Statistical Analysis Plan for the study Implementation of Evidence-Based Breathing Retraining for Patients with Asthma in Region Zealand (EmBRAiZ)

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This statistical analysis plan was registered prior to the data analysis.

Introduction

This study aims to assess the implementation of an evidence-based breathing retraining intervention into clinical care of patients with symptomatic asthma irrespective of asthma severity or comorbidities, evaluating implementation outcomes in a diverse multicentre setting. The study is a hybrid-designed prospective multicentre implementation evaluation study, in which the investigators secondarily maintain measuring the effectiveness of breathing retraining in a real-world setting including primary and secondary health care.

Methods

Intervention

The intervention consists of breathing retraining (BR) delivered by physiotherapists as an add-on to standard asthma care, structured as patient education, three individualized treatment sessions, and daily home exercises over a 2-month period. Following an initial clinical assessment, medical history, and breathing pattern observation, the treatment content focus includes respiration modification, relaxation, suppression techniques (cough/yawn/throat clearing), and breath-holding techniques. A detailed description of the clinical protocol is reported elsewhere [1], and the Danish treatment manual for physiotherapists is available via the Open Science Framework at *https://doi.org/10.17605/OSF.IO/W6KP8*.

Outcomes

The primary outcome is the Mini Asthma Quality of Life Questionnaire (MiniAQLQ). Secondary outcomes include the Asthma Control Questionnaire (ACQ5), General Anxiety Disorder-7 (GAD-7), Personal Health Questionnaire Depression Scale (PHQ-8), Fatigue Severity Scale (FSS), EuroQol (EQ-5D-5L), lung function (spirometry), physical activity (7-day accelerometer), arterial blood saturation (pulse oximetry), pharmacotherapy level (GINA steps 1–5), comorbidities, therapist-observed Key Respiratory Characteristics (KRC), and serious adverse events. Respiratory rate is dichotomized into normal (less than or equal to 16 breaths/minute) versus abnormal (greater than 16 breaths/minute). The categorical KRC variables, diaphragmatic initiation and nasal breathing, are consistently dichotomized as unsuccessful execution (No, not at all or Yes, partly) versus successful execution (Yes, only). Outcomes will be reported in different articles.

Statistical analyses

1. Baseline characteristics

Baseline characteristics of the study population will be summarized. Continuous variables will be presented as means with standard deviations or medians with interquartile ranges. Categorical variables will be reported as frequencies and percentages.

2. Analysis of effectiveness and clinical predictors

Pre-specified continuous analysis

Changes in primary and secondary continuous outcomes from baseline to 12 months will be analysed using a Mixed Model for Repeated Measures. The analysis will follow the Intention-To-Treat principle, accounting for missing data under the Missing At Random assumption by utilizing all available measurements (including 3-month data where available). Residual normality will be assessed via residual plots to verify model assumptions; log-transformation will be applied if substantial deviations are observed. Time point will be included as a fixed effect. The intra-individual correlation will be handled by an unstructured covariance matrix. The model will be fitted using Restricted Maximum Likelihood estimation with Satterthwaite approximation for degrees of freedom. Results will be reported as Estimated Marginal Means with 95% confidence intervals.

Pre-specified categorical analysis

Changes in dichotomized secondary outcomes (respiratory rate, diaphragmatic initiation, and nasal breathing) from baseline to 12 months will be analyzed using Generalized Estimating Equations with a logit link function and an unstructured correlation structure to account for intra-individual dependency. Results will be reported as Odds Ratios (OR) with 95% confidence intervals.

Pre-specified responder analysis

A net success rate will be calculated for the primary outcome, the MiniAQLQ, at 12 months. Participants will be categorized into three groups based on the minimal clinically important difference (MCID) of 0.5 points [2]: improved (change ≥ 0.5), stable (change > -0.5 and < 0.5), or deteriorated (change ≤ -0.5). The net success rate will be reported as the proportion of improved participants minus the proportion of deteriorated participants using complete-case analysis. The 95% confidence interval for the net success rate will be calculated using the Wald method for the difference of proportions.

Post-hoc responder analyses

Additional responder analyses will be conducted for the MiniAQLQ at 12 months using complete-case analysis. Participants will be classified as responders based on two thresholds: 1) an improvement of MCID (Yes/No), and 2) an improvement corresponding to the mean within-group 12-month improvement of 0.76 points observed in the intervention arm of a previous trial of the intervention [3]. The proportion of responders for both thresholds will be reported as frequencies and percentages with 95% confidence intervals using the Clopper-Pearson method.

Post-hoc analysis of clinical predictors

To identify clinical characteristics associated with treatment response, a multivariable logistic regression analysis will be performed [4]. The dependent variable will be the achievement of the MiniAQLQ MCID at 12 months. To ensure model stability and avoid overfitting, the number of predictors included will be limited by the number of participants reaching the MCID, adhering to the principle of at least 10 events per variable. The independent variables will include the KRC: 1) nasal breathing, 2) diaphragmatic initiation, and 3) respiratory rate. Provided the number of observed events allows for further complexity, the model will be adjusted for additional baseline

covariates in this prioritized order: ACQ5 (asthma control), GAD7 (anxiety), and GINA step (asthma severity). Results will be reported as Odds Ratios (OR) with 95% confidence intervals.

Post-hoc sensitivity analysis

A sensitivity analysis concerning the delivery mode will be performed by excluding all participants who underwent the hybrid mode of delivery, to evaluate the robustness of all effectiveness and predictor findings.

3. Implementation evaluation (RE-AIM framework)

- **Reach:** Representativeness will be assessed by comparing baseline characteristics (e.g., age, sex, asthma severity) between participants who complete (i.e. are therapeutically fully treated) the intervention and non-completers.
- **Effectiveness:** Described in section 2.
- **Adoption:** Reported as the proportion of general practices and hospitals that adopt the intervention, as well as the participation rate among practitioners (including pulmonologists, general practitioners, and physiotherapists).
- **Implementation (Acceptability and Fidelity):** Qualitative analysis of semi-structured interviews will explore the feasibility and acceptability of the hybrid delivery mode, including the reasons for choosing this mode of delivery. Quantitative analysis of proportion who had the hybrid-version, and the reasons related to the decisions for including or omitting the hybrid-version. Implementation fidelity will further be quantitatively reported as the proportion of participants a) completing the intervention (≥ 3 sessions), b) who were therapeutically fully treated, c) the extent they had the key aspects of breathing retraining-intervention, and d) the reasons for non-fidelity.
- **Maintenance:** Reported as the attrition rate (proportion of dropouts) at 12 months. The number and reasons for withdrawal (dropouts) will be summarized to describe the study flow.

4. Statistical software

All statistical analyses will be conducted using Altair SLC (Altair Engineering Inc., Troy, MI, USA).

References

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