Protocol Title: A Multi-Site Trial of Specialist Palliative Care in Cystic Fibrosis

PROTOCOL TITLE: A Multi-Site Trial of Specialist Palliative Care in Cystic Fibrosis

PRINCIPAL INVESTIGATOR:
Dr. Dio Kavalieratos
Department of Family and Preventive Medicine
412.805.8381
d.kavalieratos@emory.edu

EXTERNAL (NON-EMORY) COLLABORATORS
Robert Arnold, MD, University of Pittsburgh, General Internal Medicine
Andrew Althouse, PhD, University of Pittsburgh, General Internal Medicine
Laura Hanson, MD MPH, University of North Carolina, Geriatric Medicine
Elisabeth Dellon, MD MPH, University of North Carolina, Pediatrics
Marie Bakitas, DNSc CRNP, University of Alabama at Birmingham, Nursing
Sigrid Ladores, PhD RN, University of Alabama at Birmingham, Nursing
Gretchen Winter, MD, University of Alabama at Birmingham, Medicine
George Solomon, MD, University of Alabama at Birmingham, Medicine
*Jonathan Ailon, MD Msc, St. Michael's Teaching Hospital, General Internal Medicine
*Anne Stephenson, MD PhD, St. Michael's Teaching Hospital, Medicine
Douglas Conrad, MD, University of California, San Diego, Medicine
William Mitchell, MD, University of California, San Diego, Medicine
Jessica Goggin, PhD MAS RN, University of California, San Diego, Medicine

*The Toronto, ON investigators will receive regulatory approval from their institution prior to engaging in research.

VERSION: Version 2.4, March 2022.

FUNDING SOURCE: Cystic Fibrosis Foundation

REVISION HISTORY

Revision #	Version Date	Summary of Changes
2.1	9/23/20	Changed data collection interval from monthly to quarterly, with updated data analysis. Changed consent forms to reflect new total available compensation.
2.2	9/25/20	Adjusted eligibility criteria to remove FEV1% threshold.
2.3	12/18/20	Clarified that fidelity recordings of intervention visits will be destroyed after the data collection period is complete.
2.4	03/28/22	Increase target enrollment by 40 to achieve target randomization

Protocol Title: A Multi-Site Trial of Specialist Palliative Care in Cystic Fibrosis

Protocol Title: A Multi-Site Trial of Specialist Palliative Care in Cystic Fibrosis

Table of Contents

1. Study Summary 4
2. Objectives 4
3. Background 5
4. Study Endpoints 6
5. Study Intervention / Design 6
6. Procedures Involved 7
7. Data and Specimen Banking 9
8. Sharing of Results with Participants 9
9. Study Timelines 9
10. Subject Population 9
11. Vulnerable Populations 10
12. Local Number of Participants 10
13. Recruitment Methods 11
14. Withdrawal of Participants 12
15. Risks to Participants 12
16. Potential Benefits to Participants 12
17. Data Analysis, Management and Confidentiality 12
18. Provisions to Monitor the Data to Ensure the Safety of Participants 14
19. Provisions to Protect the Privacy Interests of Participants and Confidentiality of Participants' Identifiable Data 14
20. Economic Burden to Participants 14
21. Consent Process 15
22. Setting 16
23. Multi-Site Research when Emory is the Lead Site 16
24. References 17

Protocol Title: A Multi-Site Trial of Specialist Palliative Care in Cystic Fibrosis

1. Study Summary

Study Title	A Multi-Site Trial of Specialist Palliative Care in Cystic Fibrosis
Study Design	Multi-site Randomized-Control Clinical Trial
Primary Objective	Assess the effect of embedded specialist palliative care versus usual care on patient quality of life among adults with CF
Secondary Objective(s)	• Assess the effect of embedded specialist palliative care versus usual care on caregiver quality of life and burden • Assess the effect of embedded specialist palliative care on patient depression, anxiety, and coping skills • Evaluate the effectiveness of intervention implementation
Research Intervention(s)/Interactions	≥4 visits with a palliative care specialist, plus monthly check-in calls
Study Population	Adult Patients with Cystic Fibrosis, Adult Caregivers, CF Clinicians and Administrators
Sample Size	264 patients randomized (304 enrolled) 198 caregivers 10 CF team members (Aim 3 only) 5 CF clinic administrators (Aim 3 only)
Study Duration for individual participants	15 months
Study Specific Abbreviations/ Definitions	Cystic Fibrosis – CF Integrating Specialist Palliative Care to Improve Care and Reduce Suffering – InSPIRe:CF Quality of Life – QoL Functional Assessment of Chronic Illness Therapy – Palliative Care – FACIT-Pal Specialty Palliative Care - PC
Funding Source (if any)	Cystic Fibrosis Foundation

2. Objectives

This is a Phase III randomized clinical trial to compare the effectiveness of integrating specialist palliative care versus usual care alone among adults (≥18 years) with cystic fibrosis (CF). The intervention is titled Integrating Specialist Palliative Care to Improve Care and Reduce Suffering: Cystic Fibrosis (InSPIRe:CF), which was previously pilot-tested at the University of Pittsburgh in a 1:1 feasibility pilot RCT (n=50) and shown to be feasible, acceptable, and perceived to be effective. For this multisite comparative effectiveness trial, our primary endpoint is patient-reported quality of life at 12 months, with secondary outcomes including additional patient-reported outcomes (e.g., symptom burden, satisfaction with care) and caregiver-reported outcomes (e.g., caregiver quality of life). In addition to our effectiveness outcomes, we will include a rigorous mixed-methods evaluation that includes interviews with key

informants to elucidate the mechanisms by which InSPIRe:CF influences outcomes and to identify factors necessary for successful dissemination and implementation of the intervention beyond this trial.

Aim 1: Compare InSPIRe:CF to usual care for effects on patient quality of life (QoL) (primary outcome), physical and psychological symptom burden, and advance care planning.
Hypotheses: Compared to usual care, patients receiving InSPIRe:CF will report better QoL (as measured by the Functional Assessment of Chronic Illness Therapy-Palliative Care (FACIT-Pal) instrument), decreased physical symptom burden, decreased psychological distress, and higher rates of advance care planning at 12 months.
Aim 2: Compare InSPIRe:CF to usual care for effects on family caregiver QoL, psychological distress, and burden. Hypotheses: Compared to usual care, family caregivers of patients receiving InSPIRe:CF will report better QoL, decreased psychological distress, and reduced caregiver burden at 12 months.

Aim 3: Evaluate the mechanisms of action of InSPIRe:CF and its barriers and facilitators to wider dissemination and implementation. We will conduct a rigorous mixed-methods summative evaluation to understand patient, clinician, and systems-level barriers and facilitators to adoption of specialty palliative care (PC) in CF.

3. Background

Individuals living with CF and their caregivers experience unrelieved suffering and impaired QoL. CF is a progressive, multisystem genetic disease affecting >30,000 individuals in the US.[1] Despite improved outcomes with therapeutic advances, individuals with CF experience high physical symptom burden (e.g., dyspnea, fatigue, pain) and emotional distress (e.g., depression, anxiety) significantly impairing functional status and QoL. [2-5]

Treatment burden in CF is immense; adults spend a mean 108 minutes/day on treatments including airway clearance and inhaled and nebulized medications.[6] Furthermore, patients with CF must navigate complex and highly specialized healthcare, making difficult decisions about high-risk therapies, such as lung transplantation. All the while, these multifaceted burdens also negatively impact family caregivers and their QoL.

Palliative care (PC) is proven to reduce suffering and improve QoL for people with serious illness, but is untested for CF. Skilled PC clinicians are able to optimize QoL for patients and families affected by serious illness, through expert assessment and management of physical and emotional symptoms; social support; assistance with treatment decision-making; and complex care coordination. In 2016, we published a meta-analysis of 43 clinical trials testing PC interventions, synthesizing >40 years of PC research.[7] We demonstrated that PC is associated with improvements in patient QoL, reductions in symptom burden, improved satisfaction with care, and higher rates of advance care planning. However, the majority of clinical trials enrolled patients with advanced cancer; and importantly, none included individuals living with CF.

Palliative care is underutilized for patients with CF. In a 2018 retrospective chart review of 248 deaths across 71 CF care centers, use of specialist PC was rare, and, if present, was typically only at the end of life.[8] A critical reason for this underutilization is likely the lack of evidence for PC in CF. To date, the rationale for PC in CF has largely been one of analogy from the benefits seen in oncology, since no rigorous experimental evidence exists to demonstrate the benefit of PC in CF.

We therefore developed InSPIRe:CF – the first specialist PC intervention for individuals with CF with support from the Cystic Fibrosis Foundation.[9] As opposed to a standalone PC intervention that would add burden to the already complex health care demands of living with CF, we designed InSPIRe:CF as an intervention that seamlessly integrates a PC specialist within usual CF care. Informed by the Chronic Care Model and more than 5 years of formative work, InSPIRe:CF comprises 2 key components: 1) four protocolized PC encounters, delivered quarterly either in-person or via telemedicine; and, 2) monthly calls to reinforce topics and identify incident concerns. In a mixed-methods RCT (n=50), we demonstrated that InSPIRe:CF is feasible, acceptable, and is perceived by patients to improve QoL, symptoms, and psychological distress. The next logical step is therefore to conduct a fully powered efficacy clinical trial.

4. Study Endpoints

Aim 1 (Effects of InSPIRe:CF on patient-reported outcomes; all at 12 months)
Primary
Patient quality of life (as measured by FACIT-Pal instrument)
Secondary
CF-specific patient quality of life (as measured by PROMIS Global Health 10 instrument)
Symptom burden (as measured by MSAS-CF instrument)
Anxiety and depression (as measured by HADS instrument)
Coping (as measured by Brief COPE instrument)
Satisfaction with care (as measured by FAMCARE instrument)

Aim 2 (Effects of InSPIRe:CF on caregiver-reported outcomes; all at 12 months)
Primary
Caregiver quality of life (as measured by PROMIS Global 10 instrument)
Secondary
Anxiety and depression (as measured by HADS instrument)
Caregiver burden (as measured by Zarit Buden Interview instrument)
Coping (as measured by Brief COPE instrument)

Aim 3 (Summative mixed-methods evaluation of dissemination and implementation factors)
Primary
Qualitative themes related to factors relevant to future dissemination and implementation of InSPIRe:CF intervention at other sites.

5. Study Intervention / Design

In this Phase III multi-site randomized clinical trial, we will compare the InSPIRe:CF intervention versus usual care, while conducting a summative evaluation using qualitative interviews. Together, these two primary data streams will yield a comprehensive mixed-methods evaluation of the InSPIRe:CF trial.

The InSPIRe: CF intervention has two key components that work together to influence care and improve outcomes:
1) Four protocolized face-to-face or telehealth palliative care (PC) visits, delivered alongside standard CF care. Participants may receive additional PC visits at the discretion of the patient or their clinicians.
2) Monthly telephone calls from the PC clinician to monitor status and address incident concerns.

Patients and caregivers randomized to the usual care arm of the study will continue receiving care for CF without PC visits.

6. Procedures Involved

Aims 1 and 2

1) Intervention Visits.

Participants randomized to InSPIRe:CF will receive four protocolized face-to-face or virtual telehealth conferencing visits with a PC nurse practitioner (PC NP); see section 13 for details regarding randomization. Although the InSPIRe:CF intervention was developed as an in-person intervention, the COVID-19 pandemic has necessitated that we allow for telemedicine as a delivery option; individual sites will use their locally approved telemedicine solution (e.g., Zoom). Ideally, study visits will occur on the same day as participants' usual outpatient CF visits to allow for seamless communication between CF and palliative care clinicians, but may not be, given provider availability. Patients with CF typically see their outpatient CF care teams at least quarterly, therefore this intervention will last approximately one year. Participants may receive more than four visits with the palliative care clinician at the discretion of the patient and their CF care team. We anticipate the average duration of each intervention visit to range from 30 minutes to 1 hour, per our pilot data. Intervention visits will focus on the patient but will address the needs and concerns of patients' invited caregivers, regardless of whether the caregivers are also enrolled as study participants.

Reflecting the highly individualized nature of PC, specific content covered in each visit will be tailored to a participant's needs. We have developed an extensive intervention manual used to train and support the PC NP. For ease of use during visits, the NP will have a checklist that protocolizes each of the four visits. The first visit consists of a comprehensive palliative assessment, serving to build rapport between NP and participant, while identifying symptoms, psychosocial support needs, and preparation for advance care planning. Visits two and three focus on making and implementing recommendations for symptom management, psychosocial support, and advance care planning, while visit four will serve as a summary session, to reinforce concepts, make referrals for supportive services, and identify when and how to re-engage with palliative care if needed.

The PC NP will have authority to make changes to therapy, including but not limited to controlled substances, in accordance with local regulations and negotiation with the CF team. Treatment plan modifications will be communicated in real time to the CF care team via the EMR and/or in person. If a patient participant is hospitalized, the PC NP may visit the patient themselves or will liaise with the inpatient PC service to direct care. If a patient's condition necessitates more frequent outpatient follow-up, they may see the PC NP for additional visits as deemed necessary by the patient or the CF care team; analyses will control for dose effects.

2) Monthly Check-in Calls.

The PC NP will call patient participants randomized to the InSPIRe:CF arm monthly to reinforce topics covered during intervention visits, identify incident concerns (e.g., new/worsening symptoms), monitor intervention safety (e.g., adverse drug events), and track healthcare utilization otherwise uncaptured in each site's EMR (e.g., out-of-network emergency department visits). The NP will use a checklist of topics

as a method to increase intervention fidelity. We anticipate the duration of these calls to be 30 minutes on average.

Usual Care.
Per best practices in behavioral intervention research, a usual care control is the most appropriate comparator given that we aim to understand how specialist PC is additive to usual CF care. Beyond providing CF care team members with results of electronic patient-reported outcomes (PRO) screening (which we will do for both intervention and control patients), no attempt will be made to alter care received by individuals in the usual care arm. While it is arguable that PROs constitute an enhancement of usual care, integration of PRO assessment is the standard of care in CF. Patients in the control arm may be referred for specialty PC consultation if judged necessary by treating CF clinicians; however, those consultations will be delivered by PC specialists who do not have the InSPIRe:CF protocols, checklists, or training in the intervention. Based on current referral patterns, we anticipate this will be exceedingly rare.

We will collect EMR data through chart extractions; survey data through tablet, email, phone, or paper surveys; and interview data through recorded qualitative interviews. Please see below for a description of measures to be collected in this trial.

Measures to be Collected in InSPIRe:CF Trial

	Construct	Instrument	Description	Frequency
Aim 1 (Patients)	QoL (Primary)	FACIT-Pal[10]	46-item measure of generic and serious illness-specific QoL	Baseline, quarterly
	CF-specific QoL	Cystic Fibrosis Questionnaire-Revised[11]	50-item CF-specific measure of 9 QoL & 3 symptom domains	
	Symptom burden	Memorial Symptom Assessment Scale – CF[2]	32 general and CF-specific symptoms, evaluating frequency, severity, and distress	
	Psychological distress	Hospital Anxiety and Depression Scale (HADS)[12]	14-item measure of depression (7 items) and anxiety (7 items)	
	Coping	Brief COPE[13]	28-item measure assessing 14 scales of coping styles and strategies	Baseline, 12 and 15 months
	Satisfaction with care	FAMCARE P-16[14]	16-item measure of satisfaction with information-giving, availability of care, and physical care among individuals with serious illness	
	Healthcare utilization	Custom items	Emergency department visits, inpatient hospitalizations, unplanned outpatient visits, vital status (if death, CF-related or not)	
	Advance care planning		Patient's report of ≥1 of the following: living will or durable power of attorney,	

			DNR order, or having discussed end-of-life care wishes[15]	
	Demographics		Age, race, ethnicity, sex, marital status, education, income, social support, health insurance, religiosity	Baseline
Aim 2 (Caregivers)	QoL	PROMIS-Global 10	10-item measure of health-related quality of life	Baseline, quarterly
	Psych. distress	HADS[12]	See above	
	Caregiver burden	Zarit Burden Interview[16]	12-item measure of caregiver burden	
	Coping	Brief COPE[13]	See above	
	Demographics	Custom items	See above	Baseline

We will not conduct long-term follow-up of research subjects beyond this trial.

Audio recordings will be stored on study databases and deleted from their recording device. They are protected by the database security protocols and will be destroyed after the data collection period.

Aim 3

For Aim 3, we will conduct semi-structured individual interviews with the following individuals to understand the contextual factors regarding perceived effectiveness, as well as barriers and facilitators to implementation: up to 10 patients and 10 caregivers from each site (up to a total of 100 patient/caregiver participants), up to 10 CF care team members (i.e., 2 from each site), and 5 CF clinic administrators (i.e., 1 per site). These participants will be recruited from participating sites. These interviews will be conducted via phone or in-person, audio recorded, transcribed, and analyzed with the help of qualitative data analysis software. Audio files will be destroyed after transcription.

7. Data and Specimen Banking

Data will be stored in a study-specific REDCap database housed at Emory University, and paper files in locked file cabinets. Access will be limited to essential study personnel only, with further access limits based on role and site. There will be a screening database kept at each clinic storing the data of all patients screened. This database will store identifiable data with screening data to prevent re-screening and re-contact of patients who are ineligible or refuse to participate. This will consist of an Excel sheet stored behind the medical institution's firewall. We will only add identifiers to the study REDCap database after eliciting informed consent.

8. Sharing of Results with Participants

We will not share study results (study, individual, or otherwise) with participants or their clinicians outside of results presentation or publication.

9. Study Timelines

The duration of individual subject participation is 15 months (12 months for intervention, 3 months follow-up afterward).

10. Subject Population

Aims 1 and 2

Patient Inclusion Criteria
1) English-speaking;
2) Age ≥18 years;
3) Palliative needs, as indicated by the following criteria:
a) ≥1 moderate or severe symptom (captured by the Integrated Palliative Outcomes Scale [IPOS]); OR
b) Reduced QoL (as captured by the IPOS); OR
c) ≥2 hospitalizations in the preceding year

Caregiver Inclusion Criteria
1) Someone identified by the patient as "a person who knows you well and is involved in your medical care";
2) English-speaking;
3) Age ≥18 years

Patient Exclusion Criteria
1) Post–lung transplant;
2) Patient does not receive primary CF care from the study site or intends to transfer primary CF care elsewhere over the next year;
3) Received outpatient specialty palliative care within the past 12 months;
4) Lack of reliable telephone or internet access;
5) Active suicidal ideation

Caregiver Exclusion Criteria
1) Lack of reliable telephone or internet access;
2) Caregiver themselves has CF (if this rare event occurs, both will be approached for enrollment as "patient" participants)

We will exclude the following:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners
- Cognitively impaired or Individuals with Impaired Decision-Making Capacity
- Individuals who are not able to clearly understand English

Aim 3
Inclusion Criteria
1) Age ≥ 18
2) English-speaking

11. Vulnerable Populations

N/A

12. Local Number of Participants

Aims 1 and 2 (Effects of intervention on patient- and caregiver-reported outcomes)

In 2019, 318 adults with CF were cared for at the Emory Adult CF Center. To enroll 73 participants from Emory, we will screen the entire adult CF clinic population. Of those 73, we estimate enrolling caregivers at a rate of 75%, for an additional 49 participants, bringing the local total to 122.

Aim 3 (Qualitative interviews regarding dissemination and implementation)
At Emory, specific to Aim 3 we will enroll 2 CF care team members, and 1 clinic administrator, for a local total of 3.

13. Recruitment Methods

Aims 1 and 2
Research assistants (RAs) at each site will conduct weekly Electronic Medical Record (EMR) screening of patients presenting for regular outpatient CF clinic. Once potentially eligible patients are identified, the site RA will contact CF clinic staff and confirm study appropriateness of each eligible patient. Patients deemed appropriate will be contacted by either 1) the RA, if they are already previously known to the patient, or 2) a member of clinic, who will ask permission to release the patient's contact information to research staff. If agreeable, or if option 1) applies, the RA will contact the patient via phone or email, and administer additional eligibility screening using the Improved Palliative Care Outcomes Scale. Should the RA be unable to contact the patient via phone or email, the RA may approach them immediately before, during, or after their in-person or telehealth clinic visit. Again, should the RA not be known to the patient, a member of clinic staff will first approach the patient and ask if the patient is willing to speak with the RA.

If patients are eligible after the additional screening, the RA will elicit verbal informed consent and enroll them in the study. Patients will then complete baseline measures via phone, email, telehealth conferencing, tablet computer, or mailed surveys. Upon completion, they will be randomized into either the intervention or control group. Randomization will occur within the study's REDCap database. The randomization scheme (1:1 allocation) will be preloaded into the REDCap database by Dr. Althouse (statistician, Co-I), and will be stratified by site with permuted blocks of varying sizes. Randomization will occur after eligibility criteria have been confirmed and baseline data are collected as outlined above. This clinical trial will be partially masked; staff collecting/managing raw outcomes data will be masked to participants' treatment assignment, while staff conducting enrollment will be un-masked once randomization occurs.

Each site will keep a local list of ineligible patients and their screening data. This is to ensure that patients who refuse are not re-screened or re-contacted, and to prevent duplicate record entry in the study database. Identifiers stored on the local list include name, phone number, email address, home address, date of birth, and date of care. Ineligible patients will only have de-identified data added to the study database. Identifiers will only be added to the study database after eliciting informed consent from eligible patients. Once enrollment is complete, site RAs will delete all identifiers stored on the local list.

Participants will be compensated US$ 20 for each survey completed, for US$ 120 in total possible compensation. Participants will be paid US$ 20 for each survey completed, regardless of completion of previous surveys.

Aim 3
Research staff will approach potential Aim 3 participants in-person, or via phone, email, or virtual telehealth visit, and describe the interview. If the potential participants are interested, they will give

verbal informed consent and the interview will take place immediately or be scheduled. Research staff are familiar with the potential participants by way of working with them on the study. Patient and caregiver participants who complete qualitative interviews will be compensated US$ 50; clinical and administrative participants will not be compensated for completing interviews. Qualitative interview participants must complete the entire interview to receive compensation.

14. Withdrawal of Participants

The study will stop for individual subjects should any of the following events happen:
- Subject withdraws from the study
- Investigator determination that study continuation is not in the subject's best interest
- Pulmonologist determines that study continuation is not in the subject's best interest

The study will stop for all subjects should any of the following events happen:
- Evidence emerges that the intervention is placing the subjects at a risk level higher than expected

Participants may withdraw, at any time, their authorization to allow the research team to review their medical records, but if they do so, they will no longer be permitted to participate in this study. Any information obtained from a subject up to that point will, however, continue to be used by the research team.

15. Risks to Participants

The risks involved in this research are breach of data security and uncomfortable conversations involving end-of-life care. In our experience of conducting palliative care research, the latter concern is very rare.

All research staff interacting with participants will monitor for adverse events. A response to a question regarding self-harm and suicide prompts an automated real-time alert within the database, at which point study personnel will initiate a self-harm response protocol, which will include connecting the participant with a local crisis hotline and simultaneously immediately contacting the patient's CF care team. Staff may refer lesser, but concerning, observations to the patient's pulmonologist and/or PCP.

16. Potential Benefits to Participants

Individual participants may benefit from the therapeutic content delivered as part of palliative care interventions, which have been shown to improve quality of life and other patient-centered outcomes in other illnesses, but not yet in CF.

17. Data Analysis, Management and Confidentiality

The University of Pittsburgh will serve as the data coordinating center for this trial, with Dr. Andrew Althouse serving as the principal statistician. Dr. Althouse will oversee all data quality monitoring and analysis. We will first evaluate the statistical properties of baseline and follow-up outcomes, including normality, outliers, and missingness. Measures of central tendency and dispersion will be reported for continuous variables; frequency distributions will be reported for categorical variables. We will analyze and report process data before outcome data, to avoid bias in interpretation. All analyses for treatment group comparisons will use an intention-to-treat (ITT) approach, and we will present results according to CONSORT guidelines for reporting RCTs. We will conduct analyses of two pre-specified subgroups: 1) receipt of lung transplant (or evaluated/listed for transplant) during the study, and 2) CFTR modulator use.

To test the effect of InSPIRe:CF on patient QoL (Aim 1, primary outcome), we will compare patient FACIT-Pal scores at 12-month follow-up between trial arms. The primary efficacy assessment will use 12-month data as we expect the treatment effect to be maximized near the completion of InSPIRe:CF. We will also collect data at 15 months, and perform secondary analysis on that time point to assess durability of treatment effects. This will be carried out using a linear mixed-effects model, assuming normality of the outcome. The primary independent variable will be a fixed effect for allocation (InSPIRe:CF vs control). Primary analyses will also adjust for baseline FACIT-Pal score, study site, and additional patient characteristics (baseline FEV1, diagnosis of depression or anxiety, number of pulmonary exacerbations in the prior year, and use of supplemental oxygen) as fixed effects, as these are known to be associated with QoL. Additional analyses will compare differences between groups on secondary outcomes, including CF-specific QoL (CFQ-R), physical symptoms (MSAS-CF), psychological distress (HADS), coping (brief COPE), and satisfaction with care (FAMCARE) using the same approach as for the primary outcome: linear mixed-effects model adjusting for the baseline score, study site, and aforementioned patient characteristics.

Sample size calculations were based on the primary analysis for Aim 1 using the FACIT-Pal as the primary measure of patient QoL at 12 months (with quarterly assessments). Assuming a 15% attrition rate at 1 year (observed in our pilot trial), enrollment of 264 patients would provide 80% power (using alpha=0.05) to detect an effect size of d=0.4 in the FACIT-Pal by 12 months (testing the difference in slopes between the treatment groups). Notably, previous PC trials in metastatic cancer were powered to detect a larger effect size of d=0.5 between groups. However, given the lack of prior data regarding PC in CF, we designed our trial to detect a more modest effect size of d=0.4, to assure that the trial is not underpowered. We would retain 80% power to detect a larger effect size of d=0.5 with 180 patients randomized, under the same assumptions outlined above, should we have difficulty achieving the intended recruitment goal of n=264.

Analyses for Aim 2 will parallel analyses conducted for Aim 1, but instead, using data collected from caregivers, using linear mixed-effects models with a fixed effect for the patient's allocation (InSPIRe:CF vs control), with adjustment for the baseline value of each respective outcome, study site, and baseline patient covariates (baseline FEV1, diagnosis of depression or anxiety, number of pulmonary exacerbations in the prior year, use of supplemental oxygen) as fixed effects. The primary outcome for caregivers is QoL (PROMIS Global 10); secondary outcomes include mood (HADS), caregiver burden (ZBI), and coping (brief COPE).

For Aim 3, Descriptive summaries that aid the interpretation of the qualitative data will be produced, as appropriate. Audio files of Aim 3 interviews will be transcribed verbatim, and coded using NVivo qualitative software. Dr. Kavalieratos (PI) and a trained RA will analyze transcripts using template analysis, a qualitative approach that combines content analysis and grounded theory, resulting in a hybrid inductive/deductive analytic process. Consensus meetings will be held to discuss coding discrepancies. To achieve a true mixed-methods approach, we will merge results in a joint display, overlaying quantitative data from Aims 1 and 2 with qualitative themes identified in Aim 3. We will conduct member checking by sharing our findings with the trial's Steering Committee to ensure that our interpretations are credible.

To record this information and all study data, we will build a custom study database using REDCap. The database is only accessible to approved personnel, and user groups will be utilized to limit access to identifying information and partition data by site. Subjects will be informed, during the informed consent process, that all information will be kept confidential. Patient identifiers will only be recorded

on a tracking file in REDCap; all other forms, both paper and digital, will use an assigned study identification code. After the data retention period, all potential identifiers will be stripped from the dataset. The resultant dataset will be secured for long-term retention on HIPAA-compliant servers.

During patient screening, should the patient be found ineligible, each site will store a list of ineligible patients with their screening results behind their medical institution's firewall. This is in order to prevent duplicate database records of the same person, and re-contact of patients who refused to participate. Once enrollment is complete, all identifiers on these lists will be destroyed.

During data entry, a number of strategies will be employed to ensure quality of data: use of standard methods of data collection and recording already specified in the SOP, careful programming of the data management system, detailed documentation of computer operations and data editing procedures, and regular meetings with project staff to review any changes in procedure. The research coordinator will verify all data, program out-of-range data checks into data entry fields and evaluate the full data process within and across forms. A typical variable may be subjected to two kinds of range checking: impossible values (e.g., negative FEV1) and suspicious values (e.g., FEV1 > 100%). The former will be coded into the data entry system, restricting such values from being entered. The research coordinator will check suspicious values from the enrollment of the first participant to the data cleaning phase, at which point logical checks will be performed, and outliers will be analyzed.

18. Provisions to Monitor the Data to Ensure the Safety of Participants

We will use the Cystic Fibrosis Foundation's Data Safety Monitoring Board for this study. We will meet every six months at minimum to discuss recruitment, retention, and any possible safety concerns. The DSMB charter was approved in 2020. We have submitted DSMB reviews with IRB renewal.

19. Provisions to Protect the Privacy Interests of Participants and Confidentiality of Participants' Identifiable Data

The intervention will occur in a private, individual clinic room with the participant, interventionist, and caregiver present if the patient prefers. Should the visit be via telehealth, the interventionist will use a HIPAA-compliant videoconferencing service. Study sites will use the telehealth platform approved for use by their institution (e.g., Zoom at Emory University).

Participants may skip survey and interview questions they do not wish to answer, and refrain from discussing aspects of their life, health, care, or future that they do not wish to discuss with the interventionist.

In order to access PowerChart, the research staff will submit access request forms to the Departmental Access Coordinator. Once approved, they will work with clinic administrators to gain access to the Adult CF Clinic's schedule. All sites will complete their equivalent approvals to gain access to their clinical schedules.

Within REDCap, all potential identifiers will be marked as such and access restricted to essential personnel only. We will destroy identifiers once data analysis is complete. We will destroy audio recordings for Aim 1 after the data collection period ends, and after transcription for Aim 3.

No research test results will be placed into participants' electronic medical record.

20. Economic Burden to Participants

Participants will not be charged for any aspect of this study.

21. Consent Process

Aims 1 and 2

We will follow Emory IRB Policy and Procedure #44, Informed Consent when eliciting informed consent.

We are requesting 1) a waiver to elicit informed consent for medical record screening for eligibility, and 2) a waiver to elicit written consent for study enrollment.

1) Medical record screening for eligibility is impossible if we are required to elicit informed consent from every potential participant. This activity is no more than minimal risk; the only risk to patients is breach of confidentiality, and the data collection for screening is limited to the minimum needed to determine study eligibility. Patient rights or welfare are not damaged, as only essential personnel with appropriate training will conduct medical record screening. Additionally, we must store identifiers along with the screening data in order to prevent re-screening of patients and re-contact of patients who refused the additional screening questions; however, this data will be kept behind each clinic's firewall, and all identifiers will be destroyed once enrollment is complete. The time and effort required of contacting every patient at each clinic, and the risk of re-screening and re-contacting patients who refuse to participate, make this study impractical without the waiver.
2) This study poses no more than minimal risk to participants, and involves no procedures for which written consent is normally required outside of the research context. Seeing a palliative care specialist poses no more than minimal risk to participants, and (in conditions other than CF), has been proven to improve a number of outcomes, such as quality of life and symptom burden. The risks of survey and interview completion include breaches of confidentiality and feelings of unease when discussing personal concerns or medical care, neither of which fall above minimal risk.

We will elicit verbal informed consent via an in-person, phone, or telehealth conference conversation with patients and caregivers. We will send each participant a copy of the consent script via Emory University's encrypted email system before the consent discussion. The patient's pulmonologist and primary care physician will be notified of study participation.

Aim 3

Similar to Aims 1 and 2, we are requesting a waiver to elicit written consent for study enrollment. This study offers no more than minimal risk to participants, and involves no procedures for which written consent is normally required outside of the research context. The risks of interview completion include breaches of confidentiality and feelings of unease when discussing personal concerns or medical care, neither of which fall above minimal risk.

Similar to Aims 1-2, we will elicit informed consent via an in-person or phone discussion with potential participants.

All Aims

We will follow Emory's IRB Policy and Procedure #44, Informed Consent. Research assistants with appropriate training and certifications will consent participants. They will discuss the

consent script with the potential participants in private. Review of the script will take on average 10-15 minutes. Should potential participants wish, they may take time to consider their participation and enroll at a later date. The participants will be given opportunities to ask any clarifying questions during the conversation.

Non-English-Speaking Participants

Participants must speak English to be enrolled in this trial, given that the intervention content is in English, and that it is not possible to secure non-English-speaking interventionists at each study site.

Participants who are not yet adults (infants, children, teenagers)

We will not enroll children in this trial given that the concerns of children with CF differ enough from adults with CF to merit their own intervention.

Cognitively Impaired Adults

N/A

Adults Unable to Consent

N/A

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

As explained above, we request 1) a waiver to elicit informed consent for medical record screening for eligibility, and 2) a waiver to elicit written consent for study enrollment.

Medical Record Screening: We request a partial waiver of HIPAA authorization for the purpose of screening medical records for subject eligibility. We will collect names, phone numbers, email addresses, physical addresses, dates of birth, dates of care, relevant medical test results, and healthcare utilization rates. Should the patient be found ineligible, each site will store a list of ineligible patients with their screening results behind their medical institution's firewall. This is in order to prevent duplicate database records of the same person, and re-contact of patients who refused to participate. Once enrollment is complete, all identifiers on these lists will be destroyed.

22. Setting

At Emory, research will take place at the Emory Adult Cystic Fibrosis Program, a part of the The Emory Clinic. Research visits with the palliative care provider will occur at The Emory Clinic, Emory University Hospital, or via telemedicine (e.g., Zoom). Data collection (for all study sites) will occur centrally at Emory University, where research staff will be housed at the Emory Palliative Care Center (Wesley Woods Health Center).

23. Multi-Site Research when Emory is the Lead Site

Emory University will serve as the Clinical Coordinate Site and the home of the InSPIRe:CF trial. The study will be conducted at five institutions: Emory University, the University of North Carolina at Chapel Hill, the University of Alabama at Birmingham, the University of California – San Diego, and St. Michael's Hospital in Toronto, Canada. The University of Pittsburgh will serve as the Data Coordinating Site (and will not be involved in patient recruitment or study conduct). Upon approval at Emory, we will utilize the

sIRB mechanism for the sites at University of California San Diego, University of Alabama at Birmingham, and the University of North Carolina at Chapel Hill. We will adapt this protocol to the format used by St. Michael's Teaching Hospital in Toronto, ON, for approval of our international site.

The total number of people to be enrolled across all sites is 517 (304 patients, 198 caregivers, and 5 clinic administrators, and 10 CF care team members).

Recruitment methods at all sites will follow the protocol outlined here, but with their respective CF clinics.

Worksheet HRP-830 outlines the responsibilities of the Reviewing IRB, Reviewing Study Team, Relying IRB, and Relying Study Team.

Before beginning research activities, all required approvals and modifications will be confirmed and communicated to every site.

All sites will store data in accordance with this protocol.

All sites will conduct the study in accordance with applicable federal and local regulations, and report protocol non-compliance and adverse events in accordance with this protocol and local policy.

All sites will participate in at least monthly check-in meetings with the coordinating site staff. This meeting will discuss enrollment, enrolled patient progress, implementation challenges, and potential safety concerns. The breakdown of responsibilities is recorded in HRP-830.

Any problems, inclusive of reportable events, will be reported from the relying site to the Emory University site (i.e., the reviewing site) within 1 business day of event discovery. The Emory University site will be responsible for determining the reportability of the event, and if reportable, will report to the Emory University IRB, and instruct the relying site to report to the relying site's IRB in accordance with the relying site's institutional policies.

The closure of the study will be conducted on a site-by-site basis. Each site will ensure all data collection is complete and equipment is inventoried prior to ceasing research procedures. Sites will return research equipment to the coordinating site and inform their respective IRBs of study closure.

24. References

1. Cystic Fibrosis Foundation. *Cystic Fibrosis Foundation Patient Registry 2017 Annual Data Report.* Bethesda, MD2018.
2. Sawicki GS, Sellers DE, Robinson WM. Self-reported physical and psychological symptom burden in adults with cystic fibrosis. *J Pain Symptom Manage.* 2008;35(4):372-380.
3. Dellon EP, Shores MD, Nelson KI, Wolfe J, Noah TL, Hanson LC. Family caregiver perspectives on symptoms and treatments for patients dying from complications of cystic fibrosis. *J Pain Symptom Manage.* 2010;40(6):829-837.
4. Stenekes SJ, Hughes A, Grégoire M-C, Frager G, Robinson WM, McGrath PJ. Frequency and self-management of pain, dyspnea, and cough in cystic fibrosis. *Journal of pain and symptom management.* 2009;38(6):837-848.

5. Quittner AL, Goldbeck L, Abbott J, et al. Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: results of The International Depression Epidemiological Study across nine countries. *Thorax.* 2014;69(12):1090-1097.
6. Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2009;8(2):91-96.
7. Kavalieratos D, Corbelli J, Zhang D, et al. Association Between Palliative Care and Patient and Caregiver Outcomes: A Systematic Review and Meta-analysis. *JAMA.* 2016;316(20):2104-2114.
8. Chen E, Homa K, Goggin J, et al. End-of-life practice patterns at US adult cystic fibrosis care centers: A national retrospective chart review. *Journal of Cystic Fibrosis.* 2018;17(4):548-554.
9. Kavalieratos D, Moreines L, Hoydich Z, et al. Embedded Specialty Palliative Care Is Feasible, Acceptable, and Perceived to Be Effective in Cystic Fibrosis: Results of a Pilot Randomized Clinical Trial (TH371A). *Journal of Pain and Symptom Management.* 2019;57(2):396.
10. Lyons KD, Bakitas M, Hegel MT, Hanscom B, Hull J, Ahles TA. Reliability and validity of the Functional Assessment of Chronic Illness Therapy-Palliative care (FACIT-Pal) scale. *J Pain Symptom Manage.* 2009;37(1):23-32.
11. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest.* 2005;128(4):2347-2354.
12. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *Journal of psychosomatic research.* 2002;52(2):69-77.
13. Carver CS. You want to measure coping but your protocol's too long: consider the brief COPE. *Int J Behav Med.* 1997;4(1):92-100.
14. Lo C, Burman D, Rodin G, Zimmermann C. Measuring patient satisfaction in oncology palliative care: psychometric properties of the FAMCARE-patient scale. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2009;18(6):747-752.
15. Smith AK, McCarthy EP, Paulk E, et al. Racial and ethnic differences in advance care planning among patients with cancer: impact of terminal illness acknowledgment, religiousness, and treatment preferences. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(25):4131-4137.
16. Bédard M, Molloy DW, Squire L, Dubois S, Lever JA, O'Donnell M. The Zarit Burden Interview A New Short Version and Screening Version. *The Gerontologist.* 2001;41(5):652-657.