BREEZE 2

A randomised controlled trial of a complex intervention to manage breathlessness in pulmonary fibrosis

NOTE: The SPIRIT 2013 Statement provides evidence-based recommendations for the minimum content of a clinical trial protocol. “SPIRIT is intended to facilitate the drafting of protocols and improve their completeness. High-quality protocols can promote proper trial implementation, reduce avoidable protocol amendments, and facilitate full appraisal of the study’s scientific and ethical considerations”.

FULL TITLE OF THE TRIAL: A randomised controlled trial of a complex intervention to manage breathlessness in pulmonary fibrosis

SHORT TITLE: BREEZE 2

PROTOCOL VERSION NUMBER AND DATE: Version 3.3 09.APR.2025

FUNDER: National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB)

SPONSOR: Hull University Teaching Hospital National Health Service (NHS) Trust

CHIEF INVESTIGATOR: Dr Ann Hutchinson

RESEARCH REFERENCE NUMBERS:

IRAS NUMBER: 342696

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) Standard

Operating Procedures (SOPs), and other regulatory requirements as amended.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Funder and the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the UK Sponsor:
Signature:

…… Date: ……..

Name:

……

Position:

……

Chief Investigator Signature:

…… Date: ……..

Name:

……

Statistician Signature:

…… Date: ……..

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Protocol amendments since Version 1.0

Version	Date	Summary of Changes
1.1	11.07.2024	Response to initial REC response – clarification of what to do if a participant cannot be contacted after three attempts.
2.0	04.NOV.2024	Clarification of the interview consent process; addition of CRQ mastery
2.1	15.NOV.2024	Addition of clarity of CRQ mastery answer cards being provided to participants at baseline visit.
3.0	03.FEB.2025	Addition of monetary incentive SWAT and collection of additional information collected during screening.
3.1	12.MAR.2025	-Clarity on the following exclusion criteria *"Australian-modified Karnofsky Performance Status of at least 60 (60=Considerable assistance and frequent medical care required)."* AKPS score of 60 is 'Requires occasional assistance but is able to care for most needs'. -Clarity on the schedule of events that the CSRI is the HRUQ questionnaire. -pg 31 Clarification on the randomisation approach for the SWAT corrected from cluster site ranomisation to a participant level randomisation =
3.2	01.APR.2025	Correction of exclusion criteria to remove "*Australian-modified Karnofsky Performance Status of at least 60 (60=Considerable assistance and frequent medical care required)"* from an exclusion criterion and to an inclusion criteria. For clarity this inclusion criteria will be reworded to "*Australian-modified Karnofsky Performance Status of 60 or more (60=Considerable assistance and frequent medical care required*)".

3.3	09.APR.2025	Clarification to the SWAT is for patients approached in person rather than using remote methods.
3.4	30 SEP 2025	Update to SAE reporting criteria and SWAT eligibility criteria. Update to the SWAT eligibility criteria.

ROLES AND RESPONSIBILITIES OF STUDY GROUPS AND INDIVIDUALS

• **The Sponsor** (Hull University Teaching Hospital NHS Trust) will have overall responsibility for the conduct of the study in the UK. The study will be managed by the Hull Health Trials Unit (HHTU), on behalf of Dr Ann Hutchinson (Chief Investigator). The study will be monitored by HHTU in accordance with SOP to ensure compliance with UK Clinical Trial Regulations.

- **Chief Investigator(s)** - The Chief Investigator will have responsibility for the design, coordination, and management of the study.
  - Trial authorisation including responsibility for the protocol and obtaining approvals from the MHRA, Research Ethics Committee (REC) and Research & Development (R&D)
  - Ensuring that the study is conducted according to the UK Clinical Trial regulations and GCP
- **Medical Experts -** The study medical expert will have responsibility for the design, coordination, management of the study and oversight.
  - Assessment of Serious adverse events (SAEs) and expedited reporting of any Related Unexpected Serious Adverse Event (RUSAEs).
- **Hull Health Trials Unit (HHTU):** duties will be defined in the collaboration agreement.

• **Statistical Analysis**: Chao Huang will oversee statistical aspects of the study including drafting the analysis plan, conduct of analyses and reporting of results.

• **The Principal Investigator (PI):** at the participating site will be responsible for site conduct of the study. The Investigator Site File (ISF) will be maintained by the study team, overseen by the PI.

• **Site Teams:** will consist of General Medical Council (GMC) registered clinicians responsible for approaching patients, confirming eligibility, obtaining consent, and undertaking clinical assessment of Serious Adverse Events/Reactions. The PI support team will facilitate the consent process, coordinate implementation of study interventions and data collection, process safety reports and prepare for monitoring visits. Sites will conduct the study in accordance with the protocol, SOPs, study agreements, the UK Clinical Trial Regulations and GCP.

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AKPS	Australian-modified Karnofsky Performance Scale
APF	Action for Pulmonary Fibrosis
BMI	Body Mass Index
C&C	Capacity and Capability
CI	Chief Investigator
CSRI	Client Service Receipt Inventory
CRF	Case Report Form
CTIMPs	Clinical Trials of Investigational Medical Products
CTU	Clinical Trials Unit
CRQ	Chronic Respiratory Questionnaire

CBIS	Cambridge Breathlessness Intervention Service
DPIA	Data Protection Impact Assessment
EDC	Electronic Data Capture
eTMF	Electronic Trial Master File
EU	European Union
EQ-5D-5L	EuroQol
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMC	General Medical Council
GP	General Practitioner
HHTU	Hull Health Trials Unit
HIPAA	Health Insurance Portability Accountability Act
HPFSG	Hull Pulmonary Fibrosis Support Group
HRA	Health Research Authority
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal editors
ID	Identification
ILD	Interstitial Lung Disease
IPF	Idiopathic pulmonary fibrosis
ISF	Investigator Site file
ISRCTN	International Standard Randomised Controlled Trial Number
MDT	Multidisciplinary Team
MCID	Minimal Clinical Important Difference
mMRC	Modified Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NPT	Normalisation Process Theory
NRES	National Research Ethics Service
NRS	Numeric Rating Scale
PCAG	Patient and Carer Advisory Group
PF	Pulmonary Fibrosis
PI	Principal Investigator
PIS	Participant Information Sheet
PR	Pulmonary Rehabilitation
QALY	Quality Adjusted Survival
RCC	REDCap Cloud
RCT	Randomised Controlled Trial
RUSAE	Related Unexpected Serious Adverse Event
R&D	Research & Development
REC	Research Ethics Committee
RfPB	Research for Patient Benefit
RGF	Research Governance Framework
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
VAS	Visual Analogue Scale

Contents

TRIAL SUMMARY

Study title	A randomised controlled trial of a complex intervention to manage breathlessness in pulmonary fibrosis
Short title	BREEZE 2
Clinical phase	Phase 3
Trial design	Multi-centre, wait-list design, randomised, controlled trial of a complex, non-pharmacological breathlessness management intervention in people with pulmonary fibrosis (PF) and chronic breathlessness, with embedded qualitative implementation study to inform scaled NHS (National Health Service) adoption. Patients will be randomised 1:1 to fast-track or wait-list groups.
Trial participants	Adults with idiopathic pulmonary fibrosis (IPF) or another fibrotic interstitial lung disease and chronic breathlessness.
Sample size	Total study sample size is 146.
Investigation	Participants will be randomised to receive the breathlessness intervention within 1 week of randomisation (fast-track group) or be placed on a waiting-list for 8 weeks prior to receiving the intervention (wait-list group).
Planned trial period	24 Months
Follow up	Follow-up assessments will be completed at weeks 4, 8, 12 and 16 followed by every eight weeks to a maximum of twelve months or the end of the trial, depending on which occurs first. The maximum number of additional follow-up visits after week 16 will be five, with each visit taking a maximum of 15 minutes and being completed over the telephone.
Aims	1) To test the clinical and cost effectiveness of a complex intervention to manage breathlessness in people with PF and chronic breathlessness. 2) To understand how best to implement the intervention if found to be effective.
Objectives:	1) To conduct a randomised controlled trial to assess the clinical and cost-effectiveness of the intervention in Interstitial Lung Disease (ILD) centres in the UK. 2) To undertake an embedded qualitative study, using normalisation process theory (NPT) as a framework to analyse clinician interviews, to develop an implementation strategy for wide-scale adoption of the breathlessness intervention as standard of care if proven effective.
Outcomes:	**The primary outcome:** • Numerical Rating Scale (NRS) worst breathlessness score at 4 weeks follow-up **The secondary outcomes:** • NRS breathlessness scores (worst, coping & distress) at the rest of the follow-up visits • CRQ mastery domain score • Function capacity measurement using Australian-modified Karnofsky Performance scale (AKPS) • Health Status assessment using EQ-5D-5L (EQ-5D & EQ Visual Analogue Scale (VAS)] • Evaluation of health service utilization using a bespoke version of the Client Service Receipt Inventory (CSRI)

Eligibility criteria	**Inclusion criteria:** • Males and females aged ≥50 years. This age cut-off is chosen to reduce the likelihood of including patients with non-fibrotic ILD. • PF* diagnosed by multidisciplinary team (MDT) consensus in accordance with international guidelines. • If on treatment for PF (with antifibrotic or immunomodulatory medication), on same dosage for at least 1 months. • mMRC (Modified Medical Research Council) breathlessness grades 3 or 4 despite optimal management* (i.e. stops for breath after walking about 100 yards or after a few minutes on level ground or is too breathless to leave the house or is breathless when dressing). • Resting oxygen saturation ≥90% on air/using usual oxygen prescription. • Able to give informed consent. • Australian-modified Karnofsky Performance Status of 60 or more (60= Requires occasional assistance but is able to care for most needs). * Specifically, the diagnosis of PF is confirmed if a patient has: 1. A diagnosis of idiopathic pulmonary fibrosis (IPF) OR 2. A diagnosis on non-IPF pulmonary fibrosis, with fibrosing lung disease (reticulation including evidence of traction bronchial dilatation and/or honeycombing) affecting more than 10% of lung volume (estimated) on CT scan.
	Exclusion criteria: • Significant comorbid cardiorespiratory disease other than PF considered by the PI to be the primary cause of breathlessness. • Pulmonary rehabilitation: completed ≤ 3 months before study entry. • Breathlessness clinic attendance: completed ≤ 3 months before study entry or to be started in the next 16 weeks. • Acute exacerbation of PF within 3 months • Unwilling or unable to give informed consent or complete study measures.
Investigations performed	mMRC, height, weight, vital sign, physical examination, medical history, medications, one minute sit to stand test, NRS worst breathlessness, CRQ-Mastery Domain, AKPS, Health Status using EuroQol [EQ-5D-5L (EQ-5D and EQ-VAS)], safety reporting, evaluation of usual care and Health service utilization.
Planned trial sites	A minimum of 15 specialist ILD centres across the UK

STUDY FLOW CHART

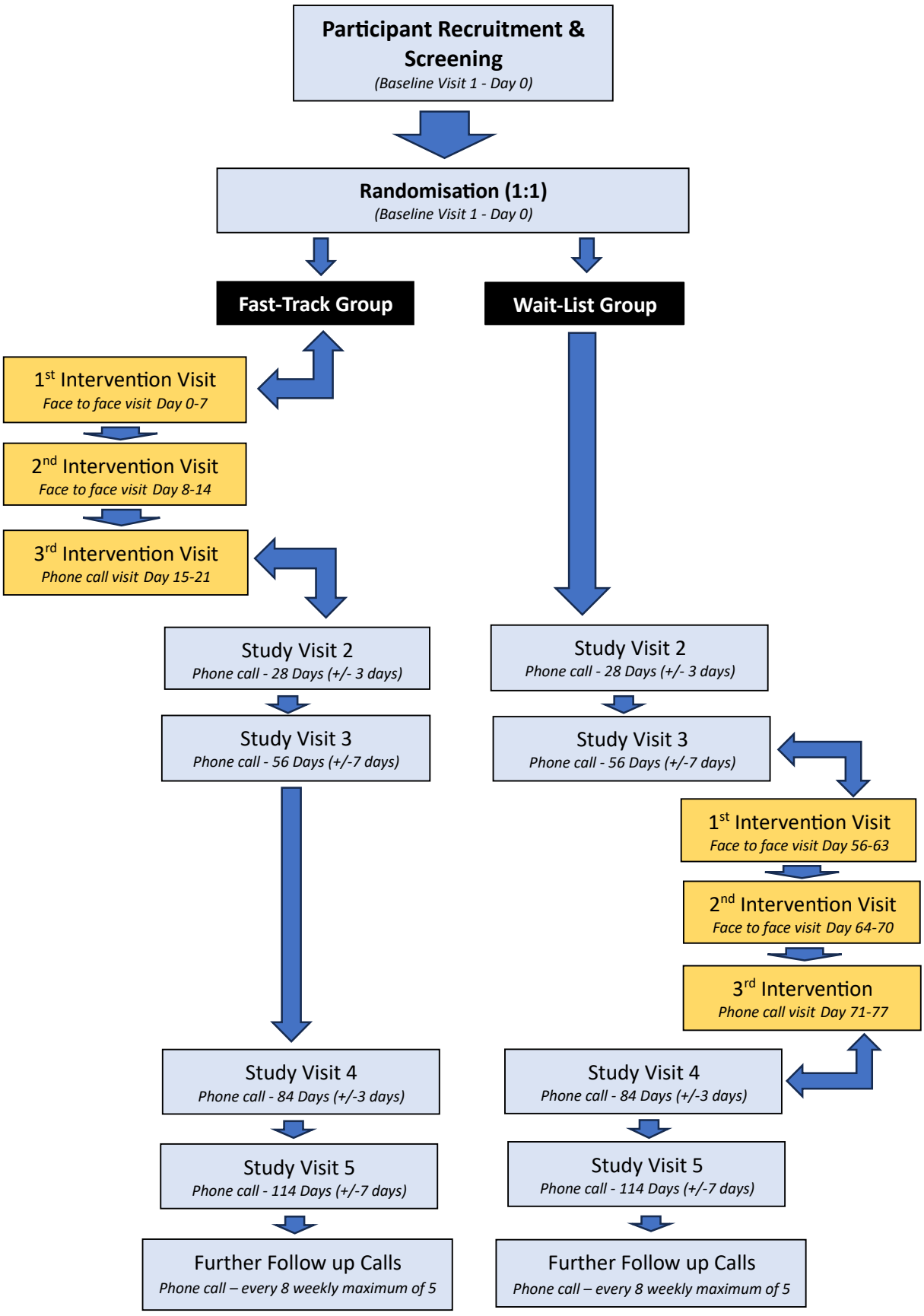

TABLE 1: SCHEDULE OF ASSESSMENTS AND PROCEDURES

	Baseline Visit 1	**Fast-Track Group Receive intervention Face to Face - Day 0-7**	**Fast-Track Group Receive intervention Face to Face - Day 8-14 (1 week after Visit 1)**	**Fast-Track Group Receive intervention Phone call - Day 15-21 (1 week after Visit 2)**	**Study Visit 2**	**Study Visit 3**	**Wait-list Group Receive intervention Face to Face - Day 56-63 (Week 8)**	**Wait-list Group Receive intervention Face to Face - Day 64-70 (1 week after Visit 1)**	**Wait-list Group Receive intervention Telephone - Day 71-77 (1 week after Visit 1)**	**Study Visit 4**	**Study Visit 5**	**Further Follow-up calls**
Visits	Onsite				Week 4 Telephone All participants	Week 8 Telephone All participants				Week 12 Telephone All participants	Week 16 Telephone All participants	Telephone All participants
Day	0				28 Days (+/- 3 days)	56 Days (+/-7 days)				84 Days (+/-3 days)	114 Days (+/-7 days)	Every 8 weeks maximum of 5 follow ups
Procedure/assessment												
Inclusion/exclusion criteria	X											
Written Informed consent	X											
Randomisation	X											
mMRC	X											
Vital sign	X											
Height & Weight	X											
Physical examination	X											
Medical History	X											
Medications	X				X	X				X	X	X
One-minute sit to stand test	X											
NRS scores *	X				X	X				X	X	X
CRQ mastery	X				X	X				X	X	X
CRQ mastery answer cards given to participants	X											
Australia-modified KPS	X				X	X				X	X	X
Health Care Utilisation **	X				X	X				X	X	X
AE					X	X				X	X	X
Evaluation of usual care received since last visit					X	X				X	X	X

*Worst Breathlessness in 24 hours, Distress due to breathlessness and Coping with breathlessness NRS.

** EQ-5D-5L, EQ VAS, CSRI (HRUQ)

1.PROTOCOL INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) and other fibrotic-interstitial lung diseases, collectively termed pulmonary fibrosis (PF), are progressive, incurable, and ultimately fatal. Breathlessness is the most common symptom and worsens over time resulting in distress and functional limitation. The James Lind Alliance Priority Setting Partnership identified treatments to 'reduce breathlessness' as a research priority[1]. PF is growing in prevalence and causes incurable lung damage[2]. PF affects around 70,000 people in the UK[3] and has a prognosis worse than many cancers. It is associated with breathlessness and cough that worsen over time, limiting daily activities and negatively impacting quality of life[4]. People with PF have a high symptom burden (chronic breathlessness, fatigue, cough)[5]. The impact of chronic breathlessness on PF patients can be profound. In addition to the detrimental impact on quality of life, chronic breathlessness is associated with anxiety and depression[6] and reduced survival[7]. Additionally, pulmonary hypertension, obstructive sleep apnoea, lung cancer, chronic obstructive pulmonary disease, ischaemic heart disease and gastro-oesophageal reflux are all common co-morbidities of PF[8]. The high symptom burden and the number of co-morbidities associated with PF emphasises the importance of a holistic approach to patient management and the complex interplay between symptoms and disease outcomes. It is essential that the importance of breathlessness is acknowledged by the medical and scientific communities and effective management strategies developed. In recognition of this, chronic breathlessness (breathlessness which persists despite optimal treatment for the underlying disease and causing disability) has been recognised as a clinical syndrome in its own right[9]. Patients attending the Hull Pulmonary Fibrosis Support Group (HPFSG) identified breathlessness as the symptom with the greatest impact on their lives; a view shared across a UK-wide support group network and the Action for Pulmonary Fibrosis (APF) voice of the patient council. Finding treatments to reduce breathlessness is one of the top ten research priorities identified by the James Lind Alliance Priority Setting Partnership on progressive pulmonary fibrosis[1]. Also, in recognition that breathlessness management is an important patient priority for breathlessness due to a range of conditions, National Institute for health and care excellence (NICE) has announced they are developing guidelines for breathlessness.

Although two therapies are now available that slow the rate of lung function decline[10, 11], providing hope for patients, these trials have failed to show improvement in symptoms or quality of life[10, 11]. There is therefore an immediate and large unmet need for evidenced-based interventions that improve patients' symptom burden and make a difference to everyday living.

Pulmonary rehabilitation (PR) is a well-recognised non-pharmacological exercise- and education-based programme usually delivered over 6 to 8 weeks. Although initially developed for people with chronic obstructive pulmonary disease, it is also effective for people with PF[12]. International guidelines[13] recommend PR for people with PF on the basis of two trials demonstrating improved walk distance, symptoms and quality of life[14, 15]. Since guideline publication, further small studies have demonstrated positive effects on quality of life, but these studies involve longer rehabilitation programs than those in the UK[16,17,18]. Despite this recommendation, access to programs varies across the UK, but even where available uptake is low in people with PF. The group nature of PR and the need for a regular commitment to an exercise-based program over 6-8 weeks prevents many PF patients from attending or completing, particularly those with worse breathlessness. While PR remains an important part of

PF management, it is not suitable for or tolerated by all patients and therefore many remain unable to access evidence-based treatments that improve symptoms and quality of life. Further, if breathlessness was managed better, some people with PF who had not attended PR due to fear of exertion-related breathlessness may be better equipped and more confident to attend.

Recognising the challenges of an exercise-based program for people with moderate to severe breathlessness, non-pharmacological breathlessness interventions (interventions focusing directly on breathing management rather that the more indirect approach through aerobic exercise programs) have been developed and evaluated in people with chronic breathlessness caused by cardiorespiratory diseases or cancer and benefits observed in terms of reduced severity of, and distress due to, breathlessness and increased breathlessness mastery[19,20,21,22].

In one trial people with non-malignant diseases receiving a breathlessness intervention as part of a randomised controlled trial (RCT) also had better survival than those in the control group[19]. Although these interventions are evidence-based[23], the studies included very few people with PF. Therefore, there is limited evidence relating to the efficacy of breathlessness strategies in people with PF. Extrapolating treatment effects from trials in other conditions has caused harm to people with PF in the past[24]. The poor prognosis, variable disease trajectory and absence of any existing, widely accessible evidence-based treatment to improve patients' symptoms sets PF apart from other causes of chronic breathlessness. Therefore, a phase 3 RCT of a breathlessness intervention in people with PF is needed.

ANTICIPATED IMPACT

Patient Impact

The potential impact of this study on patients are both direct (as a result of the study) and indirect (related to its subsequent implementation). We anticipate the following direct and indirect impact:

Direct impact

- Participation in a clinical trial has potential benefits for PF patients unrelated to the intervention.
- All participants taking part in the trial will have access to the breathlessness intervention. Our feasibility findings suggest that patients are likely to benefit from the intervention, but this requires confirmation in the definitive trial.
- Participants taking part in the definitive trial will benefit from the lessons learned during the feasibility study, with adaptations made to study visits and outcome measures increasing acceptability.

Indirect impact

- If the breathlessness intervention is found to be effective and can be implemented in clinical practice, it will positively impact the lives of many patients with PF, providing an evidence-based alternative for people unable to access pulmonary rehabilitation or for whom it is not suitable.
- The outcome of this definitive trial will inform local and national policy and service decisions with potential to improve access to the intervention for PF patients.

- Patients and members of the public involved in the conduct of the trial will benefit from increased awareness of breathlessness techniques to help them manage their own condition, and by helping to make a difference to other patients with PF.

Health Service Impact

The breathlessness intervention utilised in this trial is standardised and reproducible and therefore has excellent scope for wide implementation.

Health economic assessment in the trial will evaluate the future economic impact of the intervention, including any reduction in unplanned health service use.

The BREEZE feasibility trial

We conducted a National Institute for Health and Care Research (NIHR) Research for Patient Benefit (RfPB)-funded three-centre, wait-list design, randomised controlled feasibility trial of the breathlessness intervention compared with usual care in patients with PF (ISRCTN13784514, NIHR PB-PG-1216-20020). This showed that a phase 3 RCT was feasible, and that there was a signal to suggest that the intervention may improve patient relevant outcomes (breathlessness mastery and breathlessness-related distress, and worst breathlessness in the past 24 hours).

Participants were randomised 1:1 to either start the intervention within 1 week of randomisation (fast-track group) or to receive usual care for 8 weeks before receiving the intervention (wait-list group), delivered by a trained clinician. A wait-list design was chosen as it was felt that it was important that all study participants were offered the intervention because: i) this intervention has been shown to benefit those with breathlessness due to other chronic lung conditions, with no evidence of harm and ii) preliminary data supported the hypothesis that this intervention benefits people with PF. As there are no longer-term data on duration of effect, a crossover design was inappropriate as we do not know the duration of wash-out. By using a wait-list design, we ensured that all participants had access to the intervention, and we collected data up to 16 weeks post-intervention in the 'fast-track' arm. The 8-week wait-list period was deemed acceptable by patients and service providers.

Assessment of breathlessness and quality of life and measurement of daily activity was performed at the start of the study and repeated every 4 weeks over 16 weeks. Feasibility outcomes, including recruitment, retention, acceptability, and fidelity of the intervention were reported against pre-defined stop/go criteria. Clinical outcomes were measured to inform outcome selection and sample size calculation for a definitive trial.

Recruitment was notably higher in the tertiary ILD centre and lower in district hospitals. As PF patients are usually referred to tertiary ILD centres for their treatment, for the definitive RCT we have decided to focus recruitment from tertiary ILD centres only. An average of 2.5 patients were recruited per-month across all three sites. Most of the recruitment was from the Hull ILD centre with an average of 2 patients per month. 47 participants (38 male, mean [SD] age 73.9 [7.2] years, 35 IPF: 9 other fibrotic ILD) were randomised (25 wait-list :22 Fast-Track). The groups were well matched across key demographic factors, although a higher proportion of participants in the fast-track group reported more severe breathlessness at baseline. All feasibility outcomes were met, with almost all pre-defined

stop-go criteria achieving 'green', except recruitment rate (which was 2.5; 'green' cut off point of 3 per month) and retention at 16 weeks (which was 72%; 'green' cut off point was 80%) which were 'amber'.

Although the feasibility study was not powered to demonstrate intervention effectiveness, candidate primary outcome measures all demonstrated numerical improvement in the fast-track group at 4 weeks compared with the wait-list group. The effect size was fair and moderate respectively for the Chronic Respiratory Questionnaire (CRQ) breathlessness mastery domain and worst breathlessness in last 24 hours measured on a NRS, which is scored 0-10 where lower scores represent a lower symptom burden. The improvement in distress due to breathlessness (NRS) had a large effect size. This indicates a clinically significant signal of benefit and supports continuing to a definitive trial. Patients found the CRQ burdensome to fill out whereas the NRS scores of both worst breathlessness in the last 24 hours and of distress due to breathlessness were acceptable to them. The breathlessness distress measure is not validated, whereas worst breathlessness in the last 24 hours is, with well-established minimal important differences estimated[25]. We therefore have chosen NRS worst breathlessness in 24 hours as our primary outcome measure in this phase 3 trial.

2. AIMS AND OBJECTIVES

2.1 AIMS

1) To test the clinical and cost effectiveness of a complex intervention to manage breathlessness in people with PF and chronic breathlessness.
2) To understand how best to implement the intervention if found to be effective.

2.2 OBJECTIVES

1) To conduct a randomised controlled trial to assess the clinical and cost-effectiveness of the intervention in ILD centres in the UK.
2) To undertake an embedded qualitative study, using normalisation process theory[26] (NPT) as a framework to analyse clinician interviews, to develop an implementation strategy for wide-scale adoption of the breathlessness intervention as standard of care if proven effective.

3.TRIAL DESIGN

Phase 3, multi-centre, wait-list design, randomised, controlled trial of a complex, non-pharmacological breathlessness management intervention in people with PF and chronic breathlessness, with embedded qualitative implementation study to inform scaled NHS adoption.

3.1 OUTCOME MEASURES

Baseline measurements will be undertaken following completion of consent. Randomisation will be undertaken after completion of baseline assessments. Following randomisation and receiving the breathlessness intervention (fast-track group only), assessments will be performed at 4 weeks (primary endpoint), 8 weeks, 12 weeks & 16 weeks. Similarly, those in the wait-list group will be assessed at 4 weeks, 8 weeks, 12 weeks & 16 weeks. The outcome assessment completed for the wait-list group at 12 weeks, after they have received the intervention, will mirror the 4-week primary outcome measure after intervention delivery.

Outcome assessments in this phase of the trial will be completed remotely by the site research team. Participants will then enter the follow-up phase, which will involve completion of outcome assessments by phone. Follow-up assessments will be completed every eight weeks from week 16, for twelve months or the end of the trial, whichever occurs first. The maximum additional follow-ups will be five, with each phone-call taking a maximum of 15 minutes. This will provide additional information about longer-term maintenance of effects and continuation of the use of intervention components. The outcomes assessed during this study are detailed within table 1.

3.1.1 PRIMARY OUTCOMES

The primary outcome is the NRS worst breathlessness score at 4 weeks follow-up. Both 'worst breathlessness' and 'distress caused by breathlessness', in the past 24 hours, were identified as strong candidate measures. However, whilst there is a significant validation literature for the NRS, and justification for 'worst breathlessness' in 24 hours, there is none for 'distress caused by breathlessness', although it has been successfully used in previous trials[21]. Also, there are well documented minimal clinically important differences published for the 'worst breathlessness' in 24 hours NRS, there are none for 'distress caused by breathlessness'.

3.1.2 SECONDARY OUTCOMES

- NRS breathlessness scores (worst, coping & distress) at the rest of the follow-up visits.
- CRQ-Mastery Domain score
- Function capacity measurement using AKPS. The AKPS is a measure of functional status with 10% gradations from 0 (dead) to 100 (fully functional). The AKPS can be used across palliative care settings; patient's home, hospital/hospice inpatient and nursing/care home. AKPS predicts survival, can reflect longitudinal changes and is easier to use than previous versions.
- Health status will be assessed by using EQ-5D-5L (EQ-5D & EQ VAS) questionnaire to measure QoL and, as it will also be used for health economic evaluation.
- Evaluation of health service utilisation. Health service utilisation will be collected using a bespoke version of the Client Service Receipt Inventory (CSRI) [37] and based on the success of our feasibility study. This will include items such as General Practitioner (GP) attendance, practice nurse attendance, out-patient appointment attendance (consultant), specialist nurse review (out-patient or home-visit), emergency department attendance, hospital admission, hospice admission. Unit costs will be applied to the relevant resource use to generate cost per patient.

4. RECRUITMENT PROCESS

We will recruit 146 eligible out-patients with PF and chronic breathlessness. Participants will be screened against the eligibility criteria and identified by their usual care provider in participating ILD centres or from existing research databases.

Patients expressing an interest in the study will be provided with a participant information sheet and invited to attend the site during which screening, informed consent and a baseline sit-to-stand test will take place.

Eligible patients will be approached by a member of their usual care team and those requiring an interpreter will be offered this via usual hospital interpretation services. A local NHS Trust interpreter may be requested by the potential participant to attend study discussions and informed consent visits with the participant. All participants will be offered travel expenses to attend site visits to avoid this being a barrier to participation. If participants have no other way of travelling to the hospital for study visits, the research team may be able to arrange a taxi to take participants to and from the hospital. We aim to include out-patients from fifteen specialist ILD centres across the UK which will be chosen with support from the CRN to ensure diversity and inclusivity.

We will collect pseudonymised data on the background of patients that are screened including age, sex, ethnicity, and socioeconomic position in order to monitor the inclusivity of our study population and identify any populations that are underrepresented.

4.1 ELIGIBILITY

Inclusion Criteria:

- Males and females aged ≥50 years.
- PF* diagnosed by multidisciplinary team (MDT) consensus in accordance with international guidelines.
- If on treatment for PF (with antifibrotic or immunomodulatory medication), on same dosage for at least 1 months.
- mMRC breathlessness grades 3 or 4 despite optimal management.
- Resting oxygen saturation ≥90% on air/using usual oxygen prescription.
- Able to give informed consent.
- Australian-modified Karnofsky Performance Status of 60 or more (60= Requires occasional assistance but is able to care for most needs).

* Specifically, the diagnosis of PF is confirmed if a patient has:
1. A diagnosis of idiopathic pulmonary fibrosis (IPF)
OR
2. A diagnosis on non-IPF pulmonary fibrosis, with fibrosing lung disease (reticulation including evidence of traction bronchial dilatation and/or honeycombing) affecting more than 10% of lung volume (estimated) on CT scan.

Exclusion criteria:

- Significant comorbid cardiorespiratory disease other than PF considered by the PI to be the primary cause of breathlessness.
- Pulmonary rehabilitation: completed ≤ 3 months before study entry.

- Breathlessness clinic attendance: completed ≤ 3 months before study entry or to be started in the next 16 weeks.
- Acute exacerbation of PF within 3 months.
- Unwilling or unable to give informed consent or complete study measures.

4.2 PARTICIPANT IDENTIFICATION AND SCREENING

Participants will be identified by their usual care provider or from local research databases at study sites. All clinicians working in study sites will be trained in the study protocol including inclusion and exclusion criteria. Participants expressing an interest in the study will be provided with a participant information sheet (PIS). In addition to the PIS an Infographic Sheet will be provided to the study participants. Participants will be invited to attend their closest study site for consenting, screening, and baseline assessments.

Participants that fail screening can be re-screened if the reason for screen failure is resolved prior to completion of study recruitment. Participants entering the study following re-screening after an earlier failed screening will be allocated a new study identification (ID) and have their earlier study ID and the reason for initial screen failure recorded in their Case Report Form (CRF) and the Participant Master Index.

4.3 INFORMED CONSENT

The PI has overall responsibility for informed consent of participants at site and must ensure that anyone delegated responsibility to conduct informed consent is duly authorised, trained and competent to undertake consent according to the protocol and GCP. Informed consent must be obtained prior to the participant undergoing any non-routine study specific procedure.

Informed consent will be obtained following discussion of the study with the potential participant. The role of the participant and the procedures involved will be explained in detail. A PIS with contact details of the researcher and other local team members will have been provided.

The potential participant may have as long as they wish to make the decision about whether to take part or not. As some people will be coming a long way for their tertiary centre appointment, there might be a potential participant who wishes to enter the study immediately. Considering the low-risk intervention the researcher will use judgement as to whether it is better to prevent the patient from having another journey and to allow consent at this earlier stage. It will be made very clear to the potential participants that they do not have to participate in the study if they do not wish to and that whatever they decide to do, it will not affect their clinical care in any way. Researchers will ensure that participants understand that they are free to withdraw from the study at any time. However, we will ask participants to consent to ongoing safety reporting after withdrawal for regulatory purposes and to ensure that they are aware that their data will be used in analysis up to the point of withdrawal.

Participants will be asked if they are willing to take part in an interview and if they agree for their carer to be invited to participate in a qualitative interview. Both participant and carer (if interested) will be provided with an Interview Information Sheet and given time to review the information and ask questions. Those willing to be selected for an interview will be asked to sign an Interview Informed Consent Form (ICF). If consent is obtained, the participant (with or without their carer) may be selected to participate in a qualitative interview at a later date. Verbal reconsent will be taken at the beginning of the interview in case they have changed their mind about participation.

Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the HHTU.

4.4 PARTICIPANT WITHDRAWAL

Participants have the right to withdraw from the study at any time without giving reasons and without prejudicing their further treatment. Participants that withdraw will be provided with a contact point where they can obtain further information about the trial. The investigator(s) or sponsor may withdraw patients from treatment or the study only if indicated by safety/clinical issue or study protocol.

Participants should remain in the study for follow-up unless they request to fully withdraw. All data up to the point of withdrawal should be filed. We will ask the participants to give a reason for withdrawal whilst making it clear they do not have to give this information if they do not wish to do so.

In the event of participant withdrawal, the Investigator(s) will promptly explain to the participant that their involvement in the study will discontinue and explain why. Investigators will provide medical treatment and/or other necessary measures deemed appropriate by the investigator for the participant.

A participant who does not wish to continue in the study, will be contacted by phone or other means to offer them the opportunity to give a reason for withdrawal whilst making it clear they do not have to give this information if they do not wish to do so. This information will be recorded in the CRF.

In the event that a participant cannot be contacted after three attempts, their GP will be contacted to find out more information such as whether they have been admitted to hospital for any reason.

If a participant loses the ability to provide informed consent during the conduct of the trial, they will be withdrawn from the trial and no further study assessments/procedures will be undertaken and no data collected from the point that informed consent could no longer be provided. All data collected prior to the participant losing the ability to provide informed consent will be retained. Participants will be made aware of this in the PIS and confirm ascent during the informed consent process.

5. ENROLMENT, RANDOMISATION AND BLINDING

The HHTU will provide a web-based randomisation system within their electronic data capture system, REDCap Cloud (RCC). Participants will be randomised to receive the breathlessness intervention within 1 week of randomisation (fast-track) or to be placed on a waiting list for 8 weeks prior to receiving the intervention (wait-list group) in a 1:1 ratio using random permuted blocks stratified by site and mMRC (strong relationship between breathlessness severity and survival) [7]. The schedule of events is outlined in Table 1.

Blinding of participants is not possible and where blinding of research nurses has been attempted before in a similar intervention study, the blind was broken in nearly 50% of cases by the participant during study assessments [20]. However, the study statistician and the health economist undertaking analysis will be blinded to group allocation.

6. STUDY INTERVENTION

The breathlessness intervention will be delivered by a local clinician/therapist at participating sites trained by our study physiotherapist who is skilled in breathlessness management, thereby facilitating standardisation of content. The intervention is designed to be delivered by any suitable clinician/therapist (e.g. nurses, physiotherapists, or other suitably qualified clinicians).

All of the clinicians will be trained in the breathlessness intervention components, and the tailoring of these to the participant. The training session (maximum 2 hours) will be conducted on-line and recorded on MS Teams. The recording and a copy of the presentation slides will be made available for all of the site clinicians delivering the intervention. All sites will be provided with the intervention resources; breathlessness intervention leaflet and the handheld fans for the training session.
The intervention sessions consist of two one-hour face-to-face consultations and one phone consultation. These will be undertaken at 1-week intervals over a 3-week period with a trained clinician/therapist. The phone call consultation will be a 20-minute phone call. During the intervention sessions the trained clinician/therapist will go through the breathlessness management techniques. The schedule of events is outlined in Table 1.

If a participant randomised to the fast-track group, they will start their intervention sessions within one week of randomisation. However, if a participant randomised to the wait-list group the intervention sessions will start in week 9.
During these sessions, participants in both groups will receive training tailored in:

- Breathing control techniques (e.g. pursed lip and diaphragmatic breathing)[20, 22, 27,28,29].
- Instructions on using a hand-held fan (fan will be provided)[30,31,32].
- Pacing and breathlessness management during everyday activities, including positions for recovery from exertional breathlessness and information on the importance of exercise[22, 27, 33,34].
- Techniques to promote relaxation and manage anxiety and panic[29].

Delivery of the core intervention components will be recorded by the delivering respiratory therapist in participants' medical records and CRFs. This will form part of the assessment of intervention fidelity. The reason for failure to deliver any of the core intervention components should be recorded by the delivering therapist in participants' medical records and CRFs.

BREATHLESSNESS LEAFLETS

As part of the breathlessness intervention all participants will receive a standardised information leaflet to take home that details the breathlessness management techniques. The leaflet will cover the following breathlessness management techniques.

- The handheld fan
- Breathing control and techniques to ease breathlessness
- Positions to ease breathlessness
- Managing thoughts about breathlessness
- Relaxation
- Conserving your energy levels
- Exercise

The leaflet is adapted with permission from the Cambridge Breathlessness Intervention Service (CBIS) and used in the feasibility study. All leaflets developed by the CBIS have gone through extensive user feedback and their institutional review process. The leaflet can be accessed through below link as well. https://www.cuh.nhs.uk/our-services/breathlessness-intervention-service/patient-information-leaflets/

USUAL CARE

Usual care will be received throughout by all participants. Details of usual care received will be recorded during study visits (see Table 1) and includes any intervention that would ordinarily be offered out-with the trial setting. The sole exception is breathlessness clinic attendance, as this would be similar to our intervention which is the trial's focus. Therefore, people who have attended a breathlessness clinic during 3 months prior to recruitment will be excluded, and those enrolled on the study will be prohibited from breathlessness clinic attendance for the first 12 weeks. Usual care includes, but is not limited to, any of the following if considered appropriate by the patient's clinician: ILD clinic attendance; review and support by the ILD specialist nursing team and/or primary care provider; antifibrotic drug treatment in accordance with NICE guidelines; and home oxygen therapy. Pharmacological or other non-pharmacological breathlessness treatments (e.g. opioids or hand-held fan) delivered as part of usual care (that is, not as part of a breathlessness clinic) will not be restricted if considered appropriate by the patient's clinician but will be documented.

6.1 TRIAL VISITS

In order to maximise participant retention, we have minimised participant burden by undertaking study follow-up visits remotely (by phone), minimising the number of assessments, and using historical lung function results to characterise the study population.
In the event that the participant is unable to attend the intervention visit (for any reason) during the visit window, the visit should be rescheduled as soon as possible. The out of window visit will be considered a protocol deviation. For those randomised to the fast-track group, the Visit 3 phone call must take place before the 4 week time point and for the wait list group, before the week 8 time point in order to collect and measure study endpoint data.

6.1.1 BASELINE VISIT

The baseline visit will take place on Day 0 to confirm eligibility and will include the following interventions: inclusion/exclusion criteria, informed consent, mMRC, vital signs, height, weight, physical examination, medical history, medications, one-minute sit to stand test, NRS scores, AKPS, CRQ Mastery and Health Status EQ-5D-5L (EQ5D and EQ VAS), CSRI. A copy of the answer cards for the CRQ mastery questionnaire will be given to the participant at the baseline visit to aid in answering the questionnaire over the phone at further visits.
Data on pulmonary function and other baseline demographic and clinical characteristics will be taken from the most recent measurement documented in the clinical records (electronic health record or physical notes).

At the end of baseline visit, after baseline assessments have been completed, participants will be randomised to fast-track or wait-list groups. The research team will be informed of group allocation (See section 5 for randomisation procedures).
Following randomisation, the site research team will book the intervention appointments with the trained local clinician/therapist, following locally agreed procedures. Participants will be informed of their appointment dates and times by the research team.
With consent, the site team will notify the participants GP of their involvement using the approved GP letter.

6.1.2 INTERVENTION VISITS

Participants in both fast-track or wait-list groups will receive three intervention sessions; two one-hour face-to-face sessions and one phone consultation.
Participants randomised to the fast-track group will have their 1st face-to-face session within one week of randomisation and the 2nd face-to-face session will be one week later. The final session will be a phone call follow-up of 20 minutes after a further week.
Participant randomised to the wait-list group the intervention will start in week 9, with two one-hour face-to-face sessions and a phone call at 1-week intervals over a 3-week period.

6.1.3 STUDY VISITS

All the participants in both fast-track or wait-list groups will receive further assessments at 4 weeks (primary endpoint), 8 weeks, 12 weeks & 16 weeks on the phone. These assessments will include the following interventions: NRS scores, AKPS, CRQ Mastery, Health Status, EQ-5D-5L (EQ-5D and EQ VAS), CSRI and evaluation of usual care received since last visit including the changes in the medications and Adverse events (AE).
The fast-track group will perform the study visits after receiving their breathlessness intervention. The wait-list group will be assessed at 4 weeks & 8 weeks study visits before receiving their breathlessness intervention and the 12 weeks and 16 weeks assessments will be after that they have received the intervention, to mirror the 4-week (primary outcome) and the 8-week measure in the fast-track group.

6.1.4 FURTHER FOLLOW-UP VISITS

After completing the study visits participants will have further follow-ups, which will involve completion of outcome assessments by phone with the research team. Follow-up assessments will be completed every eight weeks from week 16 to a maximum of twelve months or the end of the trial, depending on which occurs first. The maximum number of additional follow-up visits after week 16 will be five, with each visit taking a maximum of 15 minutes and being completed over the telephone. At these visits will perform the following assessments: NRS scores, AKPS, CRQ Mastery Domain, and Health Status EQ-5D-5L (EQ-5D and EQ VAS), CSRI and evaluation of usual care received since last visit including the changes in the medications and AEs. This will provide additional information about longer-term maintenance of effects and continuation of the use of intervention components. The outcomes assessed during this study are detailed below. (Table 1 details the timing/frequency of assessments).

7. TRIAL ASSESSMENTS & DATA COLLECTION

7.1 DATA COLLECTION

Individual participant data required by the study protocol will be recorded on the study CRF. Site research staff will enter collected data from the paper CRF onto the electronic study database (RCC) provided by the HHTU.

HHTU will develop the study database and data processes in accordance with HHTU SOPs. HHTU data systems are within scope of the HHTU NHS Data Security and Protection Toolkit (Organisation Code - EE133824-HHTU).

The HHTU will adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, some minor variations may occur due to circumstances beyond the control of HHTU. All protocol deviations will be documented with a reason. Where appropriate, deviations will be detailed in the published report. The design of the CRF will:

- enable adequate collection of data
- provide an audit trail to demonstrate the validity of the study (both during and after the study)
- ensure that only the data required by the protocol are captured

The participating sites will retain a copy of the paper CRFs and a copy of the data entered on the study database to ensure that the PI can provide access to the source documents to a monitor, auditor, or regulatory agency to check for any transcription errors.

Note: The site will maintain essential documentation in an ISF
Note: Researchers are responsible for redacting personal identifiers prior to sending forms to HHTU

Participants' interview recordings and transcriptions will be stored securely on HHTU/University of Hull Box. BOX is a collaborative cloud storage with the HHTU instance administered solely by HHTU staff. The HHTU Box instance uses only EU (European Union) hosted servers. Box is ISO27001/ISO27018 certified, HIPAA (Health Insurance Portability Accountability Act) compliant and holds SOC 1,2 and 3 reports. Data is encrypted at rest and in transit. Under General Data Protection Regulation (GDPR), BOX act as a data processor on behalf of the University of Hull who is the data controller for HHTU projects.

7.2 TRIAL ASSESSMENTS

MEDICAL HISTORY

Medical history will be collected at baseline Day 0. The year of IPF or non-IPF fibrotic ILD diagnosis will be recorded. All active comorbid conditions* and any conditions occurring within the past year prior to Visit 0 will be recorded including the date of diagnosis.

* Active comorbid condition is any condition causing symptoms, functional limitation or for which the participant is receiving treatment.

MEDICATIONS

Participant's regular medications (prescribed and over the counter) will be recorded during the baseline visit Day 0 and rest of the study visits including the follow up visits.

VITAL SIGNS

Vital signs will be assessed during the baseline visit. Pulse oximetry, heart rate, blood pressure and temperature will be measured.

PHYSICAL EXAMINATION

A brief physical examination will be performed during the baseline visit and documented using a standard form. The brief physical examination will include:

- General, respiratory, and cardiovascular examinations.
- Height and weight will be measured, and Body Mass Index (BMI) calculated.

SPIROMETRY

In order to minimise participant burden, the date and result of the most recent lung function tests (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], forced expiratory ratio [FEV1/FVC], transfer factor [TLCO/DLCO] will be collected (value and as percentage of predicted value) from participants' clinical records for the purpose of characterising the study population.

EXERCISE CAPACITY

A one-minute sit-to-stand test will be performed at the baseline visit. According with a standard protocol[35] we will use a standard chair (height 46–48 cm) with a flat seat and no armrests, stabilised against a wall. Patients will be asked to sit with their legs hip-width apart and flexed to 90°, with their hands stationary on the hips without using the hands or arms to assist movement. They will be instructed to stand completely straight and touch the chair with their bottom when sitting, but that they need not sit fully back on the chair. Patients will be asked to perform as many repetitions as possible in 1 min, and after 45 s will be told "you have 15 s left until the test is over". Two sit-to-stand tests will be undertaken with the second recorded as their exercise capacity to eliminate the known learning effect.

BREATHLESSNESS

NRS will be used to assess the following aspects of breathlessness over the past 24 hours:

- Worst breathlessness in last 24 hours (primary outcome)

- Distress caused by breathlessness
- Coping with breathlessness

In this assessment patients rate their breathlessness symptoms from 0 to 10 where lower scores represent a lower symptom burden. NRS will be collected at the baseline visit and rest of the study visits including the follow up visits.

mMRC BREATHLESSNESS SCALE

The mMRC Breathlessness Scale will be used to assess the degree of baseline functional disability due to dyspnoea during the baseline visit Day 0. The mMRC breathlessness scale ranges from grade 0 to 4 where higher scores represent severity of the breathlessness. The scores are associated with patients' perceptions of respiratory symptom burden.

FUNCTIONAL STATUS

AKPS will be used to assess participants' functional status[36]. This is a 0 (dead) to 100 (fully functional) scale increasing by 10-point increments reflecting the ability to function and the level of assistance required. AKPS will be collected at the baseline visit and rest of the study visits including the follow up visits.

HEALTH STATUS [EQ-5D-5L (EQ-5D & EQ VAS)]

EQ-5D-5L is a self-administered, validated, measure of health status and consists of two sections: the EQ-5D descriptive system and the EQ VAS. The EQ-5D is a 5-question multi-attribute questionnaire. Respondents are asked to rate severity of their current problems (level 1 = no problems, level 2 = slight problems, level 3 = moderate problems, level 4 = severe problems, level 5 = unable [or extreme]) for five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The patient will be asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions.
The EQ VAS is a visual analogue self-rating scale to record the patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled 'The best health you can imagine' (100) and 'The worst health you can imagine' (0). The VAS will be used to measure participants' health outcome that reflects the participants' perception. EQ-5D-5L will be collected at the baseline visit and rest of the study visits including the follow up visits.

HEALTH SERVICE UTILISATION (CSRI)

Health service utilisation will be collected using a bespoke version of the CSRI[37] and based on the success of our feasibility study. This will include items such as GP attendance, practice nurse attendance, out-patient appointment attendance (consultant), specialist nurse review (out-patient or home-visit), emergency department attendance, hospital admission, hospice admission. CSRI will be collected at the baseline visit and rest of the study visits including the follow up visits.

EVALUATION OF USUAL CARE RECEIVED SINCE LAST VISIT

Usual care received since last visit will be collected after baseline visit at the study visits and the follow up visits. Any treatment delivered for lung disease and breathlessness such as pulmonary

rehabilitation, oxygen therapy, antifibrotics, immunosuppression (incl. steroids), morphine/other opiates therapies, breathlessness clinic attendance and existing breathlessness management strategies, will be collected.

7.3 QUALITATIVE DATA COLLECTION

An interview study will explore patient and carer satisfaction with intervention delivery and their experience of using the intervention.

A further interview study with clinicians using NPT as a framework for analysis will explore their satisfaction with the intervention training and their views on how best to implement the intervention in clinical practice.

PATIENT PARTICIPANT AND CARER INTERVIEWS

A purposive sample of approximately twenty consenting participants (plus carer if present) will be interviewed by phone six weeks after they have received the intervention. The interviews will last 30-60 minutes. Patient participants with a carer willing to contribute will be interviewed as patient-carer dyads or separately as preferred. Patient participants without a carer will still be able to participate. A patient participant interview information sheet and the opportunity to ask and receive answers to questions will be offered and written informed consent given before interviews take place. Carers will include anyone who supports the Patient participant, including relatives and friends as well as formally identified caregivers and who are nominated as such by the patient participant. Nominated carers will be invited and given a carer interview information sheet. If they are willing, they will be consented at the baseline line visit and verbal reconsent will be taken prior to interview. Patient participants will be invited to participate whether or not they have a carer and whether or not their carer agrees to take part. All participants will be assured of confidentiality, anonymity (including in any dissemination materials) and the right to withdraw at any stage without offering a reason.

The sampling frame will include age, gender, ethnicity, location, severity of breathlessness and carer status in order to achieve maximum variation. A topic guide for these patient and carer interviews developed by the study team, will be used. Interviews will be audio-recorded, transcribed verbatim, anonymised and then analysed using reflexive thematic analysis[41].

CLINICIAN AND SERVICE MANAGER INTERVIEWS

All clinicians who delivered the intervention across the participating sites will be invited to a phone interview towards the end of the recruitment period. Commissioners and service managers will also be invited to interview. The interviews will last 30-60 minutes. Clinicians, commissioners and service managers who are invited to attend an interview by members of the research team will be provided with a participant information leaflet, given an opportunity to ask questions and asked to sign an ICF prior to the interview.

A topic guide developed by the study team and informed by NPT will be used to address the study aims. Additionally, senior clinicians, commissioners and service managers across the sites and from across the United Kingdom (UK) will be interviewed on their views of how best to implement the intervention. Approximately 20 participants will be recruited for maximum variation by snowball sampling through our contacts. Interviews will be audio-recorded, transcribed verbatim and then analysed using the four constructs of NPT (coherence, cognitive participation, collective action, reflexive monitoring)[26]. Findings will be shared with the patient and carer advisory group and the wider

research group who will reflect on how findings can inform recommendations about the content and structure of an implementation strategy for the UK.

7.4 CHARITABLE INCENTIVE STUDY WITHIN A TRIAL

As part of a collaboration with the UK National Institute for Health and Care Research -funded programme, 'Implement SWATs' (www.implementswats.org), which is testing the effectiveness and cost-effectiveness of strategies aimed at improving recruitment and retention in randomised controlled trials, we would like to embed a randomised study of a recruitment strategy within the BREEZE-2 trial.

There is a lack of evidence on efficient ways to recruit participants in trials. One solution is to use a 'Study Within A Trial' (SWAT) design, where a randomised trial is embedded within another trial, such as BREEZE-2. This method, done within a single host trial or across several in a coordinated way, can produce rapid, high-quality evidence.

Monetary incentives, such as offering participants money in the form of cash or vouchers, or donation to a charity, are common strategies used by trial teams to encourage participants to enrol into trials. Systematic reviews of recruitment strategies in trials, and priority setting exercises - including by the Implement SWATs team and the International Trial Forge SWATs Network, which involved patient and public partners, have identified monetary incentives as key strategies to test for their effectiveness for recruiting participants. However, questions remain about the impacts of different types of incentives and optimal amounts, as well as their cost-effectiveness.

The Cochrane methodology review of strategies to improve recruitment in trials found monetary incentives may improve recruitment rates compared to no incentive, but the certainty of the evidence was low. One potentially effective but as yet untested incentive strategy is offering to make a charitable donation on behalf of potential participants being invited to take part in a trial. This is a patient and public involvement (PPI) led strategy, proposed by the Implement SWATs PPI group at the University of York, who suggest that potential participants may be more likely to take part in a trial if they know a donation is going to be made to a charity of their choice, or to a charity whose cause they can relate to (e.g., making an offer to donate to a well-known cancer charity when inviting participants with a diagnosis of cancer into a trial). PPI partners also suggested that such charitable incentives may not only be effective but may also be viewed by potential participants as more appealing from an ethical perspective, compared to paying participants directly with cash or vouchers for enrolling in trials.

Definitive evidence is needed on the effectiveness and cost-effectiveness of charitable donation incentives for improving recruitment rates in trials. We propose patient level randomisation with a 1:1 ratio for participants where the initial approach for the BREEZE 2 trial is being conducted to be offered a £10 charitable donation (intervention arm) or £10 cash (control arm). As is the nature of a SWAT design of this type, participants will not be informed about the SWAT, so will be blind to the SWAT hypothesis.

A potential participant is eligible to receive the SWAT pack if they are either:

-Being approached in-person in your clinic; SWAT pack contents should be given along with the study PIS and Infographic.

Or

-They have previously agreed to discuss or learn about the study (in person or by phone) and the PIS and infographic are planned to be sent to the potential participant by mail. SWAT pack contents should be sent along with the PIS and Infographic.

Potential participants that are to be sent the study details via email cannot be sent the SWAT packs and therefore are not eligible to receive the SWAT pack contents. Everybody approached for the study should be documented on the Screening log and it should be documented if they were given a SWAT pack.

To enable meta-analysis of our findings with those of approximately 20 similar studies of monetary incentives being undertaken in the UK and Ireland, anonymised quantitative patient-level data from this SWAT will be shared with Implement SWATs (funded by UK NIHR, award reference: NIHR302256), led by Dr Adwoa Parker, and based at York Trials Unit, University of York, UK - a UKCRC registered Clinical Trials Unit (UKCRC Registration ID Number 40). All datasets will be anonymised before transfer to the University of York, removing all identifiable patient information such as names and addresses, and will be encrypted before transmission to ensure security. The transfer of the data to The University of York and its storage and access will strictly adhere to the principles of data protection, including the General Data Protection Regulation (GDPR). The link to relevant information is: Data Protection - Records Management and Information Governance, University of York.

In light of this we have produced a separate protocol for the charitable incentive SWAT.

8 DATA MONITORING

A risk-based approach to monitoring will be adopted for the BREEZE 2 study. A HHTU Study Monitoring Plan will be developed and agreed by the sponsor, CI and Trial Management Group (TMG). A Data Monitoring Plan will be agreed by the sponsor, CI and statistician to provide detailed instructions and guidance relevant to database set up, data entry, validation, review, query generation and resolution, quality control processes involving data access and transfer of data to the sponsor at the end of the study and archiving.

The HHTU will maintain contact with the Investigator(s) and designated staff by email or telephone during the study.

All the information obtained about participants during the study is confidential and will be held in accordance with the GDPR 2018. Data will be monitored for quality and completeness by the HHTU. Missing data will be chased until it is received or confirmed as unavailable or the trial is at the analysis stage. Missing data items will not be chased from participants (although missing questionnaires sometimes are). The HHTU will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the HHTU. Source data verification will involve direct access to patient case notes at participating sites. There will be ongoing central collection of consent forms and other relevant investigation reports.

9 SAFETY PROCCEDURES

The AE reporting period for this trial begins after consenting to the study and ends at the participant's final study visit. Each trial participant will be questioned about adverse events at each visit. The investigator will record all directly observed AEs and all AEs spontaneously reported by the trial

participant. A pre-existing condition (i.e. a disorder present before the AE reporting period started and noted on the pre-study medical notes), is not to be reported as an AE unless the condition worsens, or episodes increase in frequency during the AE-reporting period. All adverse events (serious and non-serious) will be recorded in patients' CRFs using the adverse event report form.

All adverse events will be recorded in patients' medical records. All AEs will be followed-up until the event has resolved or a decision has been taken for no further follow-up.

9.1 DEFINITIONS OF SAFETY REPORTING

AE (Adverse event)

An adverse event is any untoward medical occurrence in a participant to whom a research intervention or procedure has been administered, including occurrences which are not necessarily caused by or related to that intervention or procedure.

SAE (Serious Adverse Event)

In research other than Clinical Trials of Investigational Medical Products (CTIMPs), a SAE is defined as an untoward occurrence that:
(a) results in death.
(b) is life-threatening.
(c) requires hospitalisation or prolongation of existing hospitalisation.
(d) results in persistent or significant disability or incapacity.
(e) consists of a congenital anomaly or birth defect; or
(f) is otherwise considered medically significant by the investigator.

Relationship to the Study Intervention

The investigator must make an assessment of the relationship of each event to the study intervention and classify it as either:

- Unrelated (where the event is definitely not or unlikely to be related to the intervention or a research procedure)
- Related (where the event likely to be related to the intervention).

Additionally, the investigator must assess whether the AE is unexpected (ie. not listed in the study protocol as an expected occurrence).

Only an SAE that is both related to the study and unexpected must be reported to the Sponsor within 24 hours of research staff knowledge of the SAE. For SAE's, the following information will be collected:

- Full details in medical terms and case description
- Event duration
- Action taken
- Outcome
- Seriousness criteria
- Causality (ie. related or unrelated to the intervention)

Hospital admissions and deaths are common in this patient group due to their underlying disease. Thus, events that meet the definition of an SAE but are not related to the study intervention will only be required to be recorded on the study adverse events log. The study adverse event log will generate a prompt to ensure the Concomitant Medication log is updated for any medication that may have been administered.

Related Unexpected Serious Adverse Events

Unexpected SAEs related to the intervention will be reported to the REC that gave a favourable opinion of the study and the sponsor (Hull University Teaching Hospitals NHS Trust R&D department) within 15 days of the chief investigator becoming aware of the event using the Non-CTIMP safety report form available from: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

Expected Serious Adverse Events

Due to the seriousness of the disease in this study, the following expected SAEs will not require reporting within 24hrs on the initial and follow-up SAE forms but will still need to be reported on the trial's AE log. All serious events that do not require reporting within 24hrs will still require recording on the trial Adverse Events log within 14 days of the researcher becoming aware of the event. Expected serious adverse events in this study include: hospital admission due to IPF/fibrotic ILD; admission to hospital or prolongation of existing hospitalisation for a pre-existing condition; death due to IPF/fibrotic ILD or known pre-existing condition; and elective surgery.

9.2 NON-CTIMP RESPONSIBILITIES FOR SAFETY REPORTING

Chief Investigator / delegate or independent clinical reviewer

- Assign relatedness and expectedness of SAE where it is not possible to obtain local assessment.
- Undertake SAE review.
- Review all Related / Unexpected events in the opinion of the PI as per protocol, or detail other review process. In the event of disagreement between PI and CI assessment, PI assessment may be upgraded or downgraded by the CI prior to reporting to the main REC.

Principal Investigator / Authorised individual

- Check for SAEs when participants attend for treatment / follow-up.
- Use medical judgement in assigning seriousness, causality and expectedness.
- Ensure all Related Unexpected Serious Adverse Event (RUSAEs) are recorded and reported to the HHTU within 24 hours of becoming aware and to provide further follow-up information as soon as available.

HHTU RESPONSIBILITIES

- Expedited reporting of Related / Unexpected SAEs to the main REC and Sponsor [dependent on Sponsor processes] within required timelines
- Preparing annual safety reports to main REC and periodic safety reports to TSC
- Notifying Investigators of Related / Unexpected SAEs which compromise participant safety.

10 STUDY OVERSITE RESPONSIBILITIES

10.1 RESEARCH GOVERNANCE

The study is funded by NIHR RfPB. The Hull University Teaching Hospitals NHS Trust is the study sponsor.

10.2 TRIAL MANAGEMENT

The day-to-day management will be conducted by the CI and personnel from HHTU. This will include a trial manager, a data manager, a trial coordinator, and a trial administrator with oversight provided by members of the HHTU senior management team. Further oversight from senior members of the research teams will be provided as needed. All activities will be performed according to the relevant HHTU SOPs.

10.3 TRIAL MANAGEMENT GROUP, TRIAL STEERING OVERSIGHT COMMITTEE AND PATIENT AND CARER ADVISORY GROUP

The Trial Management Group (TMG)

TMG is comprised of the CI, HHTU team, key external members of staff assigned responsibility for trial management including protocol development, trial set-up, data analysis, obtaining regulatory approvals, submitting contracts, completing cost estimates, facilitating TSC meetings, monitoring compliance to recruitment & qualitative intervention, auditing consent procedures, data collection, data validation, database development and trial promotion and publication of trial results.

The Trial Steering Committee (TSC)

TSC is comprised of an Independent Chair, not less than two other independent members and a patient representative. At least one of the TSC independent members will be a clinician who collectively possess a range of relevant skills and an interest in the trial. The Committee will meet approximately every 6 months. The Terms of Reference of the Trial Steering Committee are as follows:

• To provide overall supervision of the study, ensuring adherence to protocol
• To review developments during the study and recommend appropriate action

• To ensure that the rights and well-being of study participants is safeguarded and prioritised
• To review at regular intervals relevant information from other sources (e.g. other related studies), and recommend appropriate action
• To keep any issues discussed in the meetings or written in the minutes confidential, unless otherwise agreed
• The TSC will also consider matters pertaining to the implementation study aspects of the study

Patient and Carer Advisory Group (PCAG)

We have set up a PCAG made up of seven people with personal experience of pulmonary fibrosis, either themselves, or in caring for a loved one. This group includes people from across the UK, to include some of our trial sites, and will meet at regular points throughout the trial. During project set-up, the PCAG will advise on participant information materials for patients and carers, consent and any other ethical issues which need consideration to inform the ethics application. They will also help to develop the topic guide for the patient and carer interviews. As the trial progresses, they will help to resolve potential recruitment issues and drop out from the study. We will share our findings with the group for discussion, and they will then advise on ways of sharing these with trial participants and the wider public. Towards the end of the project, we plan to make an animated film about public involvement in the trial, and a podcast, with members of the group. Our Patient and Public Involvement Coordinator acts as a link between this group and the Trial Management Group, reporting on its activities, and we have also recruited two people with pulmonary fibrosis to represent patients on the Trial Steering Committee. Members of the group will participate in other activities as required throughout the lifecycle of the project.

11 STATISTICAL ANALYSIS PLAN

11.1 SAMPLE SIZE

The primary outcome is the NRS worst breathlessness score at 4 weeks follow-up. It ranges from 0-10, which evaluates the worst breathlessness in the last 24 hours (higher scores indicate worse breathlessness). The feasibility trial showed the unadjusted and adjusted mean difference at 4-week follow-up were -0.80 and -0.93 and we observed the common baseline standard deviation SD=1.7. Assuming a minimal clinical important difference (MCID) of 1 in NRS worst breathlessness score[38, 39], we will need to recruit 62 patients per group at 90% power and 0.05 significance level. Considering 87% retention rate was attained in the feasibility study, we assume 15% attrition rate. Therefore, the final sample size will be 73 patients per group (146 in total).

11.2 DATA ANALYSIS

Statistical analysis is the responsibility of the HHTU Statistician. A full statistical analysis plan will be written before any analyses are undertaken.

11.2.1 MAIN STUDY DATA ANALYSIS

We will follow the CONSORT 2010 statement[40] for analysis and reporting. Primary analyses will be conducted on intention-to-treat basis and follow a pre-specified statistical analysis plan. A flow chart will show the numbers of participants who were approached and/or assessed for eligibility, randomly

assigned for treatment, completed treatment, completed follow-up as planned and included in the main analyses in each group. Baseline demographic and health characteristics will be summarised for each group through descriptive statistics.

As the primary outcome, NRS worst breathlessness in 24 hours score at 4-week follow-up will be analysed by linear regression, adjusting for NRS worst breathlessness in 24 hours score at baseline, treatment group and stratification factors. The same regression approach, with adjustment for independent variables, will be used for the comparison of NRS worst breathlessness in 24 hours score at 8-week follow-up. Secondary outcomes (other NRS breathlessness scores, Functional Status and EQ-5D scores) will be presented at each time-point and analysed by regression approaches, adjusting for baseline score, treatment group and stratification factors.

For the wait-list group, outcome assessment at 12 weeks will be summarised. This will be after they have received the intervention and will mirror the 4-week primary outcome measure after intervention delivery in the fast-track group. In the telephone follow-up phase, continuation of the use of intervention components, outcome measure completion rates as well as longer-term maintenance of effects will be reported every eight weeks, to a maximum of twelve months.

11.2.2 QUALITATIVE DATA ANALYSIS

Reflexive thematic analysis will be used to identify, analyse and interpret themes from the qualitative interview data [41]. Nvivo software will be used to support the analysis (QSR International 2012). Clinician interview data will be analysed using thematic analysis, informed by key aspects of NPT, relating to: how clinicians understand the intervention (coherence); how they engage with it (cognitive participation); enact it (collective action); and appraise its effects (reflexive monitoring).

Any patient/carer dyad transcripts will be analysed together to examine interaction between the two participants. Initially, two researchers will familiarise themselves with the data by reading and re-reading transcripts and identifying recurring ideas and concepts (codes). They will then work systematically through the dataset in the process of coding the data (collating segments of text relevant to each code). The codes will be sorted and collated to develop potential themes and subthemes. The two researchers will discuss the development of codes and themes at regular intervals to reach consensus and take a consistent approach to analysis. This will be reviewed and refined by a third member of the research team, by checking whether the collated data extracts within each theme form a coherent pattern and by checking whether the identified themes reflect the meanings evident in the dataset as a whole. Further coding and development of themes will be conducted as necessary. The themes will then be defined and based on the collated data extracts, a detailed analysis will be written for each theme. Finally, an account will be written which analyses and interprets the data, both within and across themes [41].

The wider research team and the PCAG will review the findings, in relation to how it compares with their own clinical context and knowledge of the wider literature.

11.2.3 ECONOMIC EVALUATION

To assess the cost-effectiveness of the intervention we will collect data on health service utilisation (using the modified CSRI) and health related quality of life (EQ-5D-5L).

1. Health service utilisation will be recorded to collect participants' attendance to the GP, practice nurse, out-patient appointment (consultant), specialist nurse review (out-patient or home-visit),

emergency department, hospital admission and hospice admission. Unit costs will be applied to the relevant resource use to generate cost per patient.

We are committed to collect data on the duration of intervention delivery and members of staff involved and their grade and training requirements. We will also collect information on other costs associated with intervention delivery to generate a full cost of introducing the intervention into routine NHS practice.

2. EQ-5D-5L will be used to calculate Quality adjusted survival (QALY).

Using the costs and outcomes described above, we will conduct two main analyses, comparing the costs and effects of the breathlessness intervention with the costs and effects of wait-list control. Firstly, we will conduct a within trial evaluation, using individual patient data from the trial over the time horizon of the RCT. We will compare costs and effects in the breathlessness intervention (fast-track) group with costs and effects in the wait-list arm. We will calculate QALYs using linear interpolation of EQ5D scores at baseline and follow-up.

Secondly, though we anticipate the majority of costs and effects will occur within or around the period of the trial, we will explore whether the duration and pattern of costs/effects impacts on cost-effectiveness. As an example, if the intervention shows an increase in costs together with an improvement in outcome over the trial period, we will estimate how long the treatment effect would have to be maintained for the intervention to be cost-effective. For both analyses, we will use an NHS and PSS perspective, consistent with that taken by the NICE as most costs and benefits will fall in this sector (for example, in this patient group there are unlikely to be any impact on productivity).

Cost-effectiveness results will be expressed in terms of incremental cost-effectiveness ratios (ICERs), showing the incremental cost per additional QALY compared with usual care, and incremental net health benefits to show the difference between the health generated with a strategy and the health which could be generated elsewhere in the health care system using the same resources. We will do this for commonly used thresholds of £15,000, £20,000 and £30,000 per QALY.

11.3 PLANNED RECUITMENT

To achieve recruitment target of 146 participants, we intend to recruit for 12 months from fifteen sites. Given the recruitment rate at the ILD centre in the feasibility trial was an average of 2 per month, while recognising that not all sites will recruit at this rate and some sites will be open for recruitment for less time, we believe that we will comfortably recruit to time and target.

We will also recruit a sample of approximately twenty consenting participants (plus carer if present) for qualitative interviews. In addition, we will recruit approximately 20 clinicians, commissioners, and service managers for maximum variation by snowball sampling through our contacts.

11.4 MISSING DATA

Missing data will be assessed for any differential ‘missingness’ between randomised groups and investigated using appropriate missing data mechanisms. Details will be provided in the Statistical Analysis Plan.

11.5 ENDPOINT ANALYSIS

The end of the study will be defined as 30 days after the date of the last follow up visit for the last participant. An End of Study Declaration Form will be submitted to the REC, Health Research Authority (HRA) and site R&D within 90 days from the End of Study date and within 15 days if the study is discontinued prematurely. A summary of the study final report/publication will be submitted to the REC, HRA and site R&D within 1 year of the end of study date. Site R&D will be notified immediately of any reason to halt the study. The CI and sponsor will decide if the study should be halted temporarily. The REC and site R&D will be notified within 15 days of a decision to temporarily halt the study by submitting a substantial amendment notification.

12 QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework (RGF) [and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006 (for studies conducted in Scotland)], and through adherence to HHTU SOPs.

Investigators are required to promptly notify the HHTU of a serious breach (as defined in the latest version of the National Research Ethics Service (NRES) A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

In the event of doubt or for further information, the Investigator should contact the study Trial Manager at the HHTU.

As part of study set-up and before initiation of the trial at any participating site, the protocol, ICFs and any material to be given to prospective participants will be submitted to a national REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Each site will provide R&D and Capacity and Capability (C&C) approval before the trial can be given green light to start recruitment.

Written Informed consent will be obtained from participants prior to commencing the interview. The right to decline study participation without giving a reason must be respected. The participant must remain free to withdraw at any time without giving a reason and without prejudicing his/her further treatment. The HHTU will provide the main REC with a copy of the final protocol, participant information sheets, consent forms and all other relevant study documentation.

13 FINANCIAL AND OTHER COMPETING INTERESTS FOR THE CHIEF INVESTIGATOR, PIS AT EACH SITE AND COMMITTEE MEMBERS FOR THE OVERALL TRIAL MANAGEMENT

Any competing interests that might influence study design, conduct, or reporting will be identified, disclosed and documented in the Electronic Trial Master File (eTMF). The oversight groups will determine what it is appropriate to report; details will be in the Dissemination and Publication Plan.

Disclosure should reflect:

- ownership interests that may be related to products, services, or interventions considered for use in the study or that may be significantly affected by the study

- commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion

14 CONFIDENTIALITY

Full details will be available in the Study Data Management Plan, Data Protection Impact Assessment (DPIA) and Privacy Notice. The HHTU data management team will be responsible for insuring compliance with General Data Protection Regulation 2018.

All site investigators and research staff must comply with the requirements of the General Data Protection Regulation 2018 with regards to the collection, storage, processing, and disclosure of personal information and will uphold the Regulation's core principles.

HHTU and sponsor will maintain the confidentiality of all participant data in accordance with General Data Protection Regulation Act (2018) and will not reproduce or disclose any information by which participants could be identified. Confidentiality will be maintained at all times.

Access to personal data for this project will be limited to named individuals who will accept terms of use ahead of being granted individual user-based access. HHTU data systems have a full audit trail which cannot be edited by HHTU staff. Personal data for this specific project will be limited to participants names and their contact details for the purpose of interview.

Participants will be informed that their personal data will be entered into the cloud-based Electronic Data Capture (EDC).

Study data will be pseudo anonymised and related forms will be identified using the study ID only. Participant names and contact details will be held in a restricted folder within the same system, to enable the central researcher to undertake an interview. All hard copy data will be stored at study sites in a locked filing cabinet in accordance with data protection requirements for the retention of research data policies.

14.1 ARCHIVING

Archiving will be authorised by the sponsor following submission of the end of study report. All essential study documents including source documents will be archived in accordance with the HHTU Data and Study Document Archiving SOP. Personal identifiable data will be stored for 12 months from study completion. Plan for a minimum period of 5 years after study completion. Destruction of essential documents will require authorisation from the sponsor.

15. STATEMENT OF INDEMNITY

15.1 POTENTIAL LEGAL LIABILITY OF THE SPONSOR OR EMPLOYER

This is an NHS sponsored study and NHS indemnity covers sponsor potential legal liability for harm to participants arising from the design of the research. Protocol authors with a substantive university contract will also have indemnity cover from their employing university.

15.2 POTENTIAL LEGAL LIABILITY OF INVESTIGATORS/COLLABORATORS

If there is negligent harm during the clinical trial, the NHS body owes a duty of care to the person harmed. NHS indemnity covers NHS staff and UK based medical academic staff with honorary contracts only when the study has received confirmation of capability and capacity from the Trust R&D department.

15.3 ARRANGEMENTS IN THE ABSENCE OF LEGAL LIABILITY

NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Protocol authors with a substantive UK university contract will also have indemnity cover from their employing university. The UK universities do not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

The sponsor will not provide 'no-fault' indemnity for harm arising due to study procedures carried out as part of the study. The sponsor will not provide payment for medical costs for medical complications caused by failure of participants to follow instructions given or if the medical complication was not related to the study agent or research study procedure. Study associated staff employed by NHS and UK university will also have personal indemnity from their employers.

16. STUDY ORGANISATIONAL STRUCTURE

- **Chief Investigator (CI) –** The CI will have overall responsibility for the trial design, set-up, conduct, co-ordination, and management.
- **Medical Experts** - The study medical expert will have responsibility for the design, coordination, management of the study and oversight.
- **Trial Sponsor –** The Sponsor will be responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the HHTU as detailed in the trial contract.
- **Clinical Trials Research Unit –** The HHTU will have responsibility for trial conduct as delegated by the Sponsor in accordance with GCP standards. The HHTU will conduct trial set-up and monitoring in line with HHTU SOPs and partner SOPs (if applicable). Responsibilities include trial administration, protocol development, CRF design, trial design, main REC/HRA regulatory submissions, data management, safety reporting, randomisation design and service, database development and provision, database administrative functions, source data verification, monitoring, statistical analyses, HHTU and site training, trial reports and results dissemination.
- **Site PI / nominated clinicians –** PIs and study doctors will have a responsibility for participants eligibility assessment, consent process and adverse event assessment**.**
- **Trial Management Group (TMG) –** The TMG, is comprised of the CI, HHTU team, key external members of staff and a nursing representative will be assigned responsibility for trial set-up, trial management, trial promotion, data analysis and publishing trial results. The TMG will be responsible for:
  - protocol completion.
  - CRF development
  - obtain approval from main REC and support applications for Site Specific Assessments
  - completing cost estimates and project initiation

- nominating members and facilitating the TSC
- reporting of serious adverse events
- monitoring of screening, recruitment, and follow-up procedures
- auditing consent procedures, data collection, trial end-point validation, database development

- **Trial Steering Committee (TSC) –** The TSC, is comprised of an Independent Chair, not less than two other independent members and a consumer representative. The TSC will provide overall supervision of the trial looking in particular at trial progress, adherence to protocol, participant safety and consideration of new information. TMG members may attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum.

17. PUBLICATION POLICY

Prior to trial recruitment, the trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated on the trial, through authorship and contributions. Authorship guidelines will be provided for manuscripts submitted to medical journals. These state that authorship credit should be based only on substantial contribution to:

conception and design, or acquisition of data, or analysis and interpretation of data

drafting the article or revising it critically for important intellectual content

and final approval of the version to be published.

and that all these conditions must be met (**www.icmje.org**)

The CI, Research Fellow [if appropriate] and relevant senior HHTU staff will be named as authors in all publications. All collaborators will be listed as contributors for the main trial publication, alongside roles in trial planning, conducting, and reporting. To maintain trial scientific integrity, data will not be released before the first publication of primary endpoint analysis, either for publication or oral presentation, without TSC permission. Individual collaborators must not publish data concerning their participants before the first publication of primary endpoint analysis.

17.1 AUTHORSHIP ELIGIBILITY GUIDELINES AND ANY INTENDED USE OF PROFESSIONAL WRITERS

All publications and presentations relating to the study are required to be authorised by the TMG, who will prepare the Study Dissemination and Publications Plan.

The agreement will include:

- guidelines on authorship on the final trial report consistent with the Vancouver Recommendations from The International Committee of Medical Journal Editors
- whether participating investigators have rights to publish any of the study data
- any time limits or review requirements on the publications

17.2 DISSEMINATION POLICY

Publications for the study will meet the standards required for submission to high quality peer reviewed journals and the main trial papers will be reported in accordance with the CONSORT guidance. http://www.consort-statement.org/. On completion of the study, the data will be analysed and tabulated and a Final Study Report prepared.

The results will be disseminated in peer reviewed journals, through local and other relevant clinical networks and at national and international meetings. Participants will be sent a summary of the findings, if requested and a copy of the final accepted manuscript of the primary paper after the results have been published.

The funding source (NIHR) will be acknowledged within all publications, and a copy sent for their prior information according to their requirements. The Funder does not have publication rights of the data from the study.

The study protocol manuscript will be prepared and published. The protocol will be available on the CI and HHTU website, and the study design synopsis available on the International Standard Randomised Controlled Trial Number (ISRCTN) website.

18. REFERENCES

1. Jenkins G. James Lind Alliance Priority Setting Partnership on Progressive Pulmonary Fibrosis. https://www.jla.nihr.ac.uk/priority-setting-partnerships/progressive-pulmonary-fibrosis/top-10-priorities.htm: James Lind Alliance, 2022.

2. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An O cial ATS. ERS/JRS/ALAT Clinical Practice Guideline. American journal of respiratory …, 2020.

3. APF. Living with pulmonary fibrosis. https://www.actionpf.org/information-and-support/living-with-pulmonary-fibrosis2023.

4. Swigris JJ, Stewart AL, Gould MK and Wilson SR. Patients' perspectives on how idiopathic pulmonary fibrosis affects the quality of their lives. Health and quality of life outcomes. 2005; 3: 1-9.

5. Carvajalino S, Reigada C, Johnson MJ, Dzingina M and Bajwah S. Symptom prevalence of patients with fibrotic interstitial lung disease: a systematic literature review. BMC pulmonary medicine. 2018; 18: 1-11.

6. Johnson MJ, Bland JM, Gahbauer EA, et al. Breathlessness in elderly adults during the last year of life sufficient to restrict activity: prevalence, pattern, and associated factors. Journal of the American Geriatrics Society. 2016; 64: 73-80.

7. Nishiyama O, Taniguchi H, Kondoh Y, et al. A simple assessment of dyspnoea as a prognostic indicator in idiopathic pulmonary fibrosis. European Respiratory Journal. 2010; 36: 1067-72.

8. Raghu G, Amatto VC, Behr J and Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. European Respiratory Journal. 2015; 46: 1113-30.

9. Johnson M, Yorke J and Hansen-Flaschen J. Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. Eur Respir J. 2017: 13993003.02277-2016.

10. King Jr TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. New England Journal of Medicine. 2014; 370: 2083-92.

11. Richeldi L, Du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New England Journal of Medicine. 2014; 370: 2071-82.

12. Dowman L, Hill CJ, May A and Holland AE. Pulmonary rehabilitation for interstitial lung disease. Cochrane Database of Systematic Reviews. 2021.

13. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. American journal of respiratory and critical care medicine. 2011; 183: 788-824.

14. Holland AE, Hill CJ, Conron M, Munro P and McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax. 2008; 63: 549-54.

15. Nishiyama O, Kondoh Y, Kimura T, et al. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2008; 13: 394-9.

16. Vainshelboim B, Oliveira J, Yehoshua L, et al. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic pulmonary fibrosis. Respiration. 2014; 88: 378-88.

17. Gaunaurd IA, Gómez-Marín OW, Ramos CF, et al. Physical activity and quality of life improvements of patients with idiopathic pulmonary fibrosis completing a pulmonary rehabilitation program. Respiratory care. 2014; 59: 1872-9.

18. Jackson RM, Gomez-Marin OW, Ramos CF, et al. Exercise limitation in IPF patients: a randomized trial of pulmonary rehabilitation. Lung. 2014; 192: 367-76.

19. Allen S, Raut S, Woollard J and Vassallo M. Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end-stage idiopathic pulmonary fibrosis. Palliative medicine. 2005; 19: 128-30.

20. Higginson IJ, Bausewein C, Reilly CC, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. The Lancet Respiratory Medicine. 2014; 2: 979-87.

21. Farquhar MC, Prevost AT, McCrone P, et al. Is a specialist breathlessness service more effective and cost-effective for patients with advanced cancer and their carers than standard care? Findings of a mixed-method randomised controlled trial. BMC medicine. 2014; 12: 1-13.

22. Johnson MJ, Kanaan M, Richardson G, et al. A randomised controlled trial of three or one breathing technique training sessions for breathlessness in people with malignant lung disease. BMC medicine. 2015; 13: 213.

23. Maddocks M, Brighton LJ, Farquhar M, et al. Holistic services for people with advanced disease and chronic or refractory breathlessness: a mixed-methods evidence synthesis. 2019.

24. Bajwah S, Ross JR, Peacock JL, et al. Interventions to improve symptoms and quality of life of patients with fibrotic interstitial lung disease: a systematic review of the literature. Thorax. 2013; 68: 867-79.

25. Gift AG and Narsavage G. Validity of the numeric rating scale as a measure of dyspnea. American Journal of Critical Care. 1998; 7: 200-4.

26. May CR, Mair F, Finch T, et al. Development of a theory of implementation and integration: Normalization Process Theory. Implementation Science. 2009; 4: 29.

27. Farquhar MC, Prevost AT, McCrone P, et al. The clinical and cost effectiveness of a Breathlessness Intervention Service for patients with advanced non-malignant disease and their informal carers: mixed findings of a mixed method randomised controlled trial. Trials. 2016; 17: 1.

28. Tiep BL, Burns M, Kao D, Madison R and Herrera J. Pursed lips breathing training using ear oximetry. Chest. 1986; 90: 218-21.

29. Bausewein C, Booth S, Gysels M and Higginson I. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. Cochrane Database Syst Rev. 2008; 2.

30. Galbraith S, Fagan P, Perkins P, Lynch A and Booth S. Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial. Journal of pain and symptom management. 2010; 39: 831-8.

31. Johnson MJ, Booth S, Currow DC, Lam LT and Phillips JL. A mixed-methods, randomized, controlled feasibility trial to inform the design of a phase III trial to test the effect of the handheld fan on physical activity and carer anxiety in patients with refractory breathlessness. Journal of pain and symptom management. 2016; 51: 807-15.

32. Bausewein C, Booth S, Gysels M, Kühnbach R and Higginson IJ. Effectiveness of a hand-held fan for breathlessness: a randomised phase II trial. BMC palliative care. 2010; 9: 22.

33. Farquhar MC, Prevost AT, McCrone P, et al. Is a specialist breathlessness service more effective and cost-effective for patients with advanced cancer and their carers than standard care? Findings of a mixed-method randomised controlled trial. BMC medicine. 2014; 12: 194.

34. Yorke J, Johnson MJ, Punnett G, et al. Respiratory distress symptom intervention for non-pharmacological management of the lung cancer breathlessness–cough–fatigue symptom cluster: randomised controlled trial. BMJ supportive & palliative care. 2022.

35. Crook S, Büsching G, Schultz K, et al. A multicentre validation of the 1-min sit-to-stand test in patients with COPD. European Respiratory Journal. 2017; 49.

36. Abernethy A, Shelby-James T, Fazekas B, Woods D and Currow D. Performance status across PC settings: agreement between three versions of the Karnofsky Performance Scale. BMC Palliat Care. 2005; 4.

37. Beecham J, Hallam A, Knapp MRJ, Baines B, Fenyo AJ and Asbury M. Costing care in hospital and in the community. 1997.

38. Ekström M, Chang S, Johnson MJ, et al. Low agreement between mMRC rated by patients and clinicians: implications for practice. European Respiratory Journal. 2019; 54.

39. Johnson MJ, Bland JM, Oxberry SG, Abernethy AP and Currow DC. Clinically important differences in the intensity of chronic refractory breathlessness. Journal of pain and symptom management. 2013; 46: 957-63.

40. Schulz KF, Altman DG and Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Journal of Pharmacology and pharmacotherapeutics. 2010; 1: 100-7.

41. Braun V and Clarke V. One size fits all? What counts as quality practice in (reflexive) thematic analysis? Qualitative research in psychology. 2021; 18: 328-52.