis and/or small intestinal bacterial overgrowth (SIBO) in mouse models results not only in quantitative and qualitative changes in bacterial flora, but also decreased mucus accumulation, decreased inflammation and improved intestinal transit times(10).

CF animal models have been effective in describing the multiple GI manifestations of CF and providing an initial understanding of the complex interactions among symptoms. However, due to differences of severity among CFTR-related phenotypes between species, animal models have a limited role in therapeutic investigations necessitating an increased focus on clinical studies.

1.2 Overview of Clinical Studies

There are currently no large, multicenter prospective clinical trials examining management of many of the GI symptoms in people with CF. Current recommendations in the CF literature still are largely based on expert consensus and opinions. However, generalized GI symptoms seen often in CF include nausea, abdominal pain, abdominal distension, constipation or diarrhea, decreased appetite and weight loss and these symptoms are crucial factors that impact patient's quality of life as well as the maintenance of an optimal nutritional state in people with CF(1, 3). The majority of studies of GI comorbidities seen in CF have been investigated in small single center studies, often retrospective. For example, although constipation is common in people with CF, and a source of significant abdominal pain, available studies have focused on the less common distal intestinal obstruction syndrome (DIOS). Studies focused on the lifetime prevalence of constipation are scarce, but some report that constipation is common in pediatrics with a prevalence ranging between 26-47% and 42% in adults(2, 4). The main obstacle in formulating formal treatment recommendations for the GI symptoms in CF has been the overlap of many GI symptoms simultaneously in the same patient with CF and the lack of a focused symptom-based questionnaire that correctly identifies constipation and other GI disorders specifically in patients with CF(1, 3-5). The pathophysiology of many of these GI symptoms in CF is unique and perhaps different than what is seen in the general population with multifactorial causes which include both an increased viscosity of intestinal mucus with subsequent prolonged transit times in the stomach (gastroparesis), small intestinal bacterial overgrowth (SIBO), or colon (colonic dysmotility or fecal incontinence due to severe constipation) (5, 6). In this study, we will focus on more common GI conditions that impact the lives of a large number of people with CF.

Recently a systematic review of abdominal complaints in adult and pediatric people with CF was undertaken, called the JenAbdomen-CF Score 1.0, which is a comprehensive 17 item survey(7). This survey is based on the patient-reported outcomes measures (PROMIS) set forth by the Food and Drug Administration (FDA) in 2009 to better identify GI symptoms in the general population in order to guide future treatments(8). The JenAbdomen study included a total of 131 patients with CF of all ages and found the most common GI symptoms to be loss of appetite (99%), dysgeusia (91%), followed by abdominal pain (80%), flatulence (78%), and distension (63%). Constipation was noted by 32% of adults and 30% of children and juveniles combined using a frequently used stool consistency scale called the Bristol Stool Scale(9). Unfortunately, other important measures of constipation such as quantification of the frequency of spontaneous bowel movements (SBM), complete bowel movements (CSBM), or others in regards to an obstructive defecation seen often in CF such as fecal incontinence or rectal prolapse were not included(10). Moreover, the JenAbdomen questionnaire and PROMIS do not identify the severity of GI symptoms which may be important endpoints in CF.

Other specific questionnaires focused on GI symptoms in people with CF have been developed and studied by several investigators. These include the GI Symptom Tracker (Abbot Pharmaceuticals) which is focused predominantly on symptoms associated with pancreatic

insufficiency and inadequate pancreatic enzyme therapy. The GI CF screening questionnaire was used as a screening questionnaire for pulmonologists and other providers involved in the care of a CF individual to determine the need for referral of patients to gastroenterologists (Bozic, Freedman, Schwarzenberg, personal communication). These questionnaires are not suitable for determining prevalence of GI symptoms in CF, nor for capturing the detail necessary to develop treatment algorithms.

Several validated questionnaires exist for capturing the overlap of GI symptoms in the general population and for categorizing them into specific groups based on most likely GI diagnoses. The validated questionnaires most cited and often used by the National Institutes of Health (NIH) and accepted by the FDA for purposes of clinical drug trials are the ROME IV questionnaires(11), Patient Assessment of Gastrointestinal Symptoms (PAGI-SYM)(12), Patient-Assessment of Constipation Symptoms (PAC-SYM)(13) and Patient- Assessment of Constipation Quality of Life (PAC-QOL)(14).

ROME IV is used as a diagnostic tool for what was previously termed "Functional Bowel Diseases"; however, it does not stratify patients based on symptom intensity and was purely formed for diagnostic purposes. It is a long and laborious set of questionnaires and although also validated in children more than 4 years of age, its limitations include the inability to analyze symptom severity. In contrast, the PAC-SYM is a 12-item questionnaire that evaluates many different GI symptoms including nausea, vomiting, upper or lower abdominal pain, constipation and other questions related to stool habits(13). A higher score corresponds with worse symptoms; with a range from 1 to 4 points. In the general adult population, a decrease in score of about 1 point indicates moderate improvement and a decrease of about 0.5 points indicating minimal improvement. Another validated scale system is the Bristol Stool Scale discussed above(9, 15) which is primarily based on a pictorial identification of stool consistency and validated both in the pediatric and adult population. A lower score on the Bristol Stool Scale (Type 1 and 2) corresponds with harder stool, whereas a higher score suggests diarrhea (Type 6, 7) with total range of scores ranging from 1 to 7.

The PAGI-SYM is a 20-item questionnaire with six subscales: heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain and has good internal consistency and reliability (α=0.79-0.91) (12). This questionnaire correlates well with the PAGI-QOL scores (p value < 0.0001) and was developed in fact in conjunction with a disease-specific QOL instrument, the PAGI-QOL, making it a robust internationally utilized instrument. The PAGI-SYM is a helpful questionnaire for assessing symptom severity with good construct validity in subjects with reflux, dyspepsia, abdominal pain and gastroparesis - all symptoms and disorders which people with CF could have. The initial purpose of this questionnaire was its application in clinical trials and for assessment of effectiveness of new medical treatments.

In addition to the PAGI-QOL, other important quality of life measures also exist for constipation and would be important to capture in the CF population. The PAC-QOL has 28 questions also rated on a 5 point Likert scale from 0 to 4 which range from not at all (0) to all of the time (4) (14). These questions are focused more on the intensity of bloating and constipation, as well as covering 4 subscales including worries and concerns (11 items), physical discomfort (4 items), Psychosocial discomfort (8 items) and satisfaction of treatment (5 items).

While this project collects data needed to develop protocols for several key GI symptoms in people with CF, we have chosen constipation as the first symptom we will be addressing in our CF patient population. Clear definitions of chronic constipation in CF do not exist but are needed in establishing a diagnosis and subsequent treatment plans in the acute and chronic settings. The most commonly accepted definition of constipation has been based on ROME IV criteria defining constipation as less than 3 bowel movements a week. The FDA uses this definition in combination with endpoints such as the number of CSBM and Bristol Stool Scale Type 1 and 2 as defining constipation(16). The FDA's PROMIS also defined chronic constipation as decreased stool frequency as measured by the number of CSBM a week to assess treatment response and for the purposes of clinical trials(8). Abdominal pain and discomfort were excluded in the definition of constipation although these are common in our patients with CF(16). The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has proposed a definition of constipation in CF which considers: 1) abdominal pain and/or distention, 2) reduced frequency or increased consistency of stool in the last few weeks or months, and 3) Symptoms 1 and 2 are relieved by laxatives(17). However, this definition was primarily proposed to differentiate constipation from DIOS. It remains to be seen whether any of these definitions adequately describe the experience of constipation in a patient with CF that is relevant for clinically and/or research utility.

Most of the current recommendations for treatment of constipation in CF are based on expert practices and guidelines rather than formal clinical trials. Given the lack of clinical data, Freeman et al.(18) has come up with an algorithm for treatment of constipation in CF which is based primarily on expert opinion and which has not been formally tested yet in the clinical setting. Our proposal would use GI-symptomatology questionnaires to understand the multiple overlapping GI symptoms in people with CF. This would be followed by interventions directed at the most high-frequency symptoms.

2 STUDY RATIONALE

There are currently no large, multicenter prospective clinical trials examining management of constipation or other GI symptoms in people with CF. Current recommendations in the CF literature are largely based on expert consensus and opinions. Yet, constipation and other GI symptoms are crucial factors in QOL and maintenance of optimal nutritional state in people with CF. This study will use GI-symptomatology questionnaires to understand the multiple overlapping GI symptoms in people with CF. This would be followed by studies to improve GI outcomes through establishing evidence-based algorithms, starting with constipation. In the future, we would also like to evaluate the impact of CF modulators on common GI symptoms and evaluate how this might impact the development of symptom-specific algorithms.

2.1 Risk / Benefit Assessment

As an observational study, there is no anticipated direct benefit to subjects.

3 STUDY OBJECTIVES

3.1 Primary Objective

Assess the feasibility of electronic PROs conducted outside-the-clinic.

3.2 Secondary Objectives

- Estimate the prevalence and variability of GI symptoms occurring in pediatric and adult patients with CF
- Describe current management of GI symptoms in patients with CF
- Gather information to guide and inform on the design of future algorithm-based approaches to treating GI symptoms in people with CF

4 STUDY DESIGN

4.1 Study Overview

This is a prospective, multicenter, observational study designed to collect gastrointestinal related data in patients with CF.

Eligible subjects will be consented and enrolled in the study at the Enrollment Visit. At the visit, the subject or parent/guardian will complete the PROs using their mobile device (e.g., smartphone or tablet). The PROs will consist of four questionnaires: Patient Assessment of Constipation-Symptoms (PAC-SYM), Patient Assessment of Gastrointestinal-Symptoms (PAGI-SYM), Patient Assessment of Constipation Quality of Life (PAC-QOL) and the disease-specific questionnaire. The disease-specific questionnaire will include the Bristol Stool Scale and will collect information on presence of fecal incontinence, stool quality and frequency. At the Enrollment Visit, weight and height will be collected in addition to medical history and concomitant medication information. The subject or parent/guardian will complete the PROs outside-the-clinic setting per the Schedule of Events using their mobile device.

5 CRITERIA FOR EVALUATION

5.1 Primary Endpoint

Percentage of scheduled outside-the-clinic assessments with at least one of the four PROs fully completed.

5.2 Secondary Endpoints

Assess the feasibility of electronic PRO surveys conducted outside-the-clinic setting:

1. At each scheduled outside-the-clinic assessment, number (%) of subjects with at least one PRO fully completed
2. For each PRO, number (%) of subjects with fully completed questionnaires at each scheduled outside-the-clinic assessment and overall
3. Number (%) of completed PROs by subject, site, and other demographic and clinical features

Estimate the prevalence and variability of GI symptoms:

- Evaluate prevalence of protocol-defined constipation:
    4. Number (%) of enrolled subjects with any occurrence of constipation during 1 month of follow-up (the period prevalence)
- Evaluate frequency and severity of each GI symptom at scheduled assessments and overall:
    5. Number (%) of subjects with presence of GI symptom

6. Distribution of severity scores of GI symptom
7. Mean severity score of GI symptom
8. Distribution of stool frequency and type by Bristol Stool Scale
9. Change in distribution of GI symptoms and stool frequency/type from enrollment visit overall and by whether subjects were receiving treatment

- Evaluate PRO scores overall and by sub-scale at scheduled assessments:
  10. Mean PRO score
  11. Within and across subject variability of PRO scores
  12. Mean PRO scores (also mean differences and 95% confidence interval) comparing subjects with constipation to those without constipation
- Evaluate alternative CF specific definitions of constipation:
  13. Examine alternative definitions of constipation that are CF specific based on correlation with PRO questionnaires and maximizing the area under the receiver operating characteristic curve (ROC curve) for PAC-SYM scores
  14. Number (%) reporting constipation based on patient self-assessment. Examine concordance of self-reported constipation against protocol/alternate definitions using Cohen's kappa coefficient

Describe current management of GI symptoms:

- Evaluate treatment for GI symptoms and constipation at time of enrollment visit:
  15. Number (%) of all subjects receiving treatment
  16. Number (%) of all subjects initiating treatment
  17. Number (%) of all subjects receiving treatment by Medication class/type
  18. Among subjects with GI symptoms and constipation, number (%) receiving treatment
- Evaluate symptom scores due to treatment:
  19. Mean PRO scores (also mean differences and 95% confidence interval) comparing subjects receiving treatment for GI symptoms to those not receiving treatment
  20. Among subjects receiving treatment for constipation, mean absolute change in PRO scores over time overall and by medication type/class

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of CF who meet all of the inclusion and none of the exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. All genders ≥ 2 years of age at time of consent
2. Documentation of a Cystic Fibrosis (CF) diagnosis as evidenced by one or more clinical features consistent with the CF phenotype and one or more of the following criteria:
   - Sweat chloride equal to or greater than 60 mEq/liter by quantitative pilocarpine iontophoresis test (QPIT)

- Two well-characterized mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
- Abnormal nasal potential difference (change in NPD in response to a low chloride solution and isoproteronol of less than -5 mV)

3. Enrolled in the Cystic Fibrosis Foundation Patient Registry (subjects may enroll in the Registry at Enrollment Visit if not previously enrolled)
4. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative
5. Willing to complete questionnaires on mobile device
6. Able to use the Medidata Patient Cloud mobile application for completing the questionnaires

6.3 Exclusion Criteria

1. Presence of a condition or abnormality that, in the opinion of the Investigator, would complicate interpretation of study outcome data or interfere with achieving the study objectives
2. Presence of a pulmonary exacerbation at the Enrollment Visit
3. Hospitalization for distal intestinal obstruction syndrome (DIOS) within the 28 days prior to the Enrollment Visit
4. Current gastrointestinal (GI) or abdominal/pelvic malignancy
5. Abdominal or pelvic surgery within the 28 days prior to the Enrollment Visit
6. At the time of the Enrollment Visit, planned abdominal or pelvic surgery or bowel cleanout in the 28 days after the Enrollment Visit.
7. Initiation of new CFTR modulator therapy within the 4 weeks prior to the Enrollment Visit
8. Intent to initiate new CFTR modulator therapy within 28 days of the Enrollment Visit

6.4 Study Specific Tolerance for Inclusion/Exclusion Criteria

Subjects who fail to meet one or more of the inclusion criteria or who meet any of the exclusion criteria will not be enrolled in this study. Waivers of any of the above study entry criteria will not be granted.

6.5 Screen Fail Criteria

Any consented patient who is excluded from the study before enrollment is considered a screen failure. All screen failures must be documented with the reason for the screen failure adequately stated. If a subject screen fails prior to enrollment, they can be rescreened if the site staff feels they meet eligibility criteria. Rescreened subjects will have to complete all screening procedures (i.e., data from previous screenings cannot be used).

7 CONCURRENT MEDICATIONS

7.1 Allowed Medications and Treatments

Standard therapy for CF is allowed.

7.2 Prohibited Medications and Treatments

There are no prohibited medications.

8 STUDY TREATMENTS

Not applicable.

9 STUDY PROCEDURES AND GUIDELINES

The procedures described below will be performed at the visits noted in the Schedule of Events (Appendix) and in Section 9.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

Concomitant medications and concurrent therapies will be documented as noted in the Schedule of Events.

9.1.2 Demographics and CFF Registry ID

Demographic information (date of birth, sex, race) and CF Registry number will be recorded.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent gastrointestinal history, and information regarding underlying diseases will be recorded.

9.1.4 CF Diagnosis

CF diagnostic test date(s) and results will be recorded.

9.1.5 Weight and Height

Weight will be measured and recorded as noted in the Schedule of Events. Adults and children may remain in clothes (without shoes). A standing height will be measured and recorded as noted in the Schedule of Events.

9.1.6 Subject Questionnaire: Patient Assessment of Gastrointestinal Disorders – Symptom Severity Index (PAGI-SYM)

Subjects will complete the PAGI-SYM questionnaire as noted in the Schedule of Events. The PAGI-SYM questionnaire measures specific symptoms of patients with upper gastrointestinal disorders, specifically GERD, dyspepsia and gastroparesis. The PAGI-SYM contains 20 questions scored on a 6-point Likert response scale (0 – 5 range). The questionnaire takes approximately 5 minutes to complete. For subjects ≥ 2 years of age to < 12 years of age, the

parent/guardian will complete the questionnaire. For subjects ≥ 12 years of age, the subject will complete the questionnaire.

9.1.7 Subject Questionnaire: Patient Assessment of Constipation – Symptom Severity Index (PAC-SYM)

Subjects will complete the PAC-SYM questionnaire as noted in the Schedule of Events. The PAC-SYM questionnaire measures specific symptoms of patients with constipation. The PAC-SYM contains 12 questions scored on a 5-point Likert response scale (0 – 4 range). The questionnaire takes approximately 5 minutes to complete. For subjects ≥ 2 years of age to < 12 years of age, the parent/guardian will complete the questionnaire. For subjects ≥ 12 years of age, the subject will complete the questionnaire.

9.1.8 Subject Questionnaire: Patient Assessment of Constipation Quality of Life (PAC-QOL)

Subjects will complete the PAC-QOL questionnaire as noted in the Schedule of Events. The PAC-QOL questionnaire measures quality of life of patients with constipation. The PAC-QOL contains 28 questions scored on a 5-point Likert response scale (0 – 4 range). The questionnaire takes approximately 5 minutes to complete. For subjects ≥ 2 years of age to < 12 years of age, the parent/guardian will complete the questionnaire. For subjects ≥ 12 years of age, the subject will complete the questionnaire.

9.1.9 Disease-specific questions

The Bristol Stool Scale is a visual assessment of stool consistency. In addition, there are questions related to stool quality, frequency and presence of fecal incontinence. These will be completed as noted in the Schedule of Events. The questionnaire takes approximately 5 minutes to complete. For subjects ≥ 2 years of age to < 12 years of age, the parent/guardian will complete these questions. For subjects ≥ 12 years of age, the subject will complete these questions.

10 EVALUATIONS BY VISIT

10.1 Enrollment Visit (Day 1)

1. Review the study with the subject (subject's legal representative) and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2. Assign the subject a unique screening number.
3. Perform review of eligibility criteria.
4. Record demographics data and CFF Registry ID.
5. Record medical history, including a history of CF, diagnosis date, gastrointestinal history, and prior CF and gastrointestinal treatments.
6. Record concomitant medications.
7. Measure and record height and weight.

8. Assist with downloading and registering the Medidata Patient Cloud mobile application for completing the questionnaires into subject's mobile device (e.g., smartphone or tablet computer). Review and provide the subject with the application and questionnaire completion instructions.
9. Complete electronic PRO questionnaires (PAGI-SYM, PAC-SYM, PAC-QOL, and additional disease-specific questions) on mobile device (subject or their parent/guardian).

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

Adverse Events, including Serious Adverse Experiences, will not be collected as part of this study.

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Withdrawal of Subjects from the Study

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. This may include subjects who withdraw from completing the study visit and who decline to complete the questionnaires.

If the investigator is able to provide a reason for early subject withdrawals, it will be specified in the subject's source documents.

12.2 Replacement of Subjects

Subjects who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or the Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files. The site will report the violation to their IRB in accordance with their IRB reporting requirements.

14 DATA SAFETY MONITORING

Not applicable

15 STATISTICAL METHODS AND CONSIDERATIONS

15.1 General Considerations

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written, describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

The endpoints of this study are mostly descriptive, with all continuous outcomes such as symptom severity and PRO scores evaluated using descriptive statistics such as mean, median, standard deviation and 95% confidence intervals. Presence/absence of symptoms will be shown as percentages and corresponding 95% confidence intervals calculated using the Wilson method. Group comparisons will be made via the two-sample t-test for continuous outcomes or Fisher's exact test for categorical outcomes. Except where otherwise noted, all tests will be two-sided and statistical significance will be determined at the 0.05 level. No adjustment for multiple comparisons will be made.

15.1.1 Data Sets Analyzed

The analysis population consists of all eligible subjects who enroll into the study – the Full Analysis Set. For select endpoints, stratification of study results by age group, CF genotype, pancreatic status, and whether sites were DIGEST awardees will also be considered.

15.2 Demographic and Baseline Characteristics

The enrolled study population will be described with respect to baseline demographic and clinical characteristics such as age, gender, race, ethnicity, genotype, height, weight, pancreatic status, body mass index, and use of concomitant medications. Demographics of subjects comparing completers (those who completed all questionnaires at all assessments) to those that are not completers will also be included. To evaluate the representativeness of the enrolled study population, the demographics of enrolled subjects will be compared against the general CF population (from the CFF Patient registry).

15.3 Analysis of Primary Endpoint

The primary endpoint is the percentage of scheduled outside-the-clinic assessments with at least one PRO fully completed out of the four questionnaires administered (the PAC-SYM, PAGI-SYM, PAC-QOL and the disease-specific questionnaire). The denominator for the percentage is the expected number of outside-the-clinic assessments (# of enrolled subjects x 3 outside-the-clinic assessments/subject).

15.4 Analysis of Secondary Endpoints

Constipation is defined as <3 bowel movements in the past week and/or Bristol Stool type 1 or 2. The secondary endpoint upon which the sample size is based is the number (%) of enrolled subjects with any occurrence of constipation during 1 month of follow-up (the period prevalence). Treatment for GI symptoms and constipation will be summarized based on the percentage of enrolled subjects receiving and initiating treatment at time of enrollment visit. To evaluate whether CF subjects are adequately treated, the number and percentage of subjects with GI symptoms and constipation on treatment will be reported. All GI related treatments will be classified by medication type/class.

Individual GI symptoms will be extracted from the PAC-SYM and PAGI-SYM questionnaires. For each GI symptom, frequency and severity will be summarized at each assessment as follows: number (%) of subjects with GI symptom, severity of GI symptom (mean score and distribution of severity score) and change in severity scores from the enrollment visit by whether subjects were receiving treatment.

Mean overall (and by sub-scale) PRO scores for PAC-SYM, PAGI-SYM and PAC-QOL at scheduled assessments will be reported including evaluation of within and between subject variability. Group comparisons of mean scores by subjects receiving/not receiving treatment and by those with/without constipation will also be made. Absolute change in PRO scores from enrollment visit to scheduled assessments will be reported based on subjects receiving/not receiving treatment for constipation. To examine these effects, figures displaying mean PRO scores by scheduled assessment will be created. Additionally, mixed effects models for repeated measures will be fit with PRO scores as the outcome and covariates for visit, treatment, pancreatic status, age group and the interaction between treatment and visit.

Alternative definitions of constipation that are CF specific will be created based on different frequencies of bowel movement and Bristol stool type evaluated individually or in combination. Spearman correlations of stool frequency with the PAC-SYM score and Bristol stool type with PAC-SYM scores will be examined. The different constipation definitions will be evaluated by comparing against the area under the curve of receiver operating characteristic curve (ROC curve) for PAC-SYM scores. The percentage of subjects reporting constipation based on self-assessment and the concordance to the protocol definition/alternate definitions will be made using Cohen's kappa coefficient.

15.5 Analysis of Missing Data

Detailed summaries of missing data including the number and percentage of scheduled assessments with at least one of the four PROs completed will be provided. For each PRO, the percentage of scheduled assessments with fully completed PROs will also be provided. Other missing data methods to examine sensitivity and robustness of study results for the primary and key secondary endpoints will be described in the SAP. To minimize missing data, subjects will receive reminder notifications to complete their scheduled assessment.

15.6 Interim Review

When 100 subjects have enrolled, an interim review will be conducted by an External Advisory Committee to determine whether the study should continue or stop. The Advisory Committee decision to continue to enroll or stop will be made in consideration of several factors including but not limited to: overall rate of enrollment, adequate representation of sub-populations, missing PRO data, and prevalence of constipation as well as estimates of PRO variability. The two-stage enrollment strategy will allow for enriching enrollment based on either under-enrolled sub-populations or on the observed variability of GI symptoms for demographics-related factors such as age-group (pediatric/adult), modulator use or pancreatic status. In addition to the interim review, the TDNCC will continuously monitor enrollment and provide the Advisory Committee quarterly reports of enrollment demographics.

15.7 Sample Size

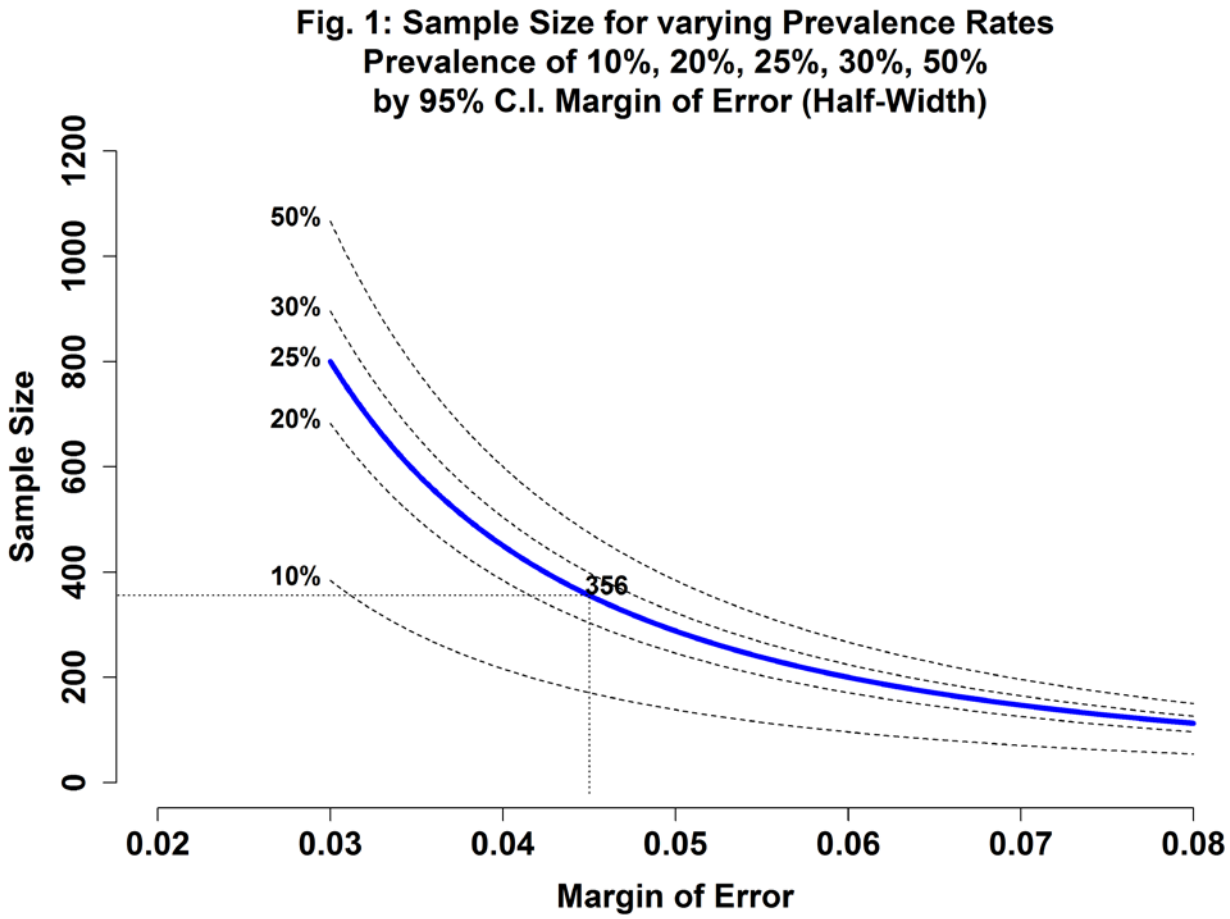
Sample size estimates for this study are based on two criteria:

a. To assess feasibility and ensure representativeness of the enrolled CF subjects

b. To estimate prevalence of GI symptoms (specifically constipation)

Period prevalence is defined as the proportion of subjects with symptom over an interval of time. Estimates of constipation prevalence in CF patients varies in the literature. A recent 2017 publication (7) showed the period prevalence of constipation over 3 months was 31% (32% adults; 30% children). Another 2010 publication (3) estimated prevalence of constipation in CF patients age ≤ 18 years in the Netherlands at 20% (annual assessment) using the ESPGHAN definition. Note that an epidemiologic review of constipation prevalence in the general population (non-CF) in North America ranged from 1.9% to 27.2% with most estimates from 12%-19% (19). Therefore, 10% will serve as the lower bound estimate of constipation prevalence. The sample size estimate for CF patients in the GALAXY study is based on a prevalence of constipation over a 1 month period in the 20% - 30% range (25% average).

Sample size estimates are based on 95% confidence intervals (C.I.) half-widths (i.e., width of one arm of the 95% CI) for proportions. While constipation is one symptom of interest, it is difficult to specify an exact prevalence estimate over a 1 month period utilizing the study specific definition of constipation. In addition, the occurrence of other GI symptoms is also of interest and will occur at varying rates. Therefore, the figure below shows what the sample size (y-axis) is for varying half-width sizes (x-axis) when prevalence estimates range between 10% to 50% (maximum). Approximately 400 subjects are needed to estimate a prevalence of constipation of 25% with a 95% C.I. half-width of 4.5% (95% C.I. = 20.5%, 29.5%) and assuming a 12% missing data rate.



With 400 subjects, this study will allow estimation of variability (between and within subject) in 160 pediatric subjects and 240 adult subjects. A recent publication (20) reported PAC-SYM variability from 2884 adult patients with chronic constipation from six randomized clinical trials (scores range from 0 to 4 per subject). The study reported a baseline variance of 0.52. With 240 adult subjects and between-subject variance of 0.52, the 95% confidence interval for variance is 0.44, 0.63 (width = 0.19).

16 DATA COLLECTION, RETENTION AND CLINICAL MONITORING

16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject who signs informed consent.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number and subject number.

If a correction is required for a CRF, the time and date stamp tracks the person entering or updating CRF data and creates an electronic audit trail.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. At the completion of the study, a copy of the CRF data will be provided to the site to be retained at the Investigator's site.

16.2 Data Management Procedures

TDNCC utilizes Medidata Solutions, Inc. (Medidata) Rave for their study database. The Medidata Rave EDC system is designed to be US Code of Federal Regulations (CFR) 21 Part 11 compliant, with a robust audit trail system and electronic signature capabilities. Study personnel at each site will enter data from a subject's visit onto electronic CRF screens via a web browser. Study subjects will not be identified by name in the study database or on any data capture screens, but will be identified by a unique subject identification number. Only study personnel at the individual sites will be able to link the study ID to the subject's name. TDNCC also utilizes the Medidata Rave eCOA/ePRO system, a regulatory compliant system which allows subjects in a study using Medidata Rave EDC to complete and submit forms and data for patient-reported outcomes electronically on a mobile device to the Medidata Rave EDC System. Study personnel at each site will register study subjects using their unique subject identification number which generates an activation code unique to that subject. Study site personnel provide the subject with their activation code. The study subject downloads the Medidata Rave eCOA/ePRO app to their mobile device and uses their unique activation code to create their ePRO login and password.

The Biostatistics and Clinical Data Management group of the TDNCC will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed. All procedures for the handling and analysis of data will be conducted using good computing practices for the handling and analysis of data for clinical trials.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, data validation checks will be applied on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented in an audit trail.

16.4 Security and Archival of Data

The Rave EDC and Rave eCOA/ePRO systems are hosted by Medidata; the data are stored at Medidata's primary data center in Houston, Texas, with fail-safe data centers in New Jersey. Data are regularly backed up by Medidata.

Medidata maintains 21 CFR Part 11-compliant electronic systems, with procedures in place to safeguard against unauthorized acquisition of data. Any authorized communication with the Medidata servers at the Houston Data Center is conducted via SSL (128-bit) encryption. Robust password procedures, consistent with 21 Part 11, are in place. Robust physical security procedures are in place at the Houston Data Center to prevent unauthorized personnel physical access to the server rooms. EDC account access is maintained and monitored by the Biostatistics and Clinical Data Management group of the TDNCC.

Other databases will be stored on Seattle Children's servers and are safeguarded against unauthorized access by established security procedures. Network accounts are password protected and maintained and monitored by Seattle Children's. Data is backed up regularly according to the Information Services group's procedures.

16.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (e.g., patient files, signed informed consent forms, copies of CRFs, Essential Document and Study Reference Binders) must be kept secured for a period of five years after database lock. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

16.6 Monitoring

By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR 21 Part 312 to ensure investigator compliance to 21 CFR Parts 50, 56 and 312.

16.7 Subject Confidentiality

In order to maintain subject confidentiality, only a site number and subject number will identify all study subjects on CRFs and other documentation submitted to the Sponsor. The subject's CFF patient registry number will also be collected. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate

hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

17.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB on record prior to study initiation. The Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB's unconditional approval statement will be transmitted by the Investigator to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the IRB, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form

(and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

During the course of the study, if modifications are made to the consent form that impact the subject, the subject will be re-consented as described above.

17.4 Consent for Collection and Use of CFF Registry ID Number

To facilitate the inclusion of retrospective and prospective information from all patients enrolled in this study, the subject's CFF Registry ID number will be collected. The Cystic Fibrosis Foundation Patient Registry (CFFPR) collects data on all CF patients who consented to participate in the CFFPR registry and who are followed at CFF-accredited care centers. The registry data includes information from clinical encounters, hospitalizations courses of antibiotics, and year-end surveys. Data also include microbiology results, spirometry results, CF genotype and other information. The patient's CF registry number will be recorded in the CRF.

17.5 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.6 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1 Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.

2 Personally conduct or supervise the study (or investigation).

3 Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.

4 Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.

5 Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

6 Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).

7 Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.

8 Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).

9 Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.

10 Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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APPENDIX. SCHEDULE OF EVENTS

	ENROLLMENT VISIT (DAY 1)	DAY 7 [A] (+ 1 day)	DAY 14 [A] (+ 1 day)	DAY 28 [A] (+ 1 day)
Informed Consent	X			
Review Eligibility	X			
CFF Registry ID, CF Diagnosis, and Demographics	X			
Medical History/GI History	X			
Concomitant Medication Review	X			
Height	X			
Weight	X			
Assist with downloading mobile application for completing questionnaires	X			
Complete PAC-SYM and PAGI-SYM questionnaires and disease-specific questions on mobile device	X	X	X	X
Complete PAC-QOL on mobile device	X			X

[A] The Questionnaire(s) will be completed outside-the-clinic.