Official Title:

An Evaluation of Physiotherapy Assessment; A Mixed Methods Study to Evaluate the Physiotherapy Assessment of Breathing Pattern Disorder

Brief Title:

The Physiotherapy Assessment of Breathing Pattern Disorder

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PHAB

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Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.
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 investigation without the prior written consent of the Sponsor
I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

This protocol has been written in accordance with the Sponsor's guidance for writing non-CTIMP protocols.

Chief Investigator (CI)		
Lizzie Grillo Advanced Physiotherapist	EJFGrillo	2/2/23
Royal Brompton & Harefield Hospitals, Guy's, and St Thomas' NHS Foundation Trust (RB&H)	Signature	Date
Principal Investigator (PI) (If different from CI)		
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1. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
Ax	Assessment
BH	Breath Hold
BORG	Borg rating of perceive exertion
BPD	Breathing Pattern Disorder
BPAT	Breathing Pattern Assessment Tool
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
D12	Dyspnoea 12 questionnaire
EQ5D	EQ-Quol Questionnaire
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
ISRCTN	International Standard Randomised
MUST	Malnutrition Universal Screening Tool
MARM	Manual Assessment of Respiratory Motion
NHS R&D	National Health Service Research & Development
NIMP	Non- Investigational Medicinal Product
NQ	Nijmegen Questionnaire
PI	Principal Investigator
PIS	Participant Information Sheet
PAG	Project Advisory Group
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SAG	Study Advisory Group
SDV	Source Document Verification
SEBQ	Short Evaluation of Breathing Questionnaire
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
6MWT	Six Minute Walk Test

2. STUDY PERSONNEL AND FACILITIES

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3. STUDY SYNOPSIS

Full study title:	An Evaluation of Physiotherapy Assessment; A mixed methods study to evaluate the physiotherapy assessment of Breathing Pattern Disorder
Short study title:	Physiotherapy Assessment of Breathing Pattern Disorder (PHAB)
Chief Investigator:	Lizzie Grillo
Medical condition/disease under investigation:	Breathing Pattern Disorder
Primary Objective:	To evaluate the measurement properties of the BPAT and its utility in the assessment of BPD • To determine the inter-observer and inter-occasion reliability of the BPAT • To determine the associations of the BPAT with other routine assessment tools used in BPD assessment • To determine the responsiveness of the BPAT to physiotherapy intervention for BPD • To determine the change over time in BPAT and other assessments (3 months)
Secondary Objective:	• To evaluate other measurements of BPD and their usefulness in monitoring the effects of treatment for BPD • To determine the feasibility of recruitment, follow up and retention of patients, and recording completed assessments (to inform future trial design) • To evaluate the acceptability, to patients and clinicians, of assessments for BPD
Study population:	**Stage One** A convenience sample of patients referred to physiotherapy outpatient from the asthma or unexplained breathlessness services for BPD. Healthy controls and asthma controls recruited from clinic. **Stage Two** Participants from stage 2 who completed the assessment and treatments of their BPD. Physiotherapists who have delivered the assessment and/or treatment aspects of BPD management
Recruitment Target:	**Stage One** 100 patients, 25 healthy controls and 25 patients with asthma and no BPD **Stage Two**

	5 patients and 5 clinicians
Recruitment Window (Months):	21 months
Methodology:	**Stage One and Two** Mixed methods, questionnaire
Eligibility criteria:	**Inclusion criteria:** **Patients with BPD** Adults aged above 18 years Outpatient referrals for 'unexplained breathlessness' or possible breathing pattern disorder Primary BPD (no other respiratory or cardiology diagnosis) Secondary BPD (patients with a diagnosis of another respiratory diagnosis including asthma or UA diagnosis) Able to complete up to four sessions of outpatient physiotherapy intervention **Healthy Control** Recruited from relative/significant other accompanying the study participant Hospital staff No respiratory or cardiac diagnosis **Patients with Asthma** Attending SARA Clinic Diagnosis of Asthma No Diagnosis of BPD ***Stage Two*** Participants from stage 2 who completed the assessment and treatments of their BPD. Physiotherapists who have delivered the assessment and/or treatment aspects of BPD management
Eligibility criteria: **Study treatment:** (i.e., dose and mode of the study drug administration if applicable)**:**	**Exclusion Criteria** **Patients** Patients with a respiratory diagnosis including COPD, ILD, Bronchiectasis and Cystic Fibrosis Pregnancy Unable to give informed consent Anyone currently participating in pulmonary/cardiac rehabilitation Anyone currently receiving treatment from a speech and language therapist for an upper airway's diagnosis (e.g., Inducible Laryngeal Obstruction ILO or Laryngeal hypersensitivity syndrome (LHS) **Healthy Control and patients with asthma**

	Not meeting inclusion criteria

Stage One

BPAT: Breathing Pattern Assessment Tool

A Clinician completed tool to look at components of breathing pattern assessment. The BPAT is a tabulated means of collating data obtained at respiratory physiotherapy assessment. Assessment components include (i) evaluation of chest/abdominal wall movement, noise of (ii) inspiratory and (iii) expiratory flow, (iv) channel of inspiration and expiration, (v) signs of air hunger (yawning, sighing and deeper breaths), (vi) RR and (vii) rhythm. Each component is given a score from 0 to 2, based on features consistent with expected normal (0) versus that present in severe DB (2), giving a total score of between 0 and 14. The BPAT is completed with a patient positioned, as per the standard assessment of resting breathing pattern (i.e., sat comfortably in a supported seat for at least 5 min) and takes approximately 1 min to collate.

Visit 1: Research Visit for administration of BPAT

Participants (including both patients and healthy controls) will attend for an initial research visit. Two physiotherapists (physio-1 and physio-2) separately and simultaneously complete a BPAT score. The patient will be asked to sit quietly in the chair while this is being completed. To reduce the patient's conscious awareness of their breathing being checked, physio-1 will 'take their pulse' whilst completing the BPAT score at the same time as physio-2, by observing their breathing for two minutes. This section of the assessment will be video recorded to enable a third physiotherapist (physio-3) to complete a BPAT score from this recording. This will be the only visit completed by the Healthy Control patients

NB: Data for asthma controls will be collected from the Systematic Assessment of Asthma Clinic (SARA) where, as part of usual care, patients get a physiotherapy assessment alongside a Nijmegen Questionnaire, Short Evaluation of Breathing Questionnaire (SEBQ), Dyspnea-12 (D-12) and BPAT. No additional visit will be required for this group.

Visit 2 (usual care): All patients will attend for a second appointment between one and three weeks later (in line with usual care) where physio-2 will complete a second BPAT within their standard physiotherapy assessment and will confirm the presence/absence of BPD, through both objective and subjective observation. The physiotherapist will be asked to record their decision by completing "Outcome Questions" which ask them to rate on a visual analogue scale how likely it is that the individual has BPD. The patients will then also complete the primary and secondary outcome measures as per usual care.

Visit 2-5 (usual care): All patients with physiotherapy-confirmed BPD will complete a course of four sessions of outpatient physiotherapy intervention in line with usual care.

Visit 5 End of Treatment (usual care): Patients will complete their final session and completion of outcomes as per usual care. Patients will be asked to rate their change in breathlessness following intervention using a using a seven point Global Rating of Change Questionnaire (GRCQ) according to the following responses: ":1: Much better"; "2: Better"; "3: A little better"; "4: The same"; "5: A little worse"; "6: Worse" and "7: Much worse". The physiotherapist (physio 2) will record their own

evaluation of the patient's response to the treatment using the same scale. Additionally, the patient will be invited to explain the reason for their answer in a free text box; this text will be recorded anonymously.

Visit 6 Follow up: Patients will be followed-up (remotely or in person as per patient request) at three months and physio-1 will complete a BPAT score.

Stage Two B

Convenience sampling of participants from study who have completed the assessment and all treatment sessions, and a convenience sample of physiotherapists who delivered the assessment and/or treatment aspects will be invited to take part after completion of the study data collection.

The experiences of physiotherapists' (n=5) and patients' (n=5) participation in the study will be explored by in-depth, semi-structured interviews lasting 30-60 minutes, conducted face-to-face or via digital platform according to national guidance and individual preference. All interviews will be audio/visual recorded, specifically, experiences of the BPAT assessment and outcome measures will be explored.

4. INTRODUCTION

4.1 BACKGROUND

In health, and at rest, human respiration is achieved through the largely subconscious rhythm of breathing at a comfortable tidal volume. Increases in both the rate and depth of breathing are triggered by temporary, physiological responses to stimuli such as exertion or anxiety[1]. In respiratory disease where there is loss of function or reserve, these patterns may be disturbed resulting in the familiar, if complex, sensation of 'breathlessness'. Non-physiological disorders in breathing pattern are known collectively as Breathing Pattern Disorder (BPD) or Dysfunctional Breathing (DB); however, there is inconsistency in the is nomenclature which clinicians describe as frustrating (Focus group paper), For this application we will use the term BPD. Individuals with BPD tend to breathe in a manner that is disconnected from their respiratory or metabolic requirements[2], in some cases leading to a decreased arterial partial pressure of carbon dioxide through hyperventilation[3].

The condition may be present in the absence of respiratory disease ('primary' BPD), or it may accompany another respiratory disorder, commonly asthma[2] ('secondary' BPD). However, there is limited knowledge on whether these presentations differ in clinically important ways. Individuals with BPD experience non-physiological breathlessness, air hunger and limitation in function[5]. Its pathogenesis is incompletely understood but probably comprises an interplay between biomechanical and biochemical stimuli and psychopathological, cognitive factors[2,3,4]. Various assessments can be used to assess BPD; however many do not capture the core components across all types of presentation.

Whether primary or secondary, BPD is not uncommon. The Nijmegen Questionnaire (NQ) is a self-completed questionnaire of 16 items, developed to assess hyperventilation but commonly used to evaluate the presence of BPD[7]. Among patients registered with a UK general practice, positive responses to the NQ were received

from 8% of 208 adults without respiratory disease[8], and from 29% of 227 adults being treated for asthma[9]; the overall prevalence of BPD measured in this way was 9.5%[8]. This figure is likely to be an underestimate of the true prevalence, as the NQ may not capture all types of BPD, it being an assessment of hyperventilation which may only be one form of BPD[10]; further, it can be scored higher in patients with physiological breathlessness and higher levels of anxiety[11].

BPD is a complex and burdensome condition; those with the condition report worse physical functioning scores than those with severe asthma[12], and are more anxious, with a poorer health related quality-of-life[13]. BPD is likely to be a key consequence of COVID-19 due to the disease's impacts on (cardio-)respiratory physiology, de-conditioning, and anxiety over prolonged recovery. The British Thoracic Society recommends that patients hospitalised with COVID-19 should, after discharge, have their breathing pattern assessed by a physiotherapist[14].

4.2 PRE-CLINICAL DATA/CLINICAL DATA

In 2016, I led the development of a straightforward, practical instrument to improve the consistency of BPD assessment[15]. The Breathing Pattern Assessment Tool (BPAT) is a tabulated means of collating data from a physiotherapy assessment. The tool was developed within our specialist centre by expert physiotherapists and was piloted in assessment clinics to support the diagnosis of BPD in a 'severe asthma' population. In preliminary testing, patients with BPD (with or without asthma) had a higher BPAT score compared with those with no BPD (as assessed by a physiotherapist)[1]. More specifically, it is suggested that the BPAT has clinical utility in patients with severe asthma or unexplained breathlessness, with a score of >4 indicative of BPD[15]. The BPAT appears to demonstrate face validity by its uptake nationally and internationally within asthma services, and more recently within post-Covid clinics to help with screening of patients for treatment of BPD[16,17]. Data from the UCLH Covid clinic (n=280), for example, show that 20% of patients had a BPAT score >4 with 90 of them being referred for (virtual) specialist physiotherapy treatment, and improvements in BPAT scores following four sessions of care[18]. Unpublished data from a private clinic in London showed that in 172 patients referred for post Covid management, average BPAT scores were 6.3 and NQ was 31 (Julie Moore, personal communication). Eighty three percent of patients showed improvements in these scores after eight weeks of a multidisciplinary intervention. Additional data have shown further validity of the BPAT compared to alternative objective assessments of BPD[19] and reliability between clinicians[20] including over a virtual platform[21] which will be important within an environment of social distancing and 'virtual' delivery of therapies.

4.3 STUDY RATIONALE AND RISK/BENEFIT ANALYSIS

The manifestations of BPD are readily misinterpreted – by both patients and clinicians – as those of asthma or similar respiratory diseases[2]. This leads to prescriptions of medications that are neither required nor effective, including inhaled or oral steroids[1]. Furthermore, BPD frequently amplifies other respiratory conditions, increasing the likelihood of excess prescriptions and the misuse of prescribing budgets[*]. In Covid-19 follow-up clinics, a high proportion of patients complain of disproportionate breathlessness, alongside symptoms of fatigue and decreased exercise tolerance[18]. While most post-Covid clinics are requesting a physiotherapy assessment of BPD as a key management step, diagnosis is hampered by there being no universally accepted terminology or method of assessment[1] since most tools do not capture the core components of BPD. Moreover, BPD does not always present in the same way, a heterogeneity that may further lead to inconsistent assessment[*].

Breathing exercises, delivered by physiotherapists, are first line treatments for BPD[22] although with limited evidence of their efficacy from high quality trials[23]. In the UK, current physiotherapy approaches are multi-component, advising modification of breathing pattern through manipulation of tidal and minute volumes, and encouragement of nasal and lower rib cage/abdominal respiration[24]. Clinical experience repeatedly shows the impact on, and relief to, individuals of a diagnosis of BPD by a physiotherapist, even before functional improvements are seen with therapy. A Cochrane review on breathing exercises in asthma[23] suggested interventions from physiotherapy breathing re-education impact positively on QoL – although with low quality evidence. Interest has recently increased following an NIHR HTA-funded RCT in patients with asthma showing a trend for a reduction in healthcare costs and improvements in quality of life[24]. The data did not include the prevalence of patients with BPD, in whom it is probable that there would have been the greatest improvements.

Breathing Pattern Disorder (BPD) is an important condition. It is associated with significant morbidity and can be treated with physiotherapy. Limited evidence exists regarding how best to assess and recognise BPD, which may limit the opportunity for patients to be referred promptly to services to receive the care they need. Additionally, the terminology used for this condition and its different presentations has limited consistency which hampers both its referral and assessment. There are promising reports of the validity and utility of the BPAT, there is a need for further examination of its measurement properties which this protocol aims to evaluate.

4.4 MANAGEMENT OF POTENTIAL STUDY RISKS

This study does not raise significant risk management issues as the assessments and treatments are part of usual care. Careful consideration has been given to management of data which will be stored and managed exclusively on a password protected server at the Royal Brompton Hospital which is backed up every 24 hours. There is a Serious Adverse Event (SAE) protocol in situ to deal with adverse events that may occur during the duration of this research. Additionally careful thought has been given to the numbers of outcome measures the patients are required to complete and have minimised this where possible. Discussion with lay representatives have suggested that if the questionnaires/assessments are justified they are happy to complete them.

5. STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVE

Objectives of the Study

- To determine the reliability of the BPAT between visits and between clinicians
- To determine the associations of the BPAT with other routine assessment tools used in BPD assessment
- To determine the responsiveness of the BPAT to physiotherapy intervention
- To determine the change over time in BPAT and other assessments (3 months)

5.2 SECONDARY OBJECTIVES

- To evaluate other measurements of BPD and their usefulness in monitoring the effects of treatment for BPD
- To determine the feasibility of recruitment, follow up and retention of patients, and recording completed assessments (to inform future trial design)
- To evaluate the validity and acceptability, to patients and clinicians, of assessments for BPD

6. STUDY DESIGN

6.1 OVERALL DESIGN

This study is a non-commercial study completed as part of a NIHR Doctoral fellowship.

Stage One
A mixed methods questionnaire study where patients will be recruited directly from physiotherapy referrals and will receive the usual care as part of the physiotherapy service for BPD in the trust. Assessments at baseline, end of treatment and at follow-up will be utilised to answer the study questions. The physiotherapist completing the baseline, end of treatment and follow up assessments will be blinded to both the physiotherapy assessment and intervention. Additionally, physiotherapist one, two and three (who will separately complete a BPAT assessment on the same patient) will be blinded to each other's BPAT score. All visits will be in line with usual care for this cohort of patients with the exemption of visit one which will be additional to collect inter-visit reliability data. The healthy controls will also be required to complete assessments, however these will all be in line with assessments usually completed in standard physiotherapy assessments.

A subsequent qualitative study with in-depth interviews will run directly after study 1, with a sample of patients who completed the assessment and treatments within the study protocol. Additionally, a convenience sample of physiotherapists who delivered the assessment or treatment aspects will be invited to take part. The experiences of physiotherapists' (n=5) and patients' (n=5) participation in the study will be explored in indepth, semi-structured interviews. Specifically, experiences of the BPAT assessment and outcome measures will be explored.

6.2 TREATMENT AND RATIONALE

Stage One
This is a study evaluating the BPAT which is used as part of usual care. Patients will not be receiving additionally interventions or treatment. Data will be collected as part of usual care for the assessment and treatment of BPD.

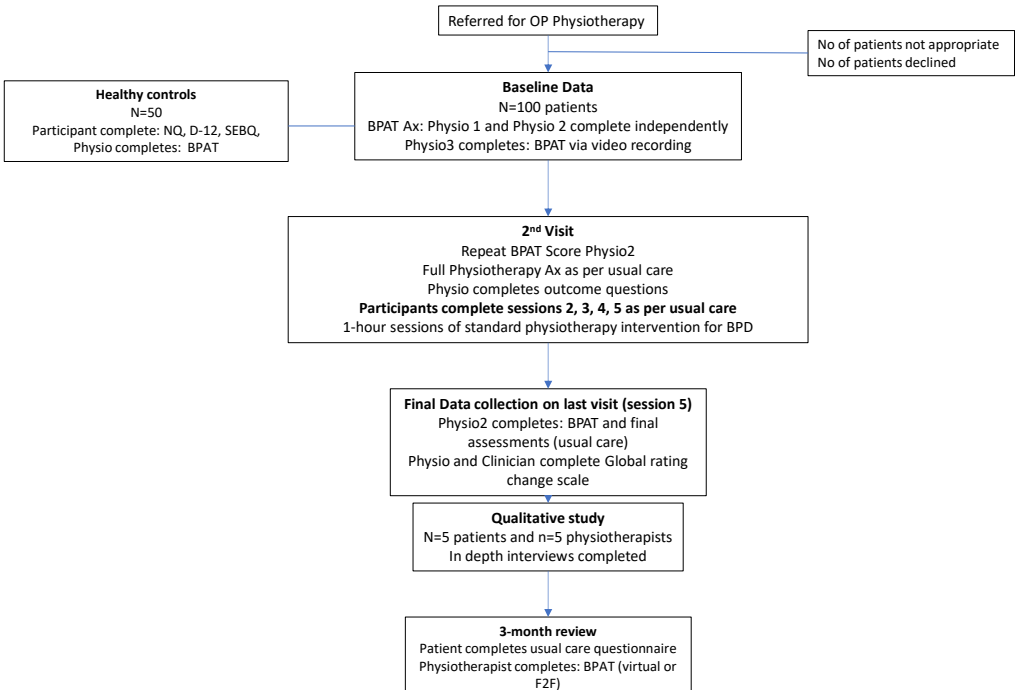
All patients recruited to the study will complete usual care as currently delivered within the service at the Royal Brompton Hospital. All sessions will be completed by physiotherapist at Band 6 and above (2-5 years of experience within respiratory physiotherapy), who will have completed departmental competencies in the assessment treatment of BPD. There will be an assessment and treatment guide for the physiotherapy staff to follow at each stage based on current clinical practice. This will aim to guide the assessment and treatment content but will not be a prescription of specific components. Therefore, the clinicians will be able to include an individually tailored programme of treatment as they do in usual care. This study is not investigating the treatment intervention, merely the response of the outcome measures after this intervention.

Patients will only be considered for final assessment and follow-up once they have completed 4 treatment sessions of physiotherapy. The patients who drop out of the study will still be included in the results and where able, the reason for dropping out/incomplete treatment will be collected in line with current service reporting.

Stage Two

Patients will be participating in the focus group only and not receiving any additional treatment.

6.3 SCHEMATIC OF STAGE 1 DESIGN



7. ELIGIBILITY CRITERIA

7.1 INCLUSION CRITERIA

Patients with BPD

Adults aged above 18 years

Outpatient referrals for 'unexplained breathlessness' or possible breathing pattern disorder

Primary BPD (no other respiratory or cardiology diagnosis)

Secondary BPD (patients with a diagnosis of another respiratory diagnosis including asthma or UA diagnosis)

Able to complete up to four sessions of outpatient physiotherapy intervention

Healthy Control

Recruited from relative/significant other accompanying the study participant

Hospital staff
No respiratory or cardiac diagnosis

Patients with Asthma
Attending SARA Clinic
Diagnosis of Asthma
No Diagnosis of BPD

Stage Two

Participants from stage 2 who completed the assessment and treatments of their BPD. Physiotherapists who have delivered the assessment and/or treatment aspects of BPD management

7.2 EXCLUSION CRITERIA

Stage One

Patients
Patients with a respiratory diagnosis including COPD, ILD, Bronchiectasis and Cystic Fibrosis
Pregnancy
Unable to give informed consent
Anyone currently participating in pulmonary/cardiac rehabilitation
Anyone currently receiving treatment from a speech and language therapist for an upper airway's diagnosis (e.g., Inducible Laryngeal Obstruction ILO or Laryngeal hypersensitivity syndrome (LHS)

Healthy Control and patients with asthma
Not meeting inclusion criteria

7.3 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS AND STOPPING RULES

All information collected in the process of this study will be retained for data analysis, including information about those not completing treatment and where possible the reason why they have withdrawn. Subjects will only be withdrawn from the study if they have expressed not wanting to continue or if another diagnosis or symptoms prevents them from completing and the clinician feels this will limit their response (e.g. A diagnosis of an acute illness).

8. SUBJECT/PATIENT RECRUITMENT PROCESS

Patient recruitment at a site will only commence once the *study* team has ensured that the following approvals/essential documents are in place:

1. Health Research Authority (HRA) approval,
2. Local Site Delegation of Duties and Signature Log is completed (if applicable).

Stage One

A convenience sample of patients referred to physiotherapy outpatient services of Royal Brompton Hospitals for BPD or unexplained breathlessness, over a 22-month recruitment period will be recruited. This sample will include 100 participants to ensure there are adequate numbers within any subgroup analyses.

Healthy control patients will be recruited from a convenience sample of a relative/significant other accompanying the study participant and will attend for one visit to complete a BPAT and other measurements. Permission will be requested from the participant to approach them prior to consenting.

Asthma control patients will be recruited from the Systematic Assessment of Asthma Clinic and data used from their completed usual care assessment. These patients will not be required to attend for any additional visits.

The medical staff referring to physiotherapy will be made aware of the study so they can inform the patients they may be contacted about it once the referral is received by the physiotherapy department.

The chief investigator will contact the patient whilst they are on the waiting list for physiotherapy to check if they are suitable and to ask them if they are happy to take part in the study. If they are then the CI will email/post them information about the study for them to consider prior to booking in of sessions.

If the patients are willing to take part, their session of physiotherapy (assessment sessions and treatment [visit 1-5]) will be block booked into the physiotherapy diary.

Study Two

Convenience sampling of participants from study 2 who completed the assessment and treatments within the study protocol. Additionally, a convenience sample of physiotherapists who have delivered the assessment and/or treatment aspects will be invited to take part. Demographic data for the physiotherapists (age, gender, current NHS band, years of experience in BPD) and participants (age, gender, respiratory diagnosis, BPAT score, employment) will be recorded.

9. STUDY PROCEDURES

9.1 INFORMED CONSENT

All stages

Consent to enter either studies will be obtained after a full account has been provided of its nature, purpose, risks, burdens and potential benefits, and the patient has had the opportunity to deliberate. The patient will be allowed to specify the time they wish to spend deliberating, usually up to 24 hours.

A copy of the signed Informed Consent Form along with a copy of the most recent approved Participant Information Sheet (PIS) will be given to the study participant. The original signed consent form will be retained at the study site (one filed in the medical notes and one field in the Study Master File (SMF)). A copy of the consent form will also be given to the participant.

Once a patient is referred to physiotherapy their data is kept on hospital systems including Anglia Ice and excel databases. The CI will review the individual's data against the inclusion and exclusion criteria. If they are eligible

for inclusion in the study the CI will make, contact with the individuals and ask if they are interested in taking part.

9.2 RANDOMISATION PROCEDURE

This section does not apply

9.3 EMERGENCY UN-BLINDING

This section does not apply

10. STUDY ASSESSMENTS

10.1 SCREENING ASSESSMENTS

No formal assessments will be included, however information from the referral and collected within the electronic record will be utilised to screen the patient for inclusion and exclusion criteria.

10.2 BASELINE ASSESSMENTS

Stage One

Physiotherapist will complete a BPAT score in addition to the assessments completed in usual care. The BPAT is a Clinician completed tool to look at components of breathing pattern assessment. It is a tabulated means of collating data obtained at respiratory physiotherapy assessment. Assessment components include (i) evaluation of chest/abdominal wall movement, noise of (ii) inspiratory and (iii) expiratory flow, (iv) channel of inspiration and expiration, (v) signs of air hunger (yawning, sighing and deeper breaths), (vi) RR and (vii) rhythm. Each component is given a score from 0 to 2, based on features consistent with expected normal (0) versus that present in severe DB (2), giving a total score of between 0 and 14. The BPAT is completed with a patient positioned, as per the standard assessment of resting breathing pattern (i.e., sat comfortably in a supported seat for at least 5 min) and takes approximately 1 min to collate.

Stage Two

No measurements will be taken from individuals in this study

10.3 TREATMENT PROCEDURE

Stage One

Visit 1: Research Visit for administration of BPAT

Participants (including both patients and healthy controls) will attend for an initial research visit. At the beginning of the assessment, two physiotherapists (physio-1 and physio-2) separately and simultaneously

complete a BPAT score. The patient will be asked to sit quietly in the chair while this is being completed. To reduce the patient's conscious awareness of their breathing being checked, physio-1 will 'take their pulse' whilst completing the BPAT score at the same time as physio-2, by observing their breathing for two minutes. This section of the assessment will be video recorded to enable a third physiotherapist (physio 3) to complete a BPAT score from this recording. This will be the only visit completed by the Healthy Control patients

NB: Data for asthma controls will be collected from the Systematic Assessment of Asthma Clinic (SARA) where, as part of usual care, patients get a physiotherapy assessment alongside a NQ, SEBQ, D-12 and BPAT. No additional visit will be required for this group.

Visit 2: Usual Care

All patients will attend for a second appointment between one and three weeks later (in line with usual care) where physio-2 will complete a second BPAT within their standard physiotherapy assessment and will confirm the presence/absence of BPD, through both objective and subjective observation. The physiotherapist will be asked to record their decision by completing "Outcome Questions" which ask them to rate on a visual analogue scale how likely it is that the individual has BPD.

10.4 SUBSEQUENT ASSESSMENTS

Stage One

Visits 2-5: Usual Care

All patients with physiotherapy-confirmed BPD will complete a course of four sessions outpatient physiotherapy intervention as part of usual care for this treatment pathway.

Visit 5: End of Treatment

Patients will complete their final session and completion of outcomes as per usual care. Patients will be asked to rate their change in breathlessness following intervention using a using a seven point Global Rating of Change Questionnaire (GRCQ) according to the following responses: ":1: Much better"; "2: Better"; "3: A little better"; "4: The same"; "5: A little worse"; "6: Worse" and "7: Much worse". The physiotherapist (physio 2) will record their own evaluation of the patient's response to the treatment using the same scale. Additionally, the patient will be invited to explain the reason for their answer in a free text box; this text will be recorded anonymously.

Visit 6: Follow up

Patients will be followed-up (remotely or in person as per patient request) at three months and physio-1 will complete a BPAT score. This is an additional visit to usual care.

Study Two *(visit 7 for those recruited)*

The experiences of physiotherapists' (n=5) and patients' (n=5) participation in the study will be explored in in-depth, semi-structured interviews lasting 30-60 minutes, conducted face-to-face or via digital platform according to national guidance and individual preference. All interviews will be audio/visual recorded, Specifically, experiences of the BPAT assessment and outcome measures will be explored. A framework of questions informed by literature will be developed with oversight from the Study Advisory Group who will review the interview guide created.

11. METHODS

11.1 Laboratory Procedures

This is not appropriate for this study design

11.2 Radiology or any other procedure(s)

Not required in this study

Techniques and Interventions

- ***Tools***

Not required in this study

Study Drugs

Not in this study

11.3 DEFINITION OF THE END OF STUDY

Stage One
The end of the study will be when the individual has completed all assessments at baseline, end of treatment.

Stage Two
When the participant(s) recruited have completed the in-depth interviews

12. SAFETY REPORTING

12.1 DEFINITION

Adverse Event (AE) — any untoward medical occurrence in a patient or clinical study subject who is administered a treatment, and which does not necessarily have a causal relationship with this treatment (*i.e.* any unfavourable or unintended change in the structure (signs), function (symptoms), or chemistry (lab data) in a subject to whom a treatment/study procedure has been administered, including occurrences unrelated to that product/procedure/device).

Serious Adverse Event (SAE) – is defined as an untoward occurrence that:

- Results in death; or
- Is life-threatening (places the subject, in the view of the Investigator, at immediate risk of death)
- Requires hospitalization or prolongation of existing hospitalization (hospitalisation is defined as an inpatient admission, regardless of length of stay; even if it is a precautionary measure for observation; including hospitalisation for an elective procedure, for a pre-existing condition)
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)

- Consists of a congenital anomaly or birth defect (in offspring of subjects or their parents taking the study drug regardless of time of diagnosis)
- Is otherwise considered medically significant by the investigator.

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed in the definition of serious will also be considered serious.

12.2 Recording Adverse Events (AEs)

All Adverse Events (AEs) will be recorded in the hospital notes and Case Report Form (CRF).
If the Investigator suspects that the disease has progressed faster due to the administration of the study treatment/procedure, then he/she will report this as an unexpected adverse event to the Sponsor and the REC as detailed in Section 12.6.

12.3 Assessment of SAEs

Classification and causality of Adverse Events (AEs) will be conducted by local PIs and reviewed by CI. The CI cannot downgrade the site PI's classification and if there is disagreement which cannot be resolved during formal discussion then the assessment of the site PI will be accepted. The CI, can however, upgrade the seriousness of an event without consultation with the site PI.

12.4 Expected AEs

Reporting of SAEs to the sponsor and the REC

The CI and their research team at RBHT are responsible for reporting SAEs to the Research Office immediately and/or within 24 hours of becoming aware of the event in accordance with the process outlined below.

An SAE occurring to a research participant will be reported to the Research Ethics Committee (REC) that gave a favorable opinion of the study, the study Sponsor (RB&HFT Research Office) and the local R&D Office where in the opinion of the CI/PI the event was:

- **'Related'**: that is, it resulted from administration of any of the research procedures; and
- **'Unexpected'**: that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs will be submitted to the REC within 15 days of the CI/PI becoming aware of the event; using the SAE reporting form for non-CTIMPs published on the HRA website and entitled non-CTIMP safety report to REC. The form should be completed in typescript and signed by the Chief Investigator (CI) prior to submission to the REC.

Reports of SAEs in double-blind studies should be un-blinded.All SAEs that are to be reported to the REC should also be forwarded to the Research Office in parallel and must be recorded, signed and dated by the Investigator at site. Research Office accepts study specific SAE forms, HRA SAE Form or RB&HFT template SAE Reporting Form available here.

Information can be submitted to the Research Office in electronic format:

- E-mail: research.reporting@rbht.nhs.uk.

Following submission by the CI, the coordinator of the main REC will acknowledge receipt of safety reports within 30 days. It is the responsibility of the CI and his/her research team to send a copy of the SAE notification and acknowledgement receipt to the Research Office.

The research team also has the responsibility to report SAEs occurring in a certain period (28 days) after a patient completes the study. Any SAEs reported to the Investigators during this phase must be documented in the patient's medical notes and submitted *via* an SAE reporting form.

12.5 THE TYPE AND DURATION OF FOLLOW UP

12.6 PREGNANCY

Not applicable to this study

12.7 ANNUAL PROGRESS REPORTS (APRS)

The Chief Investigator will prepare the APR for the study. It will be reviewed by the RO and sent to the REC by the CI within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the study is declared ended.

12.8 REPORTING URGENT SAFETY MEASURES

The Sponsor and/or the Investigator may take appropriate urgent safety measures to protect the subjects of a clinical study against any immediate hazard to their health or safety. If safety measures are taken, REC approval is not required before the measure is taken.

The Investigator will immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the REC and the study Sponsor of the measures taken and the circumstances giving rise to those measures.

In order to prevent any delays in the reporting timelines the Sponsor has delegated this responsibility to the CI/PI. Therefore, the CI/PI must report any urgent safety measures to the REC directly, and in parallel to the Sponsor. The REC coordinator will acknowledge receipt of urgent safety measures within 30 days.

13. DATA MANAGEMENT AND QUALITY ASSURANCE

13.1 CONFIDENTIALITY

All data will be handled in accordance with the Data Protection Act (2018), NHS Caldecott Principles, The UK Policy Framework for Health and Social Care Research, and the condition of the REC approval.

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The subject's study Identification Number (ID) will be used for identification.

No data will be shared with any external organisation without appropriate consent and data sharing agreement in place, as applicable.

13.2 DATA COLLECTION TOOL

Case Report Forms (CRF) will be designed by the CI and the final version will be reviewed and discussed with the study Sponsor. All data will be entered legibly in black ink with a ball-point pen. If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Delegation of Responsibilities Log will identify all study personnel responsible for data collection, entry, handling and managing the database.

13.3 DATA HANDLING AND ANALYSIS

All data will be handled in accordance with the Data Protection Act (2018), NHS Caldecott Principles, The UK Policy Framework for Health and Social Care Research, and the condition of the REC approval. Case report files will be completed digitally. They will be accessed, completed, and stored on the network drive at the Royal Brompton Hospital and Imperial College which is backed up every 24 hours. Access to the NHS and university computers requires usernames and passwords. Further access to particular network drives requires permission from senior line managers. Files within the limited access network drive will be password protected.

All data will be anonymised, and patient information removed. The focus group, nominal group and in-depth interview audio recordings will be immediately saved to the chief investigators personal drive on the NHS or Imperial College network. The transcription of these recordings will also be anonymised and saved in a password protected file

Files transferred electronically will be anonymised/encrypted and password protected and emailed through secure email addresses. No data will be shared with any external organisation without appropriate consent and data sharing agreement in place, as applicable. This is explained in the information sheet and consent form.

13.4 ARCHIVING ARRANGEMENTS

The study documents (including the Study Master File (SMF), Case Report Forms (CRFs), Informed Consent Forms along with the study database) will be kept for a minimum of five years. They will be stored in locked offices within the Royal Brompton and Harefield Hospitals. The CI is responsible for the secure archiving of study documents. The study database will also be kept electronically on the RB&HFT computer network, for a minimum of five years.

The approved repository for longer retention of local materials for studies that involve RB&H patients is Box-It Storage UK. The study documentation will be prepared for archiving by the research team in line with the Research Office Archiving SOP and the transfer will be arranged by the Research Office.

14. STATISTICAL DESIGN

14.1 SAMPLE SIZE AND RECRUITMENT

A convenience sample of patients referred to physiotherapy outpatient services of Royal Brompton Hospitals over a 20-month recruitment period for BPD or unexplained breathlessness. This sample will include 100 participants to ensure there are adequate numbers within any subgroup analyses. Recruitment will occur over a 22-month period; we anticipate recruiting 6-8 participants each month. I am in a strong position to achieve this as I sit within a renowned, specialist institution with a high patient throughput of approximately 40 patients referred per month at Royal Brompton alone.

Participants will be approached by members of their clinical team initially, asked if they are interested in taking part and if so, given the PIS to read. At this point their details can be passed to the research team if they wish to participate.

Sample size calculations:
Inter rater reliability
This calculation assumed a single-measure ICC framework with two ratings per participant (Physio 1 is always the same, physio 2 pool of 4), 80% power, alpha 0.05, and a minimum acceptable ICC of 0.85, resulting in a required sample of 25 participants.

Intra visit relaibility
The same physiotherapist assesses participants on both occasions; therefore, this analysis plans to use a two-way mixed-effects, single-measure ICC model, ICC(3,1). As no prior estimate was available for between-visit reliability, a more conservative expected ICC of 0.90 was assumed. Using a minimum acceptable ICC of 0.80, 80% power, and alpha 0.05, the required sample was 58 participants.

Construct validity (associations with other measures)
To detect moderate correlations between symptom and breathlessness scores (r = 0.30 to 0.40) requires 47-85 participants.

Construct validity (distinguish between groups)
Using a standard one-way ANOVA with 3 groups (BPD n=100/Asthma n=25 /HC n=25), alpha 0.05, and power 0.80, the required total sample is approximately 63 total (21 per group) assuming a large effect size (f=0.4)

Stage Two

Participants who have completed stage Two will be invited to take part in the qualitative study

14.2 ENDPOINTS

14.2.1 Primary endpoints

Stage One

The primary end points will be baseline assessment data for the outcome measures previously described for 100 participants. This includes BPAT data from visit 1 and visit 2, between clinician data and BPAT data compared to other completed outcome measures including NQ, D-12, SEBQ, BH, 6MWT, & MARM. Additionally change in BPAT, post physiotherapy intervention will also be collected.

Study Two
Acceptability of the BPAT to clinicians, measured by qualitative analysis

14.3.1 Secondary endpoints

Study One

- Change in NQ, SEBQ, D-12, EQ5D5L, BH, exercise test, MARM post physiotherapy intervention.
- No of patients recruited, number of patients completing follow up, number of outcome measures completed

14.3 STATISTICAL ANALYSIS PLAN

Analysis will be carried out according to a statistical analysis plan developed by Winston Banya, Trust Statistician at Royal Brompton Hospital, using STATA. Analysis will be on an intention to treat basis. A p value of <0.05 will be taken to be significant.

14.3.1Primary endpoint analysis

Study One

Reliability
Reliability will be assessed using the single measure, intra-class correlation co-efficient (ICC) of consistency. Measurement variability will be determined by calculating the standard error of measurement (SEM) and percentages of standard errors of the measurements (SEM%). This will be completed from data collected for intra-visit and inter-visit BPAT scores for all participants Cronbach's alpha will be used to assess internal consistency of the BPAT tool, and Cohen's kappa to further evaluate the qualitative agreement between physiotherapists completing the BPAT. Time between the two BPAT assessments will be recorded and included in the analysis.

Validity
Validity will be evaluated for all group data, with several factors including intercorrelation between BPAT scores, and convergent and discriminate validities by examining relationships with other measures to assess BPD (NQ, SEBQ, D-12, MARM and BH). The ability of BPAT to detect BPD will be assessed in a receiver operating characteristic analysis with estimates of sensitivity and specificity at relevant cut-off points, determined by the Youden Index. Regression analysis will assess the determinants associated with high/low BPAT scores. If normally distributed data multiple linear regressions will be completed from the raw scores. If non normal data, then logistics regression will be performed on a categorised variables with a BPAT of >4 being counted as high and BPAT< as low.

Responsiveness

To analyse the responsiveness to the intervention, the primary outcome will be the change before and after treatment in the BPAT score. Secondary outcomes including a change before and after treatment in NQ, D-12,

SEBQ, EQ5D5L and GRCQ will also be reviewed. All outcomes will be analysed as both continuous and categorical (in this case binary). When considering the outcomes as continuous, linear regression will be used to assess the effectiveness of the intervention. When considering the outcomes as categorical, they will be categorised as either 'improvement' or 'no improvement'. Improvement will be defined for all variables as an increase in the score of 1 or more, and no improvement will be defined as either no change in the score or a decrease in the score. For the binary outcomes, logistic regression will be used to assess the effectiveness of the intervention. Finally, all regression models will be conducted as both univariable analysis and multivariable analysis, adjusting for gender, age and asthma

Effect Size

Effect sizes (ES) are the most used method for interpreting and comparing changes in questionnaire scores and are calculated by measuring the difference between the mean scores pre- and post-intervention and dividing this value by the standard deviation of the pre-intervention score. A standard unit of measurement is then assigned to change in health status which helps with interpretation and comparison with other measures. The standardized response mean (SRM) is similar to the ES and is calculated by dividing the mean change in scores by the standard deviation of change in score. E and SRMs for the BPAT and other validated scores for all patients who completed measures at timepoint 1 and timepoint 2 will be reported on.

Feasibility

Feasibility outcomes will be collected, including number of patients eligible for inclusion, recruitment rate, adherence, retention rate and data completeness.

Qualitative analysis

Patient explanation for global rating of change will be explored with thematic analysis and presented descriptively.

14.3.2Secondary endpoint analysis

Stage One

Validity, Responsiveness and Effect Size

All statistics (except for reliability) will be completed for the other standard outcome measures including NQ, SEBQ, D-12, exercise test, BH, MARM and EQ5D5L.

Feasibility

Feasibility outcomes will be collected, including number of patients eligible for inclusion, recruitment rate, adherence, retention rate and data completeness.

Stage Two

Interview recordings will be transcribed verbatim, checked for accuracy and pseudonymised. Scripts will be read and re-read, and a codebook developed. Thematic analysis will be applied and NVivo 10 software used to support code development and analysis.

Taking a deductive approach codes and themes will be grouped into higher-order codes and domains. To increase rigour, a second researcher will independently conduct this process of analysis in a subset of transcripts; coding will be compared and discussed, and the codebook updated. Research reflexivity to alleviate bias pre- and post-interviews will be adhered to. An iterative process of data reduction, comparison, organisation and understanding through thematic analysis will be used to analyse each data source.

14.4 RANDOMISATION

Not applicable for this study design

14.5 INTERIM ANALYSIS (IF APPLICABLE)

Not applicable for this study design

14.6 OTHER STATISTICAL CONSIDERATIONS

Not applicable

15. COMMITTEES INVOLVED IN THE STUDY

My research timetable will be regularly reviewed with my supervisory team, who I will meet regularly either in person or via virtual calls. We will meet independently but also quarterly with all supervisors together. A Study Advisory Group (SAG) including the Principal Investigator (PI), supervisor(s), PPI representative(s) and PPI support from RBH, alongside relevant stakeholders will meet 2-3 times a year to monitor progress and performance throughout. A Professional Advisory Group (PAG) will additionally be created and used at various stages along the project when stakeholder engagement is required, including the dissemination plans.

I will take the role of PI, with responsibility for the day-to-day running of the project including 1. Maintaining frequent communication with stakeholders, recruitment and consenting of all participants, leading the data collection and analysis with the support of the statistician, ensuring all stakeholders are regularly updated at key milestones (R&D, REC, NIHR, PPI groups), including financial departments Study Advisory Group (SAG)

Study Advisory Group

This group includes myself, my supervisors, two patients with BPD and a physiotherapist not involved in the study. The patient representatives have been approached and have agreed in principle. This group will meet regularly at time points set out in the study timetable (virtual and/or in person). They will have a key role in guiding, reviewing, and informing each step in the research process (see below).

Professional advisory group (PAG)

This group includes clinical expertise through representation from the Physiotherapy for BPD group in the UK and international representation from the Bradcliff breathing group. In addition, there will be representation from Asthma UK due to the impact of BPD in asthma.

16. MONITORING AND AUDITING

The requirement for study monitoring or audit will be based on the internal Research Office risk assessment procedure and applicable Standard Operating Procedures (SOPs). It is the responsibility of the RO to determine the monitoring risk assessment and explain the rationale to the study research team.

Study monitoring and/or audit will be discussed with the CI before arrangements are made to conduct the visit.

17. DIRECT ACCESS TO SOURCE DATA

The Investigator(s)/institution(s) will permit study-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Study participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

18. ETHICS AND REGULATORY REQUIREMENTS

The Sponsor will ensure that the study protocol, Patient Information Sheet (PIS), Informed Consent Form (ICF), GP letter and submitted supporting documents have been approved by the Health Research Authority (HRA) which includes Research Ethics Committee (REC) approval if applicable, prior to any patient recruitment taking place. The protocol and all agreed substantial protocol amendments, will be documented, and submitted for HRA approval prior to implementation.

Before site(s) can enrol patients into the study confirmation of capacity and capability must be issued by the institution hosting the trial (unless HRA specifically has confirmed in the HRA approval letter that this is not required). It is the responsibility of the PI at each site to ensure that all subsequent amendments gain the necessary approvals by the participating site. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

Within 90 days after the end of the study, the CI will ensure that the REC is notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study.

The CI will supply a final summary report of the clinical study to the REC and the Sponsor in parallel within one year after the end of the study.

19. FINANCE

This study is funded by the NIHR.

20. INSURANCE AND INDEMNITY

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate.

21. PUBLICATION POLICY

Data ownership rights will lie with the institution sponsoring the study.

22. STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 2018, and with all relevant guidance relating to medicines and clinical studies from time to time in force including, but not limited to, the ICH GCP**,** the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the UK Policy Framework for Health and Social Care Research.

This study will be conducted in compliance with the protocol approved by HRA and according to RGF standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and HRA except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and the REC as soon as possible.

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