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Early View

Study protocol

A feasibility cluster randomised controlled trial of a paramedic-administered breathlessness management intervention for acute-on-chronic breathlessness (BREATHE): Study protocol

Matthew Northgraves, Judith Cohen, Victoria Allgar, David Currow, Simon Hart, Kelly Hird, Andrew Hodge, Miriam Johnson, Suzanne Mason, Flavia Swan, Ann Hutchinson

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Title: A feasibility cluster randomised controlled trial of a paramedic-administered breathlessness management intervention for acute-on-chronic breathlessness (BREATHE): Study protocol

Authors:
Matthew Northgraves[1], Judith Cohen[1], Victoria Allgar[2], David Currow[3], Simon Hart[4], Kelly Hird[5], Andrew Hodge[5], Miriam Johnson[6], Suzanne Mason[7], Flavia Swan[6], Ann Hutchinson[6]

1. Hull Health Trials Unit, University of Hull
2. Hull York Medical School / Health Sciences, University of York
3. Faculty of Health, University of Technology Sydney
4. Respiratory Research Group, Hull York Medical School
5. Yorkshire Ambulance Service NHS Trust
6. Wolfson Palliative Care Research Group, Hull York Medical School
7. CURE group, School of Health and Related Research, University of Sheffield

Corresponding author:
Matthew Northgraves
Hull Health Trials Unit
3rd Floor AMB
University of Hull
Hull
HU6 7RX
UK

Sponsor:
University of Hull
Cottingham Road
Hull
HU6 7RX
UK

Tweetable abstract/take home message

Acute-on-chronic breathlessness initiates many emergency presentations. The BREATHE protocol describes a feasibility, cluster randomised controlled trial of a paramedic breathlessness management intervention.

Abstract

Introduction: Chronic breathlessness, persistent and disabling despite optimal treatment of underlying causes, is a prevalent and frightening symptom and is associated with many emergency presentations and admission to hospital. Breathlessness management techniques used by paramedics may reduce the need for conveyance to hospital. The Breathlessness RElief AT HomE study (BREATHE) aims to explore the feasibility of conducting a definitive cluster randomised controlled trial (cRCT) for people with acute-on-chronic breathlessness who have called an ambulance, to evaluate the effectiveness and cost-effectiveness of a paramedic-administered non-pharmacological breathlessness intervention.

Methods and analysis: The trial is a mixed-methods feasibility cluster randomised controlled trial. Eight paramedics will be randomised 1:1 to deliver either the BREATHE intervention in addition to usual care or usual care alone at call-outs for acute-on-chronic breathlessness. Sixty participants will be recruited to provide access to routine data relating to the index call-out with optional follow-up questionnaires at 14 days, 1 month and 6 months. An in-depth interview will be conducted with a subgroup. Feasibility outcomes relating to recruitment, data quality (especially candidate primary outcomes), and intervention acceptability and fidelity will be collected as well as providing data to estimate a sample size for a definitive trial.

Ethics and dissemination: Yorkshire and The Humber – Sheffield Research Ethics Committee approved the trial protocol (19/YH/0314). The study results will inform progression to, or not, and design of a main trial according to pre-determined stop-go criteria. Findings will be disseminated to relevant stakeholders and submitted for publication in a peer-reviewed journal.

Introduction

Chronic breathlessness – persistent and disabling despite treatment of underlying causes[1] - is prevalent, and often frightening in cardiorespiratory disease(s). It is more common in older adults[2] with widespread impacts for patients, family carers and health systems.[1-3] Acute worsening of chronic breathlessness (acute-on-chronic breathlessness) is mostly triggered by physical and/or emotional exertion.[4] Tailored non-pharmacological interventions are effective[5] and include breathing retraining, relaxation and anxiety management techniques, pacing and prioritisation[6] and cool facial airflow, for example, from a hand-held, battery-operated fan.[7]

Severe episodes of acute-on-chronic breathlessness may be caused by a worsening/complication of the underlying disease, or when distress perpetuates and magnifies the symptom.[8] Acute-on-chronic breathlessness often triggers emergency use of health services.[9] However, approximately a third of those attending the emergency department (ED) because of acute-on-chronic breathlessness do not need hospital admission and some ED attendances might be preventable.[9] Estimates of breathlessness as a primary reason for adult ED presentations range between 2.7% and 9%[10-13]. In one UK study, acute-on-chronic breathlessness was a reason for ED conveyance by ambulance in 20% of attendances.[9] The presence and intensity of breathlessness on ED arrival predicts hospital admission[14], and return presentations.[15]

For many, the ED is necessary. For others, particularly those with advanced disease where palliation is the priority, the ED is less likely to be the optimal place for care if community-based care is working effectively.[16] People with recurrent acute-on-chronic breathlessness may have anxiety playing a significant role, and for whom targeted community-based management plans may reduce the need for ED attendances.[17]

The American Thoracic Society (ATS) recommends a dual approach to breathlessness management.[18] Initial management should be given by first responders, using evidence-based non-pharmacological breathlessness interventions. In addition, patients and carers should receive education and training in appropriate self-management techniques to reduce the need for external help. These techniques should be reinforced at every breathlessness encounter[18]. For some, an acute worsening of breathlessness can become a “teachable moment”.[19] Carers may also learn techniques by observing skilled paramedics[20] in this teachable moment. With this approach, more people with acute-on-chronic breathlessness might be managed safely in the community, or, if hospital admission is needed, have their breathlessness brought under control more quickly.

Study Aim and Objectives

The Breathlessness RElief AT HomE study (BREATHE) aims to define the feasibility and desirability of conducting a definitive cluster randomised controlled trial (cRCT) for people with acute-on-chronic breathlessness to evaluate the effectiveness and cost-effectiveness of a paramedic-administered, non-pharmacological breathlessness intervention.

Recruitment and retention rates
The feasibility of recruiting the required number of paramedic and patient participants needed for a definitive trial within a reasonable trial timeline will be assessed. This will include the acceptability to be randomised within the paramedic-participants and the feasibility of consenting the patient-participants within the time constraints of clinical priorities during an acute call-out.

Intervention
The acceptability, adherence and fidelity, and safety of the BREATHE intervention will be assessed.

Data quality
The quality of data collected during the paramedic call-out in terms of amount and pattern of missing data will be assessed.

Outcomes
The most clinically relevant primary outcome for the definitive trial will be determined by assessing data completion of candidate primary outcomes, qualitative interview data relating to patient views on relevance and acceptability and the variability around baseline measures. Using the variability values for primary outcome finally chosen, a sample size estimation for a definitive trial will be made.

Implementation issues
Any issues that could impact the implementation of the intervention will be identified and use this information to inform the development of the definitive trial. This will include the development of training materials for paramedics and subsequent implementation into clinical practice.

Methods and Analysis

Design

BREATHE is a mixed-methods feasibility cRCT with an embedded normalisation process theory-based (NPT) study. Paramedics, who will act as the cluster unit, will be randomised 1:1 to deliver either the BREATHE intervention plus usual care or usual care only during call-out to patients experiencing acute-on-chronic breathlessness.

This feasibility trial is community-based, with paramedics recruited from ambulance stations within one regional ambulance service. The first paramedic-participants were randomised in January 2020, with the first patient-participant recruited in February 2020.

The trial procedures for patient-participants are outlined in the study flowchart (Figure 1) and schedule of events (Table 1).

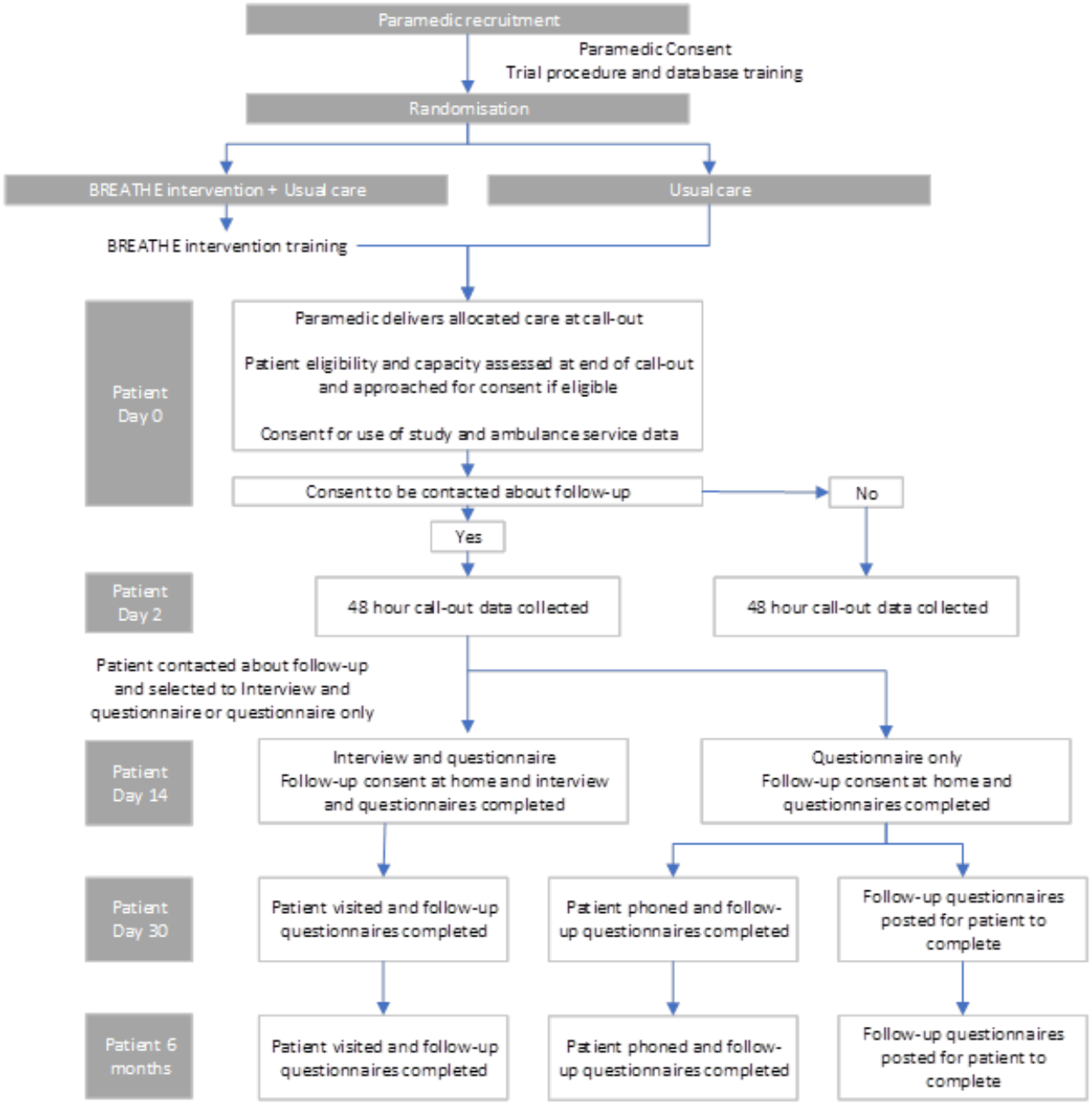

Figure 1: BREATHE Study flowchart

Table 1: Schedule of Events for patient-participants

Visit	**Call-out (Baseline)**	**48 hours**	**Day 14**	**Day 30**	**Month 6**
Day	**0**	**2 (± 0 days)**	**14 (±7 days)**	**30 (±7 days)**	**183 (±7 days)**
Procedure/Assessment					
Inclusion/exclusion criteria assessment	x				
Call-out Informed Consent	x				
NRS 0-10 breathlessness every 2 minutes (patient)	x				
Routinely collected paramedic data	x				
Demographic measures (patient and carer)	x				
Index Ambulance Call-out outcome	x				
Further call-outs in 48 hours after index call-out		x			
Follow-up Informed Consent			x		
Interview (patient and carer)			x		
Health service utilisation questionnaire (patient)			x	x	x
SF-36 (patient)			x	x	x
CRQ-Dyspnoea questionnaire (patient)			x	x	x
CRQ: Chronic Respiratory Questionnaire; NRS: Numerical Rating Scale; SF-36: Short form 36					

Study Population

Paramedic-participants will be recruited from ambulance stations in one geographical region through advertisement and will be willing to undergo training in

study measures, processes and the BREATHE intervention as required. All paramedics in the service are trained in the clinical assessment of the acutely unwell patient, with expertise in making hospital conveyance decisions either immediately at the end of their visit in accordance with nationally agreed Joint Royal College Ambulance Liaison Committee (JRCALC) guidelines on initial assessment and oxygen use.[21]

Eligible patients will be in their normal home environment receiving a 999 ambulance response from participating paramedics because of breathlessness. They will have: a self-reported diagnosis of a cardiorespiratory disease (including intra-thoracic malignancy); experience chronic breathlessness (defined as short of breath most days in the last 3 months or longer) and be able to give retrospective consent at the end of the call-out. Patients needing immediate life-saving intervention/transfer to the ED in the paramedic's clinical judgement are ineligible. They will also be excluded if they are currently enrolled on the trial or have previously participated. Carers present at call-out of any patient-participants consenting to be approached by the study team will be invited to take part in an interview.

Recruitment and consent

Paramedic-participants

The first eight paramedics to confirm a willingness to participate having read the paramedic-participant information sheet (PIS), will be invited to attend study initiation training. In the event of paramedic withdrawal prior to the training session, a paramedic from the waiting list will be invited. At the beginning of the training session an opportunity to ask any questions will be provided prior to being consented into the trial. Those randomised to BREATHE intervention plus usual care will also receive intervention training.

Patient-participants

Patient-participants will be identified and screened by participating paramedic-participants during the call-out. A two-step process will be adopted to patient-participant recruitment. From the beginning of the call-out, all paramedics will start recording the numerical rating scale (NRS) ratings of breathlessness severity. Paramedics randomised to deliver the BREATHE intervention will make an initial assessment of eligibility on arrival and deliver the intervention to those considered appropriate. At the end of the visit, whether staying at home, or being transferred, patients will be screened for eligibility, given the patient PIS and invited to participate. If willing, immediate written or witnessed verbal retrospective consent will be taken to use routinely collected clinical data from the index visit (Day 0), including the NRS measures, and details of any further call-outs in the subsequent 48 hours.

Patient-participants can opt to be contacted about participation in further follow-up. Those agreeing to contact will be phoned by a member of the research team to discuss the purpose and processes of the follow-up and have the follow-up interview/questionnaires arranged on Day 14 (+/- 7 days). In the event of admission to hospital at the initial visit, this would occur at the first opportunity after discharge home (maximum by Day 21). The patient PIS will be given to the patient-participant (and carer-participant if present) at the time of the visit and reviewed together to allow time to ask further questions before consent is taken.

Randomisation and Blinding

Following consent, paramedics will be randomly allocated (1:1, random permuted blocks) using a commercial web-based randomisation system (REDCap Cloud) to; BREATHE intervention plus usual care or usual care only.

Blinding is not possible for patient or paramedic-participants, or for members of the research team providing intervention training. As data will be collected at interview about intervention adherence and fidelity, and it is likely that patient-participants will indicate their allocation. The researcher conducting interviews will collect follow-up questionnaire data before conducting the interview in order to maximise the chances of remaining blinded to allocation until that point. After the initial follow-up visit the researcher will note their guess of the allocation to check if blinding is possible to take forward into the full trial. The researcher collecting follow-up data but not interviewing participants will remain blinded to allocation. Researchers involved in the analysis of the quantitative data will be blinded to allocation.

Intervention and comparator

This study does not interfere with routine clinical decision making which will be conducted according to the JRCALC guidelines.[21] All clinical decisions regarding place of care will be taken according to the paramedic usual practice; highly experienced professionals who make decisions regarding conveyance daily.

Training

All paramedic-participants will receive a one-hour face-to face study initiation training on consent and research procedures. This will be delivered by both clinical and non-clinical members of the research team and will include NRS training. The NRS breathlessness severity rating [22] (0 = no breathlessness now; 10 = worst possible breathlessness now) will form part of clinical assessment for all patients calling with acute-on-chronic breathlessness, irrespective of the trial. This is in line with recent calls to measure breathlessness severity as routine clinical practice. Paramedic-participants randomised to intervention only will receive face-to-face BREATHE intervention training delivered by clinicians on the research team.

Intervention

The BREATHE intervention is reported in accordance with the TIDieR checklist[23]. The intervention (Table 2) was developed based on components of evidence-based non-pharmacological breathlessness interventions[24] and the findings of in-depth interviews with respiratory and emergency clinicians. It includes i) face-to-face advice (positioning, breathing techniques, panic management, fan) ii) a laminated leaflet and iii) a breathlessness management booklet to keep and refer to later. This booklet contains information to help the patient and carer self-manage breathlessness and information on local support services. Elements of the intervention used during the call-out will be recorded to capture fidelity of delivery.

Table 2: BREATHE Intervention and Usual Care

INTERVENTION	**Examples of techniques**	**Supporting evidence**
Be reassured: *	Reassure patient and carer; a reassuring and expert presence is sometimes sufficient to start "unwinding" escalating breathlessness	[25, 26]
Resting position:	Check posture; find the most comfortable and efficient position to maximise ventilation	[25, 27, 28]
Exercises (breathing):	Use to slow breathing rate and encourage breathing out to prevent air trapping (e.g. pursed lip or "breathing rectangle"). Pursed lip breathing also provides increased end-expiratory pressure.	[25-29]
Airflow:	Use hand-held fan; airflow across lower face/nasal passages can reduce breathlessness and recovery time.	[30-32]
Time: *	"Take it easy, nice and slow"*	[25-27]
Help with fears and worries: *	Simple techniques to manage panic and fear*	[25-27]
Education of patient and carer:	Information booklet and laminated card with BREATHE intervention	[25-28]
Intervention points: a) the techniques are often simultaneously delivered and tailored to the individual b) * denotes anxiety focussed management c) The laminated BREATHE card, the information booklet and hand held fan will be packaged in a "BREATHE folder" for paramedics to take into the house of a breathless patient.		
USUAL CARE		JRCALC Guidelines[21]
Immediate clinical assessment	History, baseline vital signs and targeted examination (e.g. chest auscultation, peak flow, 12	

	lead ECG).	
Reassurance	Reassurance is a mainstay of high-quality patient care	
Oxygen	Time critical feature: oxygen saturations of < 94% or less for those patients without chronic lung diseases Target range oxygen saturation in patients with chronic lung diseases: 88-92%. If SpO2 >92%, oxygen would not be administered.	
Nebuliser	Depending on the initial assessment, the paramedic may ask the patient to use their own inhalers, or proceed to nebulisation	
JRCALC: Joint Royal Colleges Ambulance Liaison Committee; ECG: Electrocardiogram; SpO_2: Oxygen Saturation		

The BREATHE intervention has adapted everyday paramedic (first responders) practice aiming to ease acute-on-chronic breathlessness more quickly and, where the paramedic deems appropriate, prevent avoidable ED attendances in people living with chronic breathlessness. Following training, paramedic-participants allocated to intervention will use the intervention (or elements of it according to the clinical situation) during all call-outs for acute-on-chronic breathlessness irrespective of whether the patient consents to data collection.

Comparator: Usual care

The paramedic-participants will deliver usual care according to national guidelines including; initial history, baseline vital signs and tailored examination (chest auscultation, peak flow readings, 12-lead ECG).

Outcomes and Assessments

For BREATHE, the primary endpoint is the end of the index paramedic call-out. If the patient-participant stays at home, this will be at the point the paramedic leaves the house. If the patient is conveyed to the ED, this will be at any point up until the paramedic leaves the patient in the ED according to their clinical judgement.

1. Feasibility outcomes

The primary feasibility outcomes being assessed relate to recruitment. These are paramedic-participant and patient-participant recruitment and attrition overall, paramedics' willingness to be randomised, patient recruitment per paramedic and consent for Day 0 data use, and for follow-up data provision.

The following secondary feasibility outcome will be assessed:

Data quality: completeness of routinely collected data and of patient and proxy reported outcome measures.

Intervention: fidelity and adherence of the components delivered by the paramedics will be collected during the call-out. Acceptability will be assessed during patient and paramedic interviews. Whether the intervention continued to be used by patient following the initial visit will be collected at 14 days, 1 month and 6 months.

2. Potential definitive trial primary outcomes

a) Improvement in breathlessness intensity at end of paramedic visit

NRS intensity every 2 minutes till decision to transfer to ED or decision to keep at home. The 0-10 NRS is a validated measure of breathlessness intensity[22], is highly correlated with Visual Analogue Scores, is more repeatable[33] and can be provided by a proxy reporter.[34] It can be used in routine clinical practice symptom assessment.

b) Conveyance to ED (from routinely collected data)

The intracluster coefficient and sample size calculation for the candidate primary outcomes will be completed.

3. **Clinical measures**

Routinely collected clinical and service delivery data such as pulse, respiratory rate, blood pressure, capillary blood oxygen saturation level (SpO_2) with air, SpO_2 with oxygen and working impression.

4. **Health service utilisation**

Health care resource use, including primary and secondary care, use of emergency services, and self-reported use of community support services.

5. Health status

The SF-36 will be administered to patient-participants from which the SF-6D will be derived. The SF-6D is a validated health status measurement tool widely used in health economic evaluations.[35]

6. Chronic Respiratory Questionnaire (CRQ) dyspnoea domain

Includes measurement of mastery of breathlessness[36] and is recommended in addition to a unidimensional tool such as the NRS.[37]

Sample size

As a feasibility study, a formal sample size calculation has not been performed. Sixty patient-participants will be recruited over 6 months, 30 in each group, providing sufficient data to answer our feasibility and desirability questions.[38] Eight paramedic-participants allows for a 20% drop-out, with the aim of including at least six paramedic-participants each treating 10 patient-participants, considered sufficient for calculating the intra-cluster co-efficient.

Embedded normalisation process theory-based (NPT) study

A mixed-methods approach will be used to conduct an embedded NPT[39] informed evaluation to explore barriers and enablers within implementing practice change domains: coherence, cognitive participation, collective action and reflexive monitoring. Semi-structured interviews will be held with a purposive sample of patient-participants (n=20) (including carer-participants where present). At the end of patient-participant recruitment, all paramedic-participants will be invited to participate in semi structured interviews/focus groups (to explore views on study procedures/measures and issues regarding the implementation of the BREATHE intervention), and complete a NoMAD survey asking their opinion about whether and how the intervention could become part of routine clinical practice.

Data Management

The main study database will be developed by Hull Health Trials Unit (HHTU), using the commercial electronic data capture system, REDCap Cloud. The system uses validation and verification features which will be used to monitor study data quality and completeness. A study monitoring plan will be developed by HHTU who will monitor the study.

Data Analysis

The trial will be reported in accordance with the CONSORT 2010 statement extension to pilot and feasibility trials.[40]

Descriptive statistics will be reported for the feasibility outcomes: paramedic recruitment rates by ambulance station, patient-participant recruitment rate by paramedic, intervention uptake, quality of data collection, intervention delivery and fidelity.

Baseline data and summary for candidate primary and secondary outcomes are summarised overall and by trial arm both by randomisation, and separately for participants providing data to the primary end point. Data will inform a potential definitive study in terms of patient/carer self-reported needs: NRS breathlessness intensity, clinical measures assessed by paramedics, health service utilisation questionnaire, SF-6D and mastery of breathlessness (CRQ). Variability in candidate primary measures will be calculated and a sample size (power calculation) for the definitive trial will be estimated for each. Adverse events will be summarised descriptively.

Missing data will be described but not imputed. No statistical comparisons between treatment groups will be undertaken on baseline or follow-up data as the trial is not designed to test effectiveness.

The quality of data collection for the SF-6D (derived from the SF-36) and health service utilisation information will be reported descriptively, however QALYs will not be calculated.

Interview data will be analysed using framework analysis with reference to NPT [39] to determine acceptability and feasibility of a definitive trial and barriers and facilitators to implementation. Interview/focus group data will be analysed using NPT as a deductive framework whilst allowing for the inductive identification of themes.

NoMAD survey data will be presented using descriptive statistics.

Stop-go criteria

Stop-go criteria (Table 3) will be used to assess the key feasibility objectives of recruitment and intervention adherence as to inform whether a main trial is possible and whether the design or other issues needs modification in order to conduct it successfully. Remediable barriers and their solutions will be identified from the NPT study. Process data will be used to describe interpreted timelines to identify “fixable”, “manageable” and “insurmountable” challenges to site opening, training, data collection and intervention fidelity with regard to both the future main trial and clinical implementation in the event of a positive trial.

Table 3: Stop-go criteria

Recruitment	
Green	If ≥ 80% of target patient-participants are recruited to target.
Amber	Between ≥ 60% and < 80% patient-participants recruited and remediable barriers identified and addressed in main trial protocol
Red	<60% of the estimated sample size for a full trial cannot be completed by 24 months
Intervention Adherence (eligible patient-participants attended by a paramedic allocated to and trained in the intervention received the intervention):	
Green	≥ 75%;
Amber	≥ 50 and < 75%; possible if further modelled for the main trial protocol by addressing remediable factors
Red	<50%; it would be concluded that the intervention cannot be sufficiently implemented in practice and a main trial not possible
Green: Main trial feasible; Amber: Feasible with remediable factors addressed; Red: Main trial not feasible	

Ethics and Dissemination

Regulatory Approvals and Trial Oversight

The trial protocol has been reviewed and approved by the Yorkshire and The Humber – Sheffield Research Ethics Committee (REC reference: 19/YH/0314). The University of Hull is the study sponsor and the Hull Health Trials Unit is supporting trial delivery. A Trial Management Group has been convened to oversee trial delivery and operations. An independent Trial Steering Committee will provide overall supervision for the project on behalf of the Project Sponsor and Project Funder.

Safety Considerations and Adverse Event Reporting

Adverse event reporting is defined in the full study protocol. In the emergency clinical context, full safety reporting of Adverse Event (AE) and Serious Adverse Events (SAE) will be limited to events that occur during the call-out visit. Because of the inherent limitation in collecting AE and SAE outcomes, proxy-safety data relating to the number and outcome of further ambulance call-outs in the 48-hour period after the index visit will be collected using routinely collected data. In addition, the study will collect health resource utilisation information at the 14 days, 30 days and 6 months follow-up time points.

Dissemination

The study results will be disseminated to the appropriate stakeholders through presentations, conferences and peer-reviewed journals according to the BREATHE publication and dissemination policy.

Discussion

Providing it is found that delivering the BREATHE intervention is acceptable, feasible and desirable, the results will inform the number of paramedic clusters required, most appropriate primary outcome and the structure of a future definitive cluster randomised controlled trial in breathlessness patients.

Word count 2,926

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