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Protocol for *Implementation of evidence-based breathing retraining for patients with asthma in Region Zealand, Denmark; EmBRAiZ study*

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Implementation of evidence-based breathing retraining for patients with asthma in Region Zealand, Denmark; EmBRAiZ study

Background Asthma is a common, chronic, heterogeneous, and treatable disease affecting 334 million patients worldwide.[1] More than 300,000 individuals have asthma in Denmark. Asthma is characterized by airway inflammation and bronchial hyperreactivity resulting in variable airflow obstruction and symptoms of breathlessness, cough, chest tightness, and wheezing, which impair the patient' quality of life (QoL).[1,2] Treatment of asthma consists of behavioural changes such as asthma trigger avoidance, and drugs, primarily inhaled corticosteroids (ICS).[2] However, a subgroup remains having uncontrolled symptoms irrespective intense medical treatment.[2,3] Asthma is classified according to level of symptoms control (controlled, partly incomplete control, uncontrolled) and asthma severity based on the amount of medication to achieve control (mild, moderate, severe).[4] Uncontrolled asthma affects 40% of patients who need optimization of treatment, as uncontrolled asthma is a risk factor for hospital admissions, sick leave, loss of income and poor QoL.[1,4] A common and important contributing entity to uncontrolled asthma is *dysfunctional breathing* (DB), which is an alteration of the breathing pattern that results in symptoms such as breathlessness or chest tightness deteriorating physical activity and QoL for the patient.[3] DB is observed in 50% of patients with moderate-to-severe asthma.[5]

Using physiotherapist delivered breathing retraining (BR), the patient learns how to improve his or her breathing pattern in rest and during activity.[6,7] It is a low-cost and relatively easy intervention to improve asthma-related QoL in patients with mild-to-moderate asthma.[6]

Until recently, the effects of BR in patients with severe asthma were unknown.[8] However, we recently finalized a large multicentre randomized controlled trial, *Breathing Exercises in Asthma Targeting Dysfunctional Breathing (BEAT DB)* that was initiated from Næstved-Slagelse-Ringsted Hospitals and covered all regions of Denmark to investigate the effect of add-on BR to standard care of patients with moderate-to-severe asthma on asthma-related QoL.[7,9] Participants were recruited from seven respiratory outpatient clinics and one private specialist asthma care clinic (April 2017 to September 2019). The 6-month and 12-month results showed effects similar to or better than the effect of adding second controllers to ICS.[9] This was a pragmatically designed trial with less than 6% attrition and the BR was not associated with any adverse events.

Thus, BR is an intervention that aligns with an increasing awareness of initiatives that promote opportunities for the individual citizen to take as much responsibility as possible for his or her own life in relation to his or her own health.[10] Furthermore, BR counteracts the aforementioned societal and individual burden at risk, as a novel, innovative, and acceptable intervention.

With the contribution of our research, BR is shown to be a safe and effective treatment of uncontrolled asthma, irrespective of asthma severity. Thus the intervention now complies with the

The Medical Research Council (MRC) framework phase 1-3 (i.e., identify intervention; feasibility; evaluation).[11] Next step is therefore MRC phase 4: to implement BR in the Danish asthma care context to improve health for the Danish asthma population. Moreover, the implementation of BR will imply a new work area for Danish physiotherapists and ensure that patients receive appropriate and sustainable evidence-based care.

Aim This study aims to implement the evidence-based intervention *breathing retraining* into clinical care of patients with symptomatic asthma irrespective of asthma severity or comorbidities, and in a diverse multicentre setting to evaluate implementation outcomes. This will meet patients' needs and improve health and life situation in patients with uncontrolled asthma.

Project design, ethical considerations, approvals and registration This is a hybrid-designed prospective multicentre implementation evaluation study, which secondly maintains measuring effectiveness,[12] in a real-world setting including primary and secondary health care and added cross-sectorial co-operation. The intervention is safe.[6,9] All participants will be offered the intervention, including individually preferred delivery form. Ethical approval has been waived by the regional committee (EMN-2022-01229). Danish Data Protection Agency registration number REG-012-2022. Clinicaltrials.gov Identifier: NCT05531370.

Recruitment procedures, recruiting centres, and participants In Denmark, patients with mild-to-moderate asthma are treated in general practice, whereas patients with severe asthma are referred to specialist asthma care at public hospitals or private clinics.

Following international guidelines, patients with asthma will have inhalation technique checked by nurse or medical doctor at asthma visits.[2] The medical doctor (MD) (i.e., general practitioner (GP) or pulmonologist) will eligibility screen and recruit participants and consent will be obtained. Region Zealand has been chosen for the implementation evaluation, and we will recruit from:

- Næstved-Slagelse-Ringsted Hospitals (NSR): MD M.Grove. Zealand University Hospital, Roskilde (SUH): MD LC.Dongo and MD DB.Rasmussen. Holbæk Hospital (HH): MD M.Sin.
- All general practitioners (GP) in Region Zealand (direct referral to the regional physiotherapy).

Participants' inclusion criteria are: Doctor diagnosed asthma; incompletely controlled asthma or worse: Asthma Control Questionnaire (ACQ5) score ≥0.8; patients with potential asthma and/or dysfunctional breathing; residence (or asthma treatment) in Region Zealand; able to read/write Danish (e.g., by available assistance).

Participants' exclusion criteria are: Unwilling to participate or <18 years of age; unable to participate in the intervention due to physical or mental condition.

Intervention including a hybrid delivery offer Conforming the real-world setting, all participants will continue standard asthma care, i.e., acute and planned visits at GP or pulmonologist.[2] BR will be delivered by trained physiotherapists (i.e., project workers) at or online from Dep of

Physiotherapy at hospitals (NSR, SUH, HH) or primary care physiotherapy clinics. To increase the accessibility, participants will be given opportunity to choose between two delivery modes based on personal preferences, yet the content of BR is equal: A) *Ordinary delivery of BR*: Three sessions on-site at hospital. B) *Hybrid delivery mode of BR (H-BR)*: First session on-site at hospital for initial assessment and introduction + following two sessions online (MedComs VDX platform; participants access using webcam and sound on smartphone, tablet, or pc).

BR aims to normalize the inhaled volume, nasal inhalation, exhalation to the resting position of the chest (functional residual capacity, FRC), use of the diaphragm muscle, and to move lower parts of the chest in a frequency of 12-14 per minute.[7] This pattern is initially trained in rest (e.g., side lying or sitting), then during physical activity (e.g., walking). Uncontrolled coughing, frequent yawning or sighing is handled by a suppression technique. Relaxation technique is introduced as a separate activity but to be combined with the breathing pattern method. BR is given in three sessions (60+30+30 minutes) with 3-4 weeks interval during the 12 weeks of intervention. Additionally, participants are supposed to do home exercises 10 minutes twice daily. See the published, open access protocol and scientific article for more information on the intervention.[7,9]

Preparations of implementation evaluation study and fidelity activities Several activities are included: Patient booklet and BR manual used in BEAT DB-trial has been updated and improved by patients' representatives and physiotherapists. Production of open access video sessions for patients and physiotherapists (Danish). The video sessions aim to improve transparency of the intervention. The session will include all parts of the BR intervention, showing a physiotherapist who treats a consenting actor.

Stepwise inclusion of hospitals to adjust e.g., inappropriate workflow. Mandatory training of physiotherapists in delivery of BR by the principal investigator. Monthly fidelity meetings for BR delivering physiotherapists, including H-BR introduction.

Outcomes The study will be grounded in the RE-AIM implementation framework to determine the over-all health impact.[13] The chosen equal primary dimensions and levels are:

Reach (individual): proportion of the target population in Region Zealand that participate in BR.

Effectiveness (individual): success rates of improvements minus deteriorations of individual effects (see patient-related outcomes).

Adoption (organization): proportion of general practices and of hospitals that will adopt BR.

Implementation (organization): extent to which BR will be implemented as intended in real world. Fidelity and clinical processes.

Maintenance (individual and organization): extent to which BR will be sustained over time. Attrition rates. Adherence (defined as 100% of sessions).

<u>Patient-related outcomes</u>:

MiniAQLQ, change at 12-month. Asthma-specific QoL describes how living with asthma is perceived, and MiniAQLQ is frequently used in clinical trials.[2,6,8,9,14] We anticipate to find mean improvement ≥0.35 units, i.e., equal to results of BEAT-DB trial.

Other outcomes will include (references are omitted due to limited space): ACQ5, General Anxiety Disorder-7, Personal Health Questionnaire Depression Scale, Fatigue Severity Scale, EuroQol (EQ-5D), observation of breathing pattern (Brompton Breathing Pattern Assessment Tool)[15], arterial blood saturation, physical activity (accelerometer, 7 consecutive days), lung function (spirometry), pharmacotherapy level, comorbidity (e.g., severe heart disease), serious adverse events (e.g.deaths).

Data collection Online collected patient-reported outcomes (PROMS, including usage of medication) and full objective assessment at baseline, and 12-month follow ups. The BR-delivery physiotherapist will assess the participant. Nurses at the GP or the respiratory clinic will perform data extraction on asthma-related health care usage, and adverse events, at 12-month follow up. Illustration of the patient timeline, see figure 1 (attached).

A research database is built (using REDCap), approved by Danish Data Protection Agency.

See *National database EmBRAiZ-Astma*, an extension of the EmBRAiZ implementation project.

Sample size During 30 months of recruitment, we expect to include 300 participants.

Statistical Analyses All analyses will be carried out using Stata/IC 17.0 or newer version (StataCorp LLC 2021, College Station, TX, USA). Significance level of 0.05. Descriptive statistics to characterise the participants. Frequency statistics for implementation evaluation outcomes. Evaluation of the effect on MiniAQLQ score of 0.35 as an intervention-related minimal imported difference.[9] Conduct of preliminary analyses of the hybrid delivery when 40 H-BR participants have completed the 6-month follow up.

Patients' and clinicians' involvement During the project, study steering board of patients' representatives, clinicians' representatives and researchers is used, qualitative investigations of the process and the written material. Patients and clinicians are included in doing the evaluation, using RE-AIM implementation framework.[13]

Schedule (and progress) for the study

Design, protocol, applications for approvals (*finalized*)	August 2021 – June 2023
Practical preparation, training of personnel, and funding (*running*)	April 2022 – August 2024
Implementation study (*running,* 110 patients included by March'24)	May 2022 – October 2024
Data management, evaluation *(awaiting)*	October 2023 – January 2025
Disseminations of process (*running*) and results (*awaiting*)	May 2022 – August 2025

Project affiliations and project team To secure quality and completion of the implementation evaluation study, it will be conducted in a collaboration of respiratory medical experts, experienced respiratory physiotherapists, experienced innovation and implementation manager, and experienced

researchers (the aforementioned research group) who have shown successful national implementation of treatment initiatives.[16] The affiliations are: 1) Research and Implementation Unit *PROgrez*, Dep. for Physiotherapy and Occupational Therapy, Næstved-Slagelse-Ringsted Hospital. 2) *PLUZ* (Pulmonary Research Unit, Zealand Denmark), Dep. For Respiratory Medicine, Zealand University Hospital, Roskilde.

This project includes the Post Doc project for the applicant affiliated to Institute for Regional Health, University of Southern Denmark. The applicant is the principal investigator.

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National database EmBRAiZ-Astma, collection of knowledge in non-pharmacological treatment

A database named EmBRAiZ-Astma, established by PROgrez in REDCap (hosted by Region Zealand), awaiting formal registration (to be submitted April 2024) will include data from courses of non-pharmacological treatment, focused in BR, in patients with asthma despite asthma severity throughout Denmark. If possible, as well in patients without an asthma-diagnose, but with symptoms of dysfunctional breathing (DB). These data have high value concerning evaluation of relevance of permanent BR by physiotherapist in Denmark. We invite physiotherapists, certificated in giving BR, who treat asthma patients (and maybe additionally in DB-patients generally), to register their patients in REDCap. *EmBRAiZ-Astma* is an extension of *EmBRAiZ implementation project*, and data collection will be similarly to the EmBRAiZ implementations project.

Ethical considerations Patients will receive written information about the aim of collection, the use of data, and that data are passed on to EmBRAiZ-Astma, and patients will asked for consent as treatment data are used for other issues than medical (Sundhedslov §§42-43).

Dissemination of process and results of study

Updates of study process: Newsletters to the included study personnel and by request from other medical doctors and physiotherapists; *PraksisInfo*; News in local media (Region Zealand) and via Social Media channels and patient organisations (Astma – Allergi Danmark; Lungeforeningen).

Dissemination of study results: Scientific open access peer-reviewed publications (English); Articles prepared for *Fysioterapeuten* and *Ugeskrift for Læger* (Danish journals for Physiotherapists and Medical Doctors); Layman-publications of results via Social Media channels.

Work title: "Implementation evaluation of evidence-based breathing retraining in patients with asthma"; order of authors (i.e*.,* research group): Karen H Andreasson, Lars H Tang, Cecilie Egholm Anne Dalhoff, Mike Thomas, Uffe Bødtger, Søren T Skou.

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