



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 impair 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. 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, (KAVAl20QI0) 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.^{2 6 12} An adult with CF participates as a compensated coinvestigator 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

Table 1 Outcomes and instruments

Measures to be collected in InSPIRe:CF trial				
	Outcome	Instrument	Description	Frequency
Aim 1 (Patients)	QoL (Primary)	FACIT-Pal ¹⁵	46-item measure of generic and serious illness-specific QoL	Baseline, months 3, 6, 9, 12, 15
	CF-specific QoL	Cystic Fibrosis Questionnaire-Revised ¹⁶	50-item CF-specific measure of 9 QoL and 3 symptom domains	
	Symptom burden	Memorial Symptom Assessment Scale – CF ⁵	32 general and CF-specific symptoms, evaluating symptom frequency, severity and distress	Baseline, 12 and 15 months
	Psychological distress	Hospital Anxiety and Depression Scale (HADS) ¹⁷	14-item measure of depression (7 items) and anxiety (7 items)	
	Coping	Brief COPE ¹⁸	28-item measure assessing 14 scales of coping styles and strategies	
	Satisfaction with care	FAMCARE P-16 ¹⁹	16-item measure of satisfaction with information-giving, availability of care, and physical care among individuals with serious illness	Baseline
	Healthcare utilisation	Custom items	Emergency department visits, inpatient hospitalisations, 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 ²⁰	
	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, months 3, 6, 9, 12, 15
	Psych. distress	HADS ¹⁷	See above	
	Caregiver burden	Zarit Burden Interview ²¹	12-item measure of caregiver burden	Baseline
	Coping	Brief COPE ¹⁸	See above	
	Demographics	Custom items	See above	

COPE, Coping Orientation to Problems Experienced; DNR, do not resuscitate; FACIT-Pal, Functional Assessment of Chronic Illness Therapy-Palliative care; FAMCARE, Family Satisfaction with Advanced Cancer Care; InSPIRe:CF, Integrating Specialist Palliative care to Improve care and Reduce suffering; Cystic Fibrosis; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, quality of life.

an enhancement of usual care, integration of PRO assessment is the standard of care in CF.¹³ 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.¹ 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.² 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.^{1 3 4} 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.^{5 6} Reach refers to the representativeness of individuals included in an intervention. Effectiveness involves assessing positive (eg, improved QoL) and negative outcomes (eg, 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

Table 2 Assessing mechanisms of action, barriers and facilitators using the RE-AIM framework

Construct	Data source	Example questions to assess RE-AIM domain
Reach	Trial exclusion/refusal rates	% of target population excluded due to exclusion criteria or refusal
Effectiveness	Aims 1 and 2 Aim 3 interviews	Effect sizes estimated from aim 1 analysis. Perceived strengths/weaknesses: 'What about InSPIRe did you find most helpful to you?'
Adoption	Aim 3 interviews	Barriers and facilitators to implementation: 'How might the intervention be difficult for someone like yourself living with CF to participate?'
Implementation	Fidelity measures	% of intervention visits addressing $\geq 80\%$ of intervention topics
Maintenance	Aim 3 interviews	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?'

CF, cystic fibrosis; InSPIRe, Integrating Specialist Palliative care to Improve care and Reduce suffering.

CF care centres. 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.⁷ 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,^{8,9} 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, 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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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.

Patient consent for publication Not applicable.

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.

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