Breathing REtraining for Asthma Trial of Home Exercises for Teenagers; repurposing, refining and feasibility – Stage 3

Short trial title: BREATHE4T – Stage 3

This protocol has regard for the HRA guidance and order of content with modification for a non-CTIMP study (Version 1.2 March 2016)

RESEARCH REFERENCE NUMBERS

TRIAL REGISTRY NUMBER AND DATE: NCT05006703; 16th August 2021

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IRAS NUMBER: 290847

FUNDER NUMBER: PB-PG-0817-20038

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

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

For and on behalf of the Trial Sponsor:

Signature: Date:

..../...../.....

Name (please print):

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Position:

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Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

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Statistician:

Signature:

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Name: (please print):

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Position:

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KEY TRIAL CONTACTS

Chief Investigator	Professor Graham Roberts Professor and Honorary Consultant, Paediatric Allergy and Respiratory Medicine University Child Health (MP803), University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton SO16 6YD Telephone: 02381206160 Email: g.c.roberts@soton.ac.uk
Trial Co-ordinator	Stephanie Easton University Child Health (MP803), University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton SO16 6YD Telephone: 02381 205227 Email: s.e.easton@soton.ac.uk
Sponsor	University Hospital Southampton NHS Foundation Trust, Mrs Sharon Davies-Dear, R&D office, E level, Southampton Centre for Biomedical Research, Laboratory and pathology block (MP138), Southampton General Hospital, Tremona Road, Southampton, SO16 6YD Telephone: 023 8120 5424 Email: sponsor@uhs.nhs.uk
Funder(s)	National Institute of Health Research, Research for Patient Benefit
Key Protocol Contributors	**Primary care lead**: Professor Mike Thomas, Professor of Primary Care Research, University of Southampton, UK; Telephone: 02380241050; Email: D.M.Thomas@soton.ac.uk **Physiotherapy lead**: Denise Gibson; Telephone: 02381206725; Email: denise.gibson@uhs.nhs.uk **Behavioural change lead**: Professor Lucy Yardley; Professor of Health Psychology, University of Southampton, UK; Telephone: 02380594581; Email L.Yardley@soton.ac.uk With additional input from Dr Rebecca Knibb, Reader in Psychology, University of Aston, UK; Telephone: 01212043402; Email: r.knibb@aston.ac.uk **Digital intervention lead**: Dr Benjamin Ainsworth, Lecturer in Health Psychology, University of Bath, UK; Telephone: 01225383114; Email: B.Ainsworth@bath.ac.uk

	Qualitative lead: Professor Sue Latter, Professor of Nursing, University of Southampton, UK; Telephone: 02380597959; Email: S.M.Latter@soton.ac.uk **Adolescent lead**: Dr Simone Holley, Senior Research Fellow, University of Southampton, UK; Email: S.L.Holley@soton.ac.uk **Asthma UK lead**: Erika Kennington, Head of Research, Asthma UK, UK; Telephone: 02077864939; Email: ekennington@asthma.org.uk
Statistician	Dr Sam Wilding, Trial Statistician, University of Southampton, UK; Telephone: 02381205674; Email: S.A.Wilding@soton.ac.uk
Committees	Trial Management Group chaired by Professor Graham Roberts (CI) Trial Steering Committee chaired by Professor Steve Turner

i. LIST of CONTENTS

ii. LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ISF	Investigator Site File (This forms part of the TMF)
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

iii. TRIAL SUMMARY

Trial Title	Breathing REtraining for Asthma Trial of Home Exercises for Teenagers; repurposing, refining and feasibility – Stage 3
Short title	BREATHE4T – Stage 3
Clinical Phase	Phase 2a clinical trial
Trial Design	Pilot trial
Trial Participants	Young people (12-17 years) with physician diagnosed asthma, impaired quality of life. All will be under the care of a general practitioner, community asthma nurse specialist or hospital healthcare professional. Exclusion criteria: already using breathing techniques; co-existent respiratory conditions; member of the study PPI groups, learning difficulties.
Planned Sample Size	116 in pilot trial
Treatment duration	6 months
Follow up duration	6 months
Objectives	i. To assess the recruitment rate. ii. To assess the acceptability and uptake of the intervention, using both internet/telephone interviews with a sample of participants and online questionnaires at 2 and 6-month assessment; iii. To estimate the follow-up rate at the 2 and 6-month assessment (will also look at relative rates for participants recruited from primary care, secondary care and Asthma UK); iv. To monitor the change in and estimate the variance of asthma-related quality of life and asthma control in each group; v. To determine if data collection methods for process, effectiveness and cost-effectiveness endpoints are appropriate for this population by assessment of completeness of data at 2 and 6-month assessment; vi. To assess the relative uptake and quality of qualitative data collection from participants via in-person, online video platforms (e.g. Microsoft Teams) or telephone interviews, to inform format and necessary staffing requirements for a trial.
Intervention	• a theoretically informed, mobile-friendly website, based on the successful adult Breathe intervention • motivational information about the benefits of breathing retraining, • short and engaging videos demonstrating breathing retraining techniques, • supportive elements such as a daily planner and progress chart, • advice on how to integrate breathing retraining techniques into daily life, • advice addressing common barriers to engagement.

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIAL SUPPORT GIVEN
National Institute of Health Research, Research for Patient Benefit	£247,376.00
National Institute of Health Research Southampton Biomedical Research Centre	The BRC paediatric research nursing team will be able to support the project. The BRC will also support the PPI activities. Lastly the BRC management team will support the project, as required.

v. ROLE OF TRIAL SPONSOR AND FUNDER

Trial sponsor: **University Hospital Southampton NHS Foundation Trust**

The trial sponsor has delegated responsible to the Chief Investigator for:

- Obtaining required authorisations to commence the trial (clinical trial authorisation and favourable ethics committee opinion)
- Keeping records of all amendments to the authorisations and obtain approval where approvals are required
- Undertaking to allow inspection of premises in third countries if required
- Notifying all relevant bodies of the conclusion or termination of the trial within the specified timeframes
- Keeping a trial master file to hold all documents relating to that trial

The trial sponsor and Chief Investigator will be responsible for:

- Ensuring that the conditions and principles of Good Clinical Practice (GCP) are satisfied and adhered to
- Ensuring that the trial is conducted in accordance with the protocol and subsequent amendments
- Appointing named individuals responsible for archiving the trial essential documents

The trial sponsor will be responsible for:

- Notifying any serious breaches of Good Clinical Practice or the protocol, or any urgent safety measures taken to the appropriate authorities

Trial funder: National Institute of Health Research, Research for Patient Benefit

The funder will have no role in the trial design, conduct, data analysis and interpretation, and generation of publications.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES

Trial Steering Committee

Trial Steering Committee (TSC) will have an important advisory role in the study reviewing progress and data and providing feedback and guidance to the TMG. It will be chaired by an independent academic clinician with experience in clinical trials. All the members of the TMG will be represented, together with our collaborators and independent members from key stakeholder groups (eg asthma clinician, general practitioner, asthma nurse specialist, academic clinician, patient with asthma and a parent of a young person with asthma (from the PPI panels). The TSC will meet twice a year face-to-face and its activities will relate to the strategic oversight of the project to ensure it meets its overall objectives and provides robust data. The TSC will send reports to the TMG and sponsor.

Trial Management Group

Trial Management Group (TMG) will be the main operational group meeting monthly (face-to-face or webconference). It will comprise the co-investigators plus the research assistant. The TMG will be responsible for:

- Monitoring the technical and financial aspects including reviewing progress against timelines and developing a strategy to address unforeseen occurrences;
- Monitoring the ethical and safety aspects;
- Ensuring effective external (including dissemination) and internal communications;
- Developing a plan for using and disseminating the knowledge accruing through the study activities.

vii. Protocol contributors

Professor Graham Roberts, Professor and Honorary Consultant, Paediatric Allergy and Respiratory Medicine, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton.

Professor Mike Thomas, Professor of Primary Care Research, University of Southampton.

Professor Anne Bruton, Professor of Respiratory Rehabilitation (retired), University of Southampton

Professor Lucy Yardley, Professor of Health Psychology, University of Southampton

Dr Rebecca Knibb, Reader in Psychology, University of Aston

Dr Benjamin Ainsworth, Lecturer in Health Psychology, University of Bath

Professor Sue Latter, Professor of Nursing, University of Southampton

Dr Simone Holley, Senior Research Fellow, University of Southampton

Erika Kennington, Head of Research, Asthma UK

Dr Amy Whitehead, Senior Statistician, University of Southampton

Dr Sam Wilding, Trial Statistician, University of Southampton

Dr Denise Gibson, Consultant Physiotherapist, University Hospital Southampton NHS Foundation Trust

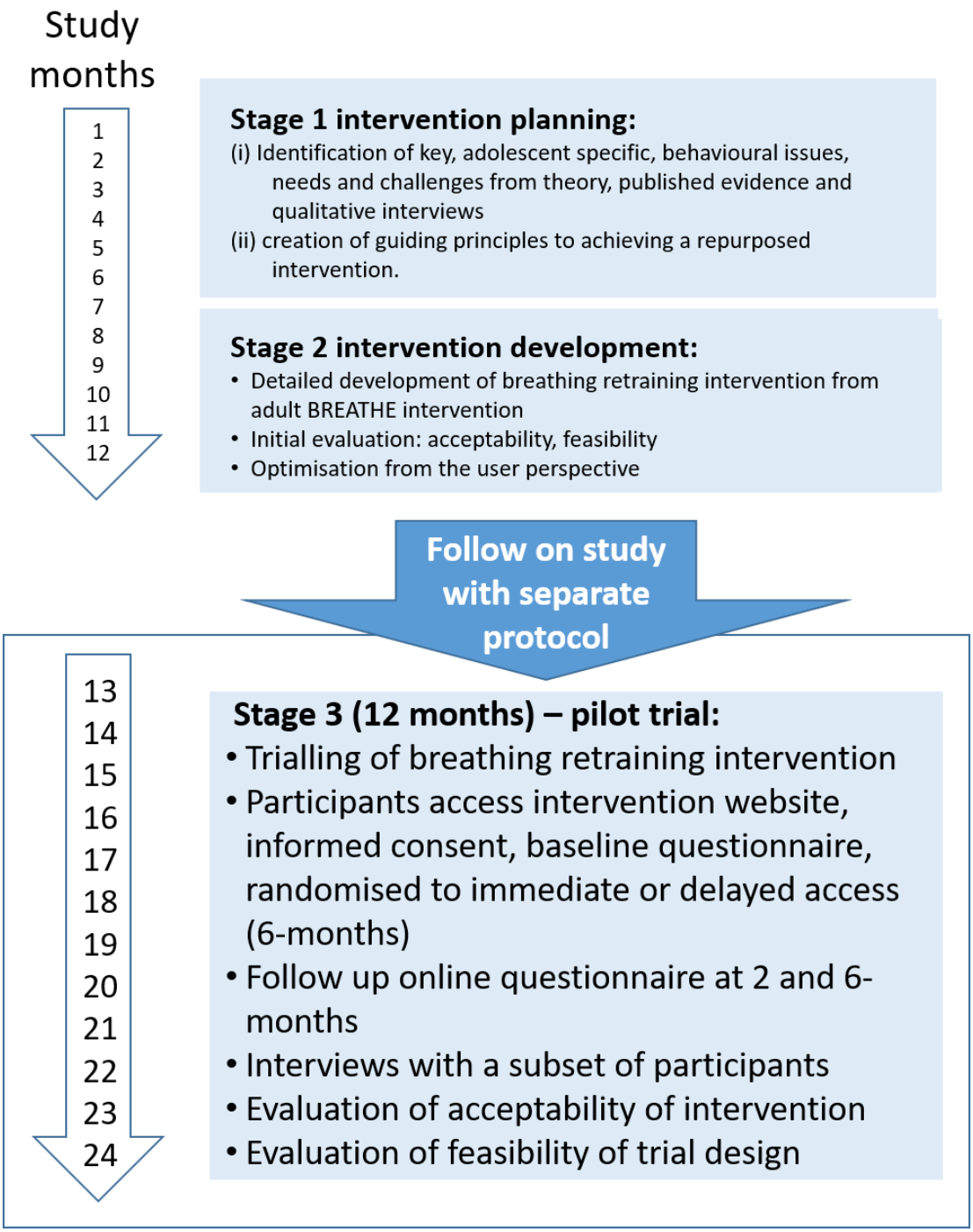
Stephanie Easton. Research Assistant, BREATHE4T study, University Hospital Southampton NHS Foundation Trust

BREATHE4T Public and Patient Involvement Committees and Michael Bahrami-Hessari, Patient and Public Involvement Officer, University Hospital Southampton NHS Foundation Trust

viii. Key words: adolescents, asthma, breathing retraining, person-based approach, development, pilot trial

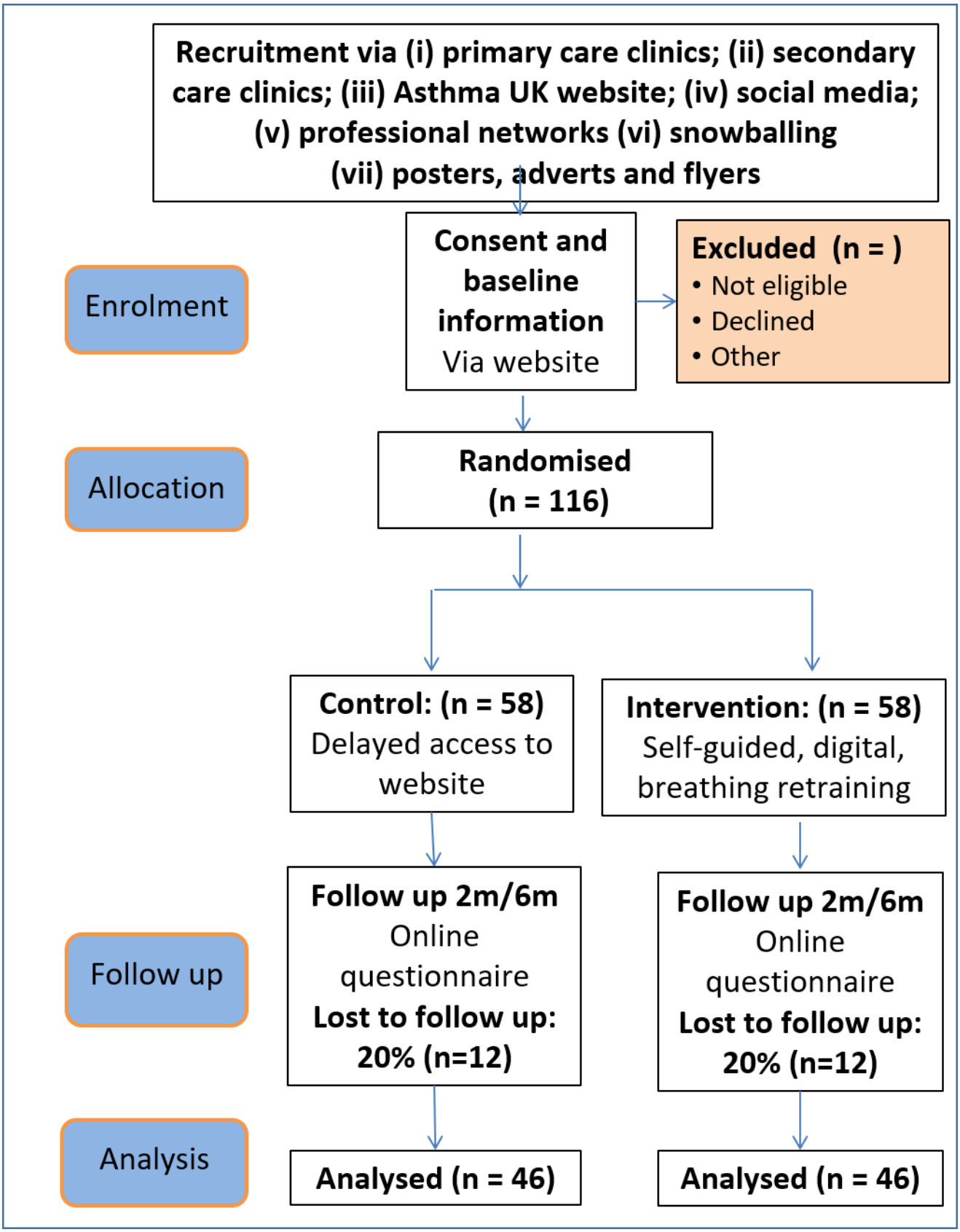
ix. Trial flow chart

Figure 1. Overview of entire BREATHE4T project



This protocol deals with Stage 3, bottom of the figure.

Figure 2. Flow of participants in the BREATHE4T pilot trial



1 BACKGROUND AND THEORETICAL FRAMEWORK

1.1 The problem – suboptimal health experience for young people with asthma

The problem we aim to address is impaired asthma-related quality of life (despite appropriate pharmacotherapy) for young people (12-17 years) with asthma [1]. A non-pharmacological intervention (breathing retraining) has been shown to be both effective and cost-effective in adults [2, 3]. Breathing retraining improved their asthma related quality of life, the key patient orientated outcome measure. Implementation of the adult BREATHE study intervention is underway. An online version of the DVD intervention is available to patients and health professionals (www.breathestudy.co.uk). This effective approach needs to be evaluated in young people with asthma, who have real potential to benefit from this simple, inexpensive intervention [4].

1.2 Why this research is important to improve the health of patients and the NHS

Asthma: Asthma prevalence is high in adolescence (around 15%) [5] and hospital admissions are more common in young people than adults. Asthma is a heterogeneous condition [6] and pharmacological approaches do not meet all patients' needs [1]. We know the majority of people with asthma continue to have symptoms and impaired quality of life [1, 7]. A personalised, holistic approach to asthma management may improve outcomes [8].

Adolescent asthma: Young people have poor asthma outcomes, particularly in relation to quality of life (1). They have different issues and needs to adults [9, 10]. For example, we and others have demonstrated that they often have limited engagement in self-managing their asthma and often inefficiently communicate with healthcare professionals [4, 11, 12]. Hence there is a pressing need to identify suitable, alternative, healthcare solutions for this group. Our recent systematic review on self-management [4] revealed that young people are reluctant to take asthma medications and attend asthma clinic reviews but, more positively and highly relevant to this application, they find technological interventions particularly acceptable. Unlike younger children, young people are able to manage interventions without parental supervision. They therefore represent a very good target for a behavioural change health intervention, especially as self-management skills support life-long asthma management.

Breathing retraining: Patients and parents are interested in non-pharmacological asthma treatments with a third of children and young people resorting to complementary and alternative medicine therapies, often without the knowledge of their clinicians [13]. One approach for asthma is breathing retraining, which we have recently demonstrated to be successful and cost-effective in adults with asthma in a large HTA funded study [2, 3] and is already being implemented. However, we know that young people will need to be engaged differently ([4], our ongoing Asthma UK funded study) and so we propose an adapted, web-based intervention. A recent Delphi exercise from the European Asthma Research and Innovation Partnership Self-Management working group highlighted behavioural strategies and new information technologies in their top three priorities for asthma self-management [14]. As per the adult intervention, once we have evidence for the effectiveness of the young person intervention, it should be easy to implement as an online training tool.

1.3 Current state of the art knowledge

Breathing retraining in adult asthma: A systematic review of studies of breathing retraining in adult asthma demonstrated improvements in asthma quality of life, control, symptoms and exacerbations [15]. This approach is now advocated in adult guidelines [16]. One problem limiting the NHS use of this treatment is the lack of respiratory physiotherapists therefore only a small proportion of patients who might benefit are able to access breathing retraining. In the HTA funded, adult, randomised controlled BREATHE study [2] an audio-visual breathing retraining programme was effective in improving asthma quality of life (adjusted mean difference 0.28, 95% confidence interval: 0.11-0.44, $p<0.001$) [2, 3]. The

number needed-to-treat to deliver a clinically important improvement of 0.5 units was 8. There was an equivalent improvement with face-to-face physiotherapy (0.24, 0.04-0.44; $p<0.05$). The process evaluations showed good patient engagement and acceptability for the DVD based intervention. Importantly, healthcare costs (mostly unscheduled care) were lower in the audio-visual DVD-based breathing retraining programme group compared to usual care, with reduced asthma healthcare utilisation outweighing the £2.85 per participant cost of the intervention.

Breathing retraining in young people with asthma: Young people with asthma also exhibit dysfunctional breathing with a recent study suggesting 55% are affected [17]. This may manifest as hyperventilation or occasionally vocal cord dysfunction [18]. These add to breathing difficulties seen with an asthma exacerbation and both respond well to breathing retraining. Young people differ cognitively, psychologically and behaviourally from adults so properly conducted studies are required before we can extrapolate from adults to younger age groups. For example, even if there are good physiological reasons as to why an intervention should be equally effective in adults and young people, it may not work in young people because they fail to take up the intervention. There are case reports and case series pointing to the effectiveness of breathing training programmes in young people [19, 20]. However, in contrast with adults, there are no well-designed published randomised controlled studies. A recent systematic review concluded that "We could draw no reliable conclusions concerning the use of breathing exercises for children with asthma" [21]. We therefore wish to test the BREATHE study approach to breathing retraining in asthma in young people.

1.4 The 'Breathing Freely' intervention

The intervention being developed in BREATHE4T – Stage 1 and 2 is a self-guided, breathing retraining digital intervention, that will be delivered via a mobile friendly, online platform. The research team has successfully used internet-based approaches to implement behaviour change for weight-loss and hand-hygiene. In addition, in the BREATHE study we developed the adult 'Breathing Freely' intervention, a DVD-based remote intervention that was shown to improve asthma related quality of life in an NIHR-funded HTA adult trial by investigators (Thomas, Bruton, Yardley) [2, 3]. The intervention was developed using the iterative, user-centred 'person-based approach [22]' in order to ensure that it was acceptable and engaging to patients. The intervention has been fully disseminated in a digital format and is available here: http://www.breathestudy.co.uk.

The existing adult intervention includes a detailed explanation and illustration of how to perform the breathing exercises alongside professionally developed footage showing a physiotherapist teaching them to patients. To ensure that the intervention is engaging to adults, both the video content and accompanying advice contain motivational components that explain the rationale of the exercises, and address common doubts and concerns. Additional 'supportive' elements were also included such as a daily planner, and progress chart, in order to support practicing and implementing the techniques into daily life.

From our ongoing research with this target population (Asthma UK funded project "It's My Asthma"), and detailed PPI input we are aware that the current BREATHE intervention is not in a format that young people are likely to interact with and will need to be adapted and refined. For example, the video content will need to use younger actors with whom they can relate and it would benefit from increased gamification and personalisation. For the motivational content, advice and support, young users will benefit from a mobile app/website (rather than a dedicated website that is appropriate for older primary care adults) that can be easily accessed on a smartphone.

1.5 The need for an adolescent version of the "Breathing Freely" intervention

In our recent Asthma UK funded adolescent asthma study we have evaluated the acceptability of a novel young person approach for asthma self-management (manuscript in preparation). From this we

know that changes to the materials and format will be required to engage this age group. For example, a young person's training package needs to be relevant for them in terms of how the intervention is explained and how it is presented. So the intervention needs to be repurposed and then optimised for this population. Age-appropriate materials and the technology platform need to be developed in collaboration with young people. Our work with this age group suggests that a smartphone/ tablet/ internet accessible intervention would be required, rather than DVD technology. We have used a 'person-based approach' [22] to develop an intervention platform and content that is acceptable and feasible, by iteratively modifying the intervention according to user feedback to maximise engagement to the intervention and effective behaviour change.

1.6 The BREATHE4T intervention

The repurposing, optimisation and acceptability of the intervention in the adolescent age group has been undertaken in Stages 1 and 2 of the BREATHE4T project. In line with the person-based approach [22], a rapid scoping review and behavioural analysis examined the key adolescent-specific issues, needs and challenges that the intervention must address. Qualitative interviews were conducted with 18 participants to explore barriers and facilitators to adolescent engagement and specific design features, which has informed the development of a mobile-friendly web application. The intervention was refined and optimised using feedback from teenagers that took part in think-aloud interviews, additional to regular input from key stakeholders, including a panel of 6 teenagers and 6 parents who met every 3 months with regular contact between meetings. Guiding principles have been created and outline the specific design needs and objectives to target the key behaviours.

2 RATIONALE

From our research and clinical experience with young people with asthma we know many have impaired quality of life despite pharmacotherapy [1]. Young people (and their parents) tell us that during an asthma attack they have to calm themselves down to control their breathing [23]. Although physiotherapist-delivered breathing retraining programmes now have a clear evidence base in adults with asthma, improving quality of life [2, 3], there is a lack of evidence assessing its use in younger patients. There is a need to redesign and develop this behavioural change intervention to make it appropriate for young people, and then assess how effective such an intervention would be in this population.

If similar results were to be seen with young people, this intervention would improve their asthma related quality of life reducing their need for unscheduled emergency healthcare for asthma exacerbations for a minimal cost.

If this intervention proves to be cost-effective, it is envisaged that an updated version of the intervention would be hosted on the web. This may be within a NHS network or within the Asthma UK website. The adult digital intervention has been made freely available to patients and professionals through the web link www.breathestudy.co.uk, and is receiving considerable traffic. We would provide similar access for this intervention in the event of a positive study. NHS professionals involved in the care of young people with asthma would be alerted to the website to disseminate it. Professionals would be able to signpost patients to the site. Additionally, patient organisations would also be able to signpost patients to the site. We will also consider using the CLAHRC/AHC networks in an implementation study.

To design this substantive trial needed to demonstrate cost-effectiveness, we have repurposed the adult BREATHE intervention. This pilot trial will provide the necessary information for a substantive cost-effectiveness trial. This includes the likely i) recruitment rate (ii) acceptability, uptake and engagement with the intervention; (iii) follow-up rate; (iv) change in and estimated variance of asthma-related quality of life and asthma control in each group; (v) effectiveness of data collection methods; (vi) determine the validity of the PEDSQL Asthma Module quality of life questionnaire [24] and (vii) uptake and quality of qualitative data collection.

A future full trial would be a randomised, controlled trial recruiting young people (aged 12-17 years) with asthma cared for in both primary and secondary care. It is expected that 300-400 participants would be required. The intervention would be the self-guided, breathing retraining digital intervention, delivered via a mobile friendly, online platform developed in this proposed project. The comparator group would experience usual UK asthma management and access to the intervention at the end of the trial. Outcome data would likely be collected via telephone and online with the primary outcome being determined by this project. The cost-effectiveness analysis would employ methods and perspective endorsed by NICE.

3 ASSESSMENT AND MANAGEMENT OF RISK

Breathing re-training is a well-known approach to managing breathing problems in children, adolescents and adults. As described above (Section 1), there is evidence for its effectiveness in treating asthma in adults and some evidence for asthma in children. In the adult BREATHE study, there was a significant improvement in asthma related quality of life.

There are no known adverse effects for breathing retraining [3]. The BREATHE study enrolled 655 adults with asthma of whom 261 were randomised to breathing retraining via DVD and 132 to breathing retraining by face-to-face teaching [3]. Adverse events were seen in 39% of the DVD group, 42% of the face-to-face group and 50% of the usual care group. Percentages experiencing severe adverse events were 4%, 3% and 8% respectively. There was one death in the DVD group and two in the usual care group; none of these were related to the intervention.

The risk for patients with asthma are asthma exacerbations which can be severe and require hospitalisation. To minimise the risk, all participants will be under the management of their general practitioner, community asthma nurse specialist or hospital healthcare professional. Patients with asthma are regularly reviewed to ensure their symptoms are controlled. Additionally, the intervention will emphasise how to recognise and appropriately respond to deteriorating asthma control. This means that participants will understand when they need to take additional therapy and seek medical help in the event of an asthma exacerbation.

4 RESEARCH OBJECTIVES

4.1 Aim: This pilot trial aims to determine the acceptability and feasibility of conducting a definitive Phase III randomised controlled trial (RCT) comparing immediate access to the breathing retraining intervention to delayed access to the intervention in young people with asthma.

4.2 Specific objectives for stage 3:

To achieve the overall aim, the pilot trial has the following objectives:

i. To assess the recruitment rate;

ii. To assess the acceptability and uptake of the intervention, using both internet/video/telephone or in-person interviews with a proportion of participants and online questionnaires at 2 and 6-month assessment;

iii. To estimate the follow-up rate at the 2 and 6-month assessment (will also look at relative rates for participants recruited from primary care, secondary care, Asthma UK and social media);

iv. To monitor the change in and estimate the variance of asthma-related quality of life and asthma control in each group;

v. To determine if data collection methods for process, effectiveness and cost-effectiveness endpoints are appropriate for this population by assessment of completeness of data at 2 and 6-month assessment;

vi. To determine whether the PedsQL Asthma Module (with and without additional emotion questions[25]) provides a valid assessment of quality of life, by comparing it with the Paediatric Asthma Quality of Life Questionnaire [26]

vii. To assess the relative uptake and quality of qualitative data collection from participants via in-person, video or telephone interviews, to inform format and necessary staffing requirements for a trial;

Achieving these objectives would allow us to develop a Phase III cost-effectiveness trial to address the questions (i) “Does breathing retraining provided via a digital intervention result in clinically important improvements in patient-related asthma measures above 'usual care'?” and (ii) “What is the cost-effectiveness of the programme?”.

5 Stage 3 – THE PILOT TRIAL

The pilot trial will be a multicentre, open-label, two-group, individually randomised, controlled trial.

5.1 Outcome measures/endpoints

As this is a pilot trial, a number of outcome measures / endpoints will be included to establish which is the optimal one for a definitive trial.

Objectives	Outcome Measures	Time point(s) of evaluation of this outcome measure
Asthma specific quality of life	**PedsQL Asthma Module** This will be assessed using the validated paediatric asthma quality of life asthma module (short form) questionnaire and presented as a total score (sub-scores will also be presented)([24]). From the adult BREATHE study [2] we expect the intervention to have most benefit on asthma related quality of life. This is also an important patient outcome. As the questionnaire does not have complete coverage for emotional issues, some additional questions will also be asked [25]. This is the expected primary outcome for the definitive phase III study.	Baseline, after 2 months and at the end of the study after 6 months.
	Paediatric asthma quality of life This will be assessed using the validated paediatric asthma quality of life questionnaire and presented as a total score (sub-scores will also be presented) [26]. It is not possible for this to be recorded for all participants as the copyright owner does not allow it to be used as an online questionnaire.	Baseline, after 2 months and at the end of the study after 6 months for participants seen in person, where they can post a paper questionnaire to the

		study team or complete it over the telephone.
Asthma control	This will be assessed using the validated asthma control test and presented as a total score [27]. This is an important asthma endpoint reflecting the presence of ongoing symptoms, impact on quality of life and likely risk of an exacerbation.	Baseline, after 2 months and at the end of the study after 6 months.
Healthcare utilisation	This will be assessed using a very short questionnaire. It will be presented as: • Episodes of prescriptions of 3 or more days of prednisolone (or similar), • attendance at emergency department for an exacerbation of asthma, • hospital admission for an exacerbation of asthma. Unplanned healthcare utilisation represents a disruption to the lives of patients and families and a major cost of the NHS.	Baseline, after 2 months and at the end of the study after 6 months.

5.2 Trial design

The pilot trial will aim to assess the acceptability, uptake and success in collecting follow up data and variance in asthma-related outcome measures. A parallel group design will be used with participants being randomised to intervention or normal management. The intervention will be a self-guided, breathing retraining digital intervention, delivered via a mobile-friendly, online platform. The intervention will continue to be used for 6 months after which both groups will be reassessed. The usual management control group will then have access to the intervention (delayed access).

5.3 Trial setting

The setting is primary and secondary care in England. Recruitment would be from primary care and hospital clinics. Asthma UK will sign-post potential recruits to the website. Participants will access the trial via a web-based platform.

5.4 Participant eligibility criteria

Inclusion criteria

i. Young people aged 12-17 years
ii. Physician diagnosed asthma
iii. Impaired quality of life (<85)
iv. Under the care of a general practitioner, community or hospital practitioner for their asthma

Exclusion criteria

i. Co-existent respiratory conditions such as bronchiectasis
ii. Already using breathing techniques
iii. Already enrolled in another interventional study
iv. Lack of informed consent
v. Learning difficulties

5.5 Trial procedures

The trial procedures are summarised in Figure 3 below.

5.5.1 Recruitment and identification

Adolescent with asthma will be recruited in a number of ways:

- 20 secondary clinics in Southampton, Isle of Wight and other centres:

  (i) database search by NHS staff with invitation letters; invitation letters will be sent; letter will invite interested adolescents;

  (ii) opportunistically via posters in clinics and clinic staff mentioning to potential participants; poster will invite interested adolescents.

- Up to 20 local primary care clinics (general practitioner, primary care nurses and community nurses) who will be study participant identification centres (PICs):

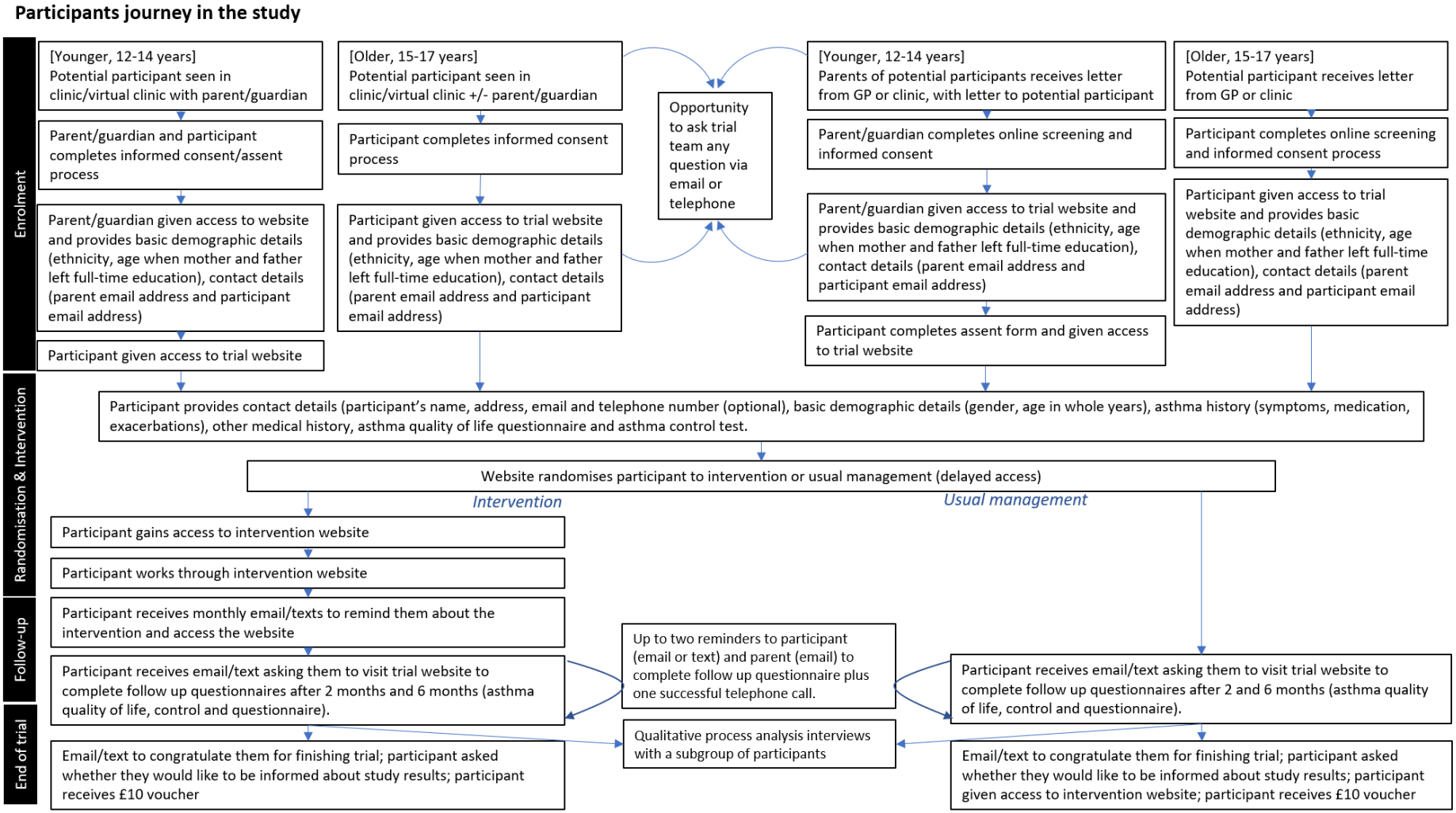
  (i) primary care staff will perform a database search; invitation letters will be sent; letter will invite interested adolescents;

  (ii) opportunistically via posters in surgeries and primary care staff mentioning to potential participants; poster will invite interested adolescents.

- Asthma UK – advert in newsletters, on website and social media inviting interested adolescents.
- Social media (eg Twitter, Instagram, Facebook) adverts and flyers - those interested will click a button/link which opens the BREATHE4T study website where they can leave their details for the study team to contact them.
- Professional networks (eg respiratory and paediatric physio teams informing patients of the study)
- Snowballing
- Posters, adverts and flyers in various local locations (examples include GP surgeries, chemists, supermarket notice boards, schools, colleges, leisure and sport clubs, coffee shops, asthma support groups and charities (e.g. No Limits), local newspapers)
- Press release

This approach will mean that we will not be able to identify the total number of potential participants who would have seen information about the trial and we will not have information about their basic demographics nor asthma status.

Figure 3. Overview of participant journey in the Stage 3 pilot study



5.5.2 Consent

In person

Study research staff will obtain informed consent prior to the participant undergoing any study activities. This process will involve:

- discussion between the potential participant and their parent/guardian and a trained research project staff member about the nature and objectives of the study and possible risks associated with their participation.
- presentation of the approved information leaflet and consent/assent documents. Two different participant information sheets will be used, for younger and older adolescents written in appropriate language.
- the aims will be framed in age and developmentally appropriate language. This will acknowledge that adolescents have different maturities. For younger teenagers (12-14 years), the process will be undertaken with their parents or guardians.
- an opportunity for potential participants and/or their parent/guardian to ask questions.
- contact point where the participant /parent or guardian may obtain further information about the trial from the research team.
- Participants aged 15 years and above will be asked to sign an informed consent form; for participants less than 15 years of age, parents will be asked to sign an informed consent form and teenagers will be asked to sign an assent form.

Via website

Parents and potential participants will be directed to the trial home page where they will be taken through informed consent/assent process. Informed consent/assent will be obtained prior to the participant undergoing any study activities. This process will involve:

- presentation of the approved information on the web pages (also available in printable leaflet form)
- information will cover the nature and objectives of the study and possible risks associated with their participation;
- participants and/or their parents will be informed that they are able to withdraw from the trial at anytime without giving reasons and without prejudicing his/her further treatment, explanation will be given about the right to withdraw permission to use previously collected data;
- an opportunity for potential participants and/or their parent/guardian to ask questions before signing consent/assent by sending a message to the trial team;
- contact point where the participant /parent or guardian may obtain further information about the trial from the research team.

For younger participants (12-14 years), when the parent consents, an invitation will be sent via email to the adolescent participant. This will take them through a similar but age appropriate assent process. Older participants (15-17 years) will be able to give their own consent to participate and will be given immediate access to the study.

5.5.3 Screening

Questions on the trial web site will assess their eligibility for the trial (age 12-17 years, physician diagnosed asthma, under the care of a general practitioner, community or hospital practitioner for their asthma, no co-existent respiratory conditions and not used breathing techniques).

5.5.4 The randomisation scheme

Participants will be randomised via the study website to the next treatment allocation in the randomisation sequence by the trial team. The list will be generated using block randomisation with variable block sizes with a 1:1 allocation ratio between the intervention and usual management. Those randomised to the intervention will have immediate access to the intervention pages. The control group will be able to access the full intervention website at the end of the trial. The website will alert the study team to a new randomisation by email.

5.5.5 Blinding

This is an open trial. It will not be possible to blind the breathing retraining intervention. Control participants will also gain access to the full intervention website once they have finished participating in the trial.

5.5.6 Baseline data

Minimal baseline information will then be collected:

- Basic demographic information: age in year, gender;
- Asthma history including treatment and any hospitalization;
- Any other significant health issues.

These data will be collected using an online questionnaire that the research team has used in previous studies [28] (Appendix 4).

5.5.7 Trial assessments

There are three assessments which will be completed online:

- Asthma quality of life: this will be assessed using the validated PedsQL Asthma Module [24].
- Asthma control: this will be assessed with the validated asthma control test [27].
- Healthcare utilisation: this will be assessed using a very short questionnaire.

The Paediatric Asthma Quality of Life Questionnaire will also be completed. As the copy write forbids this to be completed electronically, this will be completed in person or sent by post. The correlation between PedsQL Asthma Module (with and without the additional emotion questions [25] and the Paediatric Asthma Quality of Life Questionnaire will be assessed to ensure that the PedsQL Asthma Module (with and without the additional emotion questions) provides a valid assessment of quality of life.

5.5.8 Long term follow-up assessments

Participants will be re-assessed after 2 and 6 months. They will be contacted by email with a link to the study website. Instructions on the website will take them through:

- PedsQL Asthma Module
- Asthma control test
- Asthma healthcare utilisation questionnaire

These are the questionnaires they completed at baseline. Additionally, participants in the intervention arm will be asked whether or not they have used the breathing exercises.

Participants will receive two email/text reminders.

Additionally, they will complete the paediatric asthma quality of life questionnaire on paper after 2 and 6 months. This will either be at a face to face visit, will be posted to the study team, returned via email or completed over the telephone.

5.5.9 Qualitative interviews

The qualitative study will collect data both during participation and after participants finish using BREATHE4T. Qualitative interviews will seek to provide an in-depth understanding of the perspective of patients, to inform intervention and trial acceptability and to generate hypotheses about intervention mechanisms of action that can be tested in a larger trial.

Participants and sampling: Patients will be asked whether they would consent to take part in an interview at a later point in the study. Purposive sampling will then be used to select patients from the intervention group to allow for a wide range of views and experiences of the BREATHE4T programme e.g. covering age ranges, gender, asthma severity. We will also interview a small sample of control group participants to understand their experiences of trial participation. Additionally, we intend to interview participants who withdraw / drop out of the intervention arm, in order to understand reasons for doing so, to inform the larger trial design. It is anticipated that 10-20 intervention group patients will be interviewed both during and following the study. Sampling will continue until saturation is reached.

Data collection: Factors that may facilitate or diminish the acceptability of the BREATHE4T programme, adherence to implementation and mechanisms of action of the intervention will be explored, as well as acceptability of trial participation across patient interviews. Interviews will be conducted during months 4, 5 and 6 of the study. Open-ended questions within a semi-structured interview guide will be used to elicit user perspectives and experiences of the intervention, allowing participants to freely describe their experiences and views in their own way and to focus on whatever is most salient to them.

Interviews will be face to face, by telephone or video call and will be audio-recorded and fully transcribed.

Transcriptions will be anonymised (identifiable data removed) using participant numbers. To ensure that we remain open to and grounded in users' perspectives we will carry out inductive thematic analysis of all textual data, triangulated where appropriate with quantitative self-report measures and web usage data. A 10% sample of interviews will be double-coded using the initial thematic framework, to enhance the rigour of the analysis process.

The findings will be used to inform any modifications needed to BREATHE4T programme or the trial procedures for a potential future full RCT.

5.5.10 Withdrawal criteria

Where a participant or their parent or doctor wishes them to withdraw from the intervention, this will happen. Where possible follow up of the participant in the trial will continue. There will be no replacement of withdrawn participants.

5.5.11 Trial intervention

Breathe4T is a digital, self-management intervention for adolescents to control their asthma using breathing retraining exercises. The mobile-friendly website provides information about asthma and how it affects the lungs, as well as how breathing patterns can be dysfunctional, using developmentally appropriate language. Information is presented using short (30sec-2min), engaging video clips featuring a combination of physiotherapists, researchers and young adolescent role models. Users are given tips and information about their practice, including choosing a suitable time and place and building up gradually. Users can plan their practice, log how their practice went and record their confidence in using the breathing techniques in situations. There are 8 sessions to progress through. Each session includes

a video of a peer role model demonstrating the breathing exercise with a voiceover to explain the technique. Written, step-by-step instructions are also provided, in addition to a short description of the benefits of each exercise. All features and sessions can be accessed via a main dashboard where participants are also able to tailor the intervention to allow parental involvement, reminders around inactivity and their preferred format of notifications (email or text). A "frequently asked questions" section answers the common queries and concerns of breathing retraining. Users can view their asthma progress on a chart, which upon logging in requests information about their inhaler (preventer) use across time. The intervention has been designed to be easy to use on a mobile-device and with engaging colours and images.

5.5.12 Trial restrictions

There are no trial restrictions.

6 SAFETY

6.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant including occurrences which are not necessarily caused by or related to the trial intervention.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
non-IMP SUSAR	Non-IMP SUSAR is an SAE that occurs in a non-IMP trial and is: a) "Related" – that is, possibly, probably or definitely resulted from administration of any of the research procedures, and b) "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence.

"Severe" is used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

6.2 Operational definitions for (S)AEs

Exceptions including hospitalisation as a SAE are:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

Given the nature of the study, related SAEs are unlikely to occur.

6.3 Recording and reporting of SAEs

Participants will be asked to provide details of any potential AEs at the 2 and 6 month follow up assessments. An email alert will be sent to the study team.

For any SAEs, an assessment of seriousness, causality and expectedness will be made by the PI or delegate as per local reporting standard operating procedures.

Where SAEs occur, they will be notified to the Sponsor at sponsor@uhs.nhs.uk within 24 hours of the occurrence or knowledge of the occurrence, using the SAE reporting form. .

Where a non-IMP SUSAR has occurred this must be notified to the sponsor at sponsor@uhs.nhs.uk immediately upon the study teams' knowledge of the event, the sponsor will then notify the REC within 15 days using the SAE report form.

6.4 Responsibilities

Principal Investigator (PI):

Checking whether participants report AEs when they are reassessed at 2 and 6 months.

1. Using medical judgement in assigning seriousness and causality.
2. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.

Chief Investigator (CI) / delegate:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness and causality where it has not been possible to obtain local medical assessment.
3. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
4. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs.
5. Reporting safety information to the Trial Steering Committee (TSC).

Sponsor:

1. Central data collection and verification of AEs and SAEs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

6.5 Notification of deaths

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the intervention, or an unrelated event. This report will be sent to the sponsor at sponsor@uhs.nhs.uk within 24 hours of the study team being aware.

6.6 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the circumstances giving rise to those measures.

7 STATISTICS AND DATA ANALYSIS

The analysis of this trial will be mainly descriptive focusing on estimation rather than hypothesis testing. All baseline measures and outcomes will be summarised for each allocated group using the appropriate descriptive statistics and presented with their associated confidence intervals. No formal comparison of groups will take place. A Statistical Analysis Plan will be developed, setting out the details of all analyses and assumptions for the stage 3 pilot trial before the last patient is recruited.

7.1 Sample size calculation

Stage 3 represents a pilot trial so the effectiveness of the intervention is not being evaluated, therefore a formal power calculation is not appropriate. The sample size is based on a 95% confidence interval approach. For each of the expected proportions/means in the key objectives below, the precision to which we would be able to estimate the proportion/mean given this sample size is presented (nQuery and nTerim v4.0).

For the specific pilot trial objectives, the following are descriptions of the precision of our estimates with the stated assumptions:

i. *Recruitment rate*: It is estimated that the percentage of those approached who are randomised is around 30% therefore the approached sample size will be approximately 387 resulting in a half width for the confidence interval of 5%. The widest confidence interval for this approximation results when the percentage of randomised to approached is around 70% giving an approached sample size of 166 and a 95% confidence interval half width of 7%.

ii. *Acceptability and uptake of the intervention*: it is estimated that the uptake rate across those randomised to the intervention will be 90%, with 58 available participants for this estimation; this would result in a confidence interval half width of 8%.

iii. *Number of participants assessed at 6-months*: It is estimated that the dropout rate from the trial will be 20% of those randomised. With 116 participants randomised into the trial this would result in a confidence interval half width of 7% for the estimate of the dropout rate. Even when considering the statistical worst-case scenario of 50% the resulting confidence interval for this sample size has a half width of 9%.

iv. *Mean asthma related quality of life at 6 months in the control group*: with an estimated standard deviation of 1.4 from the UBIOPRED cohort (1), if data from 46 participants are available at 6 months and therefore

available for this estimation, this would give a confidence interval half width of 0.4 units approximately 0.3 standard deviations.

v. *Completeness of data for asthma related quality of life and healthcare utilisation data across the study in the two groups*: this is estimated at 95% across those randomised and still in the trial at 6 months, giving 92 participants available for this estimation therefore giving a confidence interval half width of 5%. Additionally, we plan to interview 10-20 participants in each intervention group.

7.2 Planned recruitment rate

The recruitment target for this study is 116 participants, or 58 per arm. It is planned that recruitment occurs at University Hospital Southampton, St Mary's Hospital Isle of Wight and eighteen other hospitals in England. Each site will be expected to recruit up to 5 participants over a 3 month period with the balance being recruited by University Hospital Southampton and St Mary's Hospital using 20 primary PIC sites.

7.3 Primary outcome analysis

As this stage 3 protocol outlines a pilot stage for a definitive phase-3 trial, the primary outcomes will be related to feasibility. All patients will be analysed as randomised (intention-to-treat). Feasibility outcomes include:

i. Assessing the recruitment rate by presenting the proportion of participants recruited among those approached;

ii. Assessing the acceptability, uptake and use of the intervention, by presenting the proportion of intervention patients who use the intervention website, in conjunction with findings from qualitative data collection;

iii. Estimating the follow-up rate at the 6-month assessment (additionally, looking at relative rates for participants recruited from primary care, secondary care, Asthma UK, social media, professional networks and snowballing);

iv. To monitor the change in and estimate the variance of asthma-related quality of life and asthma control in each group;

v. To determine if data collection methods for process, effectiveness and cost-effectiveness endpoints are appropriate for this population by assessment of completeness of data at 2 and 6-month assessments;

vi. To determine whether the PedsQL Asthma Module (with and without the additional emotion questions) and the Paediatric Asthma Quality of Life Questionnaire provide similar information by estimating their pairwise correlation.

vii. To assess the relative uptake and quality of qualitative data collection from participants via in-person, video or telephone interviews;

7.4 Secondary outcome analysis

There are no planned secondary outcome analyses.

7.5 Subgroup analyses

Younger (12-14 years) verses older (15-17 years) adolescents

Male verses female adolescents

7.6 Adjusted analysis

There are no planned adjustments in the analyses described above. Responses to the PedsQL Asthma Module and Paediatric Asthma Quality of Life Questionnaire will be transformed into summary scores using questionnaire-specific published methodology.

7.6 Interim analysis and criteria for the premature termination of the trial

There are no planned interim analyses or specified stopping rules.

7.7 Participant population

The trial analysis will include all participants randomised into the trial, regardless of whether they received the intervention. In addition, an analysis will be undertaken on the protocol-compliant population who will be defined as those who have covered at least half of the training sessions in the online website.

7.8 Procedure(s) to account for missing or spurious data

Participants will be encouraged to submit follow-up data via email/text reminders. Missing values will not be inputed, as completeness of data is a key feasibility outcome.

7.9 Other statistical considerations.

There are no further anticipated statistical considerations. All deviations from the Statistical Analysis Plan will be recorded.

8 DATA MANAGEMENT

8.1 Data collection tools and source document identification

Source data will be recorded on the trial website. This will downloaded into one of two CSV files:

(a) Personal data file – this will include names and contact information that is required to conduct the trial. This will be kept within the University Southampton NHS Foundation Trust IT environment.

(b) Trial data file – this will include trial data but no personal data (exception will be ethnicity coded as white/non-white and date of birth which will be coded as month/year). This will be read into statistical software (e.g. STATA, SPSS).

The exceptions will be:

- the paediatric asthma quality of life questionnaire which will be collected on paper (source document). These data will be entered into SPSS and double checked. Data will then be transferred to statistical software (e.g. STATA, SPSS).
- Transcripts of interviews which will be kept as word document (source document) and any recordings destroyed to maintain confidentiality.

8.2 Data handling and record keeping

Participants will be labelled with a unique identification number assigned by the trial website.

Copies for source data will be kept.

Source data from the trial website and paediatric asthma quality of life questionnaires will be merged to form the trial database in statistical software (e.g. STATA, SPSS). Data will be cleaned with identification of values outside set ranges and unlikely give other data; these will be corrected where possible in the trial analysis data set. A list of any edits will be kept.

8.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

8.4 Archiving

The source data and trial analysis data set with explanatory documentation will be achieved at the end of the trial. For this, the trial questionnaires will be scanned.

Documents with confidential information will be archived by University Hospital Southampton NHS Foundation Trust. All other documents will be archived by the University of Southampton. All data will be kept for a minimum of 10 years after the completion of the trial.

9 MONITORING, AUDIT & INSPECTION

The Trial Monitoring Plan is:

- Study team will monitor all trial informed consent documentation, trial data and transcripts to ensure that study conduct is as per the protocol. Additionally, the team will undertake a face to face or virtual review of activity at each site after the first participant is recruited.
- Trial management group will monitor recruitment, trial data (whole trial, not grouped) and serious adverse events at least 2 monthly.
- Trial Steering Group will review recruitment, trial data (whole trial, not grouped) and serious adverse events at 6 monthly.

It is expected that the Sponsor may also choose to monitor the study.

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Assessment and management of risk

The study team have evaluated the risks associated with the trial and classified it as low risk.

Risk	Level	Mitigation
Participant's asthma deteriorates over the course of the study and this is not adequately managed.	Low	It is likely that some participant's asthma control will deteriorate over the 6-month trial as this is the natural course of asthma and half of the participants will be in the control group. The trial website informs participants and their parents that they should contact their asthma doctor if they have increasing symptoms that are not controlled by their medication. Where a participant contacts the study team with worrying symptoms, one of the trial doctors will be involved and appropriate advice given to keep the participate safe.
Participant reveals concerning information during an interview, for example they are having suicidal ideation.	Very low	In our experience, this is very unlikely. If this was to occur, the study team will initially talk to the participant's parent or guardian and, if necessary, their doctor to ensure they are kept safe.
Data breach from the trial website	Very low	There is a need for the trial website to collect some personal data to conduct the trial, for example contact details for participants and parents. This is a very small risk of a data breach from the trial website. This will be minimised by the use of use https, SSL certificates and JWT secure tokens. Personal data will not be downloaded with trial data. Where it is downloaded to enable the conduct of the trial, it will be held on a secure NHS sever.

10.2 Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. The Chief Investigator will submit an annual progress report (APR) to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The Chief Investigator will notify the REC of the end of the Study. Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

10.3 Peer review

The NIHR RfPB panel has peer reviewed this study.

10.4 Public and Patient Involvement

We have and will involve young people and their parents in:

- Interpreting the findings of stage 1 and 2
- designing the pilot trial
- interpreting the findings of stage 3
- reporting and dissemination

We plan to achieve this with:

- Two local Patient and Public Involvement (PPI) panels: 7 young people and 7 parents – quarterly meetings, in parallel, outside school hours, facilitated by study personnel, with feedback from project and TSC – panels will receive training.
- Asthma UK – are involved in the management of the trial
- PPI representation on the Trial Steering Committee – We would support one member of each of the local young person and parent PPI panels to represent the panels' views on the trial steering committee.

10.5 Protocol compliance

Any protocol deviations will be documented in the site investigator's file. Any serious will be immediately reported to the Chief Investigator and Sponsor. A "serious breach" is a breach which is likely to effect to a significant degree: (a) the safety or physical or mental integrity of the participants of the trial; or (b) the scientific value of the trial.

10.6 Data protection and patient confidentiality

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

Personal information will be kept secure in the site investigator file. Each participant will have a numerical identifier which will be used to label the participant's CRF and transcripts.

Prior to analysis, the data will be anonymised by destroying the file linking personal details with the participants' identifiers.

Data will be stored for 10 years. Professor Graham Roberts is the data custodian.

10.7 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

None of the investigator have any commercial interests. They are though in receipt of funding from the NIHR RfPB to undertake the study. Also one of the investigators works for Asthma UK which is a charity that aims improve the life of people with asthma. A list of conflicts of interest will be reviewed at each TSC meeting and updated as needed.

10.8 Indemnity

The sponsor of the project is University Hospital Southampton NHS Foundation Trust. For NHS sponsored research HSG (96) 48 reference no.2 refers. If there is negligent harm during the clinical project when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the project. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

10.9 Amendments

Any amendments will be made by the TMG. The Sponsor will decide whether an amendment is substantial or non-substantial They will be notified to the UHS R&D office (as the lead organisation) and communicated to other participating organisations so participating sites to assess whether the amendment affects the NHS permission for that site.

10.12 Access to the final trial dataset

All the trial investigators will have access to the anonymised study dataset.

11 DISSEMINIATION POLICY

11.1 Dissemination policy

The study data will be owned by the University of Southampton. At the end of the trial, the investigators will analyse the data and generate a final trial report. The intention is that it will be published in a peer reviewed journal acknowledging the funder. It may also be presented at meeting. Additionally, a summary of the study findings will be provided to the study participants.

11.2 Authorship eligibility guidelines

Authorship will follow the International Committee of Medical Journal Editors criteria for manuscripts submitted for publication.

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13. APPENDICIES

13.1 Appendix 1 – Schedule of Procedures – Stage 3

Procedures	**Visits and timing (range)**					
	Screening	**Baseline**	**Intervention**	**2 month follow up**	**6 month follow up**	**Interviews**
	0 (-1 to 0) months	0 months	0 months	2 (2 to 3) months	6 (5 to 8) months	
Informed consent/assent	✓					
Inclusion & exclusion criteria	✓					
Demographics		✓				
Medical history		✓				
PedsQL asthma module		✓		✓	✓	
Asthma control test		✓		✓	✓	
Health utilisation		✓		✓	✓	
Paediatric asthma quality of life (paper)		✓		✓	✓	
Randomisation		✓				
Access to trial website			✓			
Web based intervention			✓ (intervention group only)			
Qualitative interviews						✓
Adverse event assessments				✓	✓	

13.2 Appendix 2 – baseline data questionnaire

1. How old are you? **___years**

2. Are you male or female? Please circle one: **Male** **Female** **Prefer not to say**

3. Which professionals do you see about your asthma? Please circle all that apply.
   General practitioner (GP) **Nurse at GPs** **Hospital consultant**
   Nurse at hospital **School nurse** **Community nurse**
   Pharmacist **Psychologist** **Other**, please state_____

4. How often do you use your blue reliever asthma inhaler? Please circle one:
   Never **Less than once a month** **Once a month**
   Once a week **2-3 times a week** **4 or more days per week**

5. What type of preventer medication do you use? Please circle all that apply:
   Clenil **Flixotide (fluticasone)** **Pulmicort (budesonide)**
   Alvesco (ciclesonide) **Seretide** **Symbicort**
   Qvar **Singular (montelukast)** **Slo-phy (theophylline)**
   Other (please specify _____)

6. How often do you miss taking your preventer inhalers? Please circle one:
   Never miss **Occasionally** **Once a week** **Half the time** **Most of the time**

7. How many courses of steroid tablets (eg prednisolone) did you need in the last 2 months?

8. How many days of school did you miss in the last 2 months because of your asthma (if you aren't sure, please estimate)?

9. How many hospital stays (over 4 hours) have you ever had because of your asthma (if you aren't sure, please estimate)?

10. How would you best describe the ethnic origin of your family? Please circle:
    White/English/Scottish/Welsh **White Irish** **White other**
    Black African **Black Caribbean** **Black other** **Indian** **Pakistani**
    Bangladeshi **Chinese** **Other**

13.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	V1.1	2021 03 26	SE	Updated consent/assent process and participant journey, to comply with feedback from REC.

Protocol amendments will be submitted to the Sponsor for approval prior to submission to the REC committee.