Add-on to NCT03280355

Statistical Analysis Plan for a long-term follow-up study in RCT "The Effects of Singing Training for Patients with Chronic Obstructive Pulmonary Disease (COPD)" (NCT03280355).

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Title of follow-up study:

Long-term upkeep of activity, effects, and impact following pulmonary rehabilitation for COPD with either Singing for Lung Health or physical exercise training.

Study Information

In our recent multicentre RCT - *Sing-a-Lung 1.0* - comparing Singing for Lung Health (SLH) with usual-care physical exercise training (PExT) within 10 week's community-based pulmonary rehabilitation (PR) for COPD (NCT03280355), we demonstrated that SLH conferred relevant short-term improvements regarding both physiological and psychological parameters and was non-inferior to PExT.[1–3] Post-hoc analyses demonstrated that effect was correlated with adherence in both groups,[4] and, moreover, suggested that SLH was associated with improved inspiratory muscle control and dyspnoea control, and that a larger proportion in SLH achieved the minimal important difference (MID) in quality of life (QoL) (measured by change in St George's Respiratory Questionnaire; SGRQ; MID = ≤4 units) than in physical capacity (measured by change in 6-Minute Walk Test Distance; 6MWD; MID = ≥30 m) (49% vs. 29%).[5]

Little is, however, known about the long-term effects of SLH including upkeep of activity, effects, and life-style changes, which is a well-known significant challenge within PR with PExT.[6–8]

Aims and hypotheses

With the present project - *Sing-a-Lung 1.1* - we will conduct a long-term follow-up study within the study cohort of *Sing-a-Lung 1.0* (n=270; SLH n=145/PExT=125) to investigate long-term upkeep of activity. Secondarily, we will investigate sustainability of effect and impact on quality of life, anxiety, depression, and dyspnoea. Furthermore, we aim to obtain deeper insight into how the study participants have integrated the tools derived from participating in either SLH or PExT.

Specifically, we aim to investigate:

Primary study outcome and hypotheses:

1. Whether level of adherence demonstrated in *Sing-a-Lung 1.0* is correlated with upkeep of activity. We hypothesise that high adherence in *Sing-a-Lung 1.0* predicts high long-term upkeep of activity after *Sing-a-Lung 1.0* and vice versa for low adherence. Moreover, we hypothesise that SLH is non-inferior to PExT in upkeeping long-term activity.
2. Whether short-term follow-up scoring values in QoL, anxiety, depression, and dyspnoea sustains at long-term follow-up. We hypothesise that SLH is non-inferior to PExT regarding sustaining of scoring and effect demonstrated in Sing-a-Lung 1.0.

Secondary study outcomes, and hypotheses:

A. Whether short-term achievement of effect in QoL – defined as achievement of MID or not in SGRQ – is associated with upkeep of activity and scoring values. We hypothese that those who achieved MID are more likely to maintain/upkeep or seek out an activity and keep up scoring values.
B. Whether self-reported long-term level of overall physical and social activity is associated with RCT randomisation, hypothesising that SLH is non-inferior to PExT.

Whether RCT randomisation is associated with self-reported satisfaction with intervention, experienced relevance, and experienced integration of the tools obtained, hypothesising that SLH is non-inferior to PExT.

C. Whether availability of a local, structured upkeeping course in physical training or a lung choir is correlated to long-term upkeep of activity, hypothesising that available local, structured offer improves likelihood of upkeep of activity. Furthermore, we hypothesise that SLH is non-inferior to PExT regarding likelihood of upkeep of activity.

Design Plan

Study type

The present study is an observational study, based on a follow-up study in the RCT cohort of *Sing-a-Lung 1.0* (n=270) (Trial registration number: NCT03280355; project title: "The Effects of Singing Training for Patients with Chronic Obstructive Pulmonary Disease (COPD)").

Blinding

The research assistant responsible for data collection is blinded to RCT randomisation. After the analysis process, blinded results (presented as A: Level of adherence 0 compared to Level of adherence 1; and B: Treatment 0 compared to Treatment 1) will be presented to the research group, who will interpret the blinded results. Prior to unblinding of the trial results, the research group will prepare two alternative conclusions for Level of adherence and two alternative conclusions for randomisation.[9]

Study design

The present study is a long-term follow-up study of upkeep of activity and sustaining of effects across RCT study groups in *Sing-a-Lung 1.0* (SLH and PExT) using validated and specially developed questionnaires to facilitate descriptive and comparative analyses and to conduct mixed-methods inspired research equivalent to our previously published, survey-based research. The validated questionnaires cover QoL, dyspnoea, and symptoms of anxiety and depression, and are all specifically validated and used for COPD. The specially developed questionnaires were developed by PostDoc, Ph.d., Mette Kaasgaard in close collaboration with Ph.d., Consultant in Pulmonology, Daniel Bech Rasmussen, and discussed and settled with the additional research group members: Professor, Ph.d., Consultant in Pulmonology, Uffe Bødtger; Professor, D.MS.c, Consultant in Pulmonology, Ole Hilberg; and Associate Professor, D.MS.c, Consultant in Pulmonology, Anders Løkke Ottesen.

Randomisation

Participants were randomised during the *Sing-a-Lung 1.0* RCT (Trial registration number: NCT03280355). The intervention phase of *Sing-a-Lung 1.0* took place between August 2017 and May 2019.

Sampling Plan

Existing Data

Already collected data from *Sing-a-Lung 1.0* include:

- Basic baseline characteristics: *e.g.* age, BMI, socio-demographics, smoking history, health care utilisation, exacerbations, medicine, comorbidities, and expectations towards benefits of singing.
- Baseline and short-term follow-up data related to *Sing-a-Lung 1.0* outcomes: Physical Capacity (Six-Minutes Walking Test; 6MWT), Quality of Life (St Georges' Respiratory Questionnaire; SGRQ), anxiety and depression (Hospital Anxiety and Depression Scale; HADS), dyspnoea (BORG-CR10 and Modified Medical Research Scale, mMRC), lung function (Forced Expiratory Volume in one Second; FEV1% predicted and Forced Vital Capacity; FVC% predicted), respiratory muscle strength and control (inspiratory pressure, breath counting scale, breath holding test), adherence, drop-out-rate, medicine consumption, number of COPD-related hospitalisations and exacerbations, and satisfaction with study intervention.

Sample size

RCT cohort of *Sing-a-Lung 1.0* (n=270). Participants who accept to participate will be included in the study. The following participants will be excluded from analyses: 1) Do not accept to participate, 2) Not reachable via telephone (after three attempts at different dates), 3) Deceased since *Sing-a-Lung 1.0*.

Data collection procedures

Participants from *Sing-a-Lung 1.0* have already provided written consent for a long-term follow-up contact. All participants will therefore be contacted directly by telephone by the research assistant Department of Medicine, Hospital Lillebaelt, Vejle, during February to May 2023 and asked for their consent to participate in the follow-up study. The research assistant will collect data by telephone and data will entered directly into web-based, software survey tool and secure database, SurveyXact by Ramboll (Rambøll Management Consulting, Aarhus, Denmark)[10] which will be used for survey distribution, data collection, and data storage. PostDoc, Ph.d., Mette Kaasgaard, is in charge of the overall data collection.

Data analysis procedures

In June 2023, data will be transferred from the database at SurveyXact by Ramboll to Microsoft Excel file and imported into statistical software STATA 17 (StataCorp LLC, Texas, USA). Data will be anonymised, cleaned and prepared (see section: Analysis plans/Modifications of specific variables of interest to be included in the logistic regression models**)** before merging with the original dataset and related 1:1 to observations from *Sing-a-Lung 1.0*. Merging and subsequent analysis process will start July 2023.

Variables

Measured variables

For the long-term follow-up study, data collection includes current smoking status, and patient-reported health care utilisation, exacerbations, and usage of COPD-related medicine since *Sing-a-Lung 1.0*. Besides, the data collection includes patient-reported knowledge on availability of local structured or unstructured offer of singing, for example a lung choir, and on availability of local structured or unstructured offer of physical training after the intervention.

Furthermore, we will collect data related to the following outcomes and variables of interest:

Study outcomes	**Measure**
Primary study outcome	
1. Long-term upkeep of activity	• Participation in local, structured or unstructured singing activity, for example a lung choir. • Participation in local, structured or unstructured upkeep course in physical training. • Participation in any other activity (physical, musical, or creative). • Overall self-evaluated level of physical and social activity compared to before intervention.
Secondary study outcomes	
2. Long-term sustaining of effect - QoL, anxiety, depression, dyspnoea, etc.	• QoL: St. George's Respiratory Questionnaire (SGRQ) • Anxiety and depression: (Hospital Anxiety and Depression Scale (HADS) • Dyspnoea: modified Medical Research Council (mMRC) (dyspnoea scale)
3. Self-reported satisfaction with intervention, experience of relevance, and experienced integration of tools obtained during *Sing-a-Lung 1.0*	• Satisfaction with the intervention • Experience of overall relevance of content of the intervention • Use and integration of tools obtained during intervention

Analysis Plan

Statistical models

Overall

Quantitative data from validated questionnaires will be analysed using standard calculators and cut-off for minimal important differences developed for the specific tools,[11–15] In lack of a formal, absolute tool for survey research analysis,[16,17] we will use a conventional approach to analyse quantitative and semi-quantitative data from the specially developed questionnaires. Hence, categorial data will be described with number and percentage (categorical data) and continuous data with either mean +/- standard deviation (normally distributed continuous data) or median and range (not normally distributed continuous data).

Differences in within-groups and between-groups effects will be investigated with relevant test for continuous data (independent samples, paired-samples, related-samples, and repeated-measures) and categorical data (Chi^2 or Fischer's test). Adjusted and unadjusted univariable and multivariable logistic regression models will be included to analyse relevant correlations. Furthermore, we will explore any potential interactions.

Baseline characteristics will be explored in the following primary and supplementary analyses: Characteristics and performance in 1) Overall total study population (baseline, short-term follow-up, and long-term follow-up), 2) Included, not accepting/not reachable, deceased, 3) Deceased (low, medium, high RCT adherence), 4) RCT randomisation (SLH, PExT).

Modifications of specific variables for analyses: 1) Adherence during RCT (ranging from 0 to 20 sessions attended; classified into three categories: zero: 0%; low: 1-49%; medium: 50-74%; high: 75-100%), 2) Intervention randomisation, 3) Sustaining of effects: QoL, anxiety, depression, dyspnoea or not (all related to minimal important difference, MID (4 units for SGRQ and 1 for HADS and mMRC), 4) Achievement of MID in RCT (SGRQ and 6MWD) or not, 5) Age categorised into quartiles, 5) FEV1% predicted categorised according to GOLD (1-4), [6,8] 6) Baseline 6MWD categorised into quartiles, 7) Available offer of singing/physical training or not.

STROBE Statement checklist for cohort studies will be used for reporting. Statistical analyses will be performed using statistical software STATA 17 (StataCorp LLC, Texas, USA). Statistical significance will be reported as $p < 0.05$.

Ethics

Written consent for long-term follow-up contact was provided in *Sing-a-Lung 1.0* and as the long-term-follow-up study, moreover, will be solely questionnaire-based, ethical approval from The Committee on Health Research Ethics was not required. The study was approved by The Danish Act on Processing of Personal Data regarding re-accesses to the raw data of *Sing-a-Lung 1.0* in order to retrieve patients' contact information and to conduct the new questionnaire-based study of the long-term-follow-up study (REG-135-2022).

Feasibility

The long-term follow-up study will be managed and facilitated by PostDoc, Ph.d., Mette Kaasgaard. The study will be conducted at Pulmonary Research Unit Zealand (PLUZ), Zealand University Hospital Roskilde and Naestved Hospital. Furthermore, Medical and Respiratory Department, Hospital Lillebaelt, Vejle, will participate with academic qualification and advice and will donate salary for the research assistant responsible for data collection.

Funding

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Dissemination

The results of the overall project will be disseminated as one or two original research papers and abstracts in international scientific journals and at regional, national, and international conferences, scientific meetings, and symposiums. Authorship will be granted according to criteria of the Vancouver authorship guidelines and "uniform requirements" (ICMJE). All results, positive, negative, and inconclusive, will be published in international peer-reviewed journals (high-impact, if possible).
Furthermore, dissemination strategy will be made, targeting *e.g.* the local and national press, the public (including social media platforms), patients, patient organisations, music teaching organisations etc.

Research group - academic consortium

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