BREATHE

Breathing **RE**training for **A**sthma – **T**rial of **H**ome **E**xercises

A controlled study of the effectiveness of breathing retraining exercises taught by a physiotherapist by either instructional DVD or by face-to-face sessions in the management of asthma in adults.

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Protocol authorised by:

Name: Mike Thomas **Role:** Chief Investigator

Signature:  **Date:** 2/8/2014

MAIN TRIAL CONTACT

Chief Investigator and Medical Expert:

Prof Mike Thomas
Professor of Primary Care Research
Primary Care & Population Sciences
University of Southampton, UK
Aldermoor Health Centre,
Aldermoor Close, Southampton
SO16 5ST

Tel: 02380 241050
Email: D.M.Thomas@soton.ac.uk

TRIAL COORDINATION CENTRE

For general trial and clinical queries e.g. subject queries, trial supplies, data collection, please contact in the first instance:

BREATHE: Clinical Trial Coordinator : Lynda Taylor

Tel: 023 80 777222
Ext: 3828
Email: L.taylor@soton.ac.uk

Address: University of Southampton Clinical Trials Unit
Mail point 131
Southampton General Hospital
Tremona Road
SOUTHAMPTON
SO16 6YD

Tel: 023 8120 5154
Fax: 0844 7740621
Email: ctu@southampton.co.uk
Web: www.ctu.soton.ac.uk

Randomisation
(Mon-Fri 0900-1700)

Tel: 023 8120 4507

SAE Reporting

Fax: 0844 7740621

SPONSOR

The University of Southampton is the research sponsor for this trial. For further information regarding sponsorship conditions, please contact the Head of Research Governance at:

Address: Research Governance Office
The University of Southampton
Room 4055, Building 37
Highfield Campus
Southampton
SO17 1BJ

Tel: **023 8059 5058**
Fax: **023 8059 5781**
email: **rgoinfo@soton.ac.uk**

FUNDER

This trial is primarily funded by the NIHR Health Technology Assessment Programme with additional financial support from local CLRN Networks.

Protocol Information

This protocol describes the BREATHE trial and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other subjects; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but sites entering subjects for the first time are advised to contact the University of Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and all other regulatory requirements, as appropriate.

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LIST OF ABBREVIATIONS

ACPRC	Association of Chartered Physiotherapists in Respiratory Care
ACQ	Asthma Control Questionnaire
AE	Adverse Event
ANCOVA	Analysis of covariance
AR	Adverse Reaction
AQLQ	Asthma Quality of Life Questionnaire
BTS	British Thoracic Society
CEACs	Cost-effectiveness acceptability curves
CI	Confidence Interval
CLRN	Comprehensive Local Research Network
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRD	Centre for Research and Dissemination
CRF	Case Report Form
CSP	Chartered Society Physiotherapy
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
DMEC	Data Monitoring and Ethics Committee
EuroQol	European Quality of Life Questionnaire
EQ-5D	European Quality of Life Questionnaire
FENO	Fraction Of Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in 1 Second
FVC	Forced Volume Vital Capacity
HAD	Hospital Anxiety and Depression questionnaire
HTA	Health Technology Assessment
ICERs	Incremental Cost Effectiveness Ratios
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
ITT	Intention To Treat
MCID	Minimal Clinically Important Difference
MRC	Medical Research Council
PCRN	Primary Care Research Network
PEFR	Peak Expiratory Flow Rate
QALYs	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UKCRC	United Kingdom Clinical Research Collaboration
UoSCTU	University of Southampton Clinical Trials Unit

KEYWORDS

Asthma, Breathing Exercise Instruction, face-to-face physiotherapist led retraining, DVD

TRIAL SYNOPSIS

Title: BREATHE
A controlled study of the effectiveness of breathing retraining exercises taught by a physiotherapist by either instructional DVD or by face-to-face sessions in the management of asthma in adults.

Sponsor: University of Southampton

Sponsor Ref Number: RGO Ref: 8568

Funder: NIHR Health Technology Assessment programme

Trial Phase: Phase 4

Indication: Asthma

Primary Objectives:

- To produce a breathing retraining programme for people with asthma (aged 16 to 70 years), incorporating breathing exercise instruction in an audio-visual format (as a DVD) with supporting written material.
- To perform a randomised controlled trial to assess the effect of the programme in comparison with usual care, on asthma-related health status, parameters of symptomatic and physiological asthma control and on asthma-related health resource use in people with impaired health status due to asthma over 12 months following the provision of the intervention.
- To perform a randomised controlled trial to assess the effect of the programme in comparison with that of 'face-to-face' physiotherapist-led retraining of similar content.

Secondary Objectives:

- To perform a qualitative process evaluation on 12-15 subjects in each arm of the trial, purposively sampled for diversity
- To estimate the cost-effectiveness of the breathing retraining interventions delivered by DVD and by face-to-face instruction, using data collected from the trial and from the GP held clinical records
- To perform an initial 'internal pilot' in 2 centres to confirm recruitment targets and protocol viability, and subsequently to extend recruitment to further centres (approximately 20)

Rationale:
Although effective drug treatment exists for asthma, many people continue to have distressing symptoms and impaired quality of life. Recent surveys show that over half of all adults with asthma in the UK are not properly controlled on their current treatment regimen, resulting in impaired quality of life, and increased costs to the community.

Many people with asthma are interested in non-drug asthma treatments, particularly in breathing exercises. Several recent studies have shown benefits from undergoing a short breathing exercises course taught by a respiratory physiotherapist for people who remained symptomatic despite usual treatment. There is currently not enough access to suitable trained

physiotherapists to provide such a service to most people with asthma in the UK. We propose to provide the same breathing retraining programme we have previously shown to be effective when taught 'face-to-face' by a physiotherapist or as a DVD, that patients can use in their own home in addition to their standard treatment. We will see whether this type of instruction is better than the 'usual care' that is currently provided, and whether it is as good as the 'face-to-face' physiotherapist instruction (which is more expensive and less convenient for patients).

We hypothesise that breathing retraining exercises taught by an audio-visual educational package consisting of a instructional DVD programme and supporting written information will result in clinically important improvements in asthma-related quality of life and in asthma control above 'usual care' and of a similar magnitude to those resulting from 'face-to-face' physiotherapist instruction.

Trial Design:
Pragmatic observer blinded 3 arm parallel group randomised controlled trial comparing breathing retraining through a DVD with 'face-to-face' physiotherapy and a 'control' of usual care for adults with asthma and impaired health status.

Sample size :
585 subjects in total. 234 in DVD arm, 234 in usual care arm, 117 in 'face-to-face' physiotherapy arm, (split by treatment group). The total number recruited may be extended during the trial to enable us to reach our target of 525 complete data sets for analysis (210 each for the DVD and usual care arms, 105 for the face-to-face arm).

Inclusion Criteria:

- Full practice registration for a minimum of 12 months prior to enrolment
- Age 16-70 yrs
- Physician diagnosed asthma in medical record
- ≥1 anti-asthma medication prescription in the previous year (determined from the physician prescribing records)
- Impaired asthma-related health status (Asthma Quality of Life Questionnaire score of <5.5)
- Informed consent

Exclusion Criteria:

- Asthma judged at the baseline assessment to be dangerously unstable and in need of urgent medical review (if unstable asthma is found, the patient will be referred back to usual primary care clinician for review)
- Documented diagnosis of Chronic Obstructive Pulmonary Disease (COPD)

We aim to allow broad entry criteria (with inclusion of smokers, and not insisting on physiological demonstration of reversible airflow obstruction) in order to allow generalisability of research findings to mild-to-moderate UK asthma populations treated in primary care NHS practice.

Duration of Intervention:

- Face-to-face physiotherapy Arm: 3 sessions lasting 30 minutes at approximately 2 weekly intervals
- DVD – For use by participants at own home as convenient

Control Group:

- Usual GP care for adults with asthma

Primary Trial Endpoints:

- Analysis of the between-group (Intention-To-Treat (ITT))
- Change in asthma-specific health status (AQLQ (short version) score)

Secondary Trial Endpoints:

- Asthma Control Questionnaire score; Lung function (FEV1, FEV1/FVC ratio, PEFR)
- Fraction of exhaled nitric oxide
- Health status (EuroQOL)
- Anxiety and depression scores (HAD questionnaire; Hyperventilation (Nijmegen) questionnaire
- Oral corticosteroid courses
- Bronchodilator use
- Asthma related health resource use
- Smoking status
- Cost effectiveness/utility
- Patient reported process evaluations (questionnaires)
- Estimates of adherence (use of exercises)

Total Number of Sites : 20 GP Practices

SCHEDULE OF OBSERVATIONS AND PROCEDURES

Visit:	Pre screen	Baseline assessment		3 physio sessions, 2 weekly intervals	6-8 weeks post baseline	3 month Follow up postal questionnaires	6 month Follow up postal questionnaires	12 month Follow up visit with study nurse
Patient Information Sheet posted	x							
mini-AQLQ questionnaire posted	x							
Informed Consent		x						
Incl /Exclusion Criteria			x					
Questionnaires: Mini-AQLQ, Nijmegen Hyperventilation, HAD, ACQ, EQ5D			x					x
Expectancy : Beliefs about asthma, First impressions (Physio and DVD only)			X (after randomisation)					
Questionnaires: Mini AQLQ, HAD, ACQ, EQ5D						x	x	
Questionnaires: Treatment experience (physio only), Treatment experience (DVD only), Treatment adherence 3 month (Physio and DVD only)						x		
Treatment adherence 6 & 12 month (Physio and DVD only)							x	x
Questionnaire: Respondent Costs						x		x
Clinical Details			x					x

Visit:	Pre screen	Baseline assessment	3 physio sessions, 2 weekly intervals	6-8 weeks post baseline	3 month Follow up postal questionnaires	6 month Follow up postal questionnaires	12 month Follow up visit With study nurse
Physiological measurements: Spirometry and FENO		x					x
Randomisation		x					
Provision of DVD & 'Booklet' Group 1		x					
Face-to-face Physiotherapy			x				
Process Evaluation Telephone interview for 12 to 15 patients in each group				x			
Medical Notes Review							x
Adverse Events		x	x		x	x	x

1. INTRODUCTION

1.1 BACKGROUND / RATIONALE

Asthma affects 5 million people in the UK and costs the NHS in excess of £1 billion. Although pharmacotherapy is effective and can provide control for many patients (1), surveys repeatedly show that outcomes remain sub-optimal. A recent European survey showed that less than half of adults with asthma achieved good symptom control (2). Many patients have concerns about taking regular medication, particularly inhaled corticosteroids.

Surveys of complementary and alternative medicine in asthma show high level of use, with up to 79% of adults and 78% of children reporting trying various treatments, include breathing modification (3). Breathing techniques are amongst the most commonly used complementary techniques, with up to 30% reporting having used them to control their symptoms (4). The James Lind Alliance and the patient organisation Asthma UK have both identified breathing exercises for asthma as a priority area for research.

Asthma encompasses a variety of phenotypes, and different therapeutic approaches may be effective in different patients (5). Symptoms attributed to dysfunctional breathing have been reported to be more frequent in people with asthma than in the general population (6,7). A number of controlled studies have investigated breathing modification techniques, and have reported beneficial outcomes. Breathing control techniques investigated have included alternative techniques such as the Butekyo breathing method (8-12) and yogic breathing (13-15). Recent studies have shown clinically important effectiveness for people with asthma in the UK from physiotherapist administered breathing exercises (16-18).

The evidence base for the effectiveness of breathing therapies for treating asthma has been assessed in several reviews. The most recent systematic review of the effectiveness of physiotherapist taught breathing training in asthma was published in Thorax in 2009 (19), as part of a review of physiotherapy interventions in the treatment of respiratory diseases in adults. This document was the report of a collaborative multi-disciplinary review undertaken by the British Thoracic Society (BTS) and the Association of Chartered Physiotherapists in Respiratory Care (ACPRC), the respiratory clinical interest group of the Chartered Society of Physiotherapy (CSP). Its purpose was to critically appraise the evidence for respiratory physiotherapy techniques in respiratory diseases, and used an explicit evidence-based methodology. This consisted of an initial literature search (conducted by the Centre for Research and Dissemination (CRD), York, UK). Papers and abstracts identified were appraised and graded by 2 trained assessors using the Scottish Intercollegiate Network (SIGN) methodology, with a third in the event of a disagreement. The assessment of breathing exercises for asthma was: 'Breathing exercises, incorporating reducing respiratory rate and/or tidal volume and relaxation training, should be offered to patients to help control the symptoms of asthma and improve quality of life. (Grade A)'. Recent papers from members of this

HTA grant application provided evidence supporting this recommendation. A prior Cochrane review of breathing exercises for asthma was performed in 2004 (20), before several large studies informing the BTS review had reported. This review stated that due to the diversity of breathing exercises and outcomes used, it was impossible at that time to draw conclusions from the available evidence. The review stated that trends for improvements were noted in a number of outcomes and warranted large-scale studies in order to clarify their effectiveness in the management of asthma. Subsequently, Slader (3) reported a double-blind randomised controlled trial (RCT) of breathing techniques in asthma and concluded that breathing techniques may be useful in patients with mild asthma who use a reliever inhaler frequently. This Australian study investigated the effects of 2 different breathing training programmes taught by physiotherapists and delivered as a videotaped instructions programme that the subjects completed at home and without face-to-face supervision. Both programmes were associated with improved health status and major reductions in bronchodilator use from baseline values. These instructional interventions have subsequently been made available as Internet downloads and have been used in Australia to improve asthma control in routine clinical practice. This study provides some evidence that breathing training programmes delivered in an audio-visual form, as planned in our study, are feasible and potentially may produce beneficial outcomes in asthma.

A 2007 UK primary care based RCT (17) demonstrated that breathing retraining and relaxation taught by a physiotherapist in face-to-face sessions significantly reduced respiratory symptoms and improved health-related quality of life in comparison with 'usual care'. The population studied consisted of community treated asthmatics with mild and moderate disease. The contents of the breathing training programme in this study were very similar to those in our proposed study, but only face-to-face instruction was investigated and no economic analysis was made. A Canadian RCT published in 2008 (12) adds further support to breathing training in asthma, also finding significant reductions in asthma symptoms. In this study, a breathing training intervention delivered by physiotherapists in a face-to-face setting was compared to the Butekyo breathing method (also taught in face-to-face sessions by a therapist). Large magnitude but similar improvements from baseline levels of health status and symptoms were seen in both groups.

The most recent and largest RCT was published in 2009 and investigated the effects of a physiotherapist-delivered breathing training intervention of very similar content to that proposed in the face-to face arm of the current trial (16). This study controlled for non-specific 'placebo-like' effect of professional contact and sympathetic attention by giving the control group the same amount of professional contact time (with an experienced respiratory nurse providing asthma education). Significant improvements from baseline were seen in patient-reported asthma outcomes for both groups after 1 month, with trends favouring the breathing training group, and at 6 months a large and significant difference between groups as found in favour of breathing training. Significant improvements were seen between groups in asthma-related quality of life, anxiety and depression and in Nijmegen questionnaire score (measuring

hyperventilation-related symptoms), and a trend was seen for an improvement in symptomatic asthma control. No effect on airway inflammation or physiology was found. No economic evaluation was made.

The inclusion of these subsequent trials to those in the Cochrane review as part of the BTS review led the authors to conclude that the evidence supporting breathing training for people with asthma was of 1++ strength. However, no recommendation on the most clinically or cost effective way of providing this intervention was made. Most of the studies contributing to the evidence base have involved 'face-to-face' interventions, and it is here that the evidence is strongest. Only two preliminary studies have investigated the use of videotaped or DVD provided instructional interventions (8,13), with some evidence that this modality may also be effective. No previous studies have compared a DVD breathing training intervention to a face-to-face breathing retraining intervention. In this study, we aim to assess the effectiveness of the intervention not only in comparison to usual care or a placebo, but also to assess its equivalence to an intervention of known benefit. The logistic and economic implications of making this intervention available to all who could potentially benefit in the UK through a face-to-face physiotherapy programme are considerable. If comparable effectiveness can be shown from a video based training programme, this is likely to provide a more efficient and economic service to patients.

The current evidence shows that a programme of breathing training comprising three or more face-to-face sessions delivered by a specialist respiratory physiotherapist is effective in improving patient-reported endpoints such as symptoms, health status and psychological wellbeing for people with asthma, and may be effective in reducing rescue bronchodilator medication usage. There are suggestions that similar beneficial effects may be achieved through the use of videotaped instructional interventions rather than face-to face instruction. However, the relative clinical and cost-effectiveness of different approaches to breathing training has not been adequately assessed. If similar benefits can be achieved without face-to-face contact with a healthcare professional, it is likely that the health resource implications of providing breathing training would be reduced, and that this technology could be realistically made available to the many people with asthma who could potentially benefit from it. Therefore, we propose to transfer the key components of the physiotherapist delivered programme that we (and others) have shown to be effective into a DVD format and to compare the effects of this intervention with that of face-to-face physiotherapist training, and with 'usual care'.

Our programme will include a full health economic evaluation, as the previous research has been focused on the clinical effectiveness, rather than the cost-effectiveness, of breathing training.

2. TRIAL OBJECTIVES

1) To produce a breathing retraining programme for people with asthma (aged 16 to 70 years), incorporating breathing exercise instruction in an audio-visual format (as a DVD) with supporting written material.
2) To perform a randomised controlled trial to assess the effect of the programme in comparison with usual care, on asthma-related health status, parameters of symptomatic and physiological asthma control and on asthma-related health resource use in people with impaired health status due to asthma over 12 months following the provision of the intervention.
3) To perform a randomised controlled trial to assess the effect of the programme in comparison with that of 'face-to-face' physiotherapist-led retraining of similar content.
4) To perform a qualitative process evaluation on 12-15 subjects in each arm of the trial, purposively sampled for diversity.
5) To estimate the cost-effectiveness of the breathing retraining interventions delivered by DVD and by face-to-face instruction, using data collected from the trial and from the GP held clinical records.
6) To perform an initial 'internal pilot' in 2 centres to confirm recruitment targets and protocol viability, and subsequently to extend recruitment to further centres (approximately 20).

3. TRIAL DESIGN

The BREATHE trial is a pragmatic observer blinded 3 arm parallel group randomised controlled trial comparing breathing retraining through a DVD with 'face-to-face' physiotherapy and a 'control' of usual care for adults with asthma and impaired health status.

Phase 1: Qualitative piloting

Development phase- transfer of programme to audio-visual media:

Development of patient educational material – 6 months

During the first 6 months the patient educational materials will be developed by members of the team including, physicians, physiotherapists, health psychologists, communications technology specialists and patient representatives. Draft scripts for the DVD and accompanying booklet will be created, consisting of:

- Detailed explanation and illustration of how to carry out the exercises, including how to adapt them to the patient's particular needs and modify them as necessary over time
- Motivational components, explaining the rationale for the exercises and addressing common doubts and concerns (e.g. about whether they will be helpful, safety issues, how to interpret and manage any symptoms they seem to provoke)

- Components to help patients adhere to the exercises, including a written plan for patients to complete (which family members can co-sign) detailing when and where they will carry them out, a chart for monitoring adherence and progress over time, advice on overcoming common barriers to carrying them out.

The draft materials will be piloted in depth with a panel of 12-18 members of the target population, purposively sampled for diversity in terms of age, gender, education and symptom profile, who have agreed to give feedback one or more times during the development process. In tape-recorded face-to-face interviews we will first use open-ended questions to explore attitudes to the proposed treatment method in the context of health beliefs and then use 'think aloud' methods (21) to elicit spontaneous reactions to all proposed materials. We will carry out immediate inductive coding of themes (22) arising in the qualitative data in order to identify when we reach saturation (i.e. no new significant themes are emerging). We will modify the scripts as necessary, based on this feedback. If substantial changes are required then time permitting, we will use further interviews to check that the modifications have successfully addressed changes needed. After professional production of the DVD and booklet we will send them out to members of our panel to try out and then provide final feedback by telephone interviews.

Phase 2: Randomised controlled clinical trial (RCT) - pragmatic observer blinded 3 arm parallel group randomised controlled trial

The methodology of this RCT is based on that of the GLAD study, a 2 armed RCT comparing face-to-face physiotherapist breathing instruction with a control of asthma education (16).

We will perform a pragmatic observer blinded 3 arm parallel group randomised controlled trial comparing a breathing retraining programme delivered through a DVD with a 'face-to-face' physiotherapist programme and a 'control' arm receiving usual care for adults with asthma and impaired health status. Three arms are needed to confirm superiority of the DVD over usual care and comparable efficacy to 'face-to-face' physiotherapy. The study is dual powered to show superiority of the breathing retraining DVD over usual care and equivalence with 'face-to-face' physiotherapist instruction. The focus of this research is on the DVD, as this is most likely to be translated into every-day practice. As the face-to-face physiotherapy already has evidence of effectiveness, and our aim is to show comparable effectiveness of the DVD and superiority of the DVD over usual care, we are using a 2:2:1 randomisation plan (DVD: usual care: face-to-face physiotherapy). This will reduce the costs and logistics of the trial, as the face-to-face intervention is associated with the largest use of time and resources. Subjects will be recruited in the setting of UK general practices who are members of the South-West Primary Care Research Network. Broad entry criteria will be used to allow representative patients to participate and so provide the trial with external validity. The RCT is described in detail below. An internal pilot will initially occur in two GP practices. An assessment of the recruitment rate and of the logistics of the trial protocol will

be made after this internal pilot, and minor protocol adjustments made as appropriate. Provided significant protocol changes are not made, it is planned to include the data from subjects participating in the pilot in the final analysis.

Phase 3: Health Economic evaluation

The resources needed to design and develop the DVD intervention will be recorded during phase 1. During the trial we will also record all resources required to provide the interventions in the DVD and the 'face-to-face' physiotherapy groups. Information will also be collected on all asthma-related healthcare costs for the 1-year follow up period.

3.1 TRIAL OUTCOME MEASURES

Outcome measures will be between-group and within-group changes from baseline to the end of the study (12 months).

The primary outcome will be an analysis of the between-group (Intention-To-Treat (ITT)) change in asthma-specific health status (AQLQ (short version) score).

Secondary outcome measures will be: Asthma Control Questionnaire score; Lung function (FEV1, FEV1/FVC ratio, PEFR); Fraction of exhaled nitric oxide; Health status (EuroQOL); Anxiety and depression scores (HAD questionnaire; Hyperventilation (Nijmegen) questionnaire; Oral corticosteroid courses; Bronchodilator use; Asthma related health resource use; Smoking status; Cost effectiveness/utility; Patient reported process evaluations (questionnaires) and estimates of adherence (use of exercises).

4. SELECTION AND ENROLEMENT OF SUBJECTS

4.1 SCREENING AND PRE-REGISTRATION / RANDOMISATION EVALUATIONS

We plan to recruit 585 patients (234 in each of the DVD and 'usual care' arms and 117 in the 'face-to-face' physiotherapy arm) from 20 general practice centres, aiming for up to 30 subjects per GP centre. All general practices now have 'asthma registers' of all patients with currently active asthma, as this is a requirement for payment under the NHS Quality and Outcomes Framework system. Patients on the practice asthma register meeting the inclusion criteria below and who have received prescriptions for any asthma medication in the previous 12 months will be identified from the practice computer records by practice staff. A mail merge will be performed at the practice sending out a study invitation letter with full information. People wishing to have more information about the trial will be provided with contact telephone numbers to enable them to speak to study staff at the University of Southampton Clinical Trials Unit (UoSCTU), or encouraged to talk to their GP. People potentially interested in study participation will be asked to provide contact details, to complete the mini-AQLQ (Asthma Quality of Life Questionnaire (23) and to

return these to the Study Co-ordinator in a pre-addressed stamped envelope. Only those with impaired health status (AQLQ score <5.5) will be recruited, as lack of impairment in health status does not allow 'room for improvement' in the primary outcome measure. In our previous work and other studies, 75% or more or people with asthma treated in the community have impaired health status.

Subjects meeting the entry criteria will be given an appointment to see the study nurse for the baseline visit, which will occur at the subject's general practice at a mutually convenient time. Any questions about the study will be answered, and informed consent obtained. A study nurse will perform the baseline assessment. This will consist of:

- Facilitating subject completion of validated questionnaires: Disease-specific health status (AQLQ) (23), Nijmegen hyperventilation questionnaire (24), Generic health status (EuroQOL, EQ-5D) (25); anxiety and depression scores (HAD questionnaire) (26), Asthma control questionnaire (ACQ) (27).
- Clinical details: Smoking status, asthma history, co-morbidities, medication, and exacerbation frequency.
- Physiological measurements: Spirometry (FEV1, FEV1/FVC ratio, PEFR), measured with standardized calibrated portable spirometer; Fraction of exhaled nitric oxide (FENO), measured with Aerocrine Mino portable monitor.

If a clinical assessment of potentially dangerous or unstable asthma is made by the trained study nurse, the subject will not enter the study but will be referred urgently back to their usual primary care asthma clinician. Participants who score greater than or equal to 16 in the HADs Questionnaire will be sent a letter from the trial team advising that they may wish to discuss this with their GP. When informed consent has been provided and the baseline assessment completed, the study nurse will telephone UoSCTU for randomisation (or use the web based system when in place). Those randomised to 'usual care' will be informed that they will be posted questionnaires in 3 and 6 months' time to complete and return to the study co-ordinator, and that a final assessment visit will be scheduled for 12 months post randomisation. Contact information will be provided. Those randomised to the DVD intervention will be provided with the written instructional material developed in phase 1 and the DVD. For those who do not have a DVD player at home, an inexpensive DVD player will be provided; it is however anticipated that most people will have access to one of these media players. Subjects will be given information that they will be posted questionnaires in 3 and 6 months to complete and return to the coordinator, and that a final assessment visit will be scheduled for 12 months. Contact information will be provided. For those randomised to the 'face-to-face' physiotherapy arm, they will be informed that they will receive 3 short sessions of contact with a respiratory physiotherapist for breathing retraining. These sessions will be approximately 30-40 minutes long and will occur at roughly 2 weekly intervals following randomisation. The retraining can occur at either the GP surgery, clinic setting or the patient's home according to convenience and preference. The content of the retraining programme

will be based on those shown to be effective in recent studies (16-18), and similar to the content of the DVD intervention.

Subjects will be informed that they will be posted questionnaires in 3 and 6 months time to complete and return to the study co-ordinator, and that a final assessment visit will be scheduled for 12 months post randomisation. Contact information will be provided for all three randomisation groups.

4.2 INCLUSION CRITERIA

- Full practice registration for a minimum of 12 months prior to enrolment
- Age 16-70 yrs
- Physician diagnosed asthma in medical record
- ≥1 anti-asthma medication prescription in the previous year (determined from the physician prescribing records)
- Impaired asthma-related health status (Asthma Quality of Life Questionnaire score of <5.5)
- Informed consent

4.3 EXCLUSION CRITERIA

- Asthma judged at the baseline assessment to be dangerously unstable and in need of urgent medical review (if unstable asthma is found, the patient will be referred back to usual primary care clinician for review)
- Documented diagnosis of Chronic Obstructive Pulmonary Disease (COPD) with a FEV1 percent predicted of 60% or lower

We aim to allow broad entry criteria (with inclusion of smokers, and not insisting on physiological demonstration of reversible airflow obstruction) in order to allow generalisability of research findings to mild-to-moderate UK asthma populations treated in primary care NHS practice.

4.4 REGISTRATION / RANDOMISATION PROCEDURES

Patients who meet the eligibility criteria for the study as determined by the inclusion and exclusion criteria will be registered with the University of Southampton Clinical Trials Unit by telephone by contacting the following number:

Randomisation Telephone: 023 8120 4507
Monday – Friday: 09.00 to 17.00hrs

All subjects will undergo screening investigations as detailed in section 4.1.

4.5 WITHDRAWAL CRITERIA

Participants are free to withdraw at any time without giving any reason.

Data collected up to the time of withdrawal may continue to be used in the study unless the participant expressly withdraws consent to the continued use of such data.

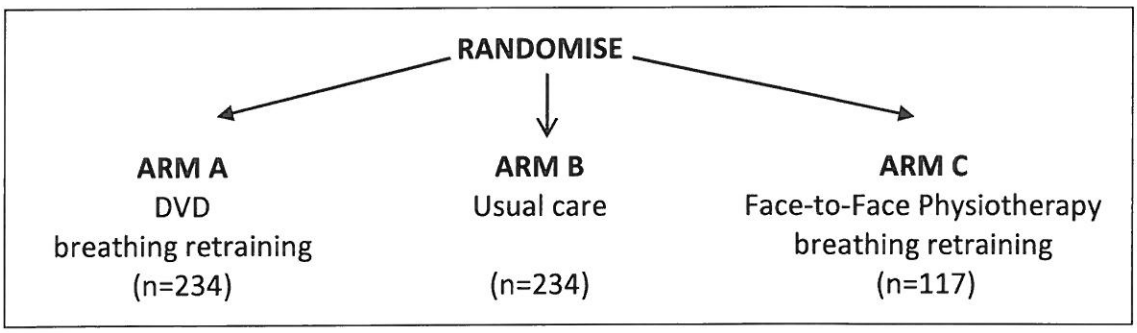
5. STUDY INTERVENTION

5.1 TREATMENT ARMS

We propose a prospective evaluation of a physiotherapy breathing retraining programme (already shown to be effective in face-to-face contact) delivered in a new DVD format. If effective, this could be used in routine NHS asthma care. The DVD breathing instruction programme will be developed in phase 1 of the project. In the subsequent randomised controlled trial (phase 2), we will assess the effectiveness of this DVD as adjuvant treatment for asthmatic adults with asthma-related health status impairment (AQLQ <5.5) despite pharmacotherapy. Consenting subjects will be randomly assigned to

- **Arm A:** Receipt of the DVD, (plus supporting written material)
- **Arm B**: Usual care
- **Arm C**: 3 sessions of 'face-to-face' physiotherapy breathing instruction (plus supporting written material)

In all 3 arms, no attempt will be made to change the standard asthma care provided in the practice.



6. ADVERSE EVENTS AND REPORTING

6.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with trial treatment or participation.

Serious Adverse Event (SAE): any untoward occurrence that:

- **Results in death**
- **Is life-threatening** – refers to an event in which the subject 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

- **Requires hospitalisation, or prolongation of hospitalisation**
- **Results in persistent or significant disability or incapacity**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AE that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Related Adverse Event: any serious adverse event thought to have resulted from administration of any of the research procedures (related) and where the type of event is not listed in the protocol as an expected occurrence (unexpected).

6.2 RELATEDNESS

The assignment of the relatedness to trial treatment of any serious event should be made by the investigator responsible for the care of the subject using the definitions in the table below.

If any doubt about the causality exists the local investigator should inform the UoSCTU who will notify the Chief Investigator. Other clinicians may be asked for advice in these cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the Ethics Committee will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any related relationship
Unlikely	There is little evidence to suggest there is a related relationship (e.g. the event did not occur within a reasonable time after the research procedure). There is another reasonable explanation for the event (e.g. the subject's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a related relationship (e.g. because the event occurs within a reasonable time after the research procedure). However, the influence of other factors may have contributed to the event (e.g. the subject's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a related relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a related relationship and other possible contributing factors can be ruled out.

6.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning

adverse event reporting should be directed to the UoSCTU in the first instance. A flowchart will be provided to aid in the reporting procedures.

6.3.1 Pre-existing Conditions

A pre-existing condition should not be reported as an AE unless the condition worsens by at least one CTCAE grade during the trial. The condition, however, must be reported in the pre-treatment section of the CRF, if symptomatic at the time of entry, or under concurrent medical conditions if asymptomatic.

6.3.2 Non serious Adverse Events

All adverse events that may be related to the study will be recorded in the relevant case report form and Adverse Event form and sent to the UoSCTU within one month of the form being due. As adults on average see their GP approximately 5 times per year for a variety of routine and unscheduled appointments (e.g. for medication review, self-limiting minor illnesses and long-term conditions unrelated to asthma), many medical encounters are of no relevance to the study. Events that will be recorded include any judged by the study nurse to be possibly related to the study. In particular, all medical encounters related to the following medical areas or symptoms will be recorded in the Adverse Events form:

Psychological morbidity: any events relating to anxiety, depression or mood disorders

Respiratory morbidity: any events relating to breathing or chest symptoms

Musculoskeletal, Abdominal and chest pain: any events relating to pain in these systems unless known to be associated with an unrelated pre-existing condition.

The study nurses are advised to record any event for which there is uncertainty as to whether it is study related or not, and to discuss with the local PI or CI.

6.3.3 Serious Adverse Events

All SAEs (including those that are expected and related) will be reported within 24 hours of the local site becoming aware of the event. The SAE form asks for nature of event, date of onset, severity, corrective therapies given or action taken, outcome and relatedness (i.e. unrelated, unlikely, possible, probably, definitely). The responsible centre Principal Investigator will assign the relatedness and expectedness of the event. Additional information will be provided as soon as possible if the event has not resolved at the time of reporting.

6.3.4 Reporting Details

An SAE form should be completed for all SAEs and faxed to the UoSCTU within 24 hours.

> Complete the SAE form & fax or email a scanned copy of the form with as many details as possible to the UoSCTU together with anonymised relevant treatment forms and investigation reports.

Or

Contact the UoSCTU by phone for advice and then fax or email a scanned copy of the completed SAE form.

The UoSCTU will notify the REC of all SUSARs occurring during the trial within 15 days. All investigators will be informed of all SUSARs occurring throughout the trial.

Local Investigators will report any Unexpected and Related Serious Adverse Events and / or SAEs as required by their Local Research & Development Office.

6.3.5 Follow Up and Post-study Serious Adverse Events

The reporting requirement for SAEs affecting subjects applies for all events occurring up to the end of the last treatment. All unresolved adverse events should be followed by the local investigator until resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's general practitioner, believes might reasonably be related to participation in this study. The investigator should notify the University of Southampton Clinical Trials Unit of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

7. ASSESSMENT AND FOLLOW-UP OF SUBJECTS

7.1 DEFINITION OF END OF TRIAL

The trial is defined as ended when the last randomised participant has a final assessment performed or the last participant withdraws from the trial.

Questionnaire assessments at 3 and 6 months

All subjects will be posted questionnaires to complete and return in stamped addressed envelopes at 3 and at 6 months following randomisation. The questionnaire will consist of: AQLQ, Asthma Control Questionnaire, HAD

questionnaire, EQ5D, Treatment experience and adherence questions (and respondent costs questionnaire at 3 months only). Those not returning the questionnaires after 3 weeks will receive a single postal reminder followed 1 week later by a single telephone call or email from the study team. The participant will be offered the opportunity to complete the mini AQLQ questionnaire over the telephone at this point.

NB- As detailed in the Patient Information Sheet, participants medical records and data collected for the study will be looked at by authorised persons from the University of Aberdeen and University of Southampton Clinical trials Unit.

All telephone calls will be carried out in a private environment by nominated UoSCTU staff with the required authorisation permissions in place.

12 months final assessment visit

Subjects will be contacted by telephone or mail to arrange the final visit, which will occur 12 months (±4 weeks) after the initial visit. Participants who do not respond will be sent a single reminder letter and given the option to complete the 12 month questionnaires by post. The study nurse performing the final assessment will be a different staff member from that performing the baseline assessment. They will be blinded to the subject's randomisation group. The assessment will consist of:

- Facilitating subject completion of validated questionnaires: Disease-specific health status (AQLQ), Nijmegen hyperventilation questionnaire, Asthma Control Questionnaire, generic health status (EuroQOL); anxiety and depression scores (HAD questionnaire), respondent costs questionnaire.
- Clinical details: Smoking status, asthma history, co-morbidities, medication, and exacerbation frequency.
- Physiological measurements: Spirometry (FEV1, FEV1/FVC ratio, PEFR), measured with standardized calibrated portable spirometer; fraction of exhaled nitric oxide (FENO), measured with Aerocrine Mino portable monitor.
- A short questionnaire exploring subject perception of the intervention they received and their experiences of being in the trial

If the trained study nurse makes a clinical assessment of potentially dangerous or unstable asthma, the subject will be referred urgently to their usual primary care asthma clinician.

Data handling

Each subject will be given a unique identifier code at randomisation. All data will be entered into an electronic database by UoSCTU staff (data officers) blinded to the subject's study status. Research staff blinded to the subject's study status will perform all statistical analyses.

Qualitative process evaluation

An open-ended qualitative study will be used to evaluate patient experiences of the trial and identify factors that may have influenced trial outcomes. We will carry out telephone interviews with 12-15 patients in each arm of the trial, purposively sampled for diversity in terms of age, gender, education and symptom profile, and seeking to ensure representation of participants with poor adherence or outcomes. The interviews will be carried out 6 to 8 weeks after baseline and will consist of open-ended questions asking about experiences of the trial, including changes, positive and negative aspects, suggestions for improvement etc. All data will be tape-recorded, fully transcribed and analysed inductively by thematic analysis (28).

Health economic evaluation

The resources needed to design and develop the DVD intervention will be recorded during phase 1. During the trial we will also record all resources required to provide the interventions in the DVD and the 'face-to-face' physiotherapy groups. Information will also be collected on all asthma-related healthcare costs for the 1-year follow up period. These will be collected using medical records to collect all asthma related NHS service use (primary and secondary care patient contacts, investigations and prescriptions) with maximum possible use of electronic records, supplemented where necessary by paper records. Respondent questionnaires will be completed at 3 month and 12 month data collection points to quantify time off work/college; and out of pocket expenses. This will constitute a societal perspective to the analysis.

Resources will be costed using appropriate local and national cost data. Total NHS and societal costs will be estimated for each group allowing estimates of the incremental costs of the breathing DVD and 'face-to-face' physiotherapy programmes compared to usual care. Health related quality of life will be assessed using the EuroQol (EQ5D) collected at baseline, 3, 6, and 12- months. These EQ5D scores will be used to generate quality adjusted life years (QALYs). No mortality differences are expected. The superiority analyses will include a cost-utility study (cost per QALY) and cost-effectiveness (cost per significant change in asthma-related health status, i.e. a change of 0.5 in the AQLQ score). If non-inferiority is proven between the face-to-face and DVD interventions, cost minimisation will be carried out. Where appropriate, incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs) will be estimated. Sensitivity analysis will be used to test any major assumptions made in the costing/analysis process. We will check for the extent of missing data at the analysis stage. If considered necessary, we will use appropriate statistical methods (for example multiple imputation) to impute missing data. This will be presented as a sensitivity analysis, i.e. in addition to the complete case analysis.

8. STATISTICS AND DATA ANALYSIS

8.1 STATISTICAL PLAN INCLUDING INTERIM ANALYSIS

Sample Size:

1. For equivalence of DVD programme and face-to-face programme.

In a previous HTA study comparing different pharmacotherapy options in asthma (the ELEVATE study, Controlled-Trials.com number, ISRCTN99132811, Price et al, 2011), treatments were deemed to be equivalent if the 95% CI for mean difference between groups in AQLQ was wholly included between -0.3 and +0.3. Our sample size calculation for equivalence therefore uses the same equivalence boundary (i.e. between -0.3 and +0.3). However, we have assumed that the SD of the between group difference in AQLQ will be a conservative 25% smaller (i.e. 0.77) than that reported in our GLAD study (1.03). The justification for this is that the proposed equivalence analysis will compare two breathing training interventions as opposed to a breathing intervention versus usual care in the GLAD study. Since this is an equivalence study, as opposed to a non-inferiority study, a two-tailed 5% significance level was used in the calculations (29). Following published guidelines (30), the equivalence margin was therefore selected to be 'the largest difference that can be judged to be clinically acceptable and should be smaller than differences observed in superiority trials of the active comparator'.

Using Nquery 7.0 (specifically the MTEOU-1 two group t-test of equivalence in means – unequal n's program), the following justification of the sample size is obtained:

Sample sizes of 210 in the DVD breathing retraining group and 105 in the 'face-to-face' physiotherapy group are required to assess treatment equivalence with 90% power using an equivalence boundary for AQLQ of 0.3. This assumes: that the expected between group difference in mean AQLQ is zero; a two tailed 5% significance level; common standard deviation for AQLQ of 0.77 and a lower/upper limit of -0.3/+0.3 for the 95% confidence interval of the between group difference in AQLQ.

In the unlikely event that the between group AQLQ standard deviation is higher than our estimated 0.77, assuming all other parameters stayed the same, we would still have 80% power to declare equivalence between the DVD breathing retraining group and the 'face-to-face' physiotherapy group as long as the between group SD was no higher than 0.89.

2. For superiority of both the DVD-delivered and the face-to-face programme over 'usual care'

For the superiority sample size calculations, there is no widely acceptable MCID for between group change in AQLQ, although the MCID for within person change in AQLQ is reported to be 0.5 (SD 0.41) (31). Therefore, we approached the superiority sample size calculation in two ways. Firstly, using the published within person MCID of 0.5 and secondly, using estimates from the GLAD study, a between group mean (SD) difference in AQLQ at 6 months of 0.38 (1.03).

Using an MID of 0.5

Nquery 7.0 (specifically the MTTOU-1 two group t-test of equal means – unequal n's program) shows that a two group t-test with a 5% one-sided significance level will have 90% power to detect a difference in mean AQLQ of 0.5 or greater, assuming that the common standard deviation is 0.41, when the

sample sizes are 10 in the face-to-face breathing retraining and 20 in the 'usual care' groups.

Similarly, a two group t-test with a 5% one-sided significance level will have 90% power to detect a difference in mean AQLQ of 0.5 or greater, assuming that the common standard deviation is 0.41, when the sample size is 13 in each of the DVD-delivered and 'usual care' groups.
Using an MID of 0.38

A two group t-test with a 5% one-sided significance level will have 92% power to detect a difference in mean AQLQ of 0.38 or greater, assuming that the common standard deviation is 1.03, when the sample sizes are 105 in the face-to-face breathing retraining and 210 in the 'usual care' groups.

Similarly, a two group t-test with a 5% one-sided significance level will have 90% power to detect a difference in mean AQLQ of 0.38 or greater, assuming that the common standard deviation is 1.03, when the sample size is 130 in each of the DVD-delivered and 'usual care' groups.

Summary:
We aim to analyse 210 in each of the DVD and usual care arms and 105 in the face-to-face breathing retraining arm). Assuming a 10% dropout rate, we will therefore aim to recruit a total sample size of 585 patients (234 in each of the DVD and 'usual care' arms and 117 in the 'face-to-face' physiotherapy arm).

Statistical Analysis:

1. Analysis plan for equivalence study
Analysis and reporting of the equivalence comparison will follow published guidelines. It is known that full analysis set or ITT may lead to bias (from protocol violators, withdrawals and dropouts) and a resultant increase in type 1 error risk. Therefore, for the equivalence study, an ITT and a per protocol analysis will run simultaneously, neither having supremacy over the other. They should hopefully lead to similar conclusions giving the study a robust interpretation.

A 95% CI will be constructed for the mean difference in 12 month total AQLQ score between the DVD arm and the 'face-to-face' breathing retraining arm. Since the equivalence boundary is set at 0.3, equivalence will be declared if the 95% CI is wholly included between -0.3 and +0.3. If equality is not evident, then ANCOVA will be used to examine whether the 'face-to-face' breathing retraining arm is superior to the DVD arm via examination of the difference (and 95% confidence interval) of 12 month total AQLQ score (and each of the four domain scores) before and after adjustment for baseline AQLQ score and potential covariates such as age, gender, practice, smoking status etc.

ANCOVA will also be used to analyse the difference (and 95% confidence interval) for the secondary outcome measures (ACQ, lung function, fraction of exhaled nitric oxide, EuroQOL, anxiety and depression score, hyperventilation and patient enablement scores) at 12 months before and after adjustment for baseline values and potential confounders. Since we have data on AQLQ, ACQ and HADS at four time points (baseline, 3, 6 and 12 months) a repeated measures analysis will be used to examine change in each of these outcomes over time. For those secondary outcomes which involve count data (i.e. oral corticosteroid courses, bronchodilator use, asthma related healthcare resource use), Poisson regression analyses with a log link function will be performed to give rate ratios (and their 95% confidence intervals) in the DVD and 'face-to-face' breathing retraining arm both before and after adjustment for potential confounders such as smoking status and sociodemographic factors.

2. Analysis plan for superiority study

Baseline comparability between the three arms of the trial will be evaluated by examination of summary statistics (the mean and standard deviation or median and interquartile range for continuous variables, dependent on their distribution, and the number and percentage for categorical variables). In accordance with CONSORT guidelines, all comparative analysis will be conducted on an intention to treat (ITT) basis with a per protocol analysis performed as a sensitivity analysis.

For the primary outcome, analysis of covariance (ANCOVA) will be used to examine the 12-month total AQLQ score (and each of the four domain scores) across the three arms with initial adjustment for baseline AQLQ score and then for other potential covariates such as age, gender, practice, smoking status etc. Pair wise comparisons of AQLQ differences will be examined between the 'usual care' arm and each of the DVD and 'face-to-face' breathing retraining arms via calculation of one sided 95% confidence intervals. If the confidence interval includes +0.3 then superiority of either the DVD or 'face-to-face' breathing retraining arms over usual care will be rejected.

In a similar way, ANCOVA will also be used to analyse the continuous secondary outcome measures (ACQ, lung function, fraction of exhaled nitric oxide, EuroQOL, anxiety and depression score, hyperventilation and patient enablement scores). Since we have data on AQLQ, ACQ and HADS at four time points (baseline, 3, 6 and 12 months) a repeated measures analysis will be used to examine change in each of these outcomes over time. The 'usual care' arm will be compared to each of the DVD and 'face-to-face' breathing retraining arms in turn.

For those secondary outcomes which involve count data (i.e. oral corticosteroid courses, bronchodilator use, asthma related healthcare resource use), Poisson regression analyses with a log link function will be performed to give rate ratios in the DVD and 'face-to-face' breathing retraining arm compared to 'usual care' both before and after adjustment for potential confounders such as smoking status and sociodemographic factors.

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the trial, including the follow-up period.

Project Timetable
This study will run over 52 months.

0 – 10 months: qualitative study
10 – 12 months: ethics/R&D submissions in and approvals obtained
12 – 14 months: pilot RCT
14 – 15 months: assess pilot outcome, file an amendment if necessary
15 months: start main RCT assuming no amendment required, (or 15 – 17 months: amendment submitted and approved, 17 months start main RCT)
15/17 months – 34 months: RCT Interventions and data collection, rolling recruitment. Qualitative assessment
34-48 months: Complete follow-ups
48-52 months: Data analysis, writing final reports

9. REGULATORY ISSUES

9.1 CLINICAL TRIAL AUTHORISATION

This trial does NOT involve the testing of any Investigational Medicinal Products (IMPs) therefore approval from the Medicines and Healthcare products Regulatory Agency is not required.

9.2 ETHICS APPROVAL

The trial protocol has received the favourable opinion of a Research Ethics Committee.

The trial will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each subject's consent to participate in the trial should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the subject to refuse to participate in the trial without giving reasons must be respected.

The subject remains free to withdraw at any time from protocol treatment and trial follow-up without giving reasons and without prejudicing their further treatment.

9.3 CONSENT

Consent to enter the trial must be sought from each subject only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed and dated subject consent should be obtained. The right of the subject to refuse to participate without giving reasons must be respected. After the subject has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the subject's best interest, but the reasons for doing so

should be recorded. In these cases the subjects remain within the trial for the purposes of follow-up and data analysis. All subjects are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

9.4 CONFIDENTIALITY

Subjects' identification data will be required for the registration process. The UoSCTU will preserve the confidentiality of subjects taking part in the trial.

The investigator must ensure that subject's anonymity will be maintained and that their identities are protected from unauthorised parties. On CRFs subjects will not be identified by their names, but by an identification code. The investigator should keep a subject enrolment log showing codes, names and addresses.

9.5 INDEMNITY

Indemnity is covered by the University of Southampton

9.6 SPONSOR

The sponsor of the trial is the University of Southampton. UoSCTU has been delegated duties by the Sponsor relating to: submissions to regulatory authorities and GCP. Other delegated duties will be assigned to the NHS Trusts or others taking part in this trial by means of the site clinical trial agreement.

9.7 FUNDING

NIHR Health Technology Assessment programme are funding this trial.

9.7 DEVIATIONS AND SERIOUS BREACHES

Any trial protocol deviations/violations and breaches of Good Clinical Practice occurring at sites should be reported to the UoSCTU and the local R&D Office immediately. The UoSCTU will then advise of and/or undertake any corrective and preventative actions as required.

A breach of the protocol or GCP is considered 'serious', i.e. if it is likely to affect to a significant degree the safety or physical or mental integrity of the study participants or the scientific value of the study. If this occurs REC will be informed by the UoSCTU on behalf of the Sponsor within seven days of it coming to attention.

9.9 AUDITS AND INSPECTIONS

The trial may be subject to inspection and audit by University Southampton, under their remit as sponsor, the UoSCTU as the Sponsor's delegate and other regulatory bodies to ensure adherence to ICH GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

10. TRIAL MANAGEMENT

The Trial Management Group (TMG) is responsible for overseeing progress of the trial. The day-to-day management of the trial will be co-ordinated through the UoSCTU and oversight will be maintained by the Trial Steering Committee and the Data Monitoring and Ethics Committee (See Appendix 1)

11. PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigator, Statistician and Trial Coordinator. Members of the TMG and the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the UoSCTU.

12. REFERENCES

1. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA et al. Can guideline defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med 2004; 170(8):836-844.

2. Demoly P, Gueron B, Annunziata K, Adamek L, Walters RD. Update on asthma control in five European countries: results of a 2008 survey. European Respiratory Review 2010; 19(116):150-157.

3. Slader CA, Reddel HK, Spencer LM, Belousova EG, Armour CL, Bosnic-Anticevich SZ et al. Double blind randomised controlled trial of two different breathing techniques in the management of asthma. Thorax 2006; 61(8):651-656.

4. Ernst E. Breathing techniques--adjunctive treatment modalities for asthma? A systematic review. Eur Respir J 2000; 15(5):969-972.

5. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. Lancet 2008; 372(9643):1107-1119.

6. Thomas M, McKinley RK, Freeman E, Foy C. Prevalence of dysfunctional breathing in patients treated for asthma in primary care: cross sectional survey. BMJ 2001; 322(7294):1098-1100.

7. Thomas M, McKinley RK, Freeman E, Foy C, Price D. The prevalence of dysfunctional breathing in adults in the community with and without asthma. Prim Care Respir J 2005; 14(2):78-82.

8. Opat AJ, Cohen MM, Bailey MJ, Abramson MJ. A clinical trial of the Buteyko Breathing Technique in asthma as taught by a video. J Asthma 2000; 37(7):557-564.

9. Bowler SD, Green A, Mitchell CA. Buteyko breathing techniques in asthma: a blinded randomized controlled trial. Med J Aust 1998; 169(11-12):575-578.

10. Berlowitz D, Denehy L, Johns DP, Bish RM, Walters EH. The Buteyko asthma breathing technique. Med J Aust 1995; 162(1):53.

11. McHugh P, Aitcheson F, Duncan B, Houghton F. Buteyko Breathing Technique for asthma: an effective intervention. N Z Med J 2003; 116(1187):U710.

12. Cowie RL, Conley DP, Underwood MF, Reader PG. A randomised controlled trial of the Buteyko technique as an adjunct to conventional management of asthma. Respir Med 2008; 102(5):726-732.

13. Cooper S, Oborne J, Newton S, Harrison V, Thompson CJ, Lewis S et al. Effect of two breathing exercises (Buteyko and pranayama) in asthma: a randomised controlled trial. Thorax 2003; 58(8):674- 679.

14. Singh V, Wisniewski A, Britton J, Tattersfield A. Effect of yoga breathing exercises (pranayama) on airway reactivity in subjects with asthma. Lancet 1990; 335(8702):1381-1383.

15. Manocha R, Marks GB, Kenchington P, Peters D, Salome CM. Sahaja yoga in the management of moderate to severe asthma: a randomised controlled trial. Thorax 2002; 57(2):110-115.

16. Thomas M, McKinley RK, Mellor S, Watkin G, Holloway E, Scullion J et al. Breathing exercises for asthma: a randomised controlled trial. Thorax 2009; 64(1):55-61.

17. Holloway EA, West RJ. Integrated breathing and relaxation training (the Papworth method) for adults with asthma in primary care: a randomised controlled trial. Thorax 2007; 62(12):1039-1042.

18. Thomas M, McKinley RK, Freeman E, Foy C, Prodger P, Price D. Breathing retraining for dysfunctional breathing in asthma: a randomised controlled trial. Thorax 2003; 58(2):110-115.

19. Bott J, Blumenthal S, Buxton M, Ellum S, Falconer C, Garrod R et al. Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. Thorax 2009; 64 Suppl 1:i1-51.

20. Holloway E, Ram FS. Breathing exercises for asthma. Cochrane Database Syst Rev 2004;(1):CD001277.

21. van den Haak MJ, de Jong MDT, Schellens PJ. Evaluation of an informational web site: Three variants

of the think-aloud method compared. Technical Communication 2007; 54:58-71.

22. Joffe H, Yardley L. Content and thematic analysis. In: Marks D, Yardley L, editors. Research Methods

23. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J 1999; 14(1):32-38.

24. van Dixhoorn J., Duivenvoorden HJ. Efficacy of Nijmegen Questionnaire in recognition of the hyperventilation syndrome. J Psychosom Res 1985; 29(2):199-206.

25. EQ-5D. A standardized instrument for use as a measure of health outcome. http://www.euroqol.org/

26. Snaith RP, Zigmond AS. The hospital anxiety and depression scale. Br Med J (Clin Res Ed) 1986; 292(6516):344.

27. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999; 14(4):902-907

28. Joffe H, Yardley L. Content and thematic analysis. In: Marks D, Yardley L, editors. Research Methods for Clinical and Health Psychology. London: Sage; 2004. 56-68.

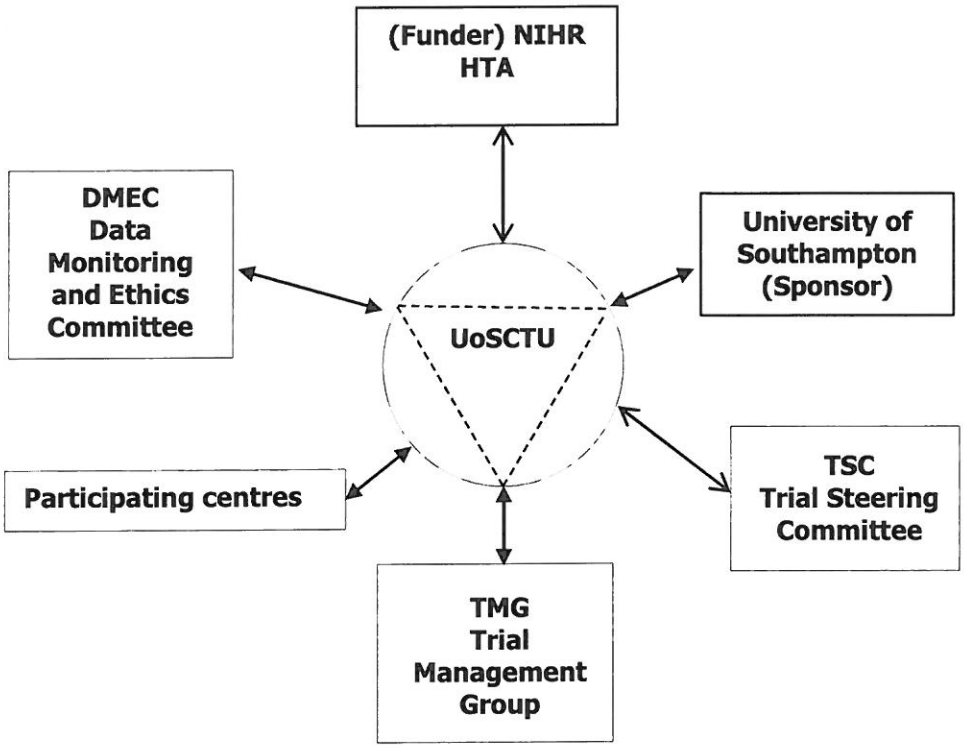
29. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA 2006; 295(10):1152- 1160.

30. Statistical Principles for Clinical Trials, E9. ICH harmonised tripartite guideline, 1998. Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf Accessed 11 April 2011.

31. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999; 14(4):902-907

APPENDICES

APPENDIX 1 TRIAL OVERSIGHT – Communication and Relationship between Parties



APPENDIX 2 BREATHE STUDY FLOW DIAGRAM