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Protocol for a multicentre randomised controlled trial to investigate the effect on asthma-related quality of life from breathing retraining in patients with incomplete asthma control attending specialist care in Denmark

Karen Hjerrild Andreasson ,[1,2] Søren Thorgaard Skou ,[1,3] Charlotte Suppli Ulrik,[4,5] Hanne Madsen,[6] Kirsten Sidenius,[7] Jannie Søndergaard Jacobsen,[8] Karin Dahl Assing,[9] Kirsten Brændholt Rasmussen,[10] Celeste Porsbjerg,[5,11] Mike Thomas,[12] Uffe Bodtger [13,14]

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For numbered affiliations see end of article.

Correspondence to
Karen Hjerrild Andreasson; khad@regionsjaelland.dk

ABSTRACT

Introduction and aim Uncontrolled asthma is a global health challenge with substantial impact on quality of life (QoL) and overall healthcare costs. Unrecognised and/or unmanaged comorbidities often contribute to presence of uncontrolled asthma. Abnormalities in breathing pattern are termed dysfunctional breathing and are not only common in asthma but also lead to asthma-like symptoms and reduced QoL, and, in keeping with this, improvement with breathing normalisation. Evidence-based guidelines recommend breathing retraining interventions as an adjuvant treatment in uncontrolled asthma. Physiotherapy-based breathing pattern modification interventions incorporating relaxation have been shown to improve asthma-related QoL in primary care patients with impaired asthma control. Despite anecdotal reports, effectiveness of breathing retraining in patients referred to secondary care with incomplete asthma control has not been formally assessed in a randomised controlled trial (RCT). We aim to investigate the effect of breathing exercises on asthma-related QoL in patients with incomplete asthma control despite specialist care.

Methods and analysis This two-armed assessor-blinded multicentre RCT will investigate the effect of physiotherapist-delivered breathing retraining on asthma QoL questionnaire (MiniAQLQ) in addition to usual specialist care, recruiting from seven outpatient departments and one specialised clinic representing all regions of Denmark during 2017–2019. We will include 190 consenting adults with incomplete asthma control, defined as Asthma Control Questionnaire 6-item score ≥0.8. Participants will randomly be allocated to either breathing exercise programme in addition to usual care (BrEX +UC) or UC alone. BrEX compiles three physiotherapy sessions and encouragement to perform home exercise daily. Both groups continue usual secondary care management. Primary outcome is between-group difference in MiniAQLQ at 6 months. Secondary outcomes include patient-reported outcome measures, spirometry and accelerometer.

Ethics and dissemination Ethics Committee, Region Zealand (SJ-552) and Danish Data Protection Agency (REG-55–2016) approved the trial. Results will be reported in peer-reviewed scientific journals.

Trial registration number NCT03127059; Pre-results.

Strengths and limitation of this study

- This trial investigates the effects of physiotherapist-delivered breathing pattern modification and relaxation on asthma-related quality of life in patients with incomplete asthma control despite attending specialist care, a resource demanding group where evidence for management strategies are lacking.
- The multicentre design including participants at secondary care centres in all regions of Denmark comparing a clinically relevant and low-cost intervention with usual care supports external validity.
- Participants and treatment providers cannot be blinded due to the nature of the intervention.

BACKGROUND

Asthma is a chronic, common, heterogeneous disease characterised by variable airflow obstruction due to airway inflammation and bronchial hyperreactivity.[1] Globally, asthma affects around 300 million people. Dyspnoea is a very important symptom, which significantly restricts physical activity and quality of life (QoL).[1 2]

Asthma-related QoL describes the subjective impairment conferred by asthma on a person's life, and is a key patient-reported

outcome.[3] It is impaired in most patients with asthma, and may be assessed by the validated MiniAsthma Quality of Life Questionnaire (MiniAQLQ).[4] Several factors affect asthma-related QoL: (a) asthma-specific such as severity and type of asthma symptoms, (b) asthma-related such as triggers and comorbidities and (c) 'patient-related' factors, such as emotional stability, overall stamina, education and income.[5–7]

Asthma-related QoL is only moderately associated with asthma control, and asthma control remains the key metric for assessing the impact of living with asthma.[6] Asthma control is currently defined as absence of key symptoms and signs of asthma (dyspnoea or coughing during nighttime or exercise, exacerbations, and emergency healthcare usage), and no asthma-related impairment of activity or QoL.[2] A tool widely used to measure asthma control is the Asthma Control Questionnaire (ACQ), which is available in 5-item, 6-item or 7-item versions, where item 7 is lung function expressed as percentage of expected forced expiratory volume in first second (FEV1 % expected).[8 9]

More than 10% of the asthma population has difficult-to-treat asthma with poor asthma control despite substantial pharmacological treatment (ie, Global Initiative for Asthma, GINA, steps 4–5).[2 10 11] This subgroup uses high levels of asthma-related healthcare resources due to increased symptom burden, medication usage, prevalence of comorbidities, smoking, sick leave, higher exacerbation rates and emergency department visits compared with patients with asthma control.[2 12] Likewise, individual costs to medication, unemployment, poorer education, sick leave, and early retirement are substantial too. True severe asthma is seldom the cause of difficult-to-treat asthma. Common causes are inadequate treatment (eg, adherence, inhaler technique), triggers (eg, smoking, allergens), erroneous asthma diagnoses or comorbidities (both: eg, non-asthma respiratory disease, obesity, rhinitis, cardiovascular diseases, dysfunctional breathing (DB), neuromuscular disease or poor cardiorespiratory fitness).[2 13–17]

Abnormalities in breathing pattern are usually referred to as DB. The extreme disordered breathing patterns range from fast and shallow to slow and deep. The first, for example, rate 20–40, thoracic breathing also known as hyperventilation, and the latter, for example, rate 5–8, diaphragmatic and whole thorax breathing, large tidal volume close to total lung capacity resulting in high ventilation volume.[18 19] However, both patterns result in increased minute volume. A patient with disordered breathing pattern may sigh often to compensate for over-inflated lung and elevated tidal volume (eg, end of tidal volume over functional residual capacity, FRC) to achieve FRC (relaxation pressure of lung plus chest wall equals the atmospheric pressure).[19 20] DB is well-recognised but ill-defined disorder that often coexists with asthma but may be an isolated problem and cause persistent or intermittent dyspnoea, coughing, loss of voice, chest tightness, anxiety and fatigue.[2 13 15 21 22] There is no consensus on diagnostic criteria.[21] The Nijmegen Questionnaire (NQ) is the commonly used screening tool,[22–24] and estimates a prevalence of DB of 25% in Danish patients with severe asthma.[25] However, the use of the NQ as a screening tool for DB in asthma has been questioned,[26] and the NQ does not predict a response to intervention in controlled trials of breathing retraining.[27 28]

In asthma, pharmacological treatment targets airway inflammation, bronchoconstriction and possible comorbidities. Non-pharmacological treatment focuses on reduction of airway inflammation by avoidance of triggers, diet and physical fitness, and (in obese) weight reduction, to improve asthma control.[2 29] Physiotherapy has gained increasing attention as part of asthma care as many patients with asthma explicit signs of DB pattern.[15 30]

Trained physiotherapists provide breathing exercises (BrEX) including re-education or modification of the breathing pattern. This involves instructions that encourage nasal route of breathing, mainly diaphragmatic respiratory movement, and normalising respiratory rate and tidal volume.[31–33]

In controlled trials in people with mild and moderate asthma (GINA steps 1–3), BrEX are safe, reduce symptoms, improve QoL and asthma control, but does not change lung function parameters or airways inflammation.[28 34–37] Interestingly, the clinical effect of BrEX is unrelated to baseline NQ scores.[26]

Recent systematic reviews of BrEX in moderate to severe asthma conclude that the methodological quality and poor methods descriptions leave insufficient evidence for a firm recommendation.[1 32 38 39]

A previous, well-performed pragmatic-designed trial investigated a similar intervention (delivered by a DVD or face-to-face by a single physiotherapist) in patients in primary care in UK.[28] The Danish healthcare system shares many similarities with the British NHS: Free health service for all citizens, all patients have a general practitioner (GP) who is the gate-keeper to secondary care. Asthma GINA steps 1–4 is the responsibility of the GPs, who can refer to the local hospital's Respiratory Service in case of diagnostic uncertainty or lack of control. There are few multidisciplinary clinics for 'difficult-to-control asthma' in Denmark (total population 5.6 million inhabitants).

However, patients with more difficult to control asthma attending secondary, outpatient respiratory clinic have not to date been studied. Therefore, we decided to perform an adequately powered, randomised controlled clinical trial of well-defined BrEX in a well-characterised cohort of patients referred from GP due to lack of control and still having suboptimal control (ACQ6 score ≥0.8) of pulmonologist-diagnosed asthma after ≥2 consultations with a pulmonologist.

Thus, the present pragmatic multicentre trial will contribute to the existing (sparse) evidence on physiotherapy in asthma concerning target group (secondary care) and intervention (multicentre), the latter improving external validity of our findings.

The aim of our randomised controlled trial (RCT) is to compare changes in the key patient-reported outcome

asthma-related QoL (MiniAQLQ scores) in patients undergoing a BrEX programme (three sessions and encouragement to do daily home exercise during 12 weeks) in addition to usual specialist care (US) with patients receiving specialist care management. Secondarily, we will investigate the effects of the intervention on important patient-reported outcomes, including lung function, gait distance and physical activity level.

METHODS AND ANALYSES

Trial design

The trial is designed as a randomised, controlled, assessor-blinded multicentre superiority trial with two parallel groups with a primary endpoint of change in asthma-related quality of life (MiniAQLQ) at 6 months from initiating the intervention, that is, 12 weeks after intervention period.

The benefits achieved at 6 months are hypothesised to be maintained at 12 months.

Main trial information is presented in online supplementary file table S1.

The trial protocol conforms to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT),[40] and the Template for Intervention Description and Replication (TIDieR) will be used.[41] The schedule of enrolment, interventions and assessments is shown in figure 1.

The trial is registered on 26 April 2017. Enrolment started at the first centre on 26 April 2017 and at the last centre in January 2019. A much lower recruitment rate than expected were observed in the first months of the trial and the following actions were taken: inclusion criteria were modified (Protocol Version 2.4, see Participants), additional recruiting centres were initiated in March 2018, October 2018, and January 2019 (Protocol Versions 2.4–2.6, March 2018–January 2019), and based also on high retention rate, the sample size was revised based on updated power calculation in May 2019. We expect to end recruitment in October 2019.

Patient and public involvement

Participants in a pilot study on breathing retraining in asthma gave formal feedback on the intervention including information, patient instruction and follow-up (KH Andreasson, ST Skou, M Thomas, U Bodtger, 2017, 'Breathing Exercise pilot study', unpublished).

Participants

The target population is patients with physician diagnosed and specialist confirmed asthma, including patients with fixed airway obstruction, cough-variant asthma or other forms without current evidence of variable airflow obstruction,[42] and incomplete asthma control despite specialist-provided asthma care and regular use of moderate-dose to high-dose inhaled steroids with or without a second controller (GINA steps 3–5). The diagnosis of asthma is not simple, and variable airflow limitation can be difficult to demonstrate in patients currently on treatment.[14 43] Restricting the trial to those able to display physiological reversibility on treatment at recruitment into the trial would have resulted in a biassed and unrepresentative sample.

Danish respiratory outpatient clinics at Naestved, Roskilde, Bispebjerg, Aalborg, Hvidovre, Silkeborg and Odense hospitals, and the private Allergy & Lung Clinic, Elsinore (*Allergi og Lungeklinikken Helsingør*) will recruit consecutively during a 30-month inclusion period. Recruitment is expected to be finalised 31 October 2019.

The recruitment target is 190 participants with incomplete asthma control, randomly allocated 1:1 to intervention or control groups. At recruitment, ACQ6 ≥1.5 is used to identify participants with uncontrolled asthma. Modification was done 1 January 2018 to improve inclusion rates: participants will need to have an ACQ6 score ≥0.8 and to be in a stable phase of their asthma defined as no treatment changes in the month preceding randomisation to be randomised, while still having incomplete asthma control.

Inclusion criteria

- Referred from GP to a secondary, outpatient respiratory clinic for lack of asthma control.
- Asthma diagnosed by a pulmonologist.
- ≥2 doctor visits at a specialised, pulmonologist-lead asthma clinic.
- Age≥18 years.
- ACQ6 score ≥0.8.
- Willing and able to give written informed consent.
- Speaks, reads and understands Danish.

Exclusion criteria

- Trained in breathing exercises by physiotherapist last 6 months.
- Pregnancy.
- Any severe disease as judged by the responsible physician.
- Participating in another respiratory interventional research project.

Recruitment procedure and consent

The trial flow is outlined in figure 2. Written advertisements in the clinics pre-inform patients on the possibility of trial participation to motivate participation. The respiratory nurse or the pulmonologist will enrol eligible participants during the scheduled visit (which routinely includes ACQ6 scoring). The nurse will provide the initial oral and written trial information, and the pulmonologist will screen for eligibility. The participant will receive thorough verbal and written trial information and will have to return for a separate visit where a nurse or a physiotherapist will provide detailed information on the trial and respond to participant queries before written informed consent is obtained. Consent paper form, online supplementary file S2. If the enrolment rate is inadequate to

	TRIAL PERIOD					
	Enrolment	Allocation	Post-allocation			
TIMEPOINT	$-t_1$	0	t_1 0 months	t_2 3 months	t_3 6 months	t_4 12 months
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Inhalation check	X					
Randomisation		X				
INTERVENTIONS:						
Breathing Exercises			3 visits			
Usual specialist care			X			
ASSESSMENTS:						
Baseline, PROM	X					
Baseline, Objective measurements	X					
Demographic data	X					
Follow up, PROM				X	X[a]	X
Follow up, Objective measurements					X	
Adverse events				X	X	X
Medication usage						X[b]

Figure 1 The figure details the schedule of enrolment, interventions and assessments of BEAT DB trial in accordance with the Standard Protocol Items: Recommendations for Interventional Trials template.[40] BEAT DB trial: this acronym is used in ClinicalTrial.gov registration. [a]Primary endpoint is at 6 months follow-up. [b]Data collection of medication usage from baseline before allocation throughout until 12 months after allocation will be done at 12-months follow-up. BEAT DB, Breathing Exercises in Asthma Targeting Dysfunctional Breathing; PROM, patient-reported outcome measures.

meet the recruitment target, more centres will be invited to participate.

Randomisation procedure and concealment of allocation

After completion of baseline assessment, participants will randomly be allocated to UC with or without BrEX in a 1:1 allocation ratio by computer-generated randomisation using EasyTrial (EasyTrial APS, Aalborg, Denmark) in fixed blocks of four stratified by centre to assure equal size of groups at the seven centres. The chief investigator and all project workers will be blinded to the generation sequence. The nurse will activate the EasyTrial randomisation function to reveal the allocated group for each individual participant. This information will be forwarded to the participants by e-mail sent from EasyTrial. After allocation, the chief investigator will be informed and will ask the local physiotherapists to invite participants in the BrEX +UC group to initiate the intervention.

Blinding

The nature of the trial precludes blinding of participants or the physiotherapists delivering BrEX. Outcome assessors are blinded to the randomisation result, and participants will be reminded not to disclose their treatment allocation to the outcome assessor. Nurses who will perform extraction of clinical data from medical reports,

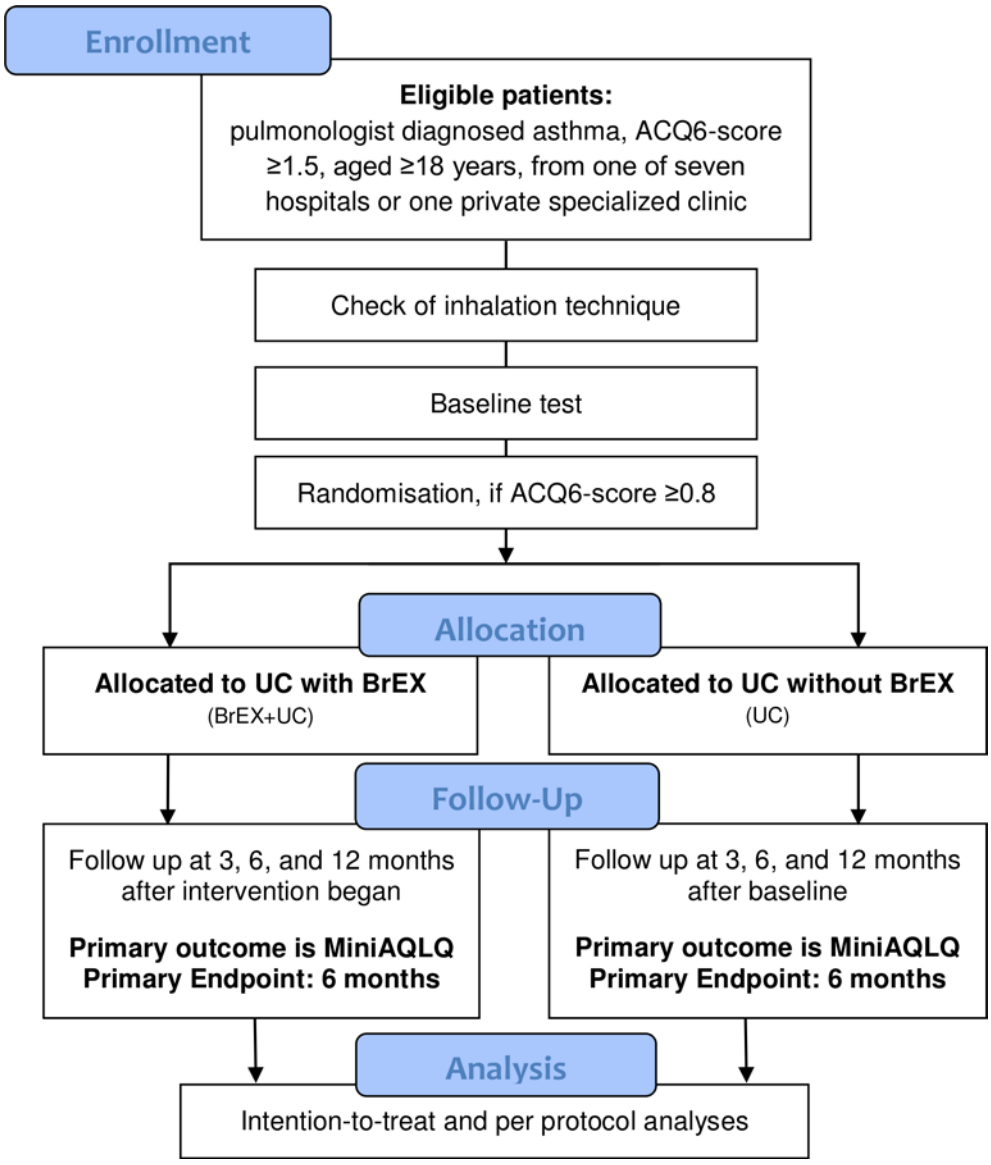

Figure 2 Patient flow through the RCT BEAT DB trial. Consolidated Standards of Reporting Trials (CONSORT) flow diagram 2010. BEAT DB, Breathing Exercises in Asthma Targeting Dysfunctional Breathing; ACQ6, asthma control questionnaire; BrEX, breathing exercises; MiniAQLQ, miniasthma quality of life questionnaire; RCT, randomised controlled trial; UC, usual specialist care.

and the statistician who will perform the analyses will also blinded to the allocation.

Blinded results (presented as group A compared with group B) will be presented to the research group, who will interpret the blinded results and prepare two alternative conclusions, prior to unblinding of the trial results.[44]

Interventions

At baseline, all participants will receive individual instruction in optimal inhalation technique by a respiratory nurse, who will also encourage the participant to use online video instructions.[45]

As the design is a pragmatic 'real-world setting' trial without standardisation of asthma therapy, the pharmacological treatment will be the choice of the responsible respiratory specialist, including changes, discontinuation or add-on of any treatment/combination. Treatment with positive expiratory pressure devices is not prohibited. The patient will be randomised to either usual care with Breathing Exercises (BrEX +UC) or usual care alone (UC).

Breathing Exercises (BrEX)

BrEX consists of three physiotherapist-sessions with duration of 60 min (initial session=week 1) and 30 min (at weeks 4 and 9, ± 7 days).

BrEX session one is t_1 in the group of usual specialist care with BrEX (BrEX +UC) figure 1.

The participant will be encouraged to do 10 min of home exercise twice daily.[32] The entire intervention combines elements of the Papworth method[46] and the Buteyko technique.[47]

Key points in the intervention are

Table 1 Overview of the BrEX intervention

Items	Description
1. Brief name	BrEX (Breathing EXercises).
2. Why	Previous studies showed the feature included in BrEX to be essential for persons with dysfunctional breathing and asthma The BrEX is simple and requires no devices to perform but fits in daily living. The goal of the intervention is that the patient incorporates an ideal breathing pattern and that this pattern becomes automated
3. What materials	The patient will be provided written materials with illustrations of elements of BrEX, including the home exercises. The physiotherapists will be provided a manual, including a schedule of anticipated progression
4. What procedure	Each BrEX session will include an initial interview (online supplementary file S4, 12-item interview list) and an observation of the breathing pattern (table 3). Features of BrEX are breathing pattern modification in rest and combined with physical activity and relaxation, breath holding exercise, handling of uncontrolled coughing, frequent sighing or yawning and patient education
5. Who provides	BrEX will be provided by physiotherapists, who are trained in the BrEX intervention at a mandatory 10-hour introduction, followed by thorough written information and telephone support (training and support given by the chief investigator), and have at least 1 year of experience in pulmonary physiotherapy
6. How	BrEX will be delivered individually and face-to-face
7. Where	In outpatient departments of physiotherapy at seven public hospitals in Denmark
8. When and how much	A 12-week intervention period featuring three physiotherapy sessions delivered in week 1, 4 and 9 (±7 days); the initial session will last for 60 min, and others for 30 min. Participants will be asked to do 10 min of home exercise twice daily throughout the 12 weeks
9. Tailoring	BrEX will be individualised in pace of progression and combinations, or of regression and simplicity according to interview at each session start and observations during the session
10. Modifications	N/A. Modifications will be reported (if any)
11. How well (planned)	Besides the introduction, the physiotherapists will adhere to a BrEX manual. Participants will be filling out a training diary
12. How well (actual)	N/A. This will be reported in the primary paper

This description is in accordance with the Template for Intervention Description and Replication, Hoffmann *et al.,* 2014.[41]
BrEX, Breathing EXercises; N/A, Not applicable.

- Modification/normalisation of respiratory rate and/or depth of breath by rhythmic, nasal inspiration, and diaphragmatic breathing, by long expiration, and by breath holding at FRC.[32 46 47] Uncontrolled, non-phlegm coughing and frequent sighing are often seen in patients with disordered breathing pattern. The participant will be trained to reduce sighing and/or coughing by a suppression-technique.[48]
- Relaxation,[32 46] especially of the neck, jaw, tongue and shoulders. We will emphasise the lowering of muscle tone in these areas and boost the feeling of gravity. The participant will be asked to 'let go' to get full support from the surroundings (pillow, plint, chair and ground) to increase feeling of being carried.
- Use of the breathing modification during walk and other physical activities.[32 46]
- Daily home exercise of BrEX.

The participant will receive a booklet covering all exercises in text and illustrations, theoretical information about breathing patterns and modification, and a page designated for an individualised home programme specified by the treating physiotherapist.

See TIDieR table (table 1) and Supplementary note for details on the BrEX intervention (online supplementary S3), and 12-item interview list (online supplementary S4). Danish version of the participant booklet and an English translation will be available on request, when the trial data collection has finished.

Usual specialist care

Participants in both groups will receive UC, which will be provided at the discretion of the responsible pulmonologist based on the individual needs of the participant's severity of disease and current level of asthma control. The UC is not a uniform intervention neither in contents nor in time spent (range 15–30 min), number of visits, nor visit intervals. The choice of pharmacotherapy is supported by step-up and step-down guidelines.[2]

The UC without BrEX group will be the control group in the trial and baseline date equals t_1 in this group figure 1.

Data collection procedure and retention

Data will be collected at baseline (t_1) and at 3, 6 and 12 months (t_2–t_4). Overview of outcome collection is showed in table 2. Before RCT initiation, all assessors will be introduced to, trained in, and supervised in the assessment procedure by the chief investigator. All assessors will be provided trial-specific assessment manuals, which have been tested in a pilot study (KH Andreasson, ST Skou, M Thomas, U Bodtger, 2017, 'Breathing Exercise pilot study', unpublished).

Patients-reported outcome measures (PROM) will be collected using online questionnaires in EasyTrial. Participants will receive invitation and links by e-mail, and—if necessary—an SMS reminder 2 weeks later (t_1-t_4 plus 2 weeks).

SenseWear (SW) data (accelerometry) will be extracted and entered by a research assistant not involved in any clinical parts of the trial.

Objective assessments will be done at the hospitals at baseline and at 6-month follow-up (±4 weeks) following a standardised procedure. The assessor will manually complete a datasheet, which will be entered as an electronic CaseReportForm in EasyTrial later.

The 6-month follow-up visit (t_3) will be planned by phone with the participant by a coordinating research assistant. Two days before the scheduled follow visit, the participant will receive standard reminders by e-mail and SMS. If the visit is not completed, no matter the cause, the coordinating research assistant will contact the participant by phone to reschedule the visit within the prespecified time frame of maximally +4 weeks.

Participants will be prompted to complete 3-month and 12-month follow-ups every second week until completion, reminders sent as SMS and e-mails after 2 weeks, and a phone call after 4 weeks.

If a participant discontinues the assigned allocation without withdrawing the consent, we will prompt him/her to remain in the trial that is, to complete the remaining follow-up visits/online questionnaires.

Reasons for non-adherence (eg, lack of interest, comorbidity reasons, exacerbation, emigration) and for non-retention (consent withdrawal, lost to follow-up) will be recorded.

Outcomes

Demographic data will be collected at baseline: gender, age, body mass index, smoking status and socioeconomic status (educational level, work status, and income).

Primary outcome

Primary outcome is the between-group mean change in Mini*Asthma Quality of Life Questionnaire* (MiniAQLQ) from baseline to 6-month follow-up.[4] MiniAQLQ is a validated, 15-item disease-specific PROM on experiences in symptoms, activity limitation, emotions and environment during the previous 2 weeks. A 7-point Likert scale (1=maximum impairment; 7=no impairment) is used, and MiniAQLQ-score is the mean of all items. In

Table 2 Overview of data collection in BEAT DB

	Baseline	3 months	6 months	12 months
Primary endpoint				
MiniAsthma Quality of Life Questionnaire (MiniAQLQ)*	@	@	@	@
Secondary endpoints				
Patient-reported information				
Asthma Control Questionnaire (ACQ6)	@	@	@	@
Nijmegen Questionnaire (NQ)	@	@	@	@
Hospital Anxiety and Depression Scale (HADS)	@	@	@	@
EuroQol-5D (EQ-5D-5L)	@	@	@	@
Global Perceived Effect rate (GPE)	N/A	@	@	@
Patient Acceptable Symptom State (PASS)	N/A	@	@	@
Treatment Failure (TF)	N/A	@	@	@
Smoking status	@		@	@
Socio-economic Status (SES)†	@			
Foster Score	@		@	
Anthropometric				
Gender	@			
Age	@			
Height, cm	@			
Weight, kg	@			
Body Mass Index (BMI)	@			
Register data				
Medication (treatment step 1–5)‡	@		@	@
Comorbidity	@		@	@
Scheduled and acute medical visits (prev.6mo)			@	@
Adverse events (AEs)	N/A	@	@	@
Adherence	N/A	@		
Functional capacity				
6 min Walk Test (6MWT)§	@		@	
Count Scale (CS)	@		@	
Breath Holding Time (BHT)	@		@	
Respiratory pattern observation	@		@	
Physical activity (SenseWear) average of 6 days¶				
Total energy expenditure (TEE), kJ (daily avg)	@	@	@	
Average METs (daily avg)	@	@	@	
Physical Activity Level (PAL) (daily avg)	@	@	@	

Continued

Table 2 Continued

	Baseline	3 months	6 months	12 months
Number of Steps (daily avg)	@	@	@	
Lung parameters**				
Expiratory volume in first second (FEV1)	@		@	
Forced vital capacity (FVC)	@		@	
Ratio (FEV1/FVC) % of predicted	@		@	
FEV1 % of predicted	@		@	
Peak expiratory flow rate (PEF)	@		@	
Maximal Inspiratory Pressure (MIP)	@		@	

*Primary outcome is MiniAQLQ at 6 month follow-up.
†SES includes educational level, annual family income, work status.
‡Reliever and controller medication.
§Including Borg CR10.
¶Subgroup will be measured. 3 month follow-up only until April 2018.
**Reference values for spirometry: GLI2012.
BEAT DB, Breathing Exercises in Asthma Targeting Dysfunctional Breathing; METs, metabolic equivalents; N/A, Not applicable.

moderate to severe asthma cohorts, MiniAQLQ has good reliability (ICC 0.83–0.86) and strong validity (criteria validity to AQLQ, $r \geq 0.80$; construct validity against ACQ, $r=0.69$).[4 49] The Danish version of MiniAQLQ is validated linguistically, although cultural adaptation is missing.[50 51]

Secondary outcome measures

Secondary (continuous) outcome measures are the between-group mean change for each. All secondary outcomes will be considered supportive of the primary outcome, that is, conclusions will only be guided by the primary outcome.[52 53]

Patient-reported outcomes

ACQ6 is the 6-item questionnaire version on asthma control addressing five symptoms using a 7-point Likert scale (0=fully controlled; 6=severely uncontrolled), and reliever medication use (0=No use; 6=More than 16 puffs most days) during the previous 7 days. Test–retest reliability of ACQ is excellent (ICC 0.83–0.90).[8 9] ACQ6 is valid in moderate to severe asthma; Cronbach's α is 0.86 (KH Andreasson, U Bodtger, ST Skou, M Thomas, J Comins, 2019, 'Rasch validation of the Asthma Control Questionnaire', unpublished results). ACQ score <0.75 corresponds to well-controlled asthma, ACQ score ≥1.5 denotes uncontrolled asthma, whereas ACQ from 0.75 to 1.5 correspond to incomplete asthma control or partly controlled asthma.[2 8 54]

NQ is a reliable 16-item screening questionnaire designed to assess subjective sensations compatible with hyperventilation during previous 7 days.[23]

Hospital Anxiety and Depression Scale (HADS) contains seven items concerning anxiety, and seven concerning depression and uses 4-point Likert scales; a low score indicates least mental health problems.[55] Asthma and disordered breathing pattern are known as associated with anxiety and depression.[56 57]

Global perceived effect (GPE) rate will be used as a retrospective evaluation of effect of asthma-related QoL as well as asthma control on a 7-point Likert scale.[58 59] This global transition rating enables investigation of the validity and the interpretability of the primary outcome.[59 60] This will be followed by the dichotomous *Patient Acceptable Symptom State* (PASS) that evaluates treatment success from the participant's perspective related to level of asthma-related QoL and to asthma control.[61] If the participant considers the symptom state to be 'non-acceptable', the participant will be asked whether he/she considers the state so unsatisfactory that *Treatment Failure* (TF) has occurred, answered by 'yes' or 'no'. GPE, PASS and TF will be used at all follow-ups.

EuroQol-5Dimension is a generic QoL tool consisting of a 5-dimension descriptive index (ranging from −0.59 to 1.00) and a Visual Analogue Scale (ranging from 0 to 100) describing self-perceived health status.[62 63]

Foster Score will be used to define the numbers of days (0–7) per week that the participant reports having taken his/her medication as prescribed.[64]

Objective performance outcomes

Physical activity level (PAL), metabolic equivalents, numbers of steps, and total energy expenditure (TEE) will be measured by a two axial *accelerometer* (SenceWear, SW) (BodyMedia *SenseWear*, Pittsburgh, PA, USA) monitoring activity during 6 days.[65] This is measured in all participants included May 2017–May 2018, hereafter only in participants from Naestved and Hvidovre Hospitals.

Functional capacity will be measured by *6 min Walk Test* (6MWT). The 6MWT is a validated measure of response to physical activity intervention in respiratory research.[66]

Dyspnoea level will be measured before and after 6MWT. To rate perceived dyspnoea the validated *Borg CR10* will be used,[67] as well as the *Count Scale* (CS).[68] CS implies that the participant loudly counts starting from one to as high as possible at a constant speed of 2 counts per second, guided by a metronome, during one exhalation from maximum inspiratory level.

*Breathing pattern observation during 60*s, following a non-validated 10-item observational list assesses the respiratory pattern at rest. See table 3.

Breath Holding Time (BHT)[69] will be measured in seconds from respiratory resting position (eg, FRC) until first involuntary respiratory muscle motion.

Spirometry (MedikroPro, M915, OY Finland) will be used to measure FEV1, forced vital capacity (FVC), FEV1/FVC ratio and peak expiratory flow rate.[70] Predicted values will be calculated using GLI2012.[71]

Table 3 Breathing pattern, 10-item observational list

Items observed for 60 s			
Respiration frequency	RF:		
Rhythmic respiration	Yes	No	
Inspiration initiated upper thorax	Yes, only	Yes, partly	No
Inspiration initiated by diaphragm	Yes, only	Yes, partly	No
Nasal inspiration	Yes, only	Yes, partly	No
Clearing of throat (cough slightly)	Number:		
Sighing (solitary large inhalation and exhalation)	Number:		
Yawning	Number:		
Coughing (non-productive)	Number:		
Bodily movement	Yes	No	
Method			
The participant is at rest in sitting position. The observer sits a little beside the viewpoint of the participant. The observer sits facing the participant, uses a time watch, and follows instruction: Introduce to the participant: *I will observe your breathing pattern for 1 min* *I will inform you, when the minute starts* *You are supposed to sit calm* *We are not allowed to talk meanwhile* Start the time watch after a participant's expiration Observe and judge subjectively the rhythm, the inspiratory movement initiation, bodily movement and the route of breathing Count clearings of throat, sighs, yawns, and coughs Stop observing after 60 s. Note results in the table.			

This list of observation items includes features that can define the breathing pattern. Karen H. Andreasson developed the list for the BEAT DB trial. Version 30 April 2019.
BEAT DB, Breathing Exercises in Asthma Targeting Dysfunctional Breathing; RF, respiration frequency.

Inspiratory muscle strength (Maximal Inspiratory Pressure, MIP) will be measured by KH2 (POWER Breathe, Southam, Warwickshire, UK).[72]

Register data from medical records

We will extract medication prescriptions and comorbidity at baseline, and medication prescriptions, comorbidity, adverse events (AEs; eg, emergency room visits), and number of consultations at specialist care respiratory nurses and/or pulmonologists from baseline until 12-month follow-up from electronic medical records.

Adherence

Participants in BrEX +UC group will be asked to complete a BrEX home training diary during the 12 weeks of intervention. Number of exercising days and minutes used will be described. At sessions 2 and 3, the physiotherapist will evaluate the adherence to the home exercise programme in a numeric rang scale 1–5 (1=no adherence, 5=excellent adherence). The physiotherapist will re-schedule any missed appointments. Good adherence with BrEX is defined as completion of three treatment sessions.

Data management and data monitoring

Data storage follows requirements in GDPR and will be kept confident and safe in EasyTrial during and after the trial. The Danish Data Protection Agency (REG-55–2016) has approved the trial. Only the chief investigator will have access to the full dataset. Security is enforced by personal password and SMS passcode accompanied with limited assignation at different levels of EasyTrial to the individual worker. All paper forms are designated pseudonyms and transported in code-locked bag to locked file cabinet at Naestved Hospital.

All paper-based data will be verified by an independent duplicate data entry.

No stopping guidelines are scheduled and no Data Monitoring Committee is involved, as the interventions and assessments are deemed safe in former trials.

Sample size

As argued by Norman *et al*,[73] no universal minimal important difference (MID) exists, as MID depends on the clinical setting, population and the intervention. However, it can often be estimated as half a standard deviation (SD).[73] Thomas *et al*. (breathing exercises vs education by a nurse in mild to moderate asthma) found a 0.38 change in MiniAQLQ score.[27]

We will use the effect size found in Thomas *et al*[27] as MID in our sample calculation (with a calculated SD of 0.76) and expect to find a similar or higher effect size, as (a) BrEX will be an add-on intervention to standard specialist care instead of a head-to-head comparison as in Thomas *et al*, and (b) as this secondary care asthma population is expected to have a higher disease burden due to asthma, that is, greater room for improvement.

There is an inherent risk of the trial being underpowered because the SD of MiniAQLQ after BrEX in secondary care is unknown. However, based on previous studies,[27 28] we expect that our SD will be sufficient to reflect the population.

For the present trial, the sample size needed is 172 to detect a 0.38 unit difference between groups in MiniAQLQ score (SD of 0.76, power of 90%, and p value of 0.05 (two-sided)). To allow for drop-outs, we will aim to randomise 190 participants.

Statistical methods

Analysis of primary and secondary outcomes

Data will be analysed on an intention-to-treat basis, thus regardless of protocol adherence, using appropriate parametric or non-parametric tests depending on data distribution. Primary endpoint (between-group difference in change in the MiniAQLQ at 6-month follow-up) and other continuous variables will be analysed using a mixed effects model with subject being a random factor and visit (ie, baseline, 3 months and 6 months) and treatment arm (BrEX +UC or UC) being fixed factors and adjusted for baseline imbalance and treatment centre. These analyses will start in April 2020. Per protocol analyses in participant with good adherence

will be done. Data at 12 months will be included in subsequent secondary analyses of long-term treatment results.

Imputations will only be done to explore results of SW, and sensitivity analyses (with and with-out imputation) will test robustness of these results. We will conduct an analysis of SW data to explore the effect of the intervention on PAL, TEE and steps per day.

Secondary analyses include a numbers-needed-to-treat (NNT) estimation and trial-specific cut-offs for clinically relevant differences in MiniAQLQ (primary outcome) to guide the clinical interpretation of the results. We will estimate NNT as formula 1/(TER–MER), TER being the event rate (proportion of responders, ie, participants improving at least corresponding to the clinically relevant difference, 0.5 units)[49] in the BrEX group, and MER the event rate in the usual care group. We will calculate the trial-specific MID/responder threshold by subtracting the mean MiniAQLQ score for those reporting to have experienced a 'small but not important change' in GPE from those reporting 'important change' in GPE at 6 months.

Both adjusted and unadjusted results will be reported including 95% CIs. No interim analyses will be made. STATA 15.0 (StataCorp LP) will be used. P values<0.05 will be regarded statistically significant. Statistical analyses plan will be made publicly available before any analyses and unblinding of data.

ETHICS, DISSEMINATION AND PERSPECTIVES OF THE TRIAL

Ethics and auditing

Region Zealand Research Ethics Committee approved this trial (SJ-552), and it will be conducted in agreement with the Helsinki declaration. Written informed consents will be obtained from all participants. At the recruitment interview, the participants will be informed that if they are allocated to usual care group they will be provided physiotherapy (BrEX) later, given the RCT will find a clinically relevant benefit.

Before informed written consent is obtained, potential participants will receive written information about the trial, after which research team members (nurse or physiotherapist, trained and supervised by chief investigator) will inform about the trial and answer any questions from the potential trial participant. The Regional Committees on Health Research Ethics are annually selecting a number of trials for auditing. The audit process is independent of research groups and sponsors.

Adverse events

We will ask participants about experienced AEs at every follow-up using open-probe questions, and record on standardises forms for reporting and analysis. Additionally, the medical records will be checked at 12 months follow-up for all AEs occurring during period of trial. We define an AE as respiratory events or other events during the trial, which may be related to aspects of trial participation leading to contact with the GP or hospital. All serious AEs, defined as life threatening or resulting in hospitalisation,[74] will be recorded. If a participant sustains a trial related harm, the hospital assurance covers him/her.

Dissemination of results and protocol amendments

All results will be published, regardless positive, negative or inconclusive, in peer-reviewed journals in due time after trial completion and to follow the Consolidated Standards of Reporting Trials (CONSORT) statement.[52]

Exclusion criteria were modified on first of March 2018 when (a) other known cause of dyspnoea (eg, cardiovascular disease, other respiratory disease) and (b) neurological disease (cannot follow an instruction or close lips) were deleted.

Any important protocol modification will be reported to the Ethics Committee for approval, and they will be registered at ClinicalTrials.gov.

Perspective and additional knowledge for clinical practice

The present trial will provide evidence of the effectiveness of the BrEX programme in patients with incomplete asthma control despite attending specialist care and adhering to moderate to high doses inhaled corticosteroids (ICS) with/without a second controller (GINA steps 3–5).[2] Asthma control is not obtained in the majority of patients,[14 75 76] and new measures to improve patients' daily life with asthma are needed. The trial results will add pivotal information to future evidence-based guidelines and clinical practice. Although primarily an effectiveness trial, we will also gain potential insights into the characteristics of responders and into the mechanisms of effectiveness. In particular, we will explore the predictive value of reduced BHT, comorbid anxiety and depression (HADS), socioeconomic status, smoking status, and PAL at baseline.

Author affiliations
[1]Department of Physiotherapy and Occupational Therapy, Næstved-Slagelse-Ringsted Hospitals, Naestved, Region Zealand, Denmark
[2]Department for Regional Health Research, University of Southern Denmark, Odense, Syddanmark, Denmark
[3]Research Unit for Musculoskeletal Function and Physiotherapy, Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark
[4]Department of Respiratory Diseases, Hvidovre Hospital, Hvidovre, Denmark
[5]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[6]Department of Respiratory Medicine, Odense University Hospital, Odense, Denmark
[7]Allergy & Lung Clinic, Elsinore, (private specialised clinic), Helsingør, Denmark
[8]Department of Physiotherapy and Occupational Therapy, and Pulmonary Disease Unit, Diagnostic Centre, Silkeborg Regional Hospital, Silkeborg, Midtjylland, Denmark
[9]Department of Respiratory Medicine, Aalborg University Hospital, Aalborg, Denmark
[10]Department of Respiratory Medicine, Zealand University Hospital Roskilde, Roskilde, Zealand, Denmark
[11]Department of Respiratory Medicine, Respiratory Research Unit, Bispebjerg and Frederiksberg University Hospitals, Copenhagen, Denmark
[12]Primary Care, Department for Population Sciences and Medical Education, University of Southampton, Southampton, UK
[13]Department for Regional Health Research, Naestved Hospital, University of Southern Denmark, Naestved, Denmark
[14]Department of Respiratory Medicine, Naestved-Slagelse-Ringsted Hospitals, Naestved, Denmark

Twitter Karen Hjerrild Andreasson @KarenAndreasson and Søren Thorgaard Skou @STSkou

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Contributors KHA, UB, STS and MT (Research group, ie, 'steering committee') contributed substantially to the concept and design of this trial. The chief investigator (KHA) developed manuals for recruitment, assessment, and treatment, written information, applications for grants, and approval assignments, made registry at ClinicalTrial.gov, introduced and supervised the recruitment, assessment, and treatment procedures to all involved physiotherapists and nurses, and led the data collection. UB, STS, and MT gave feedback. STS specifically contributed in description of the statistical analyses.KHA drafted the manuscript. All authors (KHA, STS, CSU, HM, KS, JSJ, KDA, KBR, CP, MT, and UB) provided intellectual feedback to the manuscript and approved the final version.

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Competing interests STS is an associate editor of the Journal of Orthopaedic & Sports Physical Therapy, has received grants from The Lundbeck Foundation, personal fees from Munksgaard, all of which are outside the submitted work. He is co-founder of GLA:D®, a not-for profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

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ORCID iDs
Karen Hjerrild Andreasson http://orcid.org/0000-0002-8752-9614
Søren Thorgaard Skou http://orcid.org/0000-0003-4336-7059
Uffe Bodtger https://orcid.org/0000-0002-1231-9209

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