ISRCTN13662540 https://doi.org/10.1186/ISRCTN13662540

Management of breathlessness for people with pulmonary fibrosis

Submission date
14/10/2024

Recruitment status
Recruiting

Registration date
29/10/2024

Overall study status
Ongoing

Last Edited
10/02/2025

Condition category
Respiratory

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
This study aims to find out if breathlessness management training can help people with pulmonary fibrosis, a disease that causes scarring of the lungs and makes it hard to breathe. Medications can slow the disease but do not improve symptoms or quality of life. Shortness of breath is the most common and impactful symptom. This study will help doctors and policymakers make better treatment decisions.

Who can participate?
Men and women aged 50 years or older with a diagnosis of pulmonary fibrosis can participate.

What does the study involve?
Participants will be randomly assigned to receive breathlessness management training either within one week (Fast-track Group) or after eight weeks (Wait-list Group). Both groups will continue with their usual care. Participants will visit their local hospital for an initial assessment and then attend three appointments for breathlessness management training. The first two appointments will be in person, and the third will be a phone call. Participants will learn various techniques to manage their breathlessness and receive an information leaflet to help them at home. Everyone will receive the training, but the timing will be random. Participants will also receive phone calls every four weeks during the first 16 weeks and then every eight weeks for up to one year.

What are the possible benefits and risks of participating?
Participants will gain access to breathlessness management training, which may help them manage their symptoms better. However, those in the Wait-list Group will have to wait eight weeks before receiving the training. Usual care will continue during this time, but there might be a slight delay in receiving breathlessness management training compared to normal care.

Where is the study run from?
The study is run by Hull University Teaching Hospitals NHS Trust (UK) and the University of Hull (UK)

When is the study starting and how long is it expected to run for?
April 2024 to April 2026

Who is funding the study?
NIHR Research for Patient Benefit programme (UK)

Who is the main contact?
Dr Ann Hutchinson (ann.hutchinson@hyms.ac.uk)
Grant Constable (breeze2@hyms.ac.uk)

Contact information

Type(s)
Scientific, Principal Investigator

Contact name
Dr Ann Hutchinson

Contact details
Wolfson Palliative Care Research Centre
Hull York Medical School
University of Hull
Hull
United Kingdom
HU6 7RX
-
ann.hutchinson@hyms.ac.uk

Type(s)
Public

Contact name
Mr Grant Constable

Contact details
Hull Health Trials Unit
University of Hull
Hull
United Kingdom
HU6 7RX
-
breeze2@hyms.ac.uk

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
342696

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 63570, NIHR206252

Study information

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

Acronym
BREEZE-2

Study objectives
The breathlessness intervention will reduce the score of worse breathlessness (0-10) at the 4-week follow-up appointment compared to usual care.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 11/09/2024, West of Scotland REC 5 (West of Scotland Research Ethics Service, Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, United Kingdom; +44 141 314 0213; WoSREC5@ggc.scot.nhs.uk), ref: 24/WS/0113

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Management of breathlessness for people with pulmonary fibrosis

Interventions

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).

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. However, the study statistician and the health economist undertaking analysis will be blinded to group allocation.

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 online 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.

If a participant is randomised to the fast-track group, they will start their intervention sessions within one week of randomisation. However, if a participant is 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)
- Instructions on using a hand-held fan (fan will be provided)
- Pacing and breathlessness management during everyday activities, including positions for recovery from exertional breathlessness and information on the importance of exercise
- Techniques to promote relaxation and manage anxiety and panic

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 the following link: Cambridge Breathlessness Intervention Service

Usual care
Usual care will be received throughout by all participants. Details of usual care received will be recorded during study visits and include any intervention that would ordinarily be offered outside 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 in 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.

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.

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 and Health Status EQ-5D-5L (EQ5D and EQ VAS), CSRI. 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 the 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. 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.

Intervention visits
Participants in both fast-track and 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 first face-to-face session within one week of randomisation and the second face-to-face session one week later. The final session will be a phone call follow-up of 20 minutes after a further week. Participants randomised to the wait-list group will start the intervention in week 9, with two one-hour face-to-face sessions and a phone call at 1-week intervals over a 3-week period.

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

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, the following assessments will be performed: NRS scores, AKPS, Health Status EQ-5D-5L (EQ-5D and EQ VAS), CSRI, and evaluation of usual care received since the last visit, including changes in 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).

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
Participants' regular medications (prescribed and over the counter) will be recorded during the baseline visit (Day 0) and the 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
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 to a standard protocol, 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 they need not sit fully back on the chair. Patients will be asked to perform as many repetitions as possible in 1 minute, and after 45 seconds will be told "you have 15 seconds 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 the 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 the 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 the severity of breathlessness. The scores are associated with patients' perceptions of respiratory symptom burden.

Functional status
AKPS will be used to assess participants' functional status. 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 the 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 the 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 outcomes that reflect the participants' perception. EQ-5D-5L will be collected at the baseline visit and the 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 and based on the success of our feasibility study. This will include items such as GP attendance, practice nurse attendance, outpatient appointment attendance (consultant), specialist nurse review (outpatient or home-visit), emergency department attendance, hospital admission, and hospice admission. CSRI will be collected at the baseline visit and the rest of the study visits, including the follow-up visits.

Evaluation of usual care received since last visit
Usual care received since the last visit will be collected after the 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 (including steroids), morphine/other opiates therapies, breathlessness clinic attendance, and existing breathlessness management strategies, will be collected.

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 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. Patients with a carer willing to contribute will be interviewed as patient-carer dyads or separately as preferred. Patients without a carer will still be able to participate. A participant 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 patients, including relatives and friends as well as formally identified caregivers who are nominated as such by the patient participant. Nominated carers will be invited and given an information sheet. If they are willing, they will be consented prior to the interview. Patients will be invited to participate whether or not they have a carer and whether or not their carer agrees to take part. 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 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.

Clinician and service manager interviews
All clinicians who delivered the intervention across the fifteen 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). 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.

Intervention Type
Other

Phase
Phase III

Primary outcome measure
Worst Breathlessness in the past 24 hours measured using the patient reported NRS worst Breathlessness score assessed at 4 week follow-up (Primary time point). NRS worse Breathlessness score will also be collected at the 8 week, 12 week and 16 week follow-up.

Secondary outcome measures
1. NRS Coping with Breathlessness in the past 24 hours measured using the patient reported NRS Coping with Breathlessness score. This will be collected at the 4 week, 8 week, 12 week and 16 week follow-up
2. NRS Distress due to breathlessness in the past 24 hours measured using the patient reported NRS Distress due to breathlessness score. This will be collected at the 4 week, 8 week, 12 week and 16 week follow-up
3. Functional capacity measurement using the Australia-modified Karnofsky Performance scale (AKPS). This will be collected at will be collected at the 4 week, 8 week, 12 week and 16 week follow-up
4. Health status and quality of life assessed using the patient reported EQ-5D-5L (EQ-5D scale and EQ-VAS). This will be collected at the 4 week, 8 week, 12 week and 16 week follow-up. It will also be used for the health economic evaluation
5. Health service utilisation collected using a bespoke version of the Client Service Reciept Inventory (CSRI) 37). This will be collected at the 4 week, 8 week, 12 week and 16 week follow-up

Overall study start date
30/04/2024

Completion date
29/04/2026

Eligibility

Key inclusion criteria
1. Males and females aged ≥50 years. This age cut-off is chosen to reduce the likelihood of including patients with nonfibrotic ILD
2. PF* diagnosed by multidisciplinary team (MDT) consensus in accordance with international

guidelines
3. If on treatment for PF (with antifibrotic or immunomodulatory medication), on the same dosage for at least 1 month
4. 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)
5. Resting oxygen saturation ≥90% on air/using usual oxygen prescription
6. Able to give informed consent

* Specifically, the diagnosis of PF is confirmed if a patient has:
2.1. A diagnosis of idiopathic pulmonary fibrosis (IPF)
OR
2.2. A diagnosis of 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

Participant type(s)
Patient

Age group
Mixed

Lower age limit
50 Years

Sex
Both

Target number of participants
Planned Sample Size: 146; UK Sample Size: 146

Key exclusion criteria
1. Significant comorbid cardiorespiratory disease other than PF considered by the PI to be the primary cause of breathlessness
2. Pulmonary rehabilitation: completed ≤ 3 months before study entry
3. Breathlessness clinic attendance: completed ≤ 3 months before study entry or to be started in the next 16 weeks
4. Acute exacerbation of PF within 3 months
5. Unwilling or unable to give informed consent or complete study measures
6. Australian-modified Karnofsky Performance Status of at least 60 (60=Considerable assistance and frequent medical care required)

Date of first enrolment
02/12/2024

Date of final enrolment
31/10/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Hull Royal Infirmary
Anlaby Road
Hull
United Kingdom
HU3 2JZ

Sponsor information

Organisation
Hull University Teaching Hospitals NHS Trust

Sponsor details
Hull Royal Infirmary, Anlaby Road
Hull
England
United Kingdom
HU3 2JZ
+44 1482 624067
james.illingworth3@nhs.net

Sponsor type
Hospital/treatment centre

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type

Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The results will be disseminated in high-impact 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.

Intention to publish date
01/05/2026

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from the Hull Health Trials Unit (hhtuenquiries@hyms.ac.uk)

IPD sharing plan summary
Available on request