TITLE	Fan Feasibility Randomised Controlled Trial (RCT) for people living with COPD and high SABA intake (FanFIRST)
PROTOCOL NUMBER	R2924, version 1.1
STUDY INTERVENTION	The FanFIRST intervention is a brief, complex breathlessness intervention structured around use of the hand-held fan. The intervention is deliverable in ~10 minutes by a clinician
LEAD STUDY INVESTIGATOR	Dr Michael G Crooks Senior Clinical Lecturer in Respiratory Medicine Correspondence Address: Academic Respiratory Medicine Castle Hill Hospital Cottingham HU16 5JQ Tel. 01482 624067 Mobile. 07515528984 Email. Michael.crooks@nhs.net
DATE OF PROTOCOL	29/08/23
STUDY SPONSOR	University Teaching Hospitals NHS Trust R&D Department, 2nd Floor Daisy Building, Castle Hill Hospital, Cottingham, HU16 5JQ Tel. 01482 461903: Fax: 01482 461886
RESEARCH REFERENCE	IRAS Project ID: 318320 Sponsor No: R2924 ISRCTN no: xxxxx Funder Reference: NIHR204349
Confidentiality Statement	Information in this protocol should not be disclosed, other than to those involved in the execution or ethical review of the study, without written authorisation from the Sponsor.
Regulatory Statement Protocol Preparation	All study procedures will be conducted within ICH GCP guidelines and all other regulatory requirements. This protocol has been prepared in accordance with CONSORT guidelines. It complies with Guidelines for Good Clinical Practice in clinical research.

PLAIN ENGLISH SUMMARY

Chronic obstructive pulmonary disease (COPD) is a lung disease that tends to affect older adults. Breathlessness is the most common symptom which greatly impairs quality of life. COPD is mainly treated using inhalers taken once-or-twice every day, but another type of inhaler, called a short-acting beta agonist (SABA), is only meant to be used when needed to provide short-term symptom relief.

People with COPD often don't know how best to manage their breathlessness and can become reliant on their SABA, using it too often, risking side effects. Those with COPD that use their SABA frequently have worse breathlessness and are more likely to have COPD 'flare-ups'. We believe that teaching COPD patients how to use a hand-held-fan (HHF), and other techniques to manage their breathlessness (the FanFIRST intervention), may improve their breathlessness and reduce how often they need their SABA. SABA inhalers contain a strong greenhouse gas that contributes to global warming. Therefore, reducing how many SABA inhalers are used each year has potential dual-benefits to both COPD patients and the environment.

The FanFIRST intervention takes about 10-minutes and includes providing a fan and teaching people how to use it, alongside guidance on positions and breathing techniques to help manage breathlessness. Written information about breathlessness and anxiety and how to manage this will also be provided.

A large trial is needed to tell if the FanFIRST intervention can help people manage their breathlessness and reduce SABA inhaler use. But, before we start, there are a number of questions which need to be answered. For example:

- Can we recruit enough people to a trial?
- What sort of health services are best to recruit people from?
- Do people like the FanFIRST intervention; and What do people with COPD (and their carers) think about the trial design, and the questions that it is designed to answer?

To answer these questions and more, we will first undertake a smaller study called a feasibility trial. We will invite 80 people with COPD that use their SABA inhaler frequently. Eligible participants will be chosen at random to receive either the FanFIRST intervention, or usual care. Regardless of study condition, all participants will be given devices that attach to their SABA inhaler to count how often they are used. We will measure usage throughout the study and compare use at the start of the study

with usage at the end of the study. People will take part for 4 months in total, with breathlessness questionnaires and other measures completed every 28 days during the study. A total of 40 participants (and their carers) will also be invited to take part in an interview with a researcher.

The results of the feasibility study will tell us two important things. First, whether a larger trial is possible, and if so, how best to run it. Second, if provisional results are deemed effective, how best to roll-out the FanFIRST intervention across the NHS.

PROTOCOL SYNOPSIS

Sponsor	Hull University Teaching Hospitals NHS Trust
Intervention	A brief (deliverable in 10 minutes), complex breathlessness intervention comprising provision of a rechargeable hand-held fan (HHF). Also provided as part of the intervention are verbal and written instructions in its use, guidance on positions/breathing techniques and exercises to relieve breathlessness; and written information about managing anxiety to improve breathlessness.
Study Number	IRAS ID: 318320 Funder Reference: NIHR204349
Title of Study	Fan Feasibility Randomised Controlled Trial (RCT) for people living with COPD and high SABA intake (FanFIRST)
Study Centres	- Castle Hill Hospital, Cottingham, HU16 5JQ - Holderness Health, St Nicholas Surgery, Queen Street, Withernsea - HU19 2PZ - Bradford Teaching Hospitals NHS Foundation Trust, Duckworth Lane, Bradford, BD9 6RJ - The Bloomsbury Surgery, Handel Street, London, WC1N 1PD
Phase of Development	Feasibility
Aims and Objectives	***Aim*** We will: i. Assess the feasibility and optimal design for a Phase-3, RCT comparing HHF-based breathlessness management (FanFirst intervention) with usual care in people with COPD and high SABA use, and ii. Explore barriers and facilitators to NHS-wide implementation of the FanFIRST intervention. ***Objectives*** In order to achieve the study aims, the study is designed to address uncertainties regarding: 1. Feasibility of recruiting participants and collecting sufficient outcome and implementation data 2. Baseline measure variability to enable sample-size estimation for the future Phase-3 trial 3. Intervention delivery with fidelity 4. Relevance and acceptability of the intervention and proposed outcomes to participants and clinicians

	5. How different settings characteristics constrain or enable implementation, and their implications for intervention flexibility and development of an implementation strategy
Study Design	A multicentre, parallel-group, open-label, randomised controlled, hybrid Type-I effectiveness-implementation feasibility study of the FanFIRST intervention in COPD patients with high SABA-use. A schedule of assessments and procedures is provided in Table 1. A flow chart of the study is provided in Figure 1.
Number/Type of Participants	Eighty eligible, consenting people with COPD and high SABA-use in the year prior to recruitment.
Inclusion Criteria	• Adults aged ≥30 years • Clinician diagnosed COPD with airflow obstruction, confirmed on spirometry (FEV-1/FVC ratio <0.7) • Current or ex-smokers with ≥10 pack-year smoking history • Modified Medical Research Council Dyspnoea Scale (mMRC) breathlessness score ≥2 • Patients receiving optimal guideline recommended inhaled treatment for COPD, including a minimum of dual-acting bronchodilator therapy (long-acting beta-agonist and long-acting muscarinic antagonist) with or without an inhaled corticosteroid. • Patients prescribed ≥12 SABA inhalers/canisters within the past year with self-reported SABA use most days. Only those prescribed a pressurised metered dose inhaler (pMDI) SABA are eligible for inclusion. • Provision of written informed consent • Willing and able to comply with all required study activities
Exclusion Criteria	• Those with significant cardiorespiratory disease, other than COPD, considered the primary cause of their breathlessness/high SABA use. • Those with a COPD exacerbation requiring oral corticosteroids and/or antibiotics and/or hospitalisation within 4-weeks before recruitment (taken from last day of exacerbation treatment). • Those with a planned pulmonary rehabilitation attendance during the study (pulmonary rehabilitation referral will be offered one on completing trial participation if appropriate).
Study Treatment(s)	Participants will be randomised to receive either 1. FanFIRST intervention plus usual care, or 2. Usual care without the FanFIRST intervention.
Study Endpoints and Statistical Methods	*Feasibility* Feasibility outcomes will be assessed against stop-go/traffic-light criteria (underlined and detailed in Box.1) for definitive trial progression:

	- **Recruitment and retention**: recruitment rate (per site and aggregated), eligibility to consent ratio, screen failures and participant retention. - **Data quality and integrity**: Amount and pattern of missing data (SABA inhaler use) - **Outcomes:** acceptability of proposed outcomes (qualitative interviews) and integrity of outcome data - **Intervention:** feasibility, acceptability and fidelity of the intervention will be assessed *Efficacy* *Primary Outcome* The proposed primary outcome is change in mean daily SABA use from baseline (days -28-0) at days 56 - 84. Smart inhaler technology supplied by Propeller Health, USA, will objectively count SABA actuations each day. Baseline data will inform intra- and inter-individual SABA use variability, as well as provide an optimal monitoring duration for the definitive trial. Daily SABA use will be recorded throughout the trial to enable evaluation of change in use and any potential degradation of intervention effect over-time. *Secondary Outcomes* - COPD Assessment Test (CAT) score - Breathlessness numerical rating scales for 'worst', 'distress caused by' and 'coping with' breathlessness within the past 24 hours - Modelled annual SABA inhaler/cannister pick-up rate (based on number of actuations at baseline (days -28 – 0) and between days 56 and 84) - Health-related quality-of-life: EQ-5D-5L and VAS - Healthcare-resource-utilisation - Modelled CO2e (for COPD treatments alone and combined for COPD treatments, study intervention and healthcare-resource-utilisation). *Safety* All adverse events (AEs) and serious adverse events (SAEs) will be recorded *Health Economics* The feasibility of collecting health economic data will be evaluated to inform aspects for full health economic evaluation in the definitive trial.
Safety Analyses	AEs/SAEs will be listed and summarised using descriptive statistics
Sample Size Rationale	Since this is a feasibility study, a formal sample-size calculation has not been performed. We will recruit 80 patients over 12 months.

Table 1 Schedule of Assessments and Procedures

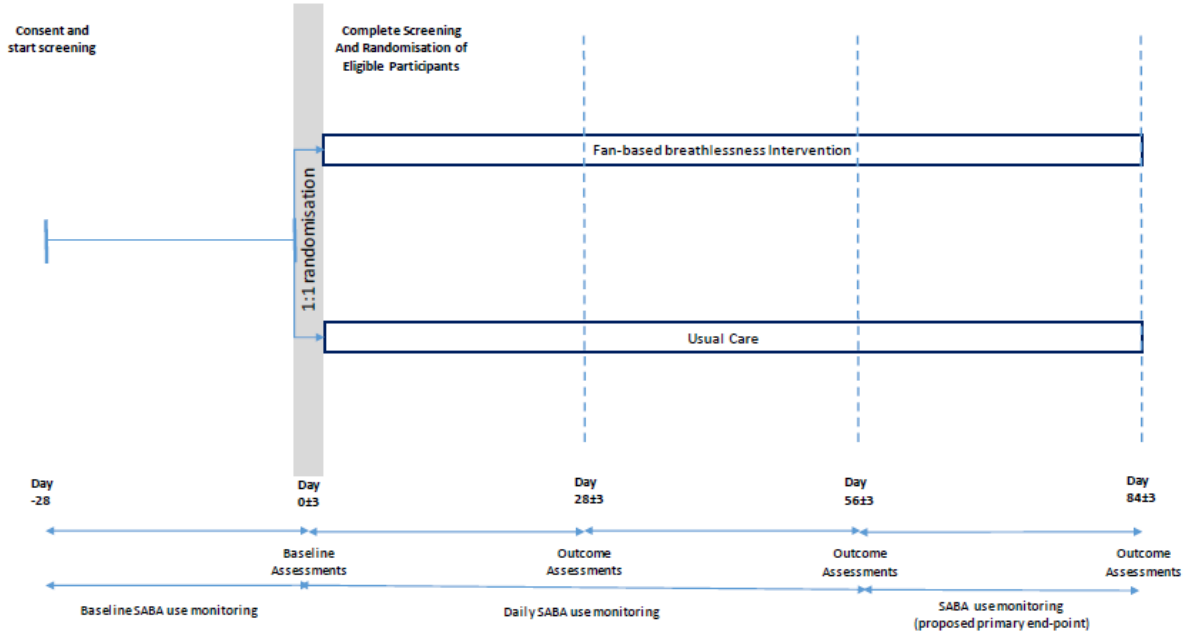
Visit	**Consent/ Screening Start of baseline**	**Baseline Visit End of baseline**		**Study Visit 1** (Face-to-face or remote)^^	**Study Visit 2** (Face-to-face or remote)^^	**Study Visit 3**
Day	**-28**	**0**		**28 (±3 days)**	**56 (±3 days)**	**84 (±3 days)**
Procedure/Assessment						
Inclusion/exclusion criteria	x					
Written Informed Consent	x					
Medical History	x					
Vital signs	x	x				x
Weight and Height	x					x
Physical Examination	x*					
Spirometry	x^					
AE Monitoring	x	x		x	x	x
Inhaler technique assessment	x					
SABA Use Monitoring	x	x		x	x	x
Breathlessness NRSs	x	x		x	x	x
CAT Score	x	x		x	x	x
mMRC	x					
EQ5D-5L	x	x				x
Invitation Experience survey	x					
Healthcare resource Utilisation		x		x	x	x
Qualitative Interviews						x
Evaluation of usual care received since last visit**		x		x	x	x
Randomisation		x				
Study Experience Survey						x

Randomisation (Day 0)

CAT: COPD Assessment Test, mMRC: modified Medical Research Council, NRS: Numerical Rating Scale, EQ-5D-5L: EuroQual 5 dimensions 5 level.

Schedule of events ** Physical examination to be performed on 1 occasion during screening (on either day -28 or day 0 visit prior to randomisation). **Usual care received will be evaluated following each study visit to capture i) new treatments initiated, ii) changes to pre-existing COPD treatment and iii) self-management interventions undertaken since the last visit. A standardised questionnaire using non-leading questions will be used to capture elements of non-pharmacological breathlessness self-management used by each group. ^ Spirometry should be done during the screening visit where possible, but can be done anytime between the screening and baseline visit, in accordance with local capacity/infection control procedures. ^^ Participants that have linked their smart inhaler sensor to their smartphone, enabling remote assessment of sensor function and recording, can have visits 1 and 2 undertaken remotely (via telephone).*

Figure 1 Study Flow Chart



CONTENTS

1. BACKGROUND AND RATIONALE

Over-reliance on short-acting beta agonist inhalers (SABA) in COPD can reflect uncontrolled breathlessness, can cause side effects (tremor/palpitations), and is harmful to the environment. We will conduct a feasibility randomised controlled trial (RCT) of a simple and scalable breathlessness management intervention in COPD patients who over-use SABA to investigate i) the feasibility and optimal design of a definitive trial investigating the potential to improve symptom control and reduce SABA reliance in COPD, and ii) explore factors impacting wide-scale adoption of our intervention across the NHS.

SABA are the most prescribed inhalers in England. They relax airway smooth muscle, temporarily relieving symptoms caused by airway narrowing (bronchospasm). However, SABA over-use is linked with poor patient outcomes and environmental damage.

High SABA use is well delineated in asthma where it is associated with exacerbation risk, health-care-resource utilisation and excess mortality[1,2]. Although less studied, high SABA use in COPD is associated with worse quality-of-life and exacerbation risk[3,4,5]; events that drive disease progression and mortality[6-8]. Where policy and guidelines are helping drive down SABA use in asthma, less is known about how to achieve this in COPD.

COPD typically affects older adults and is associated with deprivation. Breathlessness is common in COPD[9], impairs quality-of-life[10], physical and social function[11], and leads to dependence on health services[12,13]. Breathlessness causes vicious cycles of activity avoidance, deconditioning, and anxiety-panic, worsening breathlessness[14]. Optimal symptom and disease-control is therefore crucial in COPD. However, despite availability of evidence-based, non-pharmacological breathlessness interventions such as the hand-held fan (HHF)[15,16], pharmacological strategies such as SABA are often prioritised, risking over-use and over-reliance.

SABA's role in managing daily variations in chronic breathlessness in COPD is poorly understood[4] with people with COPD typically already established on long-acting bronchodilators[17]. Managing major symptom components with the HHF and addressing unhelpful breathing patterns and anxiety, may be more effective than, and reduce, SABA use.

~94% of the 21 million SABA prescribed in England each year are greenhouse gas containing metered dose inhalers[18]. Consequently, SABA account for 70% of the UK's inhaler-related carbon footprint, totalling 863 kilotonnes CO_2e annually[19]. Mitigating the health risk from climate change is a World

Health Organisation (WHO) global priority[20]. Where primary care contracts previously incentivised reducing SABA over-reliance in asthma, with quality improvement programmes developed to achieve this[21], no such incentives or interventions exist in COPD. There is therefore an unmet need for evidence-based interventions to achieve this important goal.

We will undertake a feasibility, randomised controlled trial of HHF-based breathlessness management (the FanFIRST intervention) in COPD patients with high SABA use to assess the feasibility and optimal design of a definitive trial to evaluate the impact of the FanFIRST intervention on SABA use, symptoms, quality of life, health care resource utilisation, environmental impact, safety and cost effectiveness. Our proposed feasibility trial will address uncertainties relating to fundamental trial elements, thereby favouring a stand-alone feasibility trial rather than an internal pilot. Taking an overall effectiveness research perspective[22], our feasibility study incorporates a theory-based approach to assess how processes, impact mechanisms and contextual factors shape outcomes. If proven effective, the FanFIRST intervention would be the first evidence-based, implementation-ready intervention to reduce SABA over-reliance in COPD with both patient and environmental benefits. The simple and scalable nature of the intervention means that FanFIRST has significant potential to lead to a step change in the way that breathlessness and high SABA use is managed in COPD.

2. STUDY AIMS AND OBJECTIVES

Aims

The aims of the study are to:

i. Assess the feasibility and optimal design for a phase-3, RCT comparing HHF-based breathlessness management (FanFirst intervention*) with usual care in people with COPD and high SABA use, and
ii. Explore barriers and facilitators to NHS-wide implementation of the FanFIRST intervention.

***The FanFIRST intervention is a brief (deliverable in 10 minutes), complex breathlessness intervention comprising provision of a rechargeable HHF. Verbal and written instructions in the HHFs use, positions/breathing techniques and exercises to relieve breathlessness; and written information about managing anxiety to improve breathlessness, are also provided as part of the intervention*.

Objectives

In order to achieve the study aims the study is designed to address uncertainties regarding:

1. Feasibility of recruiting participants and collecting sufficient outcome and implementation data.
2. Baseline measure variability to enable sample size estimation for the future Phase-3 trial.
3. Intervention delivery with fidelity.
4. Relevance and acceptability of the intervention and proposed outcomes to participants and clinicians.
5. How different settings characteristics constrain or enable implementation, and their implications for intervention flexibility and development of an implementation strategy.

3. STUDY DESIGN

Multicentre, parallel-group, open-label, randomised controlled, hybrid Type-I effectiveness-implementation feasibility study. Patients will be randomised to either usual care or the FanFIRST intervention in a 1:1 ratio using random permuted blocks. Randomisation will be stratified by site and based on self-reported HHF usage (any reported HHF-use) within the past month.

Taking an overall effectiveness research perspective, consistent with the MRC's updated framework for developing and evaluating complex interventions[2222], the study incorporates a theory-based approach to assess how processes, impact mechanisms and contextual factors shape outcomes[232323].

3.1 Patient and public involvement

The study design, intervention and documents have been informed by a dedicated FanFIRST patient and public involvement (PPI) group. The Patient Advisory Group is made up of four members and includes patients and carers who have experience living with, or caring for somebody with, COPD and/or chronic breathlessness. All PPI group members are members of Involve Hull; a network developed to ensure that patients and their carers are empowered to have the opportunity to shape research. The FanFIRST PPI Group was formed using funding from the University of Hull and convened prior to the Stage 1 submission. Following success at Stage 2, two more experienced PPI members have been recruited to join the Trial Management Group and a further two to join the Trial Steering Committee. Further detail on both of these groups is provided in Section 12.

3.2 Study Sites

The trial will recruit from four National Health Service (NHS) study sites. A list of the sites can be found in the Investigator Team section on page 3. In addition, where requested by study sites, a participant identification centre (PIC) will be used to identify suitable study participants (see PIC site already identified on page 3).

4. STUDY POPULATION

Eighty eligible consenting people with COPD and high SABA-use^ during the year prior to study recruitment. Participants that do not meet all of the eligibility criteria will not qualify for enrolment. A study screening and enrolment log will be kept to include all potential participants sent a participant information sheet, recording reasons for ineligibility when applicable. All consenting participants will be provided with an automatically generated subject identification number (SIN) and enter study screening. For participants that do not pass screening, reasons for failure will be recorded on the screening log and within REDCap.

^*For this study, high SABA-use will be defined as 12 or more SABA prescriptions issued during the prior 12-months with self-reported SABA-use most days.*

4.1 Inclusion Criteria

- Adults aged ≥30 years
- Clinician diagnosed COPD with airflow obstruction, confirmed on spirometry (FEV-1/FVC ratio <0.7)
- Current or ex-smokers with ≥10 pack-year smoking history
- Modified Medical Research Council Dyspnoea Scale (mMRC) breathlessness score ≥2
- Patients receiving optimal guideline recommended inhaled treatment for COPD, including a minimum of dual-acting bronchodilator therapy (long-acting beta-agonist and long-acting muscarinic antagonist) with or without an inhaled corticosteroid.
- Patients prescribed ≥12 SABA inhalers/canisters within the past year with self-reported SABA use most days. Only those prescribed a pressurised metered dose inhaler (pMDI) SABA are eligible for inclusion.
- Provision of written informed consent
- Willing and able to comply with all required study activities

4.2 Exclusion Criteria

- Those with significant cardiorespiratory disease, other than COPD, considered the primary cause of their breathlessness/high SABA use.
- Those with a COPD exacerbation requiring oral corticosteroids and/or antibiotics and/or hospitalisation within 4-weeks before recruitment (taken from last day of exacerbation treatment).
- Those with a planned pulmonary rehabilitation attendance during the study (pulmonary rehabilitation referral will be offered on completing trial participation if appropriate).

4.3 Participant Identification and Screening

Participants will be identified by study sites. Participant identification centres (PICs) will be considered if requested by the participating sites, particularly if a PIC would support inclusion of minority or underserved communities. Participants will be identified and approached in two ways:

1. Participants will be identified by their usual care team during delivery of usual care, or through electronic health record search, and provided with information about the study in one of the following ways: 1) In person, e.g. during a clinic attendance, 2) Verbally, e.g. during a phone or video consultation, 3) In writing, e.g. via postal services and/or digital platforms. Each method of information delivery should be conducted in accordance with sites usual practice and standard operating procedures (SOPs). Following this, consent will be sought to share the participant's details with the research team, who will provide further information about the study, the participant information sheet (PIS), and answer any questions relating to the study.
2. Potential participants that have previously provided consent for their details to be retained on a clinical trial or research database for the purpose of future research participation will be contacted directly by the site research team and provided with study information, including the PIS, and provided with an opportunity to ask questions.

Written informed consent will be obtained for all participants in accordance with Good Clinical Practice.

All patients who are approached for the study will be invited to complete a short 'Trial Invitation Experience Survey' assessing their experience of recruitment and their reasons for why they consented to participate or declined.

Participants that fail screening on first attempt will be eligible for re-screening, provided the reason for screen failure is resolved prior to completion of study recruitment. This does not apply to cases where screen failure is related to SABA-use during the prior 12-months being below the threshold for study inclusion. In these case, re-screening will not be permitted. Those participants who become eligible following re-screening will be assigned with a new SIN. Participants that screen fail will be replaced.

4.4 Participant Withdrawal

Participants have the right to withdraw from treatment or the study at any time. The investigator(s) or sponsor may withdraw patients from treatment or the study, only if indicated by a safety or clinical issue, or where a deviation from study protocol has occurred.

Participants should remain in the study for follow-up unless they request to fully withdraw. All data up to the point of withdrawal will be retained. Both participants who withdraw, or complete, will be invited to complete a short survey e.g., The Study Experience Survey. This survey is designed to understand participants' experience of study participation, any reasons for withdrawal, and to indicate their willingness to participate in a future interview.

In the event of participant withdrawal, the Investigator(s) will promptly explain to the participant that their involvement in the study will discontinue and explain why. In the cases where medical intervention is warranted, investigators will facilitate provision of medical treatment and/or other necessary measures deemed appropriate for the participant. A participant who does not return for follow-up visits but who has not consented to complete a study experience survey will be followed up by phone or other means, as far as is possible, to offer them the opportunity to give a reason for withdrawal; which will be recorded in the CRF. It will be made clear to participants that they do not have to explain their withdrawal, if they do not wish to do so.

As well as self-withdrawal, other primary reasons for participants withdrawing from the study will be due to: AE(s), participant deterioration of disease, participant death, participant lost to follow-up, significant protocol violation. All provided reasons for study discontinuation will be collected on the participants CRF.

5. STUDY INTERVENTION

5.1 Summary

Intervention

All participants will receive ***usual care*** as per local guidelines. This will include, but not be limited to, inhalers (minimum dual long-acting bronchodilator therapy), oral medications and oxygen therapy when indicated. Participants' use of breathlessness self-management strategies will be recorded at baseline and throughout the study.

Participants randomised to ***the FanFIRST intervention*** will be given a rechargeable HHF. *Verbal and written instructions in the HHFs use, guidance on positions/breathing techniques and exercises to relieve breathlessness; and written information about managing anxiety to improve breathlessness will also be provided.* The intervention is designed to be deliverable by a clinician during a standard consultation, taking ~10 minutes to complete (further details specified in Table 2 FanFIRST Summary Intervention components mapped using TIDieR checklist).

5.2 FanFIRST Intervention Delivery

The FanFIRST intervention will be delivered immediately following participants' successful randomisation to the FanFIRST arm of the study[+]; after completion of baseline assessments. The intervention can be delivered by clinicians (nurses, doctors and/or allied health professionals) within the site clinical / research team that have received appropriate training and have had FanFIRST intervention delivery delegated to them by the PI. A record of training and delegation of intervention delivery will be recorded on the appropriate logs.

Delivery of the FanFIRST intervention will be recorded using an intervention checklist to facilitate assessment of intervention fidelity (see section 5.3 for further details).

[+] *Participants randomised to receive usual care will receive the intervention during the final study visit, following completion of all other study measures and activities.*

5.3 Intervention Fidelity

Formal training for FanFIRST intervention delivery will be provided for clinicians at study sites by members of the research team experienced in delivery of the intervention.

Table 2 FanFIRST Summary Intervention components mapped using TIDieR checklist

Component	Why	What	Who	How	Where	When/How much	Tailoring & modifications	How well
Clinician Training	Clinician lack of knowledge and poor communication about breathlessness and its management with patients [44 45] Training programmes with Breathing, Thinking, Functioning (BTF) model and non-pharmacological interventions improves clinicians knowledge and confidence to manage breathlessness [46]	**Teaching session** • Chronic breathlessness and management with BTF and non-pharmacological interventions (a toolkit) • SABA overuse • Demonstrate, rationale, and practice delivery intervention components –a), b), c) and d) **Materials** • On-line video, paper copy of training session and links to resources	Clinicians on the research team	Delivery of face to face and/or on-line teaching session	AMB, University of Hull and/or on-line via Zoom.	Before start of recruitment 20-30 minutes max training session	If face to face not possible then on-line teaching session Video resource of teaching session on-line	Breathlessness knowledge and skills assessment, feedback form, interviews
Resting Position (a)	Forward lean position to maximise ventilation [47-49]	**Procedure:** • Demonstration of comfortable position, forward lean, and flop and drop shoulders	Doctor, nurse	Delivery face to face	Outpatient hospital, GP practice	Beginning of trial. 2 minutes	Modify resting position to patient preferences	Fidelity Patient feedback from interviews clinician.
Breathing exercise (b)	Lengthen breath out e.g. pursed lip breathing (PLB) or "breathing rectangle". [47 50] increases end-expiratory pressure and reduces breathlessness[48 50]. Evidence to support use with COPD [51]	**Procedure:** • Demonstration of "breathing rectangle" and PLB • Focus on lengthening breath out	Doctor, nurse	Delivery face to face	Outpatient hospital, GP practice	Beginning of trial. 2 minutes	Modify breathing exercises to patient preferences	Fidelity Patient feedback from interviews clinician.
Hand-held fan (c)	Fan provides relief of breathlessness and reduces recovery time from exercise [21 22 31] Fan delivery important [52] Patient fan use instead of a SABA inhaler [23 31]	**Procedure:** • Demonstration of fan • Explain fan mechanism and use • Patient fan practice	Doctor, nurse	Delivery face to face	Outpatient hospital, GP practice	Beginning of trial. 3 minutes	Modify fan position, airflow speed to patient preference	Patient feedback from interviews clinician.
Thoughts (d)	Relationship between thoughts – anxiety and breathlessness. [53 54] BTF model anxiety can perpetuate breathlessness [55] and ATS statement endorses use of action plan [6].	**Procedure:** • Listen and acknowledge patients' thoughts about breathlessness • Action plan for anxiety **Materials** • Paper information leaflets with pictures to guide on components a), b), c), and d) • **Laminated Action plan*** • Link to on-line resources	Doctor, nurse	Delivery face to face	Outpatient hospital, GP practice	Beginning of trial. 5 minutes	Modify to patient thoughts and what they believe about breathlessness	Fidelity Patient feedback from interviews clinician.

***Laminated Action Plan for Breathlessness**
I am going to lean forward (a)
Focus on breathing out for longer (b)
I am going to use my fan (c)
I can do this – I am ok (d)

Delivery of the core components of the breathlessness intervention should be documented by the delivering clinician within the participant's medical record and eCRF (Appendix C). If a core component of the breathlessness intervention has not been delivered, then the reason for this must be documented in the participant's medical record and eCRF. Delivery of the intervention in accordance with the protocol will be assessed during monitoring visits.

During each participants study visit, both groups will be asked to report any breathlessness management strategies that they have been instructed in and/or have used as part of their usual care and therefore not as a result of the studied intervention.

6. OUTCOMES AND MEASURES

This is a feasibility trial and therefore the primary outcome measures address areas of uncertainty relating to design and delivery of a Phase 3 randomised controlled trial. These outcomes are termed feasibility outcomes. As part of this trial a number of clinical outcomes will also be evaluated.

Eligibility criteria will be assessed at day -28 to ensure only eligible participants will proceed with baseline assessments. Pre-baseline, assessments will be undertaken on day -28. Baseline monitoring of SABA usage via smart inhaler will be undertaken over 28-days (from day -28 to day 0) to allow for adequate baseline SABA-use data collection. Questionnaires will be completed on Day -28 and Day 0 to establish measure stability; with Day 0 considered the baseline visit, baseline end, and start of study. Spirometry (post-bronchodilator) will be performed at day -28 (or as soon after as possible depending on availability/infection control procedures at sites) to confirm eligibility and assess COPD severity. Where spirometry cannot be completed at day -28 due to a lack of availability at site and/or imposed local infection control procedures, participants will proceed with SABA use monitoring, with spirometry completed and eligibility confirmed, prior to undertaking further baseline assessments at day 0. Participants will be randomised on Day 0 with assessments every 28-days thereafter to complete 84-days follow-up.

6.1 Feasibility Outcomes

The feasibility outcomes and when assessments will take place are outlined in Table 3. The feasibility and fidelity of the intervention will be measured through adherence in delivery and uptake of the intervention (as a whole and individual intervention components) as documented in the eCRF. Overall intervention acceptability will be assessed via qualitative interviews.

Table 3 Feasibility outcomes and timing of assessments

Recruitment	Data quality and integrity	Outcomes[+]
• Eligibility to consent ratio; recruitment rate (per-site and aggregated) • Screen failure points (SFPs) • Participant retention/ follow-up rates at each time point	• Completion of clinical outcomes (questionnaires and other assessments) at each time point • Amount/patterns of missing data for the study measures.	• Acceptability of proposed outcomes (assessed through qualitative interviews) and integrity of outcome data
ASSESSED AT:		
Consent/Screening visit, Baseline [D0], Visit 1 [D28±3], Visit 2 [D56±3] and Visit 3 [D84±3].	(Baseline [D0], Visit 1 [D28±3], Visit 2 [D56±3] and Visit 3 [D84±3])	

[+]*A traffic light system will be used for feasibility outcomes (see section 12.2).*

6.2 Clinical Outcomes

6.2.1 Primary Outcome

The proposed primary outcome is:

- Change in mean daily SABA use from baseline (days -28-0) at days 56 to 84 (see trial flow chart).

Smart inhaler technology* (Propeller Health, USA) will be used to objectively count SABA actuations each day. Baseline data will inform intra- and inter-individual SABA use variability and optimal monitoring duration for the definitive trial. Daily SABA use will be recorded throughout the trial to enable evaluation of change in use and any potential degradation of intervention effect over-time.

**The Propeller sensor attaches to participants' own SABA inhaler and automatically records each inhaler actuation. A range of sensors are available to fit different inhaler devices as necessary. Each participant will be provided with 2 sensors to account for patients often having more than 1 SABA inhaler. Participants will be asked to only use SABA inhalers that have the sensors attached during the study. Participants will be provided with training in use of the sensor and in transferring*

the sensor from one inhaler to another when their SABA runs out. Participants will be reminded to change over sensors (if necessary) during each study visit.

Sensor SABA use data will not be made available to participants or site teams during the course of the trial to prevent this influencing SABA use through biofeedback. However, HHTU and sites will have access to a Clinician Portal (provided by Propeller Services) where they will be able to see enrolled participants, identified by their SIN, for administrative purposes. Syncing of inhaler sensors will be monitored centrally by HHTU, with site teams alerted in the event of apparent failure of data recording for 7 days.

6.2.2 Secondary Outcomes

- COPD Assessment Test (CAT)

The COPD assessment Test (CAT) is an 8-item patient-completed questionnaire that is designed to quantify the impact of COPD on an individual's life. The Minimum Clinically Important Difference (MCID) for CAT is 2 units.

- Breathlessness numerical rating scales: 'worst', 'distress caused by' and 'coping with' breathlessness in the past 24-hours

Numerical rating scales (NRS, scored 0-10) will be used to assess the following aspects of breathlessness over the past 24 hours: best breathlessness / past 24 hours, worst breathlessness / past 24 hours, distress caused by breathlessness / past 24 hours, coping with breathlessness / past 24 hours. The NRS or visual analogue scale (VAS) is recommended as a unidimensional measure of breathlessness in palliative care studies[24]. The NRS is preferable to the 0-100mm VAS[25, 26]. It is highly correlated with VAS scores, but has better test-retest reliability[27], utility and research in pain shows that patients find them easier to use than VAS scales[28].

- Modelled annual SABA inhaler/canister pick-up rate (based on number of actuations at baseline (days -28 -0) and between days 56 and 84)

Annual SABA canister pick-up rate has been reported in large observational studies in asthma and COPD[2, 4]. Mean daily SABA use measured in our trial will be converted to estimated annual SABA canister pick-up rate for the purpose of enabling comparison with previous observational studies. This estimate will be based on the average SABA inhaler containing 200 doses/actuations and therefore 7 actuations per day[29] equates to approximately 12 SABA canisters per year.

- Health-related quality-of-life: EQ-5D-5L and VAS (assessed at days -28, 0 and 84)

The EuroQol 5 dimension 5 level (EQ-5D-5L) is a general measure of health status and is used to calculate quality adjusted life years (QALYs) in health economic analysis. The EQ-5D-5L has two components:

- The EQ-5D descriptive system comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
- EQ-VAS is a vertical visual analogue scale on which patients self-rate their health from the 'best heath you can imagine' to 'the worst health you can imagine'.

- Healthcare-resource-utilisation

Healthcare resource use will be assessed by self-report and by reviewing participant's electronic health record. Specific health service use that will be recorded includes: GP attendance, practice nurse attendance, out-patient appointment attendance (consultant), specialist nurse review (out-patient or home-visit), emergency department attendance (and whether an ambulance was used to get there), hospital admission including intensive care unit admission (number of events and length of stay in days), hospice attendance/admission (and whether an ambulance was used to get there), other community service contact (e.g. physiotherapy, occupational therapy, telehealth service, home oxygen service). Where health care resource utilisation is identified, additional detail will be recorded including nature of contact (face-to-face or virtual) and duration of contact (e.g. length of hospital stay). Health care resource utilisation data will enable evaluation of the feasibility of health economic and environmental impact evaluation in the definitive trial.

- Modelled CO2e (for COPD treatments alone and combined for COPD treatments, study intervention and healthcare-resource-utilisation).

The environmental impact of the intervention will be calculated for both groups based on the Greenhouse gas (GHG) emissions associated with i) participants prescribed inhaled therapies (non-SABA), ii) SABA use and iii) participants health care resource utilisation. As this is a feasibility study, we will focus on assessing the feasibility of collecting this data and calculating associated GHG emissions while providing preliminary data on treatment effect.

The PrescQIPP database will be used to obtain carbon footprint data for all inhaled therapies in order to quantify the GHG emissions related to inhaler use during trial participation.

The carbon footprint of the HHF will be estimated based on typical CO2e per £ for medical devices and we will conduct a sensitivity analysis to assess the impact on the overall data.

The carbon footprint associated with specific health care visit types will be obtained from the Sustainable Healthcare Coalition emissions data.

6.2.3 Health Economic Assessment

The following measures will be collected and presented to allow a preliminary assessment of the intervention on costs and patient outcomes:

- Health service utilisation will be recorded including: GP attendance, practice nurse attendance, out-patient appointment attendance (consultant), specialist nurse review (out-patient or home-visit), emergency department attendance, hospital admission, hospice admission.
- We will collect data on the duration of intervention delivery and members of staff involved and their grade. We will also collect information on other costs associated with intervention delivery in order to assess the impact of introducing the intervention into routine NHS practice.
- Measures: Data required to estimate health-related utility and QALYs in a subsequent trial will be collected using the EQ-5D-5L and EQ-VAS.

Quality adjusted life years (QALY) will not be calculated due to the short time horizon of this trial and exploratory nature of data collection.

6.2.4 Participant Feedback Surveys:

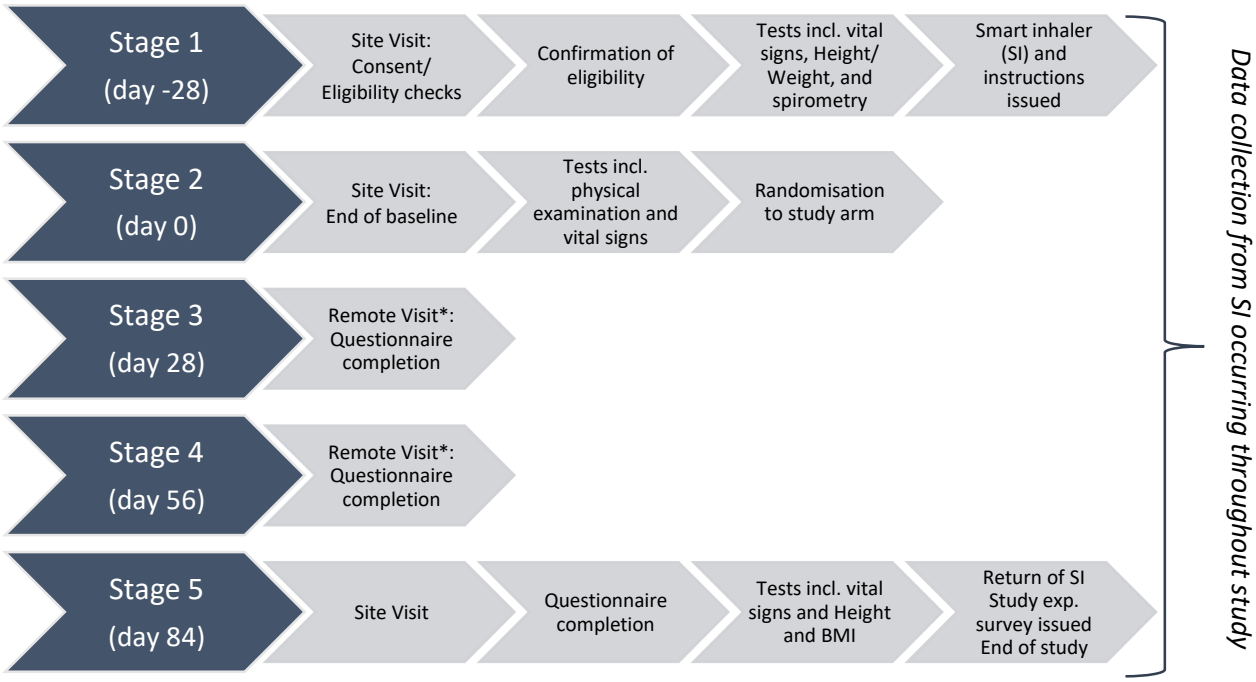
- Invitation experience survey. Reasons why patients agree to participate or decline involvement will be explored using a survey. The survey will be given to patients at the end of the recruitment encounter. Responses will be anonymous and therefore the survey should be completed by participants independently and placed in an envelope which is sealed by the participant prior to being returned to site staff. Sealed envelopes will be collated at the sites and returned in batches to HHTU where they will be opened and data analysed.
- Study experience survey. This will be given to participants during their final visit or posted to participants at study completion or withdrawal; if they have consented to this aspect on the trial consent form. Experience of the study, including reasons for withdrawal if relevant (trial

or intervention) will be explored. A pre-paid postage envelope will be included, addressed to HHTU, for return of the questionnaires.

7. STUDY PROCEDURES

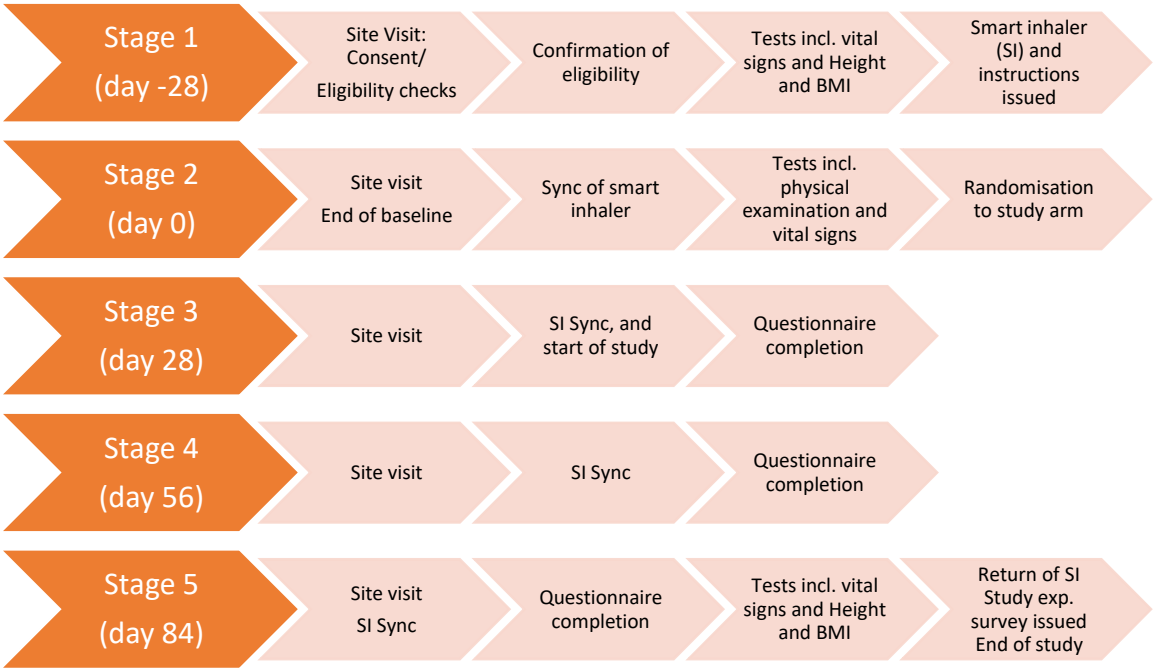
There are 5 or 6 stages to the study (qualitative interview – 6th stage) as presented in Table 1 Schedule of Assessments and Procedures. Detailed descriptions of the assessments are provided in section 7 of this protocol. The 5 stages, with key activities highlighted, are outlined in Figure 2, and Figure 3. These will be provided to participants in the PIS.

Figure 2 Participant flow diagram of study stages 1-5 for participants with mobile app



** A remote visit can be conducted over the telephone or using a video conferencing platform, based on usual practice at the site and informed by participant preference.*

Figure 3 Participant flow diagram of study stages 1-5 for participants not using mobile app



7.1 Stage 1: Participant consent, screening and study enrolment (day -28)

7.1.1 Participant Consent

In order to be screened for the study, participants will need to give informed consent. Only participants identified as eligible after screening (see section 4.3 for details on participant identification) will be enrolled onto the trial.

All participants will be given opportunity (in time and physical capacity) to consider the study and what will be required of them in full and to formulate questions following receipt of the participant information sheet (PIS). Any questions will be addressed and answered fully by a member of the site research team. An actual time period for consideration of participation is not specified, as this will be determined in part by the person's condition and circumstances at the time. However, length of time for consideration will usually exceed 24 hours. In the case that a potential participant wishes to enter the study immediately, the researcher will use their judgement on whether this should be facilitated. All potential participants will be given a Participant Feedback Questionnaire to complete and return.

Participants will also be asked if they consent to be invited to participate in qualitative interviews by the site study team. If consent is obtained and the participant is selected to take part in this element of the study, the participant will be provided with an additional qualitative-specific PIS, and given an opportunity to review the information and ask questions. A time limit will not be

applied to this process. Selected participants that wish to participate will be asked to also sign a separate informed consent form for this part of the study.

All consent forms will be stored in accordance with local requirements. The original signed copy is to be filed in the ISF; one copy of the consent form(s) will be given to the participant, and one copy will be entered into the participant's clinical record. In addition, a copy will be uploaded into the electronic study database provided by HHTU for central monitoring purposes.

The PI has overall responsibility for informed consent of participants at their site and must ensure that anyone delegated responsibility to conduct informed consent is duly authorised, trained, and competent to undertake consent according to the protocol and GCP.

This study will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

7.1.2 Enrolment

All consenting and eligible individuals will be enrolled in the study. Written confirmation of consent, will be uploaded to the study database by a member of the site study team during the enrolment of the participant onto the trial. The items listed below are also required for enrolment on the database:

- Participant details: initials, sex, date of birth
- Name of trial research site and site code
- Person conducting enrolment

Completing this information will generate a pseudonymised Subject Identification Number (SIN), which will be used to identify the participant for the remainder of the study. SINs will be created according to the format FF-XX-XXX, where FF refers to the study (FanFIRST), XX is the site code number, and XX is the sequential study number e.g., FF-01-01 for the first participant enrolled at Site 1, FF-01-02 for the second participant enrolled at Site 1.

7.1.3 Screening for Eligibility

Participants potentially deemed eligible for entry into the study and who have been given information about the study, and have given consent, will undergo eligibility screening.

Information about eligibility will be obtained from discussion with the potential participant and review of the participant's medical record. Eligibility criteria will be recorded in the eCRF, including details of any reason that a potential participant is not eligible

Eligibility criteria will be assessed at day -28 to ensure only eligible participants will proceed with baseline assessments. Where spirometry cannot be completed on day -28 due to availability at site and/or local infection control procedures, participants will proceed with SABA use monitoring with spirometry completed and eligibility confirmed prior to undertaking further baseline assessments at day 0. Consenting participants that fail screening will be replaced.

7.1.4 Consent/Screening Visit

- Participants will be invited to attend their local study site on day -28. Consent and enrolment (subject to non-failure of screening points) will take place as outlined in Table 1. During this visit, participants' inhaler technique will be assessed and training provided as required. Participants will be asked to bring their SABA inhaler(s) with them to the screening visit (included in PIS and during visit booking).
- Consent and Enrolment
- Eligibility assessment against criteria. See Table 4 for day -28 requirements and screen-fail points (SFP)
- The Participants SABA inhaler prescription and their SABA inhaler, brought to the screening visit, will be reviewed in order that the appropriate Propeller Sensor can be issued. If a participant's SABA is prescribed by the generic drug name (e.g. salbutamol pMDI) rather than brand (e.g. Ventolin Evohaler or Salamol pMDI), the participant should be provided with a Study SABA Information Card (SAIC). The study clinician will write the name of the SABA branded device that the patient brought with them to the SAIC. Participants will be instructed to show the SAIC to the pharmacist when they collect any new SABA prescriptions and thus ensure that they are issued with the same SABA for the duration of the study. This will enable the easy transfer of the provided Propeller Sensor(s) to any replacement inhalers.
- Provision of and training in the use of the Propeller Sensors for SABA monitoring.

Table 4 Day -28 processes and SFPs

Medical History[†]	Questionnaires	Medical tests/Equipment provision
SFP1: If FEV-1/FVC ratio >0.7 on screening spirometry. Check and record results of last recorded historical Spirometry for all participants **SFP2:** If pulmonary rehabilitation is planned to occur during study participation, are they happy to wait to receive post-study? **SFP3**: Is significant cardiorespiratory disease, other than COPD, considered the primary cause of their breathlessness/high SABA use? **SFP4:** Has a COPD exacerbation requiring oral corticosteroids and/or antibiotics and/or hospitalisation occurred within 4-weeks before recruitment (taken from last day of exacerbation treatment). Record number of COPD exacerbations for the last 12 months, including dates, treatments received, and whether ED attendance and/or hospitalisation occurred **SFP5a:** Does participant self-report <daily SABA use? **SFP5b:**Have they had <12 SABA inhalers/canisters prescribed within the past year. Record Name, dose and number of prescriptions within the past 12-months for all	• mMRC. **SFP8:** Score <2 • Breathlessness Numerical Rating Scale (NRS) • COPD Assessment Test (CAT) • EQ-5D-5L Quality of life questionnaire • Patient Feedback Questionnaire*	Vital signs: (Body Temperature, Pulse Rate, Respiration Rate, Blood Pressure) Height, weight and BMI Start SABA-use monitoring: Participants will be provided with the Propeller sensors to apply to their prescribed SABA inhalers. Training on their usage will be provided onsite, with written instructions to also be provided. Participants who will not be using the app will have their sensor synced onsite through a site specific app. Provide a 'Study SABA Information Card'(SAIC) if the participant's

Medical History†	Questionnaires	Medical tests/Equipment provision
inhaled medications. Note the current SABA prescription and confirm that it is a pressurised metered dose inhaler (pMDI). **SFP6:** Have they been receiving optimal guideline recommended inhaled treatment for COPD^? Smoking status. **SFP7**: <10 pack per year smoking history (see questionnaire section for **SFP8)**. History of HHF use: Question 1: 'Have you used the HHF in the past month – Yes/No. If 'Yes' is ticked, follow up question 'How often 1) Every day, 2) Most days, 3) Occasionally or rarely Record of Health Care Resource Use in the past 4-weeks. See section 7.4.3 for details of this		SABA is prescribed using the generic drug name rather than by brand.

^Optimal treatment is defined as a minimum of dual-acting bronchodilator therapy (long-acting beta-agonist and long-acting muscarinic antagonist) with or without an inhaled corticosteroid.

†In addition, to the information collected in Table 4, the following demographic information will be collected: age, gender, ethnicity, socioeconomic status [obtained from postcode], educational attainment

**All individuals undergoing screening will be asked to complete a voluntary, anonymous survey 'Invitation Experience Survey' whether they consent to take part in the study or not. If people agree to complete the questionnaire this will be taken as implied consent for the information they provide in the survey to be used for the purposes of this study. Participants will complete the survey independently and will be asked to place it in a sealed, pre-paid envelope that will be sent to the HHTU, so that it is not viewed by site staff.*

7.2 Stage 2: Baseline data collection incl. physical examination and vital signs – Day 0

7.2.1 Baseline Visit (Day 0)

All eligible participants from day -28 will be invited to attend the study site for this visit to undergo the following baseline assessments:

- Spirometry and eligibility confirmation (if not completed during day -28 visit, **SFP1**)
- Vital sign measurement
- Physical examination (general, cardiac and respiratory examinations)
- Safety/Adverse Event (AE) monitoring
- Breathlessness NRSs
- CAT Score
- EQ5D-5L
- Healthcare Resource Utilisation
- Evaluation of usual care received since the last visit
- SABA use: baseline-data download and sync from inhaler sensors, for those without the app

7.2.2 Randomisation

Randomisation will be at the individual level using a specially designed randomisation programme based on site and their self-reported prior hand-held fan use, to receive the FanFIRST intervention . Participants will be randomised in a 1:1 ratio using random permuted blocks to study arm (i) the FanFIRST intervention, or study arm (ii) usual care, stratified by site and self-reported HHF-use within the past month. The randomisation sequence will be prepared by an independent HHTU statistician and a bespoke randomisation system built within the commercial web-based system by HHTU. All trial staff and sites will remain blinded to the sequence. Prior to recruitment starting, a test system will be made available to the research team for training purposes. Any user comments or suggestions on the usability of the system will be fed back to the HHTU before the system is made live.

Randomisation will occur after informed consent has been obtained, eligibility has been established, and baseline measures have been collected from patients. The allocation schedule will be concealed to research staff, with the study arm only confirmed once eligibility is confirmed by researchers. Site staff will access the online randomisation system and enter the required

patient details with allocation results returned immediately. The research nurse will inform patients and services of allocation to treatment.

7.3 Stages 3 and 4: Questionnaire completion – Days 28 (±3 days) and 56 (±3 days)

7.3.3 Study Visits 1 and 2 (Days 28 (±3 days) and 56 (±3 days))

Participants will either

i) attend their local study sites - if not using the propeller app to sync inhaler use data; or

ii) undertake a remote (telephone or video call) visit - if using the propeller app to sync inhaler use data, for the procedures detailed below

- Safety/AE monitoring
- Evaluation of usual care received since the last visit
  - Healthcare Resource Utilisation
- Breathlessness NRSs
- CAT Score
- Questions on HHF usage to ascertain fidelity of intervention arm
- SABA use data upload from inhaler sensors for participants not using app and visiting the site on these days.

7.4 Stage 5: Final measurements incl. vital signs and height and weight - Day 84 (±3 days)

7.4.1 Study Visit 3 (Day 84 ±3 days)

All participants are required to attend the study site for this visit.

Participants will undergo the following assessments:

- Vital sign measurement
- Height and Weight Measurement
- Safety/Adverse Event (AE) monitoring
- Breathlessness NRSs
- CAT Score
- EQ5D-5L
- Evaluation of usual care received since the last visit
  - Healthcare Resource Utilisation
- Questions on HHF usage to ascertain fidelity of intervention arm
- Questions on HHF usage to ascertain new HHF-use in the usual care arm

- SABA use data upload from inhaler sensors

At the end of the final visit, participants will return their inhaler sensors, which will be retained at the site until the end of the trial. A study experience survey will be issued to the participant for immediate completion. Participants will place the completed survey into a pre-paid envelope, which the site will post back to the HHTU.

After completion of all study assessments, participants that were randomised to receive usual care will be offered the FanFIRST intervention.

7.4.2 Questionnaires

The following questionnaires will be administered at baseline and during each study visit:

- Numerical Rating Scales (NRS) ranging from 0-10
    - NRS will be used to evaluate the following aspects of breathlessness:
        - Best breathlessness in the last 24 hours
        - Worst breathlessness in the last 24 hours
        - Distress caused by breathlessness in the last 24 hours
        - Ability to cope with breathlessness in the last 24 hours
- COPD Assessment Test Score

The COPD assessment Test (CAT) is an 8-item patient-completed questionnaire that is designed to quantify the impact of COPD on an individual's life. The MCID for CAT score is 2 units.

- Modified Medical Research Council Breathlessness Scale

The modified Medical Research Council breathlessness scale (mMRC) is a patient-completed five-level numerical rating scale that measures an individual's perceived breathlessness. mMRC has been demonstrated to be a simple and valid tool in COPD to assess disability and reflects health-related quality of life.

- EQ-5D-5L and EQ VAS
    - This is a well validated generic quality of life questionnaire.

- Participant fidelity to intervention

7.4.3 Fidelity check questions for all participants on use of SABA inhaler(s)

These questions will be asked to all participants, regardless of study arm, from day 0

1. Did you use another SABA inhaler without the sensor at any stage? Y/N
    a. If Y, provide details at which stage this occurred, and over how many hours/days inhaler use was not recorded for. If more than one event, please detail each event
2. Did you forget to transfer the sensor to another SABA inhaler at any stage? Y/N
    a. If Y, provide details at which stage this occurred, and over how many hours/days inhaler use was not recorded for. If more than one event, please detail each event
3. During the last 28 days, on average, how many times per day do you think you have used your SABA inhaler?

7.4.4 Health Care Resource Utilisation

Healthcare resource use will be assessed by self-report and by reviewing participants electronic health record and recorded in the eCRF. Specific health service use that will be recorded includes: GP attendance, practice nurse attendance, out-patient appointment attendance (consultant), specialist nurse review (out-patient or home-visit), emergency department attendance, hospital admission, hospice attendance/admission, other community service contact (e.g. physiotherapy, occupational therapy, telehealth service, home oxygen service). Where health care resource utilisation is identified, additional detail will be recorded including nature of contact (face-to-face or virtual) and duration of contact (e.g. length of hospital stay including anytime in a critical care setting [e.g. Respiratory high dependency unit, general high dependency unit or intensive care unit]). Health care resource utilisation data will enable evaluation of the feasibility of health economic evaluation in the definitive trial and evaluation of the environmental impact of the intervention.

7.4.5 Allowable Therapies

Usual care will be provided throughout the study to all participants. Participants will be asked to report details of usual care received and this will be recorded in the eCRF during study visits. Usual care includes any intervention that would ordinarily be offered within the trial setting. The only exceptions to this are pulmonary rehabilitation and/or specialist breathlessness clinic attendance as these interventions have potential to impact outcome assessment. Pulmonary rehabilitation

referral will be offered to participants following completion of the trial where it is felt appropriate to do so by the site clinicians.

Usual care includes, but is not limited to, any of the following if considered appropriate by the patient's clinician: outpatient clinic attendance; review and support by the specialist nursing team and/or primary care provider; inhaled, nebulised and/or oral treatments for COPD in accordance with national guidance; and home oxygen therapy. Pharmacological or other non-pharmacological breathlessness treatments (e.g. opioids or hand held fan) will not be restricted if considered appropriate by the patient's clinician but use will be documented during study visits.

8. QUALITATIVE STUDY (FEASIBILITY AND IMPLEMENTATION EVALUATION)

Aligned with the revised MRC Complex Interventions Framework, we will use a theory-based approach to explore how mechanisms and context interact and therefore how change is brought about in relation to the intervention.

8.1 Aims

By exploring differences in the acceptability of trial processes and how the intervention is implemented at each centre, we shall identify:

1. Key feasibility issues for the design and delivery of a future trial.
2. Factors that would impact NHS implementation at-scale, if the intervention is in future found to be effective.

8.2 Methods

8.2.1 Design and methods

We shall investigate these feasibility and implementation issues using semi-structured interviews with a purposive sample of patients, clinicians and service managers at each of the four centres. The six key uncertainties are:

1) Willingness of patients to be randomised (and the reasons why/why not).
2) Willingness of clinicians to randomise patients (and the reasons why/why not).
3) Acceptability of outcome measures, including environmental outcomes that are not directly-related to an individual's health.

4) Acceptability of the FanFIRST intervention (to both patients and clinicians) and reasons for variation in intervention fidelity and delivery, in particular how patients' relationship to SABA (as part of their overall COPD management) affects this.
5) Feasibility of delivering the FanFIRST intervention during a standard clinical consultation and the feasibility and acceptability of fan provision/purchase by sites (to inform the definitive trial) and NHS services (to inform scaled implementation).
6) Whether willingness or acceptability on any of the above factors differs by ethnic group.

8.2.2 Qualitative study population

Two different groups of participants will be invited to take part in semi-structured interviews of maximum 60 minutes duration as below:

Group 1: Adult COPD patients (n=5) who completed, withdrew, or did not start the main RCT, and, optionally, their nominated carer(s)

Group 2: Clinicians (n=3), and service managers (n=2) who were involved in the main RCT. In total 40 participants will be invited across the two groups, and from across the four study sites.

A sampling grid will be constructed to enable a purposive sample inclusive of profession, gender, and ethnicity, and those who did not start, withdrew, or completed.

8.2.3 Identification and informed consent of patient and carer participants (Group 1)

Study site staff will provide patient participants at Day -28 with a qualitative study-specific participant information sheet and informed consent form for them to take away with them. This will allow participants the opportunity (in time and physical capacity) to consider the study, formulate questions and have these answered. At Day 0, after having completed baseline measures, patient participants will be asked if they would like to participate in an interview (if selected) to explore their experiences and views. Informed consent will be taken from all participants expressing a wish to be considered for an interview. The consent form will include an option for patient participants to nominate a carer, who is a relative or friend, to also participate in the interview. Nominated carers will also be provided with an information sheet, and consented-in if the person they care for is later invited to an interview.

Consent will be taken face-to-face with a researcher. Patient participants selected to take part in an interview will be contacted by a member of the site study team in order to arrange a mutually convenient time to have the interview with the researcher based at the University of Hull. Prior to

conducting the interview, the qualitative researcher will verbally reconfirm their consent with them.

8.2.4 Identification and informed consent of health care practitioners (Group 2)

Healthcare practitioners who have been involved with the implementation of the intervention will be identified by the central study team. Those that express an interest in taking part will be provided with a PIS and consent form. All participants will be given opportunity (in time and physical capacity) to consider the study and formulate questions. Potential participants will be given the opportunity to have any questions addressed and answered fully by a member of the research team. An actual time period is not specified but this will usually exceed 24 hours between receipt of the PIS and providing consent. Consent for the healthcare practitioner group will be taken either face-to-face with a researcher at the study site, or online using DocuSign.

**DocuSign is a product of DocuSign Inc., a San Francisco based company. DocuSign enables signatures to be captured on a number of electronic devices. Once signed, everyone receives a copy of the document that they can access at any time. Changes cannot be made to the document once fully executed.*

8.2.5 Booking of interviews

After a participant has been identified using the sampling grid (for patient participants) or through their involvement with the study for Group 2 participants, the site team will arrange the qualitative interview using an electronic study specific booking system within a restricted access Microsoft Outlook calendar held at HHTU. Access to the booking system will be restricted to the central study team and authorised research staff at the respective study sites. An interview time-slot will be chosen at a time convenient to the participant and qualitative researcher. Site staff will select a time-slot in the booking system and enter only the unique Subject Identification Number (SIN) ensuring that no patient identifiers are recorded. As no personally identifiable data will be entered into the booking calendar, it will be possible to use a central calendar which will cover all the study sites. In order for the qualitative researcher to be able to contact the participant, site staff will enter the participant identifiers (patient name and telephone number) into the REDCap Cloud eCRF database at the time of the participant agreeing to participate in the qualitative study. If it is not possible to book an interview at the time of the first telephone call, the participant can either arrange the interview at a later date by contacting the University of Hull researcher directly, or agree to be contacted by the UoH researcher directly. Only the SIN is to be held outside of the REDCap eCRF database.

8.2.6 Conduct of interviews

The qualitative researcher based at the University of Hull will make contact at a time agreed with the participant to conduct the interview. Both participant groups will be offered the opportunity to have the interview conducted either on the phone or using a video-conferencing platform e.g., Microsoft Teams, or Zoom. For both participant groups, the qualitative researcher will verbally re-confirm consent with the participant at the start of the interview.

The interviews will follow a group-specific topic guide and last approximately 30-60 minutes. Interviews will be recorded on an encrypted Dictaphone and audio files uploaded to a secure HHTU Box folder. Interviews will be transcribed verbatim by a University of Hull (UoH) approved transcription company e.g., one that has confidentiality agreements in place with UoH. Audio-recorded data will be destroyed once transcription and the allocation of unique identifiers have been assigned.

Interviews will be conducted using an interview guide structured using the Theoretical Framework of Acceptability (TFA)[30]. This theory, developed following a systematic review and consensus group exercise, breaks down the 'acceptability' of delivering or receiving a healthcare intervention into seven component constructs for investigation as listed below:

1	**Affective attitude**	How an individual feels about the intervention
2	**Burden**	The perceived amount of effort that is required to participate in an intervention
3	**Ethicality**	The extent to which an intervention fits with an individual's value system
4	**Intervention coherence**	The extent to which an individual understands an intervention and how it works
5	**Opportunity costs**	The extent to which benefits, profits or values must be given up to engage in an intervention
6	**Perceived effectiveness**	The extent to which an intervention is perceived as likely to achieve its purpose
7	**Self-efficacy**	The extent to which a person is confident that they can perform the behaviour(s) required to participate in an intervention

The TFA can be applied prospectively, concurrently, or retrospectively, and therefore has sufficient flexibility for use in a process evaluation.

8.2.7 Participant Withdrawal

Participants have the right to withdraw from the study at any time. The investigator(s) or sponsor may withdraw participants from the study only if indicated by a safety/clinical issue that may prevent them taking part in an interview. Participants that choose to withdraw from the study will be reminded that data collected up to that point will be used in the data analysis but that it will be anonymous and will not identify them in anyway. Participants will have consented to this in the ICF following reading the PIS. If participants continue to express concern about having their data used it may be excluded from data analysis wherever possible unless it is deemed to have a significant negative impact on the scientific value of the study findings. All participant study documentation will be kept for monitoring and inspection purposes until the study documentation archiving period has ended in line with regulatory body guidelines.

8.3 Patient safety and wellbeing during qualitative interviews

There is potential that some participants may feel upset during the interview as a result of talking about their life circumstances and the effect COPD and its treatment has on them. However, this is not more than would be expected in any clinical encounter. Participants will be listened to sensitively, allowed breaks or to withdraw from the interview, if they wish. It will not be the Qualitative Researcher's role to offer any counselling to participants, but if their distress persists, with their permission, the Qualitative Researcher would pass their concerns on to their usual care team or recommend that the participant contacts their usual care team or GP for a review. Participants may find some benefit from taking part in an interview as they will be given time to speak about their situation, an opportunity that some may find helpful.

8.4 Qualitative Data Analysis

Interview transcripts will be pseudo-anonymised, and transcripts will be imported into NVivo, a qualitative data management software. The analysis of the qualitative interview data will be conducted using a matrix-based approach to qualitative data analysis. The TFA constructs will be used as a thematic framework for initial deductive coding and exploration of data, followed by inductive coding and development of themes where appropriate (including existing concepts such as 'safety objects' that are relevant to the hand-held fan). The analytic process will progress from classification of data to synthesis of themes that explain acceptability in relation to the seven

constructs of the TFA, and which can be mapped back to each of the seven key uncertainties as outlined in section 8.2.6.

9. SAFETY ASSESSMENTS/ADVERSE EVENTS

The adverse event (AE) reporting period for this trial begins at screening and ends at the participant's final study visit. Each trial participant will be questioned about adverse events at each visit. The investigator will record all directly observed AEs and all AEs spontaneously reported by the trial participant. A pre-existing condition (i.e. a disorder present before the AE reporting period started, and noted on the pre-study medical notes), is not to be reported as an AE unless the condition worsens or episodes increase in frequency during the AE-reporting period. All AEs (serious and non-serious) will be recorded in patients' data collection forms (eCRFs) using the AE report form. All adverse events will be recorded in patients' medical records, and followed-up until the event has resolved, or a decision has been taken to discontinue follow-up.

9.1 Definitions

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

Serious adverse event (SAE):

In research other than CTIMPs, a *serious adverse event* (SAE) is defined as an untoward occurrence that:

a) results in death;
b) is life-threatening;
c) requires hospitalisation or prolongation of existing hospitalisation;
d) results in persistent or significant disability or incapacity;
e) consists of a congenital anomaly or birth defect; or
f) is otherwise considered medically significant by the investigator.

9.2 Relationship to the Study Intervention

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

- unrelated e.g., where the event is definitely not; or unlikely to be; related to the intervention or a research procedure, ***OR***
- related e.g., where the event is likely to be related to the intervention.

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

9.3 Serious Adverse Events

The investigator is required to determine if each adverse event is an SAE, as defined in section 9.1. Any SAE that is related to the study and unexpected must be reported to the Sponsor within 24 hours of research staff knowledge of the SAE. For SAE's, the following information will be collected:

- Full details in medical terms and case description
- Event duration
- Action taken
- Outcome
- Seriousness criteria
- Causality i.e., if event is related or unrelated to the intervention

Hospital admissions are common in this patient group due to their underlying disease. Thus, admissions related to their COPD, or co-morbidities, will be classified as an expected SAE. In expected SAE cases, the report will not have to be submitted within the timeframe of 24 hours as is expected in related or unexpected SAEs, but can be submitted for CI review within 14 calendar days.

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

9.4 Expected Serious Adverse Events

Due to the seriousness of the disease in this study, the expected SAEs detailed below will not require reporting within 24hrs on the initial and follow-up SAE forms, but will still need to be reported on the trial's AE report form.

Expected serious adverse events in this study include:

- hospital admission due to COPD exacerbation
- admission to hospital or prolongation of existing hospitalisation for a pre-existing condition; and
- elective surgery.

All serious events that do not require reporting within 24hrs will still require reporting within 14 days of the researcher becoming aware of the event.

10. DATA HANDLING AND QUALITY ASSURANCE

10.1 Data Collection, Database, Data Handling and Quality Assurance

HHTU will develop the study database and data processes in accordance with HHTU SOPs. HHTU data systems are within scope of the HHTU NHS Data Security and Protection Toolkit (Organisation Code - EE133824-HHTU). An electronic case report form (eCRF) will be used for data capture. The eCRF will be developed by HHTU under their licence for a commercially available system (REDCap Cloud). Granular role-based permissions will ensure site staff can enter and view the information required for their own site only. Site staff will receive training from the central study team and enter data onto the eCRFs in accordance with the eCRF Completion Instructions.

RedCap Cloud (RCC) is a cloud-based EDC system provided by nPhase. Data is stored on dedicated RCC hardware in EU datacentres (including real-time backup) managed by Amazon Web Services to industry standards outlined in ISO 27001, PCI DSS, SOC 1 - 3, FISMA, CIS, CSA, NIST and UK Cloud Security Principles. Data is encrypted at rest and in transit. RCC themselves deliver compliance to HIPAA, CFR Part 11, and EMEA Annex 11. The University of Hull's contract with nPhase establishes them as a data processor and under GDPR they act solely on the instruction of the University of Hull.

Access to personal data for this specific project will be limited to named individuals at participating sites or the research team at The University of Hull. HHTU data systems have a full audit trail which cannot be edited by HHTU staff.

Participants will be informed that their personal data will be entered into the cloud-based EDC. Study data will be pseudo anonymised and related forms and questionnaires will be identified using a Subject Identification number only (SIN). Participant names and contact details will be held in a restricted eCRF within the same system, to enable the central researcher to undertake phone interviews. All hard copy data will be stored at study sites in a locked filing cabinet in accordance with data protection requirements for the retention of research data and local site data management policies.

10.2 Propeller-specific data collection

The services provided by Propeller Health Services will be outlined both in a service level agreement (SLA) and incorporated data processing agreement (DPA), and underpinned by a data protection impact assessment (DPIA). There will be a requirement for each of the following parties to sign terms of use: i) a suitable representative from each study site, ii) a suitable representative from the University of Hull. There is no need for patient participants enrolled into the study to sign Propeller Health Services 'Eligible User Agreement' due to the slimmed down version of the app they will receive, while some participants will not use an app. Consequently, where these would normally form part of the collaboration agreement, they have been removed.

The data collected through the use of Propeller sensors will be pseudo anonymised, with participants entered using their SIN only. SABA usage data collected from participants smart inhalers are stored on a web server in Dublin, Ireland**.** As the study is non-interventional i.e., participants will not be able to see their usage and change their behaviour as a result of feedback, study sites will be blinded to the data collected from the sensors. However, each site will have access to a Clinician Portal (as provided by Propeller Services) with which they will be able to see enrolled study participants. While sites are blinded to the minute sensor usage data, they will be alerted by HHTU if participants who are using the Propeller app to sync have not synced their sensor in 7 days. This exception will be enabled in order that sites can check with participants if there is a problem. For example, participants may have forgotten to transfer the sensor over when starting a new inhaler, or, for whatever reason, may not be complying with the study procedures.

For participants that are not using the mobile application, the sites will sync the participant's sensor(s) with the Clinician Portal mobile app at each of the five visits. The full usage data from across participating study sites will be provided by a separate web login by Propeller to the central study team at University of Hull via a web portal. A nominated person will be able to see all of the usage data for all participants at all sites, but will not be able to alter data. This facility will be provided as a double-measure to identify any potential issues with fidelity to protocol and in order that issues can be raised directly with the respective site.

Responsibility of study site: Each respective study site may be requested by Propeller Health (sensor supplier), to engage in a two-way consultation. The consultation may be requested and conducted either during the study, or upon termination of the agreement with the UoH and Propeller Health. These consultations will be specifically undertaken for Propeller to learn more about the use and effectiveness of deploying the sensor(s) to participants as a component of the FanFIRST Study. Study sites should not unreasonably deny partaking in such a request.

11.STATISTICAL METHODS

The trial, including the flow of individual participants through each stage, will be reported in accordance with the CONSORT 2010 statement extension to pilot and feasibility trials[31].

For the primary outcomes, the feasibility criteria will be recruitment rate, eligibility to consent ratio, retention rate, data quality and integrity, acceptability of the proposed outcomes and intervention fidelity. The recruitment rate, consisting of the eligibility and consent rate will be calculated with 95 % confidence intervals (CI). Feasibility outcomes will be presented in a table with reference to performance against traffic light / stop-go criteria. A table showing baseline demographic and clinical characteristics for each group will be presented to indicate any between group differences. Patient characteristics will be summarised using appropriate statistics. Medians (IQR) will be reported for ordinal data, mean (standard deviation) for continuous data and raw count (number (%) will be reported for nominal data.

For patient clinical outcome data, descriptive statistics: mean (standard deviation) for continuous outcomes, medians (IQR) for ordinal data and raw count (%) for categorical outcomes, will be reported. This will be presented for each group at each time point: day -28, baseline (day 0), day 28, day 56, and day 84. Due to the nature of this feasibility study, no formal statistical tests will be undertaken. The effect sizes will be calculated with 95% CIs at each time point to compare groups.

GHG emissions will be calculated for both groups using health care resource utilisation and inhaler prescribing (non-SABA inhaled therapy) and use (SABA therapy) data between days 0 and 84. Change in GHG emissions associated with inhaled therapies between baseline and days 56-84 will be calculated with 95%CI for each group.

Safety data will be summarised using descriptive statistics.

11.1 Economic Assessment

We will present health-related resource use data and Health Related Quality of Life (EQ5D5L) for treatment and control groups. Within the funding envelope available we will not conduct a full cost-effectiveness analysis using probabilistic sensitivity analysis. Therefore, assessment of the value of conducting further research (using Value of Information techniques) will not be possible. Instead, we will consider the results of the feasibility work and the potential impact on costs and the effects on well-being and health related quality of life, that might result from a larger trial.

11.2 Mixed Methods Synthesis

Quantitative and qualitative data will be synthesised to address questions regarding optimal trial delivery, and most relevant primary outcome for a subsequent phase-3 RCT.

This mixed methods study uses an embedded design, collecting data concurrently, analysing data separately, and then bringing together the two data sources to explain the results. Therefore, the quantitative and qualitative data will be analysed separately using appropriate methods to provide descriptive statistics for the quantitative data and a thematic analysis of the qualitative data. The analysis will involve looking across the quantitative results and qualitative findings to make inferences from the data. Data will be tabulated to present side-by-side comparisons to determine how the qualitative data can augment or explain the quantitative data. The quantitative data provides a more generalised understanding of the problem (e.g. what proportion of eligible patients were consented) and the qualitative data can provide a more nuanced explanation of these findings. For example, if the trial identifies a low eligibility to consent ratio, the patient questionnaire data and extracts from the qualitative interviews will be presented alongside the quantitative data to enable convergent and discrepant findings to be identified and discussed by the research team. These findings will be discussed in light of the red/amber/green criteria and will inform decisions about the definitive trial. This may result in the redesign of study information or procedures, advice about presenting the trial, or discussions about participant eligibility.

Issues related to trial design and conduct that may be responsible for poor recruitment will be discussed with the research team to inform recruitment for the definitive trial. This may include redesign of study information, advice about presenting the study, or discussions about equipoise.

Table 5 Study endpoints and outcomes

	Eligibility levels	**Eligibility: consent ratio**	**Recruitment rate**	**Retention rate**	**Completion of study tests**	**Completion of questionnaires**	**Acceptability of intervention and outcomes**	**Fidelity of intervention (adherence, delivery, uptake)**
Quantitative Data	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
Qualitative Data (interviews & questionnaire)	*yes via screening log*	*Yes – recruitment questionnaire & interview*	*No*	*Yes, drop out questionnaire and interview*	*Yes – ask patients about acceptability of inhaler use monitoring*	*patient acceptability & views about relevance of questionnaires*	*Acceptability of fan use and written information. Acceptability of SABA use monitoring and environmental outcomes.*	*patient perspective & observations of staff*

12.TRIAL MANAGEMENT

12.1 Trial Oversight

Hull University Teaching Hospitals NHS Trust will act as sponsor for the trial. HHTU will support overall trial management, site contracting and set-up, provide data management and randomisation systems, and support data analysis. Two oversight committees will be convened for trial management and supervision: a Trial Management Group (TMG) and a Trial Steering Committee (TSC).

Research management will be the responsibility of M Crooks as CI with TMG support. Day-to-day management of the trial will be overseen by the CI with support from a HHTU clinical trial manager. Trial management at sites will be delegated to site PIs with oversight from the CI. MC, CH, AW, and MP will be responsible for data analysis. An authorship group will be convened to oversee dissemination activities.

The TMG will meet monthly during trial setup (months 1-4), every 3 months during trial recruitment/participation (months 4-20), and monthly during evaluation and dissemination activities. Additional meetings will be organised as required. The TMG will consist of the CI (MC), site principle investigators (PIs), named co-applicants, and two experienced PPI representatives. TMG meetings will be virtual with support provided to PPI representatives to facilitate attendance. These committees will function in accordance with HHTU standard operating procedures/NIHR terms of reference.

The TSC will provide overall supervision for the trial, particularly in relation to the progress of the trial, adherence to the protocol, participant safety, and the consideration of any new relevant information. The TSC provides advice through its independent Chair, and is responsible for making executive decisions about the continuation of the trial. In addition to the independent Chair, the TSC will include an independent statistician, as well as other independent expert members with clinical or other expertise relevant to the project. The TSC will also include two experienced PPI members; different to those that will sit on the TMG. The CI will take the role of a non-voting member. In addition, observers from the TMG (e.g. trial manager, trial statistician), Funder and Sponsor can be invited to attend TSC meetings at the discretion of the Chair.

12.2 Success Criteria

Operational Criteria

Progress will be assessed against set milestones and monitored by the TMG. Failure to meet milestones will be addressed by MC and contingency planning agreed with the TMG.

Feasibility Criteria

A traffic light system will be used. 'Red' suggests the definitive trial is unfeasible without major protocol modification, 'amber' means minor modification needed and 'green' means no modification required. The following targets will be applied:

12.3 Box. 1 Feasibility Outcomes: Traffic Light Criteria

RECRUITMENT	**Target**
Eligibility to consent ratio	Red >9:1 Amber 9:1 – 6:1 Green <6:1
Recruitment Rate *Only overall recruitment will be considered red. Site recruitment below green criteria will be considered amber and inform site selection for the definitive trial.	Red* < Avg 5 per month Amber Avg 5 - 6.5 per month (Site: <1.5 per month) Green ≥ Avg 6.5 per month (Site: ≥1.5 per month)
Retention	Red <60% Amber 60-75% Green >75%
DATA QUALITY AND INTEGRITY	
SABA Inhaler Use Data	Red <80% Amber 80-90% Green ≥90%
Questionnaire Completion	Red <80% Amber 80-90%

	Green ≥90%
OUTCOMES	
Acceptability of proposed outcomes	Acceptability of the proposed outcomes will be assessed through qualitative interviews, completion of study experience surveys and through recruitment and retention.
INTERVENTION	
Fidelity	Red <80% Amber 80-90% Green ≥90%

13. PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

13.1 Ethics

The protocol, patient information leaflet (PIL), informed consent form (ICF) and appropriate related documents must be reviewed and approved by a REC. Any protocol amendment and/or revision to the PIL or ICF will be resubmitted to the REC for review and approval (except for changes involving only logistical or administrative aspects of the study).

A signed letter of study approval from the REC Chairman must be sent to the Principal Investigator with a copy to the Sponsor prior to study start. If the REC decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the REC to the Sponsor.

Before any site can enrol patients into the trial, NHS HRA permission will be agreed and a Capacity and Capability assessment with site Research & Development (R&D) departments will be completed. For any amendment that will potentially affect sites NHS permissions, the CI/PI or designee will confirm with that site R&D department that NHS permission is ongoing (note that both substantial amendments and amendments considered to be non-substantial for the purposes of REC may still need to be notified to NHS R&D).

Study progress is to be reported to RECs annually (or as required) by the Investigator(s) or Sponsor, depending on local regulatory obligations. If the Investigator(s) is required to report to the REC, he/she will forward a copy to the Sponsor at the time of each periodic report. The Investigator(s)

or the Sponsor will submit, depending on local regulations, periodic reports and inform the REC of any reportable AEs as per ICH guidelines and local REC standards of practice. Upon completion of the study, the Investigator(s) will provide the REC with a brief report of the outcome of the study, if required.

13.2 Patient participant benefits

Patients selected at random to be in the intervention group will be able to start the breathlessness treatment straightaway, which is not currently available as part of usual care. Those not randomised to receive the FanFIRST intervention straightaway will be able to start after all other aspects of their participation have concluded.

By participating in this study, patient participants will be helping us to design a full trial of the FanFIRST intervention for treatment of breathlessness in COPD patients. This has the potential to benefit others with COPD in the future.

Patient participants, that are selected to take part in the qualitative interview, may find some benefit from taking part in an interview as they will be given time to speak about their situation, an opportunity that some may find helpful.

13.3 Identified patient participant burden

We do not anticipate that patients will experience any significant disadvantages from taking part in this study. However, they will be made aware through the PIS and ICF as well as through discussion with the study team that the study will involve commitment in terms of time and travel. These are discussed in more detail below.

Time

Participants will be required to make between 3 to 6 visits to their identified study site. These visits will vary in amount of time taken to complete, but the first two visits will last approximately 1-2 hours with subsequent visits taking less than 1-hour. For those invited to participate in a telephone or video interview, this will require up to an additional hour of their time. This will be clearly laid out in the PIS and ICF so that participants can carefully consider the commitment that will be required of them.

Travel

Patient participants will be expected to arrange their own transport for attending the study site visits. To help reduce the burden of this, participants will be reimbursed. The amount of money that they will receive will depend on how far away from the site that they live. Each study site will be responsible for informing participants how they can claim back incurred travel expenses. Patient participant claims will be processed in accordance with the respective study sites local administration procedures. Should participants be happy to receive travel reimbursements via a ClinCard, they will need to tick the optional consent box on the Informed Consent Form (ICF); thereby agreeing to the processing of limited personal data by Greenphire. See section 13.7 for further details on this. In order to be as inclusive as possible we may consider offering the reimbursement of taxis for those that cannot easily travel in to their study site using public transport. This is something that will be considered on a case by case basis rather than offering a blanket approach.

13.4 Participant Information and Informed Consent

As part of the informed consent process, the Investigator(s) must explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each participant must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating clinician.

This informed consent should be confirmed by the signing of the REC approved consent form by the participant. The participant should understand the information in the patient information leaflet and the statements on the consent form before signing and dating it. The participant will be given a copy of the signed form. The participant will be asked to sign the consent form prior to any study-specific procedures being performed.

The form must be signed and dated by an appropriately trained member of the research team after the participant. The original signed ICF for each participant will be kept in the Investigator Site File.

The participant should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information should be documented.

13.3 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.

Any substantial change to the protocol requires a written protocol amendment that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of participants or the scientific quality of the study require additional approval by the REC and HRA. These requirements should in no way prevent any immediate action from being taken by the Investigator(s), or by the Sponsor, in the interest of preserving the safety of all participants included in the study. If an immediate change to the protocol is felt by the Investigator(s) to be necessary for safety reasons, the Sponsor must be notified promptly and the REC must be informed as soon as possible.

Changes affecting only administrative aspects of the study are known as non-substantial amendments and only require HRA notification.

The Investigator(s) will conduct the study in strict accordance with the protocol.

13.4 Monitoring Procedures

The HHTU trial team will oversee trial monitoring activities, ensuring the trial is conducted in accordance with agreed SOPs (HHTU or Sponsor), to ensure compliance with the International Conference on Harmonisation of Good Clinical Practice (ICH GCP guidelines), as applicable under the UK Clinical Trials Regulations and the UK Policy Framework for Health and Social Care Research. All trial related documents will be made available upon request for monitoring by HHTU monitors.

A risk-based approach to monitoring will be adapted for the study. Full details will be given in the Trial Monitoring Plan, which will be developed and agreed by the Sponsor, CI, TMG and TSC, based on the trial risk assessment. Monitoring will be a combination of central, remote and on-site monitoring, with appropriate risk adaptations considered during the risk assessment process. HHTU will coordinate and perform monitoring, submit reports to the sites and Sponsor, and escalate findings as required.

Data will be monitored for quality and completeness by HHTU. Missing data will be chased until it is received or confirmed as unavailable. Participants with missing data items will not be chased directly by HHTU. HHTU will reserve the right to intermittently conduct source data verification

exercises on a sample of participants; which will be carried out by staff from HHTU. There will be ongoing central collection of consent forms.

HHTU will conduct internal audits on trial management at quarterly intervals.

13.5 Recording of Data

In order that data are accurate, complete, and legible, the following criteria are to be maintained:

- The Investigator(s) will enter the information required by the protocol onto the CRFs.
- Paper records will be kept by the Investigators in a secure location at the investigational site during the conduct of the trial.
- When data are corrected, the previous data is still visible and the reason is written next to the correction.
- The Principal Investigator signs off the eCRFs after checked and confirmed as fully completed by Investigators.
- Data reported on the eCRF that are derived from source documents, should be consistent with the source documents, or have any discrepancies explained.
- The Investigator(s) will use the SIN to identify participants.

13.6 Retention of Records

At completion or termination of the study, the Sponsor and Principal Investigator have the responsibility to retain all study documents, including but not limited to the protocol, copies of eCRFs, regulatory agency documents, ICFs, and REC correspondence. The study documents should be retained for 5 years following study completion/termination. The end of the study is defined as the submission of the End of Trial Report.

Archiving will be authorised by the Sponsor following submission of the End of Trial Report. All essential trial documents including source documents will be archived in accordance with the HHTU Data Management Plan and Archiving SOP. The archiving of trial documents and data at site (including consent forms) will be done according to participating site Trust policies and SOPs. Access to data, including the Trial Master File, will be restricted to the sponsor. Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive.

13.7 Greenphire – ClinCard

Participants in the FANFirst study can choose to receive reimbursement for travel expenses incurred from attending study visits through a ClinCard. This card is supplied by Greenphire†; a company working on behalf of University of Hull. In order that Greenphire can facilitate reimbursement, they will need to have access to the following personal data: Subject ID, Name, Address, and Date of Birth. This information will be collected by the FANFirst site staff and given to Greenphire. If participants decide not to provide the required personal data, University of Hull will make a different method of payment available.

†Greenphire are based in the United States. Any personal information supplied by participants to Greenphire will only be used to process reimbursement. As is required by law, Greenphire will retain transactional ClinCard data for at least 7 years from study close out.

13.8 Publication of Results

A publication policy will be developed and a core publication group will be appointed. The publication policy will contain guidelines on how to approach authorship and a regularly updated publication plan.

The study team are obliged, by the terms of its contract, to notify the NIHR RfPB programme of any intention to publish the results of NIHR funded work either at submission or at least 28 days in advance of publication. This also applies to public oral and poster presentations, newsletters, dissemination events for participants, press releases, media interviews and the final project report.

13.9 Protocol Deviations

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, and will require immediate action. In some instances, repeated protocol deviations could be classified as a serious breach.

13.10 Participant Insurance and Indemnity

This is an NHS-sponsored research trial. If there is negligent harm to a participant during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff and medical academic staff with honorary contracts, only when the trial has been approved by the HRA and the Trust R&D department has confirmed there is the capacity and capability to perform the trial. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Where the PI is employed by the University of Hull, the University has an insurance policy that includes cover for no-fault compensation in respect of accidental injury to a research patient, only if caused by the University.

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