Short title: Reducing chronic breathlessness in adults by following a self-guided, internet based supportive intervention (SELF BREATHE)

Full title: A multicentre, randomised controlled trial comparing usual NHS care to a self-guided internet-based intervention (SELF-BREATHE) plus usual NHS care to reduce breathlessness in adults living with chronic breathlessness

ACROYNM: mRCT SELF BREATHE.

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CONTENTS

KEY WORDS

Chronic breathlessness, self-management, advanced disease, digital health, physiotherapy

LIST OF ABBREVIATIONS

AE	Adverse Event
CAG	Confidential Advisory Group
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
COVID	Coronavirus disease (COVID) an infectious disease caused by the SARS-CoV-2 virus
CRF	Case Report Form
DMC	Data Monitoring Committee
GAfREC	Governance Arrangement for NHS Research Ethics
HRA	Health Research Authority
HTA	Human Tissue Authority
ICF	Informed Consent Form
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SAE	Serious Adverse Event
SELF-BREATHE	A self-guided internet-based intervention for individuals living with chronic breathlessness
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File

1 STUDY SUMMARY

STUDY OVERVIEW	
Full title	A multicentre, randomised controlled trial comparing usual NHS care to a self-guided internet-based intervention (SELF-BREATHE) plus usual NHS care to reduce breathlessness in adults living with chronic breathlessness
Objective(s)	To determine if using SELF-BREATHE plus usual NHS care (intervention) for six weeks reduces worst breathlessness over the last 24 hours, quantified on 0-10 numerical rating scale (NRS) in patients living with chronic breathlessness compared to those receiving usual NHS care (Control).
Type of trial	A multicentre randomised controlled trail (RCT) of SELF-BREATHE in patients living with chronic breathlessness, using a mixed methods approach.
Trial design and methods	A statistician blind, multicentre, parallel, two arm randomised controlled trial with participants allocated to 1) intervention group (SELF-BREATHE + usual NHS care) or 2) control group (usual NHS care). (superiority randomised controlled trial)
Health condition(s) or problem(s) studied	Adults living with chronic breathlessness due to malignant and non–malignant diseases.
Target sample size	246
Trial duration per participant:	12 weeks
Main inclusion/exclusion criteria:	**Inclusion criteria** • Adults ≥ 18 years of age • Chronic Breathlessness at rest and / or exertion • Chronic Breathlessness (CB) defined as breathlessness that persists (**>3months**) despite pharmacological treatment of the underlying disease including, but not limited to; cancer, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), bronchiectasis, chronic fibrotic lung disease following SARS-CoV2 infection • Medical Research Council (MRC) dyspnea score ≥ 2 (MRC 2= *short of breath when hurrying on the level or walking up a slight hill* • Availability to a computer, tablet, or smart phone with internet access • Able to provide informed consent.

	Exclusion criteria • Breathlessness of unknown cause • Primary diagnosis of chronic hyperventilation syndrome • Currently participating in a rehabilitation programme e.g., pulmonary/cardiac rehabilitation (patients that have completed PR >4-weeks will be eligible).
Statistical methodology and analysis:	Informed by CONSORT guidelines and MORECARE statement, a single analysis will occur once all follow up data have been recorded and accounted for. The primary outcome analysis will be on an intention to treat (ITT) basis. Linear regression will be used to estimate the difference between groups in numerical rating scale (NRS) 0-10, worst breathlessness at seven week (primary end point) and twelve weeks, adjusting for baseline NRS worst breathlessness, minimisation factors and any other pre-specified important factor. Sensitivity analysis will explore the robustness of our findings. Other (secondary) outcomes will be analysed using a similar method. Explanatory qualitive interviews will be transcribed verbatim, NVivo software will be used to support a conventional content analysis.
STUDY TIMELINES	
Study Duration/length	4 years (48 months)
Expected Start Date	February 2024
End of Study definition and anticipated date	February 2027 The end of the study is defined as the date the database is locked.
Key Study milestones	IRAS/HRA approvals in place = January 2024 King's College Hospital (KCH) open to recruitment = February 2024 1st patient recruited = March 2024 All study sites open = August 2024 50% recruitment achieved = October 2025 Last patient recruited = November 2027 Database lock = Feburary 2028 Final report = July 2028

2 BACKGROUND AND RATIONALE

Over 3 million people experience chronic breathlessness (despite optimal treatment of underlying diseases) each year in the UK. This includes up to 98% of the 1.2 million people diagnosed with chronic obstructive pulmonary disease (COPD)[1] , over 50% of the 200,000+ with incurable cancer and 50% of the 2 million with chronic heart failure [2]. More than two-thirds of those living with chronic breathlessness have multimorbidity [3]. It is a transdiagnostic problem, worsened by social, environmental, and economic problems.

Clinical management of breathlessness is challenging; optimal pharmacological treatment of the underlying disease is the first step. Disease specific management alone does not guarantee symptom control. Breathlessness increases with disease progression, becoming chronic resulting in high symptom burden, poor quality of life [4], increased disability, high health and social care costs [6], driven by repeat Emergency Department (ED) attendance and hospitalization [5-7].

Even before the COVID-19 pandemic, the burden of chronic breathlessness on individuals, family, society, and health systems was substantial, increasing with population ageing and multimorbidity. People living with long COVID (Post-acute sequelae of SARS-CoV-2 infection (PASC), also known as long COVID and defined as ongoing, relapsing, or new symptoms or conditions present 30 or more days after infection) commonly have breathlessness and struggle to manage it, further increasing the demand for breathlessness supportive services [8, 9] .

A proactive approach to tackle breathlessness is required to build capacity and resilience within health systems, especially given rising health and social care costs, and workforce challenges. SELF-BREATHE is one potential solution. SELF-BREATHE is an innovative digital approach to support those living with breathlessness [10, 11]. SELF- BREATHE provides online unlimited access education and non-pharmacological breathlessness self- management interventions e.g., breathing control, pursed lipped breathing, pacing, goal setting [10, 11].

There is good evidence for face-to-face delivered breathlessness supportive services (BSS) [12, 13]. BSS provide educational and self-management techniques e.g., breathing techniques, exercise to improve physical functioning, breathlessness crisis self-management planning [12]. A systematic review and

meta-analyses of BSS demonstrated reductions in distress due to breathlessness (n=324; mean difference (MD) -2.30, 95% CI -4.43 to -0.16, p=0.03) and Hospital Anxiety and Depression Scale (HADS) depression scores (n=408, MD -1.67, 95% CI -2.52 to -0.81, p<0.001) favoring BSS, delivered over a 4–6-week period [22]. BSS models demonstrate cost-effectiveness [13]

However, an implementation gap remains as there are no NHS-commissioned BSS. BSS are recommended by international COPD [14] and Oncology [15] guidelines. Establishing BSS outside of the research setting will take resource (re)allocation. Workforce shortages and training issues and the on-going legacy effects of the COVID-19 pandemic need consideration. The NHS long term plan highlights the need for alternative and sustainable approaches such as digital interventions to support those living with respiratory disease [16]. In the UK, 95%, of the population have internet access [17] . Approximately 70% of patients with chronic respiratory disease (UK) have internet access [18, 19], with 50% accessing the internet daily [18] . SELF-BREATHE builds upon BSS. SELF-BREATE is an innovative digital intervention which aims to build capacity and resilience with the NHS to improve the lives of people living with chronic breathlessness [10, 11].

A single blind feasibility RCT of SELF-BREATHE compared to usual NHS care was conducted between February 2021 and February 2023. Fifty-two participants with severe chronic breathlessness due to advanced disease took part in this study [10]. The study predefined feasibility a priori criteria were successfully achieved; 30% of eligible patients, given an information sheet, consented to take part, >60% of patients, allocated to the SELF-BREATHE, logged on to SELF-BREATHE at least once, >70% of patients reported the study design and intervention were acceptable [10]. These data support the feasibility of moving to a fully powered, randomised controlled trial to test the clinical efficacy of SELF-BREATHE.

Post intervention qualitative interviews demonstrated that SELF-BREATHE was valued by users, providing interventions that improved their breathlessness [10];
"My main goal as part of SELF-BREATHE, was to go walking because I really enjoyed walking. Since I'd had COVID, that all came to a stop. I was battling [with breathlessness] to get to the front door. So, I've managed to get out. Obviously, at the beginning somebody had to be with me. But now, I've actually ventured out on my own with the dog." ***Female, Asthma 61-70 years.***

SELF-BREATHE improved both physical and mental health:

"I was sceptical I have to be honest, but after a week or so I started to see the benefits of how to control my breathing when moving around and walking, it [SELF-BREATHE] also encouraged me to set my own goals, one being to walk more steps in a day, I'm now above 5,000 steps a day. It takes commitment from you to take part but is so very worth it. I know I can't be cured but it has certainly helped me in controlling my breathing and also my mental health." **Male, ILD, 51-60 years.**

In addition, SELF-BREATHE was found to be helpful at point of breathlessness crisis:

"It was good SELF-BREATHE, because obviously when you have a breathing attack you automatically just clam up and panic. But it was nice to be able to have that information to hand [SELF-BREATHE]." **Female, COPD, 41-50 years.**

These data support the feasibility of moving forward to a fully powered RCT, with minor modifications i.e., multiple methods of obtaining consent and data collection i.e., face-to-face, telephone and postal options for participants [10] .

3 Research aim

To determine the clinical efficacy of a self-administrated internet-based intervention (SELF-BREATHE) plus usual NHS care for adults living with chronic breathlessness compared to usual NHS care.

4 OBJECTIVES

Primary Objective

To determine if using SELF-BREATHE plus usual NHS care (intervention) for six weeks reduces worst breathlessness over the last 24 hours, quantified on 0-10 numerical rating scale (NRS) in patients living with chronic breathlessness compared to those receiving usual NHS care (Control) [10].

Secondary Objectives

- To determine whether using SELF-BREATHE plus usual NHS care for six weeks improves health-related quality of life (HRQoL) (measured using the EQ5D-5L [20] and the chronic respiratory questionnaire 22]), illness perception. (measured using the brief illness perception questionnaire [21]), and patients' behavioural responses to breathlessness (measured using cognitive behavioural responses questionnaire (short)) [22, 23]) compared to those receiving usual NHS care.

- To explore the sustained use of SELF-BREATHE after the six weeks and what impact this has on breathlessness, HRQoL and ED attendances.

- To explore factors (positive and negative) influencing the use of SELF-BREATHE after six weeks, to inform implementation planning.

5 STUDY DESIGN

Methodology

Methodology follows the MRC framework for developing and evaluating complex interventions [24], MORECARE statement [25] and the IDEAS (Integrate, DEsign, Assess and Share) framework for the development of digital behavioural change interventions [26], CONSORT statement [27] and SPIRT statement [28].

Study design

A statistician blind, multicentre, parallel, two arm randomised controlled trial with participants allocated to 1) intervention group (SELF-BREATHE + usual NHS care) or 2) control group (usual NHS care) (superiority randomised controlled trial).

Trial flowchart

Patient identification

Inclusion criteria: Adults ≥ 18 years of age, chronic breathlessness at rest or on exertion. Chronic Breathlessness (CB) defined as breathlessness that persists (**>3months**) despite pharmacological treatment of the underlying disease including, but not limited to; cancer, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), bronchiectasis, chronic fibrotic lung disease following SARS-CoV2 infection. MRC dyspnoea score ≥ 2, access to computer, tablet or smart phone with internet access. Able to provide informed consent.

Exclusion criteria: Breathlessness of unknown cause, primary diagnosis of chronic hyperventilation syndrome. Currently participating in a rehabilitation programme e.g., pulmonary/cardiac rehabilitation (patients that have completed PR >4-weeks will be eligible).

↓

Informed consent

↓

Baseline assessment (T1)
Primary outcome: worst breathlessness over the last 24 hrs (NRS 0-10)
Secondary outcomes: health related quality of life, symptom burden, health service use
Mediators: illness perception, cognitive behavioural responses

↓

Independent Randomisation (1:1 randomisation) (KCL CTU)
Minimization factors: malignant vs non-malignant disease MRC ≥ 3 or not, ethnicity, presence or not of an informal caregiver, recruitment site

↓

Control group
NHS usual care (6 weeks) (n- 123)

Intervention group
SELF-BREATHE+ NHS usual care
(6 weeks) (n- 123)

↓

Primary end – point: 7 weeks post randomisation follow up (T2) (visit window+/- 5 days)
Primary outcome: worst breathlessness over the last 24 hrs (NRS 0-10)
Secondary outcomes: health related quality of life, symptom burden, health service use
Interviews: n = 30 SELF-BREATHE users

Intervention arm: SELF-BREATHE

SELF-BREATHE is a complex, theoretically informed intervention developed with patients following the IDEAS and MRC frameworks [10] . Participants allocated to the intervention group (SELF-BREATHE) will continue to receive their usual NHS care, but they will also be given a username and password, which provides unlimited access to SELF-BREATHE. SELF-BREATHE has seven core components, delivered via multi model media i.e., animations, written text, audio files, pictures, and instructional videos [10].

1. **Patient education** about chronic breathlessness and self-management.
2. **Self-monitoring of breathlessness**; breathlessness severity, distress due to breathlessness, impact of breathlessness on life, with real time algorithm based automated feedback.
3. **Breathing exercises and techniques** to improve breathlessness self-management e.g., breathing control exercises, pursed lipped breathing, body positions to relieve breathlessness.
4. **Breathlessness self-management planning:** patients can formulate a personalised breathlessness crisis plan, which will include the breathlessness management techniques used at points of breathlessness crisis e.g., breathing control.
5. **Improving physical activity:** advice on how to increase daily activity levels, self- directed and self- monitored home exercise programme of bed, chair and standing based exercises.
6. **Personalised Goal Setting:** self-guided support for patients to set personalised goals and track achievement and success.
7. **Ask the expert:** inbuilt messaging service where patients can ask a question or get advice about any specific aspect of SELF-BREATHE (minimal response time of 48 hours).

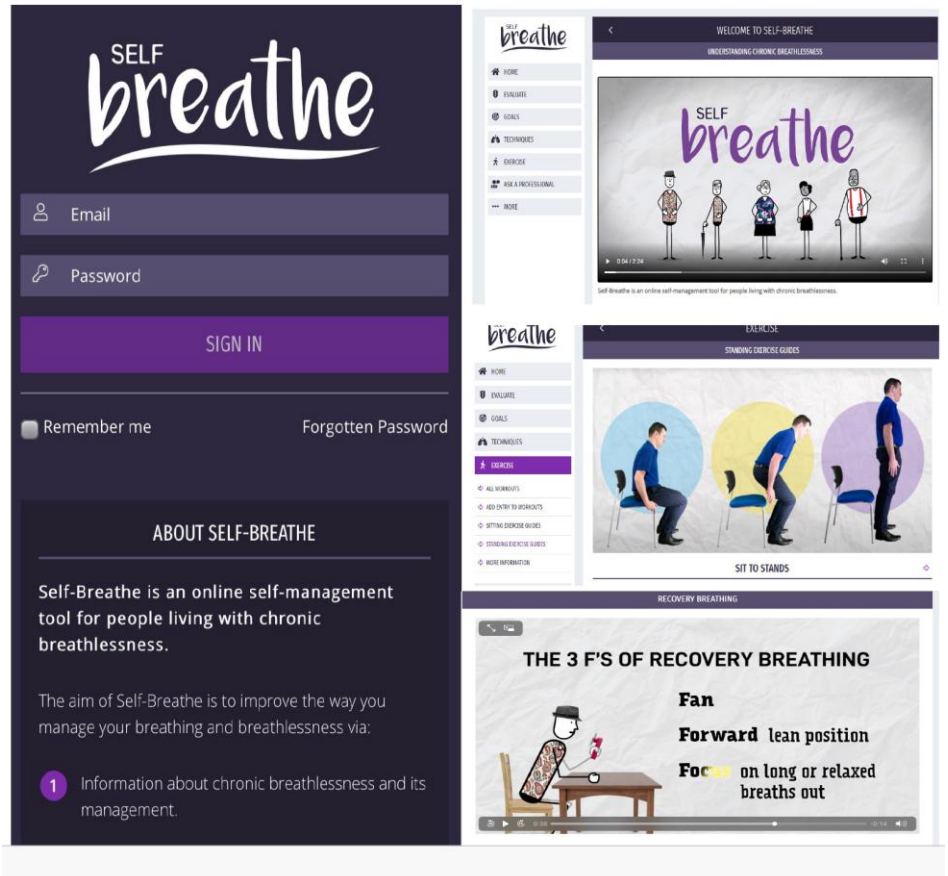
Behaviour change techniques within SELF-BREATHE include; information about health consequences, self-monitoring, demonstration and instruction, practice and rehearsal, goal setting, action planning [10].

SELF-BREATHE is accessible via any internet enabled device. The expectation is that participants log on to SELF-BREATHE within 48-hrs of receiving their log on details and weekly thereafter (minimum twice weekly), working through the 7 component sections, personalising and implementing suggested interventions e.g., breathing control exercises, home exercise. Establishment of these self-management techniques within participant's day-to-day life is supported through interactive

components of SELF-BREATHE e.g., self-monitoring of symptoms, automated feedback about usage, goal setting and achievements. SELF-BREATHE has inbuilt software that will record log on frequency, duration, resources used etc.

Participants will be provided with information via guidance document as how to log on and use SELF-BREATHE, electronically via email and / or in paper format via the post (as per individual patient preference). Participants will have a telephone/video call(s) from the SELF-BREATHE administrator 24-48 hours after been sent their log on details and answer any questions they may have e.g., troubleshooting technical problems. Participants will be provided with both an e-mail and telephone contact which can support them without any technical issues they may have while using SELF-BREATHE. Participants will receive daily/weekly automated prompts to log into SELF-BREATHE, to ensure optimal use.

Figure 1: Example of the SELF-BREATHE user interface



Control arm: usual NHS care

Participants randomised to the control group continue with usual NHS care, as was available to them prior to entry into the trial. There are no NHS commissioned BSS, therefore the comparator is usual care. Prior to recruitment usual care will be defined at each site and within each site using a muti-method approach; usual care questionnaires, 1 to 1 interview or focus groups to define what 'usual' is.

Setting

Participants will be recruited from general and specialist hospital and out-patient clinical services where there is a high prevalence of chronic breathlessness e.g., respiratory, cancer out-patient clinics, Integrated Respiratory Teams, Therapy services e.g., Physiotherapy, and Palliative Care services, across study sites.

The study will be promoted via internal/external organisational communications services e.g., newsletters, hospital intranet, hospital website to raise the profile of the study within clinical teams to facilitate recruitment. Patient facing posters will be displayed within clinical areas to prompt patients to ask if they may be eligible to take part in the study. This is approach to empowering patients to ask about potential involvement in research has been driven by the PPI group supporting this study and was successfully used with the feasibility RCT of SELF-BREATHE.

Population

Patients living with chronic breathlessness due to malignant or non-malignant disease.

Screening

Patients living with chronic breathlessness at rest or on exertion due to malignant or non-malignant disease and have been approached to take part in the trial will be screened for trial entry. All participating trial sites will be required to complete non – randomisation logs for all patients screened for entry into the trial but who did not go on to be randomised. This information will be collected from trial sites on a regular basis. Documented reasons for ineligibility or declining participation will be document in the pre-screening log.

Summary data, which includes patients, age, gender, ethnicity, MRC dyspnoea score and diagnosis and clinical specialty/ department/recruitment site the patient was identified from will be summarised using frequency statistics and appropriate summary statistics. Information on non - randomised participants including reasons for ineligibility e.g., lack access to the internet, declining trial participation or other reasons for non-randomisation will be summarised from the non- randomised log. Data will be summarised per study site.

Inclusion criteria

- Adults ≥ 18 years of age
- Chronic breathlessness at rest or on exertion
- Medical Research Council (MRC) dyspnoea score ≥ 2 (*MRC 2 = short of breath when hurrying on the level or walking up a slight hill)*.
- Chronic breathlessness (CB) defined as breathlessness that persists (**>3months**) despite pharmacological treatment of the underlying disease including, but not limited to; lung cancer, mesothelioma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), asthma, interstitial lung disease (ILD), bronchiectasis, chronic fibrotic lung disease following SARS-CoV2 infection.
- Access to a computer or tablet or smart phone with internet access
- Able to provide informed consent.

Exclusion criteria

- Breathlessness of unknown cause
- Primary diagnosis of chronic hyperventilation syndrome
- Currently participating in a rehabilitation programme e.g., pulmonary/cardiac rehabilitation (patients that have completed PR > 4-weeks will be eligible).

Withdrawal criteria

Participants will be withdrawn from the study if they no longer wish to take part. Their data will continue to be included.

Recruitment

Clinical teams will identify potential participants in three ways:

1. Opportunistically as they come in to contact with primary and secondary care teams e.g., routine outpatient hospital clinics (face to face / virtual), community clinics / services, hospital wards (including virtual wards)
2. Using existing research / audit registers (if available) of patients including those that have declined or completed pulmonary rehabilitation
3. Using the NIHR UK Clinical Trials Gateway to contact suitable patients who have consented to be contacted about research

Recruitment from opportunistic contact with primary and secondary care teams e.g., routine outpatient hospital clinics (face to face / virtual), community clinics / services, hospital wards (including virtual wards)

Patients will be recruited from specialist out-patient clinics / services (virtual and face to face) where there is high prevalence of chronic breathlessness. Across the study sites recruitment will be from out-patient clinics; respiratory medicine, lung cancer, bronchiectasis, interstitial lung disease (ILD), cystic fibrosis (CF), respiratory physiotherapy, Covid clinics, integrated respiratory team (IRT), and palliative care (inclusive of hospital based, out-reach / community services). Patients will also be recruited from the in-patient and virtual wards, predominately general respiratory, palliative care and oncology.

Clinical staff will check the eligibility of patients during their routine hospital consultation (face to face or virtual). If eligible, clinical staff will ask the patient for permission to pass their contact details to the designated researcher(s). Clinical staff and / or the research team will provide the potential eligible participants with a copy (paper or electronic) of the patient information sheet (PIS) and consent form. After receiving the PIS, the study researcher(s) will contact the patient after 24 hrs (min) to discuss the study and answer any questions regarding the study. If the patient is happy to partake in the study, verbal and written consent for participation will be obtained prior to randomisation by a designated member of the research team.

Recruitment from existing research, audit registers and / or NIHR UK Clinical Trials Gateway

If an individual is identified by the clinical team as eligible to partake in the study from a clinical database/ research register / NIHR clinical Trials Gateway, they will be written to and followed up with by telephone call to see if they would like to receive additional information about the study. With their consent the clinical team / research team will send a copy (paper and/ or electronic) of the patient information sheet (PIS), consent form and pre-paid self-addressed return envelope so that they can return a copy of their consent form to the research team, if they consent to take part in the study.

After the potential participant has received the PIS, the study researcher(s) will contact the patient after 24 hrs (min) to discuss the study and answer any questions regarding the study. If the patient is happy to partake in the study, verbal and written consent for participation will be obtained prior to randomisation.

Consent

Based on the data from the published feasibility randomised controlled trial of SELF-BREATHE [10] and PPI recommendations a multi modal approached to gaining consent will be used to reflect patients' needs and preferences. All participants will be given the opportunity to discuss the PIS and have any questions they have answered prior to giving consent.

Potential participants can complete the consent in person with a member of the research team at location that is most appropriate and convenient to them e.g., following a routine out-patient clinical appointment, separate research visit or in their own home. Alternatively, potential participants may opt to have a copy of the consent form via the post. For such participants, the researcher will go through the consent form in full with them over the telephone, and answer any questions they have about the study and participant information sheet.

Finally, the researcher will ask the participant if they verbally consent to partake in the study. If they do the researcher will ask the participant to sign and date the consent form. Thereafter, the participant will be asked to return a copy of their consent form to the research team. Finally, a fully signed consent form which includes the signature from the person taking consent will be sent to participants via the post.

Consent process for qualitative interviews

Participants (SELF- BREATHE Users and SELF-BREATHE Research Staff) will be provided with a qualitive interview specific Participant Information Sheet and Consent Form in advance of the interview. Written and verbal consent will be obtained prior to starting of the interview and audio-recording in line with ethical approval. Consent will cover participation in the interview, audio recording, and use of anonymised quotes in reporting. Participants will be informed that they may withdraw at any time without giving a reason.

Sample size

Based on the primary outcome, NRS worst breathlessness over the last 24 hours, to detect a mean difference of 1 (the minimally clinically importance difference (MCID)) with a standard deviation of 2 [29] and a 5% significance level, power 90%, 86 patients per group (172 in total) are required. The feasibility RCT had 30% attrition; thus, allowing for a loss to follow up of 30% at six weeks, our recruitment target is 246 patients over 42 months, i.e., 6 patients per month. (Superiority RCT design).

The feasibility RCT demonstrated an average recruitment rate of 3 patients per month at one centre;. King's college Hospital NHS Foundation TRUST (KCH), hence the anticipated recruitment from KCH over 42 months is 126 patients. To achieve our sample size, 8 – 10 recruitment sites will be required which will include KCH, Guy's and St Thomas' NHS Foundation Trust, others to be confirmed. Feasibility data and data from potential recruitment sites to date support achieving our recruitment target.

Justification for provision to increase the sample size by 10% (25 Participants) if required

To enhance the representativeness and generalisability of our findings, we propose a provision to increase the sample size by up to 10% (an additional 25 participants) if the initial recruitment target is met but there is underrepresentation of men and individuals from minoritised ethnic communities. This targeted increase would be implemented within the existing timelines outlined in the protocol and would not compromise the integrity of the power calculation.

This approach is consistent with the NIHR's ambition to improve the representation of minoritised groups in research, particularly in clinical trials. By increasing diversity in our sample, we aim to strengthen the relevance and applicability of our findings across different population groups and address known disparities in research participation.

We will look to adopt the NIHR Race Equality Framework https://www.nihr.ac.uk/nihr-race-equality-framework across different elements of the trial. We are also keen to work collaboratively with trial sites to explore practical strategies for improving representation at the individual site level.
This provision ensures that our study remains inclusive and reflective of the broader population, while maintaining scientific rigour and adherence to the approved protocol timelines.

Randomisation and blinding

A web-based randomisation system will be designed, using the bespoke King's clinical trials unity (KCTU) randomisation system. The randomisation system will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within Kings College London (KCL). Randomisation will be at the level of the individual using the method of minimisation. Randomisation will include minimisation to balance five potential confounders between trial arms: malignant versus non-malignant, breathlessness severity MRC ≥3 or not, ethnicity (white vs other), presence (or not) of an informal caregiver, and recruitment site [10].

Blinding

All participants, Chief Investigator, Site Principal Investigators, and research staff will be unblinded throughout the trial. The senior statistician will also be fully blinded, but the junior statistician will be unblinded from the 1st DMC meeting with data onwards. Blinding of the senior statistician minimises the risk of performance and detection bias.

Justification for our blinding approach:

- Unable to blind participants as the intervention is a self-guided (self – administered) online intervention that requires participants to log and use.
- Blinding of the recruitment sites i.e., PI's and research staff, is logistically very challenging, expensive, and not required as research teams will have on direct input to the delivery of the intervention (SELF-BREATHE).
- High rate of unblinding failure identified in the development of protocol, from working with researchers at sites and PPI members which further informed the decision to have the sites

unblinded.

- Primary and secondary outcome measures are self-reported / self- complete, so assessor input / blinding not required.

Data entry

Randomisation will be undertaken by recruiting site staff, by authorised staff onto the randomisation system by going to www.ctu.co.uk and clicking the link to access the randomisation system. A full audit trail of data entry will be automatically date and time stamped, alongside information about the user making the entry within the system.

Security

The CI or delegate will request usernames and passwords from the KCTU. System access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the randomisation system are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g., Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g., Trial Manager) in the first instance.

Participant initials and date of birth will be entered on the randomisation system. Whereas NHS number, email addresses, participant names and addresses and full postcodes will not be entered into the randomisation system. No data will be entered onto the randomisation system unless a participant has signed a consent form to participate in the trial.

Data Quality Processes

The CI team will undertake appropriate reviews of the entered data, for the purpose of data cleaning. No data can be amended in the system, however CI or delegate (e.g., Trial Manager) may request King's Clinical Trials Unit to add notes against individual subject entries to clarify data entry errors.

Database Lock

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate.

Following randomisation, an automated generated email will inform the SELF-BREATHE designated administrator / researcher at each site of the participants s study allocation via secure e-mail. The designated administrator/ researcher will contact patients allocated to the intervention arm via telephone, email and/or post providing them with their website username, temporary password, SELF- BREATHE user guide and 'go live' date. This will be followed up (48 hrs later) with a telephone call by the designated administrator / researcher, to ensure that the participant has been able to log into SELF-BREATHE and help with any technical questions / issues the participant may have. The senior trial statistician will be blind to randomisation allocation.

Data collection

Data will be collected simultaneously in both groups, the self-reported questionnaires can be administrated and completed in person (face to face) or via or postal questionnaires or video call or over the telephone. Questionnaires will be completed by participants prior to randomisation (T1) and at 7 weeks (primary endpoint) (T2) and 12 weeks post-randomisation (T3). A web based electronic data capture (EDC) system will be designed, using the InferMed Macro 4 system, by King's Clinical Trials Unit (KCTU).

Data entry

The EDC will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL. Source data will be entered by recruiting site staff within 30 days of data collection by authorised staff onto the EDC by going to www.ctu.co.uk and clicking the link to access the MACRO 4 EDC system. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

Security

The CI or delegate will request usernames and passwords from the KCTU. Database access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the EDC are not shared, and that only those authorised to access the system are allowed to

do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g., Trial Manager) in the first instance. Participant initials and possibly date of birth will be entered on the EDC. Whereas NHS number, email addresses, participant names and addresses and full postcodes will not be entered into the EDC system. No data will be entered onto the EDC system unless a participant has signed a consent form to participate in the trial.

Data Quality Processes

The CI team will undertake appropriate reviews of the entered data, [in consultation with the project analyst] where appropriate for the purpose of data cleaning and will request amendments as required The KCTU will provide the study team with Data management plan for Elsevier InferMed MACRO EDC once the system is made live and ready for use.

Database Lock

At the end of the trial, the site PI will review all the data for each participant [and provide electronic sign-off] to verify that all the data are complete and correct. At this point, all data can be formally locked for analysis. Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate.

Definition of the end of the study

The end of the study is defined as the data base lock.

Demographic data

Participant demographic data will include age, sex, ethnicity, living status, informal/formal carer status, educational level, employment status, confidence in using the internet and post code (used to calculate index of multiple deprivation (IMD)).

Outcome measures

The number of outcome measures (questionnaires) included in this study were used and judged to be acceptable by participants in the feasibility randomised controlled trial of SELF-BREATHE study [10],

with a questionnaire item completion rate >95% and 45-minute completion time. Outcome measures align with the APEASE criteria [30] (affordability, practicability, effectiveness, acceptability, spill-over effects and equity), therefore the results are more likely to inform policy, service provision and implementation planning.

Primary outcome

The primary outcome is patient rated intensity of worst breathlessness over the previous 24 hours, using a validated 11-point (0-10) numerical rating scale (NRS), where 0 = no breathlessness, and 10 = worst imaginable breathlessness [31-33] (Patient self-reported out-come measure)

NRS worst breathlessness encompasses both chronic and acute-on-chronic breathlessness crisis. NRS worst breathlessness, aligns with Leventhal's common-sense model of self-regulation, the theoretical model underpinning SELF-BREATHE [10]. NRS worst breathlessness has an established minimum clinical important difference of 1 [29]. NRS worst breathlessness was the primary outcome of choice of our PPI members, as in their opinion NRS worst breathlessness reflects what is most important to them.

The feasibility RCT of SELF-BREATHE supports NRS worst breathlessness as the primary outcome for this study [10]. Differences between groups in NRS worst breathlessness at seven weeks (primary endpoint) and 12 weeks post randomisation will be compared.

Secondary outcomes

The following validated and responsive patient self-reported outcome measures (PROMs) will be measured at baseline (T1), 7 weeks (T2) and 12 weeks (T3) post-randomisation.

- **Distress and severity of breathlessness** in the previous 24 hours quantified on a 0–10 numerical rating scale (NRS) at rest, and on exertion [10].
- **Self-efficacy for managing breathlessness,** quantified on a 0–10 numerical rating scale.
- **Dyspnoea 12** quantifies breathlessness using 12 descriptors that incorporates the physical and affective aspects of dyspnoea [34].
- **The London Chest Activity of Daily Living Scale (LCADL)** measures the functional impact of

breathlessness on activities of daily living e.g., personal care [35]

- **Chronic Respiratory Disease Questionnaire** is a 20-item validated health-related quality of life (HRQL) questionnaire across 4 domains: dyspnoea, fatigue, emotion and mastery [36]

- **EQ-5D-5L and EQ-VAS** (visual analogue scale) provides a valid measure of health status in advance disease. The EQ-5D-5L consists of five dimensions and estimates responses into a single health index score, which typically ranges from 0 (equivalent to death) to 1 (equivalent to full health).

Mechanisms of Change

The following validated and responsive patient self-reported outcome measures (PROMs) will be measured at baseline (T1), 7 weeks (T2) and 12 weeks (T3) post-randomisation to explore mechanisms of change to understand how and why SELF-BREATHE may result in therapeutic benefit (s)

- **The Brief Illness Perception Questionnaire (Brief IPQ)** is a 9-item questionnaire designed to rapidly assess cognitive and emotional representations of illness [21].
- **Cognitive Behavioural Responses Questionnaire (CBRQ) (Short version)** explores patients' cognitive and behavioural responses to their symptoms [37].
- **The Acceptance scale** is a 9 – item subscale measuring pain willingness, taken from the Chronic Pain and Acceptance questionnaire [38] to focus on willingness to accept breathlessness. Participants will be asked to rate each item as it applies to them on a 7 – point Likert Scale (0 = Never true to 6 = always true); where a higher score will indicate greater acceptance.

Health service use & associated costs

The Client Service Receipt Inventory (CSRI) is an established and validated user self- reported outcome measure in chronic breathlessness [12] and will be used to quantify heath service use; GP contacts, planned and unplanned hospital and emergency department attendances are the main cost drivers associated with chronic breathlessness and associated cost. The CRSI will be completed at the time points (baseline, 7 weeks, and 12 weeks). Interventional (SELF – BREATHE) costs will include; development costs, running, maintenance / long term hospital costs (and options) cost per user etc.

These data will help inform the cost effectiveness component of SELF-BREATHE.

SELF-BREATHE specific outcomes

- **SELF-BREATHE acceptability questionnaire:** based on the theoretical framework of acceptability (affective attitude, burden, perceived effectiveness, intervention coherence and self- efficacy). This patient self-reported questionnaire was developed and tested as part of the feasibility RCT [10].
- **Usage:** automated data (analytics) captured within SELF-BREATHE will include; frequency and duration of log ins, completion of breathlessness crisis plans and personal goal attainment, log in failures and technical faults.

Qualitative interviews with SELF-BREATHE users

To explore individuals' experiences of using and perceived benefits of SELF-BREATHE, participants randomised into the intervention arm (SELF-BREATHE) will be invited to take part in two semi-structured qualitative post-interventional interviews at 7 and 12 weeks (data collection window =+/- 10 days) post randomization i.e., each participant will have two interviews. Interviews will be conducted with 30 - 40 participants allocated to SELF-BREATHE purposively sampled by age, sex, ethnicity, diagnosis, geographical location, continued user or not. Interviews will be conducted in patient's homes/location of their choice, face to face or via telephone/video call and digitally recorded.

Interview with SELF-BREATHE users' objectives

- To understand the mechanisms underpinning sustained use, or not of SELF-BREATHE
- To explore how personal factors such as age, socio-economic status, sex and ethnicity may influence motivations for sustained use of SELF-BREATHE
- To explore and identify barriers, enablers and strategies to further inform the development of an implementation strategy for SELF-BREATHE (if positive)

Qualitative interviews with SELF-BREATHE Research Staff

To complement the quantitative findings of the SELF-BREATHE RCT, we will conduct qualitative interviews with research staff involved in recruitment across participating sites. The aim of these interviews is to explore staff experiences, identify enablers and barriers to recruitment, and

understand factors contributing to the trial's recruitment success and challenges e.g., the underrepresentation of individuals from minoritised ethnic communities.

Qualitative interviews with SELF-BREATHE Research Staff objectives

- To explore research site staff experiences of recruiting into the SELF-BREATHE RCT.
- Investigate the impact of study design, site resources, and central team support on recruitment.
- Explore staff experiences of approaching patients, including interest levels and feedback.
- Examine potential reasons for underrepresentation of minoritised ethnic communities in this clinical trial and potential solutions.
- Identify lessons learned that can inform future trials and wider implementation of SELF-BREATHE.

We will seek to recruit at least one member of the research team from each participating site. This may include research nurses, principal investigators (PIs), referring clinicians or other staff directly involved in recruitment activities, to ensure representation across sites and roles. Recruitment will continue until pragmatic saturation is achieved (i.e., sufficient information gained to address the study aims). We anticipated this would occur after recruitment of approximately 10 - 15 participants. Interviews will be conducted via video call or telephone, depending on individual preference and availability. Each interview will follow a semi-structured topic guide and is expected to last approximately 45–60 minutes.

Interview scheduling will be coordinated directly with participants to accommodate their availability and preferred mode of communication. Flexible scheduling will be offered, including options outside of standard working hours if needed, to ensure participation is convenient and minimally disruptive to clinical duties.

Analysis plan: quantitative data

Informed by CONSORT guidelines [27] and MORECARE statement [25, 39], a single analysis will occur once all follow up data have been recorded and accounted for. Baseline participant demographics and flow data from the eligibility screening to completion will be summarised overall and by site. Missing data will be summarised for each outcome, each arm and time point, where available reasons for missing data will be provided. SELF- BREATHE use / compliance data will be summarised using descriptive statistics.

The primary outcome analysis will be on an intention to treat (ITT) basis. Linear regression will be used to estimate the difference between groups in NRS worst breathlessness at seven weeks (primary end point) and 3 months, adjusting for baseline NRS worst breathlessness, minimisation factors and any other pre-specified important factor. Sensitivity analysis will explore the robustness of our findings [40] . Other outcomes will be analysed using a similar method.

Using the IPR and CBRQ mediation analyses will assess SELF-BREATHE mechanism(s) of change [41]. All outcome analyses will be outlined in a detailed Statistical Analysis Plan which will be written with support from the trial statistician, with supervision of the Senior Statistician, and signed off ahead of any data analysis.

Qualitative interviews analysis

Interviews will be transcribed verbatim. NVivo software will be used to support a conventional content analysis [42]. Categories will be created inductively, with attention to terms and content from the interview data. A process of concurrent recruitment and analysis, with iteration and constant comparison of categories and their properties, will be used until data saturation is indicated. If appropriate a summative approach may be employed to quantify patterns in views. Reflexivity, member checking and engagement with PPI members and the broader research team will be used to enhance rigor and trustworthiness [43]

6 STUDY SCHEDULE

1 Patient screening by clinical teams
2 Eligible patients will be provided with a PIS
3 Informed consent
4 Completion of baseline questionnaires
5 Randomisation
6 Participants informed of allocated study arm Intervention (SELF-BREATHE plus usual NHS care) or control (usual NHS care)
7 Participants allocated to SELF-BREATH provided with log in details / instructions
8 Participants allocated to SELF-BREATH receive a technical support call 24-48hrs after receiving log in details
9 7 weeks post randomisation (primary endpoint) all participants complete research questionnaires.
10 7 weeks post randomisation qualitative interviews conducted with subset of SELF-BREATHE users
11 12 weeks post randomisation (secondary endpoint) all participants complete research questionnaires.
12 12 weeks post randomisation qualitative interviews conducted with subset of SELF-BREATHE users
13 Once the last 12 weeks post randomisation qualitative interview is completed, the study will be closed

7 PATIENT AND PUBLIC INVOLVEMENT (PPI)

PPI in this research has been, and will continue to be, guided by the NIHR Centre for Engagement and Dissemination. We will continue to actively work with PPI groups and individual members from diverse backgrounds and cultures, using a variety of approaches (face-to-face and virtual meetings). We will work with PPI groups linked to organisations e.g., the Cicely Saunders Institute (via the online forum www.csipublicinvolvement.co.uk), Asthma + Lung UK, the NIHR Research Design Service, and the Centre for Ethnic Health Research, Leicester. PPI input to date includes development and early testing of SELF-BREATHE and writing of Dr Reilly's NIHR Advanced Clinical academic Fellowship, which provides the funding to support this multi-centre randomised controlled trial of SELF-BREATHE. For the latter, PPI members fed back and refined the trial design. PPI members' lived experience has ensured the project is focused on what matters to them.

Example of PPI involvement:

- PPI members influenced the narrative and study design of this application. They identified what matters to those living with or supporting those with chronic breathlessness (i.e., improved breathlessness self- management, resulting in reduced breathlessness). This is reflected in our theoretical model underpinning this work and study primary outcome worst breathlessness experienced.
- PPI members highlighted the importance of testing SELF-BREATHE in a multicentre randomised controlled trial.
- The plain English summary as part of the IRAS / HRA application has been co-written by 4 PPI members.

Summary chart of study assessments	**Baseline (T1)**	**7 weeks (T2)** **Primary endpoint** **(+/- 5 days visit window)**	**12 weeks (T3)** **Secondary end point** **(+/- 5 days visit window)**
Demographics questionnaire	X		
MRC Dyspnea Score	X	X	X
NRS Breathlessness rest (24hrs)	X	X	X
NRS Breathlessness exertion (24rs)	X	X	X
NRS worst breathlessness (24hrs)	X	X	X
NRS Distress due to breathlessness (24hrs)	X	X	X
NRS Confidence in managing your breathlessness	X	X	X
Dyspnea 12	X	X	X
Chronic Respiratory Questionnaire (CRQ)	X	X	X
The London Chest Activity of Daily Living Scale (LCADL)	X	X	X
EQ-5D-5L & EQ-VAS	X	X	X
The Brief Illness Perception Questionnaire (Brief IPQ)	X	X	X
Cognitive Behavioural Responses Questionnaire (CBRQ) (Short version)	X	X	X
SELF-BREATHE user acceptability questionnaire		X	X
The Acceptance Scale	X	X	X
		7 weeks (T2) **(+/- 10days visit window)**	**12 weeks (T3)** **(+/- 10 days visit window)**
Qualitative interviews (will be conducted with a subset of patient n=30-40, two interviews per participant)		X	X

8 FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the KCH R&I Office and deemed sufficient to cover the requirements of the study. The research costs for the study have been supported by HEE / NIHR ICA Advanced Clinical and Practitioner Fellowship https://fundingawards.nihr.ac.uk/award/NIHR302904.

Role of Funder / Sponsor in the design / conduct / data analysis of the study:

The funder / sponsor has had no role in the study design, nor will they have in data collection, data analysis, data interpretation or writing of reports and /or manuscripts for publication.

9 DATA HANDLING AND MANAGEMENT

The Chief Investigator will act as custodian for the trial data. All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and in accordance with the General Data Protection Regulation and the Data Management Guidelines per individual NHS organizational guidance. All personal data stored as manual files (e.g., consent forms) will be kept secure in locked cabinets, in a locked office at a designated location at each study site.

All personal data stored as digital files (e.g., interview recordings) will be encrypted and stored on password protected NHS computer. In all cases, access will be restricted and controlled. Audio recordings of interviews will only be transferred using encrypted data transfer services to professional transcribers. Anonymised transcripts will be encrypted and stored on the password protected NHS computer (King's College Hospital NHS Foundation Trust) Risk of breach of confidentiality of data is therefore minimal. Contact details collected for purposes of arranging interviews at the participant's convenience will be destroyed after the study is completed. The end of study will be defined as the date the data based is locked.

10 PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by KCH R&D. The Sponsor considers the procedure for obtaining funding from (NIHR) to be of sufficient rigor and independence to be considered an adequate peer review.

The study was deemed to require regulatory approval from the following bodies (list). Each approval will be obtained before the study commences.

- HRA
- REC

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the UK policy framework for health and social care research and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.
The Chief Investigator (Dr Charles Reilly) will submit a final report at conclusion of the Clinical trial to; R&I Department at King's College Hospital NHS Foundation Trust, NIHR (study funder), the REC and the HRA within the timelines defined in the Regulations.

11 ADVERSE EVENTS AND INCIDENT REPORTING

11.1 Definitions of Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the intervention/treatment/procedure involved.
Serious Adverse Event (SAE).	Any adverse event that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

11.2 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness, and expectedness as described below.

Severity

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

Causality

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

Expectedness

Category	Definition
Expected	An adverse event which is consistent with the available information about the intervention/treatment/procedure in use in this study.
Unexpected	An adverse event which is not consistent with the available information about the intervention/treatment/procedure in use in this study*

* this includes listed events that are more frequently reported or more severe than previously reported

11. 3 Procedures for recording adverse events

All adverse events will be recorded in the medical records in the first instance. All Adverse events will be recorded in the CRF following consent. All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. All adverse events will be recorded in the CRF until (e.g., the participant completes the study).

11. 4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the medical records and the CRF.

All SAEs (except those specified in section 11.5 not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form. The PI or designated individual will complete an SAE form and the form will be preferably emailed to the (Chief Investigator/Trial Manager/Research Nurse). within 1 working day of becoming aware of the event. The Chief Investigator or an appropriate delegated member of the research team in their absence e.g., annual leave, sickness) will submit all SAE reports to the R&I Office (kch-tr.research@nhs.net). Where the event is unexpected and thought to be related to the intervention/treatment/procedure this must be reported by the Investigator to the REC and Health Research Authority, using the SAE Report form for non-CTIMPs (available from the HRA website) within 15 days.

11. 5 Events not to be classified as SAE's in the SELF-BREATHE RCTt

The following events will **not** be classified as SAEs within this trial and therefore not to subject to **expedited** reporting (however, they will be recorded as an Adverse Event e.g., death reported on the CRF.

- Death as a result of disease progression
- Hospitalisation or admission into a hospice, nursing home or palliative care unit due to
- Caregiver burden
- Expected deterioration related to underlying lung disease (cancer / ILD/ COPD)
- Routine treatment or monitoring of the studied indication or any know comorbid conditions not associated with a deterioration in conditions
- Treatment which was elective or pre -planned for a pre – existing condition not associated with any deterioration in condition e.g., pre – planned hip replacement operation which does not lead to further complications

- Any admission to hospital or other institution for general care where there was no deterioration in condition
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given the above and not resulting in hospital admission

11. 6 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC, Health Research Authority and R&I office of the measures taken and the circumstances giving rise to those measures.

11. 7 Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI will monitor protocol deviations.

A protocol violation is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or

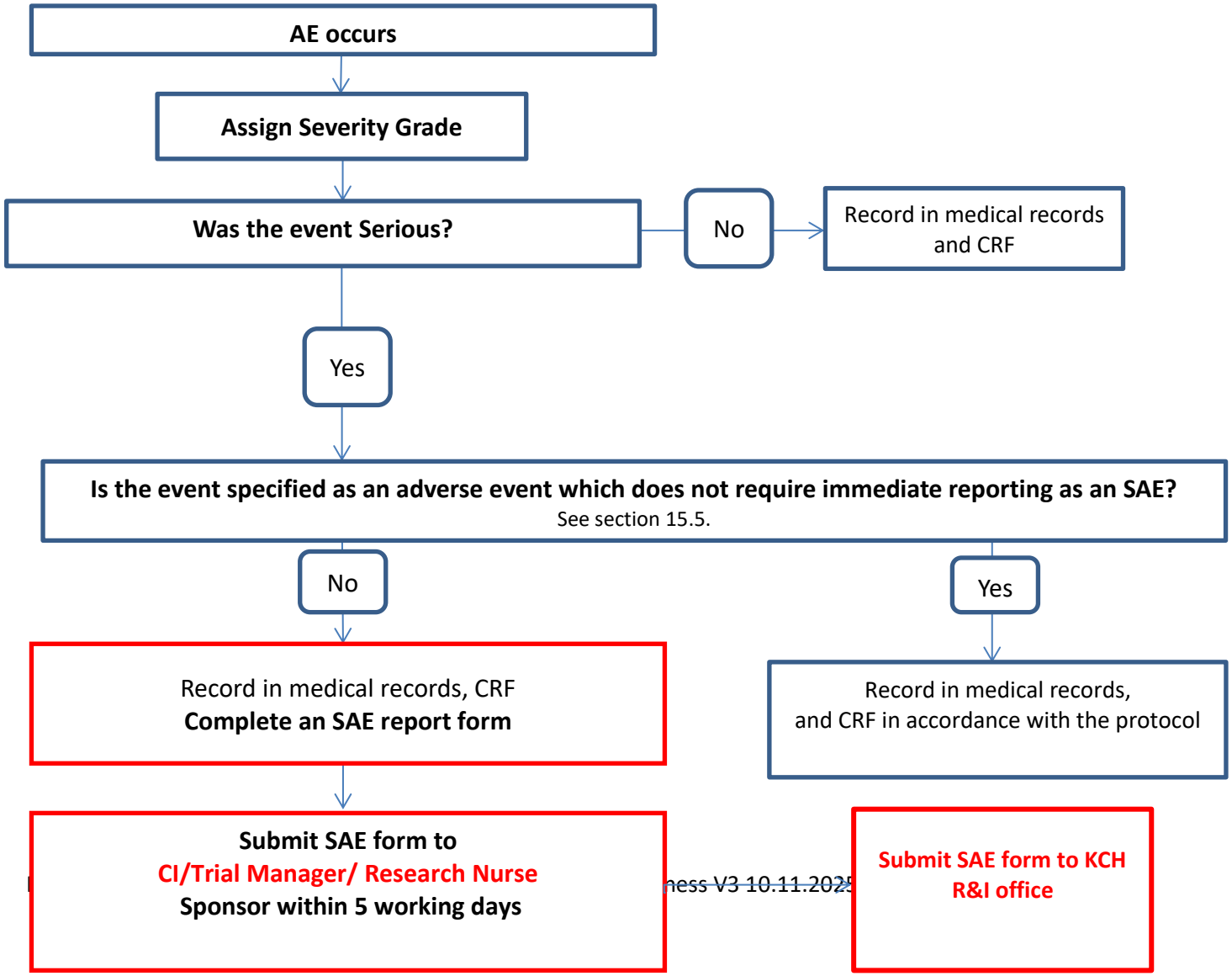
(b) the scientific value of the study.

The CI and R&I Office should be notified immediately of any case where the above definition applies during the study conduct phase.

SELF breathe

King's College Hospital NHS
NHS Foundation Trust

Flow Chart for SAE reporting



11.8 Trust incidents and near misses to follow individual study site trust guidelines

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.

b. It is contrary to specified or expected standard of patient care or service.

c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.

d. It puts the Trust in an adverse position with potential loss of reputation.

e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported following individual trust reporting procedures as soon as the individual becomes aware of them.

A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

12 MONITORING AND AUDITING

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g., patients' case sheets).

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality. The Chief Investigator will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

12. 1 Trial Management Group (TMG)

The TMG, comprising the CI, Trial Manager, a representative of from the King's College London Clinical Trials Unit (KCTU), and other key internal / external members of staff involved in trial (e.g., Professor Irene Higginson, Professor Matthew Maddocsk, Ms Parmjote Kaler – research nurse). The group will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

12.2 Trial steering committee (TSC)

The TSC will provide overall supervision of the trial, in particular the trial progress, adherence to the protocol, patient safety and consideration of new information. It will include an independent chair, not less than two other independent members. The CI and other members of the TMG may attend the TSC meeting and present and report progress. The committee will meet annually as a minimum, as documented in the TSC terms of reference.

12. 3 Data monitoring and safety committee (DMSC)

The DMSC will include independent membership and will review the safety and ethics of the trial. The DMSC) will assess unblinded outcome data and adverse events ensure patient safety. It will comply with the DMC charter. The committee will meet annually as a minimum.

13 TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files.

14 INTELLECTUAL PROPERTY

All intellectual property rights and know-how in the protocol and in the results arising directly from the study but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to King's College Hospital NHS Foundation Trust (KCH). Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to KCH and to disclose all such know-how to KCH, with the understanding that they may use know-how gained during the study in clinical services and teaching to the extent that such use does not result in disclosure of KCH/KCL confidential information or infringement of KCH/KCL IPR.

15 INDEMNITY ARRANGEMENTS

KCH will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&D Department. The Trust cannot accept liability for any activity that has not been properly registered, and Trust approved. Potential claims should be reported immediately to the R&I Office

16 ARCHIVING

Consent forms, anonymised transcripts and demographic information will be saved for 7 years after the end of the study. All study sites will archive their own documents as per their individual NHS organisational guidelines. The CI will retain the trial master file that collates all the site files at the end of the trial. The trial master file will be kept secure in locked cabinets in a locked office, and data stored as digital files will be stored on password protected NHS computer.

17 PUBLICATION AND DISSEMINATION POLICY

The findings from the trial will be disseminated regardless of results significance. We anticipate sharing the findings approximately 12 months from closing the study. We will utilise a broad strategy to maximise dissemination of our findings

. These will include:

- A plain-English summary for participants who opt to receive this on their consent form
- Sharing of scientific findings via open-access publications in journals and presentations at international meetings
- Plain English summaries of findings for public bodies and websites (e.g., CLAHRC, Asthma & Lung UK, patient.co.uk)
- Use of social media (e.g., Twitter, YouTube, blogs)
- Public engagement via talks and open public events at King's college Hospital NHS Foundation Trust and / or Cicely Saunders Institute, King's College London.

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19 APPENDICES

Appendix 1: PROTOCOL VERSIONS

Versions No	Version Date	Status
3	10.11.2025	Current
2	14.08.2025	Old / superseded by v3 10.11.2025
1	15/01/2024	Old / superseded by v2 14.08.2025