Integrating specialist palliative care to improve care and reduce suffering: cystic fibrosis (InSPIRe:CF) – study protocol for a multicentre randomised clinical trial

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ABSTRACT

Introduction Cystic fibrosis (CF) is a life-limiting genetic disorder estimated to affect more than 160,000 individuals and their families worldwide. People living with CF commonly experience significant physical and emotional symptom burdens, disruptions to social roles and complex treatment decision making. While palliative care (PC) interventions have been shown to relieve many such burdens in other serious illnesses, no rigorous evidence exists for palliative care in CF. Thus, this study aims to compare the effect of specialist palliative care plus usual CF care vs usual CF care alone on patient quality of life. Methods and analysis This is a five-site, two-arm, partially masked, randomised superiority clinical trial. 264 adults with CF will be randomly assigned to usual CF care or usual CF care plus a longitudinal palliative care intervention delivered by a palliative care specialist. The trial’s primary outcome is patient quality of life (measured with the Functional Assessment of Chronic Illness Therapy-Palliative care instrument). Secondary outcomes include symptom burden, satisfaction with care and healthcare utilisation. Outcomes will be measured at 12 months (primary endpoint) and 15 months (secondary endpoint). In addition, we will conduct qualitative interviews with patient participants, caregivers, and palliative care and CF care team members to explore perceptions of the intervention’s impact and barriers and facilitators to dissemination. Ethics and dissemination Human subjects research ethics approval was obtained from all participating sites, and all study participants gave informed consent. We will publish the results of this trial in a peer-reviewed journal. Trial registration number ISRCTN53323164.

INTRODUCTION

People living with cystic fibrosis (CF) and their caregivers experience multidimensional suffering and impaired quality of life (QoL).1,2 CF is a progressive, multisystem genetic disease occurring in an estimated >160,000 people worldwide.3 4 Therapeutic advances, including cystic fibrosis transmembrane conductance regulator (CFTR) modulators, have increased life expectancy and lung function in CF, yet people with CF continue to experience high physical symptom burden (eg, dyspnoea, fatigue, pain) and emotional distress (eg, depression, anxiety), both of which significantly impact functional status and QoL.5–8 Furthermore, many people living with CF must navigate complex and highly specialised healthcare, making difficult decisions about high-risk therapies such as lung transplantation. Meanwhile, these burdens also negatively affect family caregivers and their QoL.9

Specialist palliative care is appropriate for individuals with serious illness regardless of prognosis. PC has been shown to reduce suffering and improve QoL for people with cancer and heart failure (and their caregivers) but remains untested in CF. Skilled PC clinicians attempt to optimise QoL for patients and families affected by serious illness through expert assessment and management of physical and emotional symptoms; social support; promoting coping strategies, assistance with treatment decision making; and complex care coordination. In 2016, we published a meta-analysis of 43 clinical trials testing PC interventions.10 We demonstrated that a palliative approach is associated with improvements in patient QoL, reductions in symptom burden, improved satisfaction with care, and higher rates of advance care planning.
planning. However, most clinical trials enrolled patients with advanced cancer; and importantly, none included individuals living with CF.

Palliative care is underused for patients with CF. In a 2018 retrospective chart review of 248 deaths across 71 CF care centres, use of specialist PC was rare, and, if present, was typically only at the end of life.11 A critical reason for this underutilisation 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. US Cystic Fibrosis Foundation consensus guidelines recommend primary (or ‘generalist’) PC delivered by CF care team members as part of routine care for adults with CF, and consultation with specialist palliative care clinicians for patient needs that cannot be met by the CF team.1 In addition, no studies have evaluated when in the disease trajectory specialist PC should be introduced for lifelong, progressive, genetic conditions, including CF; findings from this study may inform clinical and research interventions regarding the role, scope and timing of palliative care in other genetic illnesses.

Considering the gap in clinical evidence, we developed Integrating Specialist Palliative care to Improve care and Reduce suffering:CF (InSPIRe:CF) (online supplemental file 1) an intervention to embed palliative care specialists within multidisciplinary care teams and processes comprising usual outpatient CF care. In a formative pilot clinical trial, we randomised 50 adults with CF to usual care vs usual care plus quarterly visits with a palliative care specialist. We found that adding PC was acceptable to patients, with 91% of patients reporting moderate or greater improvement in physical or mood symptoms or QoL (manuscript under review). In the current study, we are evaluating the effectiveness of InSPIRe:CF plus usual care vs usual care alone. We hypothesise that adults with CF randomised to the intervention group will have better QoL at 12 months than participants randomised to receive usual CF care alone. Our secondary endpoints include symptom burden, psychological distress and advance care planning for patients and QoL, psychological distress and burden for family caregivers.

METHODS AND ANALYSIS

Study overview

This phase III, multisite, randomised clinical trial sponsored by the Cystic Fibrosis Foundation cff.org, (KAVAL20Q10) compares care as usual by a CF clinic team, versus usual care plus palliative care by a palliative care specialist. The study aims are to (1) compare InSPIRe:CF to usual care for effects on patient QoL and symptom burden; (2) compare InSPIRe:CF to usual care for effects on caregiver QoL and (3) evaluate the mechanisms of action of InSPIRe:CF and barriers and facilitators to wider dissemination. The study has been registered on the ISRCTN Registry (ISRCTN53323164).

Patient and public involvement

This intervention was developed using qualitative analysis of patient and caregiver needs in CF.2612 An adult with CF participates as a compensated co-investigator for the study and is an active contributor to study design, development of recruitment and interventionist materials, assessment of intervention and data collection burden, and outcomes selection. The patient co-investigator is active in interventionist training, as well as data monitoring and analysis. Results will be shared at national CF conferences.

Setting

We are recruiting adults with CF and their caregivers from CF clinics at five academic medical centres in North America: Emory University (Atlanta, Georgia, USA), University of North Carolina at Chapel Hill (Chapel Hill, North Carolina, USA), University of California San Diego (San Diego, California, USA), University of Alabama at Birmingham (Birmingham, Alabama, USA) and St. Michael’s Hospital (Toronto, Ontario, Canada).

Study population

Adults with CF are eligible to participate if they are age ≥18, English-speaking, and have palliative needs as indicated by: ≥1 moderate or severe symptom captured by the Integrated Palliative Outcomes Scale (IPOS) and/or ≥2 CF-related hospitalisations in the past year. The IPOS addresses physical, emotional and psychosocial concerns including cough, pain, weakness, feelings of anxiety or depression and having enough information about one’s illness. Participants are asked whether each concern affected them in the past week on a scale of: not at all, slightly, moderately, severely or overwhelmingly. Exclusion criteria include CFTR-related disorder, lack of reliable telephone or internet access, pregnancy, active suicidal ideation, lack of decision-making capacity, receipt of specialist PC in past 12 months or intent to transfer primary CF care elsewhere in the next year. In addition, adults with CF are excluded if they have received lung transplantation, because post-transplant care is often centred in transplant clinics rather than CF care centres. Participants may remain in the study if they undergo transplant or become pregnant during the study period. Adults with CF need not have a caregiver to participate. Eligible caregivers are individuals identified by patient participants as ‘a person who knows you well and is involved in your medical care’ who is English-speaking, age ≥18 and does not also have CF.

Recruitment

Study staff review CF clinic schedules weekly to identify potentially eligible participants based on chart-based criteria. After confirming potential eligibility with CF...
clinic staff, study staff contact patients via telephone or during clinic visits to conduct additional eligibility screening, including administration of the IPOS instrument. Eligible and interested participants are invited to suggest a caregiver to join the study and are sent study description materials before undergoing a verbal informed consent process.

Randomisation
We randomise patient participants to the intervention or control (usual care) arm in a 1:1 ratio using randomly permuted blocks (sizes 4, 6 and 8) that are stratified by study site. The randomisation sequence is preloaded into the study data management system (REDCap) but hidden from the staff responsible for enrolling participants into the study; when enrolling a new patient, staff are unaware of the next allocation until they have randomised the patient. Caregivers are enrolled into the same arm as the patients they support. Postrandomisation, the trial is ‘open label’ as it is not possible to blind the patient and care team to their assignment; however, the investigative team is blinded to treatment assignment on all study-related reports except for the unblinded statistician.

Study Intervention
Participants randomised to the treatment arm receive at least four protocolised face-to-face or telehealth visits with a board-certified PC nurse practitioner or physician. Originally, we intended to test the effect of embedding a palliative specialist to provide care in person in the CF clinic; however, the COVID-19 pandemic changed many aspects of CF clinic operations to reduce infection risk, including an increase in telehealth visits. Consequently, we changed our interventionist manual and training programme to accommodate primarily telehealth visits. All interventionists completed approximately 10 hours of training that included an overview of CF across the life course, perspectives from people living with CF and caregivers and palliative care communication skills in the context of CF. Interventionists observed demonstrations and participated in practice sessions on building rapport with patients and caregivers in a telehealth environment. All interventionists were required to complete an individual skills demonstration with standardised patient actors and feedback from a pulmonologist and a palliative care physician trained in Vital Talk (https://www.vitaltalk.org/), a serious illness communication programme.

Because of COVID-19, intervention visits do not necessarily coincide with participants’ quarterly CF clinic visits, a departure from the initial pilot protocol. 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 min to 1 hour. Intervention visits focus on patient needs, but caregivers, whether enrolled or not, are welcome to attend visits if the patient chooses.

Reflecting the highly individualised nature of PC, specific content covered in each visit is tailored to a participant’s needs, but the study manual sets a checklist for each visit to define a basic dose of intervention content and enhance intervention standardisation. The first visit consists of a comprehensive palliative assessment, serving to build rapport between interventionist 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 serves 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. However, reflecting the variable nature of CF, study interventionists are encouraged to alter the timing of intervention content to meet individual patient needs.

The PC interventionist has 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 are communicated in real time to the CF care team. If a patient participant is hospitalised, the PC interventionist may visit the patient themselves or consult on inpatient management. If a patient’s condition necessitates more frequent outpatient follow-up, they may see the PC interventionist for additional visits as deemed necessary by the patient or CF care team; analyses will control for dose effects.

The PC interventionist calls treatment arm patient participants monthly to reinforce topics covered during intervention visits, identify incident concerns (eg, new/worsening symptoms), monitor intervention safety (eg, adverse drug events), and track healthcare utilisation otherwise uncaptured in each site’s electronic medical record (eg, out-of-network emergency department visits). The interventionist uses a checklist of topics as a method to increase intervention fidelity. Per pilot data, we anticipate the duration of these calls to be 10 min on average.

Usual Care
Per best practices in behavioural intervention research, a usual care control is the most appropriate comparator given that we aim to understand whether and how specialist PC adds to usual CF care. Beyond providing CF care team members with results of electronic patient-reported outcomes (PRO) from eligibility screening (IPOS 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 the IPOS scores 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 study protocols, checklists or training in the intervention. Based on current referral patterns, we anticipate this will be rare.

Study outcomes

Primary outcome

The strongest evidence for palliative care is its association with improved QoL and reduced symptom burden. The Functional Assessment of Chronic Illness Therapy-Palliative care (FACIT-Pal), a disease-generic measure, will be used to assess the primary study outcome, patient-reported QoL. FACIT-Pal is a 46-item measure that evaluates overall QoL (27 items) and contains a palliative subscale measuring factors particularly salient to individuals living with serious illness (19 items). Although not specifically validated in CF, the FACIT-Pal is one of the most widely used QoL instruments in PC intervention trials across a number of disease groups, including oncology and cardiology. The FACIT-Pal closely aligns with the content and purpose of a PC intervention such as InSPIRe:CF.

Secondary outcomes

Secondary outcomes for patients (aim 1) and caregivers (aim 2) and their instruments and collection schedules are listed in Table 1.

Evaluation using RE-AIM framework (aim 3)

We will evaluate InSPIRe:CF implementation using the RE-AIM framework as described in Table Y. RE-AIM is a 5-part framework that is widely used to evaluate barriers and facilitators to intervention impact. Reach refers to the representativeness of individuals included in an intervention. Effectiveness involves assessing positive (e.g., improved QoL) and negative outcomes (e.g., excess burden on clinic staff). Adoption refers to uptake of an intervention within a specific setting. Implementation in this context relates to fidelity. Lastly, Maintenance reflects the ability of an intervention to be sustained over time; here, we are interested in the likelihood of InSPIRe:CF to be integrated into usual CF care at diverse settings.
Table 2  Assessing mechanisms of action, barriers and facilitators using the RE-AIM framework

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<th>Example questions to assess RE-AIM domain</th>
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<td>Trial exclusion/refusal rates</td>
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<td>Adoption</td>
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<td>Maintenance</td>
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<td>Clinic likelihood to integrate intervention in standard of care: ‘How might or might not this intervention be integrated into standard care for people living with CF?’</td>
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CF, cystic fibrosis; InSPIRe, Integrating Specialist Palliative care to Improve care and Reduce suffering.

We will evaluate InSPIRe:CF using data as described in table 2.

We will train graduate research assistants to conduct and analyse interviews with up to 10 patient and 10 caregiver participants of the intervention at each site (up to 100 total across 5 sites); 10 CF care team members (two per site, not part of study team); and 5 clinic coordinators (1 per site). Participant interviews will be completed after the participant has completed their 12-month survey (primary endpoint). Clinic team and administrator interviews will be completed after all intervention participants have completed study visits at a site. Interviews will be conducted via phone, videoconference or in-person, digitally recorded, transcribed and analysed aided by qualitative data analysis software (NVivo).

Study procedures

Because of the COVID-19 pandemic, study coordinators will approach prospective participants by phone or in clinic observing local safety protocols and will obtain verbal informed consent after sharing study documents electronically or by mail. Patient participants who enrol in the study will have the opportunity to invite a caregiver to join them. Baseline assessments will be completed online or by phone. Patient participants will be randomly assigned to a study arm after completing baseline surveys; caregivers will be assigned to the same arm as their patient. Quarterly surveys for all participants will be completed online or by phone. Participants are paid US$20 for completing each outcomes survey. Patients in the intervention arm will also be contacted by the research coordinator to complete the IPOS before the palliative care appointments at months 3, 6 and 9.

Palliative care appointments will be conducted by telehealth platform or, if the patient prefers and if clinic safety protocols permit, in person during regular CF clinic visits. The palliative interventionist calls patients in the intervention arm to check in during months 1, 2, 4, 5, 7 and 8. Interventionists record notes about topics covered on the call for fidelity monitoring, but no other outcomes are collected on monthly calls. Although PC visits are intended to occur every 3 months, they can occur sooner if the patient and clinician determine that it would be beneficial. The outcomes survey schedule remains quarterly (months 3, 6, 9, 12, 15) regardless.

Data will be housed in a secure REDCap server at Emory University. Unblinded data will be available only to an unblinded statistician and study operations manager. Study personnel will be given access to the minimum necessary data to complete their role. Each site will house screening data locally on a secure, cloud-based server, with identifiable data (eg, email address) uploaded to REDCap only for individuals who enrol and provide informed consent. The unblinded statistician will assess data monthly for missingness, valid ranges and safety concerns.

Potential barriers to recruitment

Substantial reductions in symptom burden for some people using CFTR modulator therapy may reduce interest in palliative care. The time burden of intervention visits and privacy concerns about telehealth appointments may also be barriers to recruitment.

Possible solutions

An important finding of the pilot study was the lack of correlation between lung function and patient-reported symptom burden. Following discussion with CF clinicians and patient advisors, to allow broader participation the study team eliminated forced expiratory volume in 1 s (FEV1)% predicted as an eligibility criterion. The change prioritises participants’ perceived symptom burden rather than clinical measures of disease progression as a potential indicator for initiating palliative care. This reflects the prevailing philosophy that palliative care is appropriate at any stage of illness and should not be viewed as an option of last resort to be used only when disease-directed therapies stop working.

Retention

In the pilot trial of InSPIRe:CF, 100% of intervention group patients (23) completed all study visits on time. Because most PC visits will be delivered via telehealth and at a different time than CF clinic appointments, we anticipate intervention visit participation may be lower than...
in the pilot. Reductions in symptom burden associated with CFTR modulator use also may reduce participant motivation to complete study visits. However, research coordinators will work with the CF team to engage and schedule patients for future PC appointments during CF clinic visits if necessary.

Data analysis
The University of Pittsburgh is the data coordinating centre for this trial. Baseline characteristics will be presented with measures of central tendency (mean, median) and dispersion (SD, range) for continuous variables; frequency distributions will be reported for categorical variables. We will analyse and report process data before outcome data, to avoid bias in interpretation. All analyses for treatment group comparisons will use an intention-to-treat approach, and we will present results according to Consolidated Standards for Reporting Trials (CONSORT) guidelines for reporting randomised controlled trials.14 We will conduct analyses of two prespecified 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 focus on the contrast at the 12-month time point, as we expect treatment effect to be maximised 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. The primary analysis will be done with a linear mixed-effects model (with a random intercept for each patient) to allow inclusion of repeated measures from each participant during the trial. 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 in CF patients. The test of treatment effect will be the estimated contrast between the expected FACIT-Pal for patients assigned to InSPIRe:CF vs patients assigned to the control group at 12 months, estimated from the mixed effects model. Additional analyses will compare differences between groups on secondary outcomes, including CF-specific QoL (CFQ-R), physical symptoms (MSAS-CF), psychological distress (Hospital Anxiety and Depression Scale), coping (brief Coping Experience to Problems Experience) and satisfaction with care (Family Satisfaction with Advanced Cancer Care) using the same approach as for the primary outcome: linear mixed-effects model adjusting for baseline score, study site and patient characteristics. We will conduct exploratory analyses of dose-response by including the number of study visits completed as a covariate in regression models.

Analyses for aim 2 will parallel analyses conducted for aim 1, but instead, using data collected from caregivers, we will use 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 (Hospital Anxiety and Depression Scale), caregiver burden (Zarit Burden Interview) and coping (Brief COPE).

Sample size and power
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. Assuming quarterly measurements of the FACIT-Pal over a 1-year follow-up period, a 5% type I error rate, and a 15% attrition rate at 1 year (observed in our pilot trial), 264 patients would provide 80% power to detect an approximate effect size of Cohen’s d=0.4 in the FACIT-Pal at 12 months. Given the lack of prior data regarding PC in CF, we designed our trial conservatively for a modest effect size of d=0.4. Should we fall short of this recruitment target, we would retain 80% power to detect effect sizes of 0.5 with 180 patients, respectively.

Qualitative data analysis
A trained qualitative analyst will lead coding and analysis of aim 3 data. We will code data deductively using components of the RE-AIM framework (eg, acceptability of the intervention) and inductively to identify additional insights that may influence intervention design, timing or implementation. We will conduct constant comparison between groups (eg, participants’ perceptions at each site or by modulator use) to examine consistency of findings.

Study implementation
The funder is not involved in study design or data collection, analysis or interpretation.

Data safety monitoring
The Cystic Fibrosis Foundation’s Data Safety Monitoring Board (DSMB) serves as an independent reviewer of patient safety, study performance and data integrity. The DSMB includes clinicians with expertise in CF, researchers, statisticians and an adult living with CF. The DSMB reviews data semiannually throughout the study. Adverse events will be reported in REDCap and reported to the lead and site investigators. Serious adverse events are those that are life-threatening (eg, suicidal ideation).
or result in death. Minor adverse events include new onset depression, anxiety or distress.

The investigator team meets monthly to review data and assess recruitment, retention, data collection and quality, and safety. Serious adverse events, such as suicidality, are reported to the local and parent IRBs and DSMB.

Fidelity monitoring
All interventionists received more than 10 hours of training on clinical aspects of CF, palliative needs specific to CF, communication and study operations (online supplemental appendix table 1). To monitor consistent delivery of the intervention, all palliative interventionists are required to record their study visits with trial participants and complete a checklist indicating the topics discussed at each visit. A sample of 20% of visit recordings are reviewed by blinded reviewers to assess the completeness of each intervention visit. A study training team comprising palliative care experts with Vital Talk training provides feedback to individual interventionists as needed, with periodic interventionist team meetings to address common challenges.

Limitations
This study includes several limitations. First, palliative care is highly individualised to patient needs. The study employs extensive training and fidelity monitoring for the intervention team, but intervention visits will be tailored to participant priorities. It is possible for an intervention visit to fall short of full fidelity but still provide patient-centred care. Second, both the optimal time to initiate specialist palliative care and the patient subgroups most likely to benefit from palliative care are unknown. Third, the clinical course of CF has changed substantially for some patients who are taking and find benefit from CFTR modulator therapy. It is unknown whether CFTR modulator therapy improves overall QoL. If the primary hypothesis of improved patient QOL fails, the study will still yield important insights into (1) what aspects of palliative care are most beneficial for adults with rare or genetic diseases, (2) when in the disease course to initiate palliative care and (3) what symptoms or disease markers are most likely to indicate potential benefit from palliative care.

DISSEMINATION
Results of the trial will be reported in a peer-reviewed journal for publication using CONSORT. Additional papers are expected to report results of qualitative analysis of intervention participants’ experiences (aim 3) and the role of CFTR modulator therapies on symptom burden. Results of the trial will be presented at the North American Cystic Fibrosis Conference and the American Academy of Hospice and Palliative Medicine’s Annual Assembly.

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Contributors
PK designed the trial protocol with input from JL, EPD, AS, RA, AA, MB, WH and KC. DK procured funding for the trial with input from EPD, AS, ED, JS, CH, RA, AA, MB, JG, WH, DC and LH. JL, DK, ED, AS, RA, AA, MB, JG, SL, GS, JA, DC, WM and LH contributed to ethics/governance applications at their hospitals. JL drafted the first version of the manuscript. AA contributed to the sample size, data management and analysis sections of the manuscript. All authors read and approved the final manuscript.

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Competing interests
None declared.

Patient and public involvement
Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Ethics approval
This study involves human participants and was approved by Emory University Institutional Review Board (STUDY000071). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data availability statement
Data are available in a public, open access repository. Trial results will be published in the Palliative Care Research Cooperative Group’s deidentified data repository.

Supplemental material
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### Appendix Table 1: Training topics

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<th>Content</th>
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<td>• Introductions and roles</td>
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<td>• Overview of intervention and trial</td>
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<td>o Transitions from pediatric to adult care</td>
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<td></td>
<td>• Daily life with CF</td>
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<td>• Discussion: Similarities and differences between CF and other serious illness</td>
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<tr>
<td>Establishing therapeutic</td>
<td>• Asking about history and symptoms</td>
</tr>
<tr>
<td>alliance</td>
<td>• Eliciting patient understanding of and interest in prognosis</td>
</tr>
<tr>
<td></td>
<td>• Communicating with CF care team</td>
</tr>
<tr>
<td>Skills presentation</td>
<td>Short (15 minute) mock encounter with standardized patient (SP)</td>
</tr>
<tr>
<td>Skills demo</td>
<td>Interventionists will rotate through conversations about prognostic understanding with three SPs representing different patient scenarios (e.g., reluctant to discuss, interested in knowing more).</td>
</tr>
<tr>
<td>Introducing goals of care in</td>
<td>• Identifying surrogate</td>
</tr>
<tr>
<td>CF</td>
<td>• Previewing future conversations</td>
</tr>
<tr>
<td></td>
<td>• Identifying patient worries</td>
</tr>
<tr>
<td>Skills presentation</td>
<td>Short mock encounter with SP</td>
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</tr>
<tr>
<td>Skills demo</td>
<td>Interventionists will rotate through conversations introducing GOC/ACP with three SPs representing different patient scenarios (e.g., reluctant to discuss, interested in knowing more)</td>
</tr>
</tbody>
</table>
| Recap: role in study| • Responsibilities for each intervention encounter  
• Plans for intervention team discussions  
• Study support staff and resources |
| Technology and support| • Responsibilities for data collection  
• Introduction to REDCap  
• Fidelity monitoring and feedback: how to record encounters |
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

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


FUNDING SOURCE: Cystic Fibrosis Foundation

REVISION HISTORY

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<thead>
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<th>Revision #</th>
<th>Version Date</th>
<th>Summary of Changes</th>
</tr>
</thead>
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<tr>
<td>2.1</td>
<td>9/23/20</td>
<td>Changed data collection interval from monthly to quarterly, with updated data analysis. Changed consent forms to reflect new total available compensation.</td>
</tr>
<tr>
<td>2.2</td>
<td>9/25/20</td>
<td>Adjusted eligibility criteria to remove FEV1% threshold.</td>
</tr>
<tr>
<td>2.3</td>
<td>12/18/20</td>
<td>Clarified that fidelity recordings of intervention visits will be destroyed after the data collection period is complete.</td>
</tr>
<tr>
<td>2.4</td>
<td>03/28/22</td>
<td>Increase target enrollment by 40 to achieve target randomization</td>
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# Protocol Title: A Multi-Site Trial of Specialist Palliative Care in Cystic Fibrosis

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1. Study Summary

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<tbody>
<tr>
<td>Study Design</td>
<td>Multi-site Randomized-Control Clinical Trial</td>
</tr>
<tr>
<td>Primary Objective</td>
<td>Assess the effect of embedded specialist palliative care versus usual care on patient quality of life among adults with CF</td>
</tr>
</tbody>
</table>
| 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
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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. 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.

Treatment burden in CF is immense; adults spend a mean 108 minutes/day on treatments including airway clearance and inhaled and nebulized medications. 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. 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.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.
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We therefore developed InSPIRe:CF – the first specialist PC intervention for individuals with CF with support from the Cystic Fibrosis Foundation. 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 Burden 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.
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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 uncharted 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.

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

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<table>
<thead>
<tr>
<th>Demographics</th>
<th>DNR order, or having discussed end-of-life care wishes&lt;sup&gt;15&lt;/sup&gt;</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>QoL</td>
<td>PROMIS-Global 10&lt;sup&gt;10&lt;/sup&gt; 10-item measure of health-related quality of life</td>
<td>Baseline, quarterly</td>
</tr>
<tr>
<td>Psych. distress</td>
<td>HADS&lt;sup&gt;12&lt;/sup&gt; 12-item measure of caregiver burden</td>
<td>See above</td>
</tr>
<tr>
<td>Caregiver burden</td>
<td>Zarit Burden Interview&lt;sup&gt;16&lt;/sup&gt; 12-item measure of caregiver burden</td>
<td>See above</td>
</tr>
<tr>
<td>Coping</td>
<td>Brief COPE&lt;sup&gt;13&lt;/sup&gt; 12-item measure of caregiver burden</td>
<td>See above</td>
</tr>
<tr>
<td>Demographics</td>
<td>Custom items 12-item measure of caregiver burden</td>
<td>Baseline</td>
</tr>
</tbody>
</table>

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
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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)
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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

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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.
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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.
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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
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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
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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 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
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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

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