STATISTICAL ANALYSIS PLAN

A randomised controlled trial of culturally adapted pulmonary rehabilitation for people living with post-tuberculosis lung disease in Kyrgyzstan

(RECHARGE Kyrgyzstan)

SAP Version: V1.0

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Based on protocol: Culturally adapted pulmonary rehabilitation for adults living with post-tuberculosis lung disease in Kyrgyzstan: protocol for a randomised controlled trial with blinded outcome measures (BMJ Open 2022;12:e048664. doi:10.1136/bmjopen-2021-048664)

Trial registration: International Standard Randomised Controlled Trial Number: ISRCTN11122503.

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List of abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
CAT	COPD Assessment Test
CCQ	Clinical COPD Questionnaire
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CSR	Clinical Study Report
ESWT	Endurance Shuttle Walk Test
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GLMM	Generalized Linear Mixed Model
HADS	Hospital Anxiety and Depression Scale
ISWT	Incremental Shuttle Walking Test
ITT	Intention To Treat
MCID	Minimum Clinically Important Difference
MRC	Medical Research Council
PTLD	Post-Tuberculosis Lung Disease
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TB	Tuberculosis
VAS	Visual Analogue Scale
WPAI	Work Productivity and Activity Impairment

Contents

Introduction

This Statistical Analysis Plan (SAP) describes the planned analyses and reporting for a randomised controlled trial of culturally adapted pulmonary rehabilitation for people living with post-tuberculosis lung disease (PTLD) in Kyrgyzstan (RECHARGE Kyrgyzstan).

This SAP should be read in conjunction with the most recent version of the clinical trial protocol.

The purpose of this SAP is to outline the planned analyses that are to be performed on the data to support the completion of the Clinical Study Report (CSR). The SAP will be amended if there are substantial changes to the planned analyses, and in any case will be finalised before the database lock for this study. Exploratory post-hoc or unplanned analyses not necessarily identified in this SAP may be performed on these data as required. These analyses will be clearly identified in the CSR.

Study objectives

Primary objective

The primary objective of the trial is to evaluate the effectiveness of adapted 6-week pulmonary rehabilitation on maximal exercise capacity (assessed by the incremental shuttle walking test (ISWT)) as an add-on to usual care.

Secondary objectives

The secondary objectives are to assess:

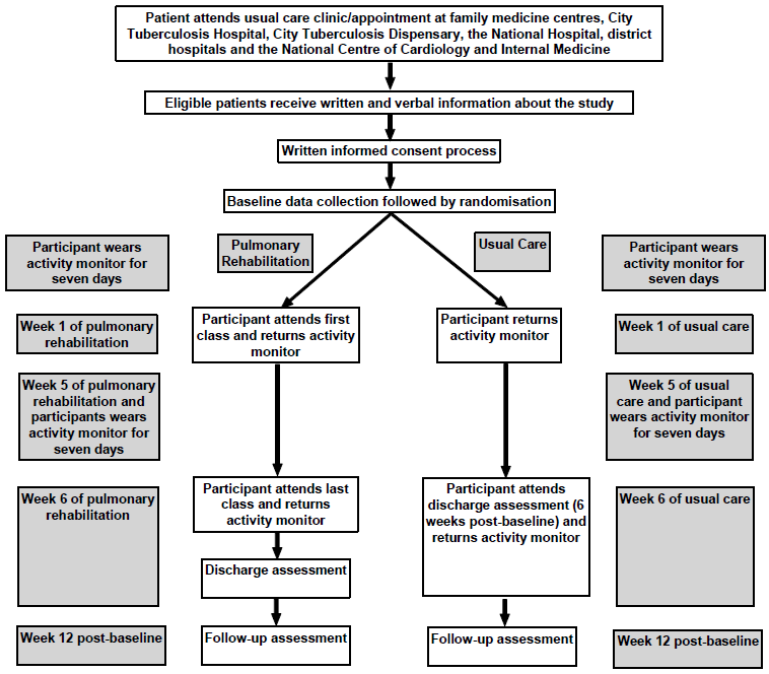
1. Safety
2. Health status and respiratory symptoms
3. Physical function
4. Economic impact/cost-effectiveness
    a. EQ-5D-5L
    b. Work productivity and activity impairment

Trial design

Overview

This is a single-centre, assessor-blind, randomised controlled trial to assess the clinical and cost-effectiveness of pulmonary rehabilitation compared to usual care, in patients with PTLD. A 6-week programme of hospital-based pulmonary rehabilitation, comprising twice-weekly 2-hour sessions of exercise and education in accordance with international guidelines (American Thoracic Society/European Respiratory Society) will be delivered. Changes in outcome will be assessed immediately post intervention (within 1 week of completing the intervention). An overview of the trial design is provided.

Figure 1: Schematic of trial design for RECHARGE Kyrgyzstan



Participants

Participants will be aged ≥18 years with a confirmed diagnosis of PTLD and be confirmed as TB-negative using a Ziehl-Nielsen stain or GeneExpert method; having completed TB treatment and with a Medical Research Council (MRC) dyspnoea score of 2 or higher.

Reasons for ineligibility will be the presence of comorbidities such as severe or unstable cardiovascular, other internal diseases and locomotor difficulties that preclude exercise; malignant disease such as lung cancer; evidence of active TB on chest X-ray or sputum tests within 1 month of assessment; or unable or unwilling to provide informed consent.

Usual care

Usual care will comprise their usual prescription medications and an educational booklet regarding PTLD self-management, including the importance of exercise, healthy diet, smoking cessation and avoiding biomass smoke.

Sample size

Recruitment of 114 participants with a drop-out rate of 30% will be sufficient to give 80% power at the 5% significance level assuming 35m difference in the ISWT measured at baseline and after completion of the intervention.

Randomisation and blinding

The University of Leicester will supply a web-based randomisation system from a third party (Sealed Envelope Ltd). Participants will be randomised 1:1 to pulmonary rehabilitation or usual care. This will be set up as a blinded randomisation process, whereby a blinded randomisation code is allocated to a participant which corresponds to either pulmonary rehabilitation or usual care. Decoding lists are held by unblinded personnel and available via Sealed Envelope.

It will not be possible to blind participants and staff delivering the intervention to group allocation due to the nature of the intervention. The outcome assessors and statistician will be blinded to the treatment groups. There are no incidences where emergency unbinding will be required.

Visit schedule

Table 1: Schedule of procedures

Assessment	Screen	Randomised treatment (visit window ±7 days)			
	V0	V1: Baseline	V2: 6 weeks (effectiveness end-point)	V3: 12 weeks (6-week post-trial follow-up)	
	In-person	In-person	In-person	In-person	Telephone
Consent	x				
Eligibility review	x				
Randomisation		x			
Socio-demographics		x			
Lung health		x			
Medical history	x				
Medications/treatments		x			
Chest x-ray	x				
TB status	x				
Safety AE/SAE		x	x	x	x
Anthropometrics		x	x		
ISWT		x	x		
ESWT		x	x		
Sit-to-stand		x	x		
MRC scale		x	x	x	x
CCQ		x	x	x	x
CAT		x	x	x	x
HADS		x	x	x	x
WPAI		x	x	x	x
EQ-5D-5L		x	x	x	x
TB symptoms		x	x	x	x
Physical activity		x	x		

CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire score; ESWT, Endurance Shuttle Walk Test; HADS, Hospital Anxiety and Depression Scale; ISWT, Incremental Shuttle Walk Test; MRC, Medical Research Council; TB, tuberculosis; WPAI, Work Productivity and Activity Impairment Questionnaire.

Outcomes and other variables

Primary outcome

Definition and derivation of primary outcome

The primary outcome is change in the incremental shuttle walking test (ISWT) distance. The minimal clinically important difference (MCID) will be 35m (1). The outcome will have a minimum score of 0m and a maximum score of 1020m in 10m increments.

Hypothesis to be tested

H_0: The difference in walking distance based on the ISWT is less than or equal to 0.

Secondary outcomes

Definition and derivation of secondary outcomes

The secondary outcomes are:

1. Safety
    a. AE event rate in the 12 weeks of the trial from V1
    b. SAE event rate in the 12 weeks of the trial from V1
2. Patient reported outcomes (V1, V2, V3)
    a. MRC dyspnoea score
    b. Clinical COPD Questionnaire (CCQ)
        i. Total score
        ii. Domains
            1. Symptoms
            2. Mental
            3. functional
    c. COPD Assessment Test (CAT)
    d. Hospital Anxiety and Depression Scale (HADS)
        i. Anxiety score
        ii. Anxiety classification (normal, mild, moderate, severe)
        iii. Depression score
        iv. Depression classification (normal, mild, moderate, severe)
    e. Euroqol EQ-5D-5L
        i. Domains
            1. Mobility
            2. Self-care
            3. Usual activities
            4. Pain/discomfort
            5. Anxiety/depression
        ii. Visual analogue scale (VAS)
    f. Modified work productivity and activity impairment
        i. Percent work time missed health
        ii. Percent impairment while working health
        iii. Percent overall work impairment health
        iv. Percent activity impairment health
3. Physical measures
    a. Incremental shuttle walking test
        i. Distance (m)
    b. Endurance shuttle walk test
        i. Time (sec)
    c. 5-times sit-to-stand test
        i. Time (sec)

Hypotheses to be investigated

H0: The treatment group (pulmonary rehabilitation) will have outcomes that are worse than or equal to those of the control group (usual care).

Intervention adherence

Attendance to pulmonary rehabilitation classes (12 classes scheduled; twice weekly for 6 weeks) will be monitored. The number of additional scheduled classes will be reported with any changes recorded in the CRF. A summary will be provided for the intervention group. Deviations from protocol including loss to follow-up, withdrawal by study team and withdrawal of consent will be included.

Analysis sets/populations

Protocol deviations

Major deviations

Protocol deviations that will affect inclusion in trial populations are:

- Participants found to be ineligible after randomisation
- Participants who receive the wrong study treatment

Minor deviations

All other (non-major) protocol deviations will be reported but will not affect analysis populations e.g., visit assessments delays less than 2 weeks, visit assessments earlier than scheduled.

Intention-to-treat population

The intention-to-treat population will be comprised all the participants randomised in to the trial (regardless of whether they received the pulmonary rehabilitation intervention) analysed in their allocated group, outcome data obtained from all participants will be included in the data analysis (i.e regardless of study completion or data completeness). All data up to the time of study discontinuation will be included for participants who withdrew prematurely.

Modified intention-to-treat population

The modified intention-to-treat will be comprised all the participants randomised to the trial (regardless of whether they received the pulmonary rehabilitation intervention), analysed in their allocated group, where data is available. Therefore, participants with missing outcome data will be excluded from the analysis (i.e complete case analysis). No imputation will be carried out for the missing data.

Per-protocol population

The per-protocol population will comprise all participants recruited in to the trial who had their intervention administered and who do not have major protocol deviations.

Other analysis populations

None.

General issues for statistical analysis

Derived/computed variables

Body mass index (BMI): This will be derived as per WHO Guidelines, BMI measures as Kg/m2.

Age: Age will be measured in years and will be derived from the date of birth at the randomisation date.

Clinical COPD Questionnaire (CCQ): The CCQ is a 10-item health-related quality of life questionnaire that is divided into three domains: symptoms, functional and mental.

COPD Assessment Tool (CAT) score: The CAT consists of 8 items with scores ranging from 0 to 5 (0= no impairment). An overall score will be calculated by adding the score from each item with total scores ranging from 0 to 40, higher scores indicating a more severe health status impairment or a poorer control of COPD.

Hospital Anxiety and Depression Scale (HADS): The HADS is used to determine levels of anxiety and depression. The questionnaire consists of 14 questions with a 4-point Likert scale, and two 7-item subscales (scored 0-21) for anxiety and depression. Subscales are categorised as Normal (score 0-7), Mild (score 8-10), Moderate (score 11-15) or Severe (score 16-21).

Euroqol EQ-5D-5L: The EQ-5D-5L comprises five domains: Mobility, Self-care, Usual activities, Pain/discomfort, Anxiety/depression, each with five possible responses ranging in severity. The questionnaire also comprises a visual analogue scale (VAS) (scored 0-100), where the participant identifies their health from 'the best you can imagine' (score of 100) and the 'worst you can imagine' (score of 0).

Modified work productivity and activity impairment: The modified WPAI questionnaire is composed of the following eight questions reflecting the following: Currently employment status; hours of lost work due to illness (past seven days); hours of lost work due to other reasons (past seven days); hours worked for pay (past seven days); how much did illness affect productivity while you were working for pay (past seven days, 0-10 scale); ; how much did illness affect ability to do regular daily activities (past seven days, 0-10 scale); hours unable to perform regular household duties (past seven days); how much relied on other household members to do your regular household duties due to illness (past seven days, 0-10 scale).

Multiple testing

Adjustments for multiple comparisons will be performed using the mhtexp method (2) with 95% Cis and p-values provided.

Interim analysis

There is no interim analysis planned. Recruitment and disposition will also be presented in a Consolidated Standards of Reporting Trials (CONSORT) diagram.

Analysis software

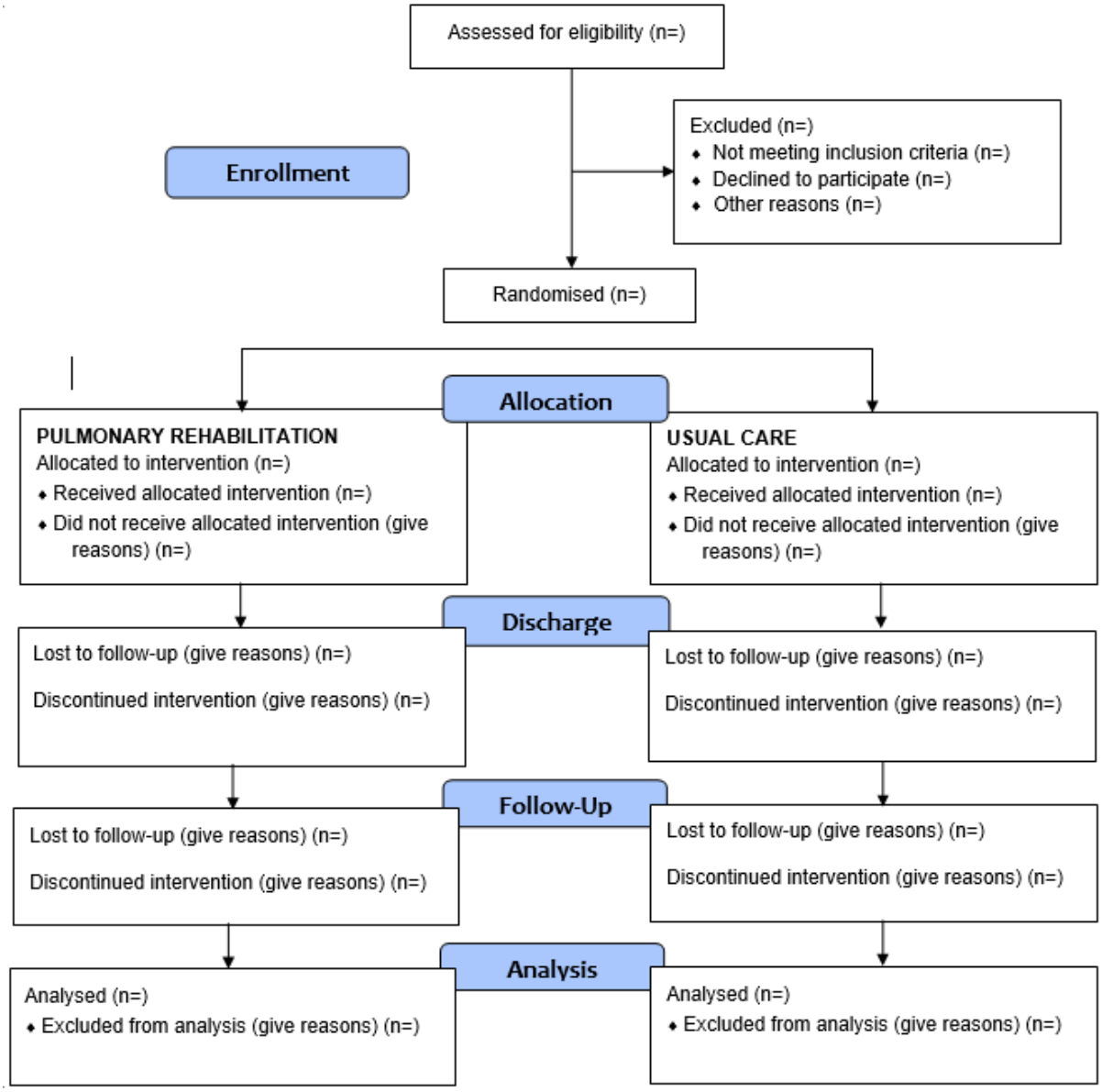
It is anticipated that the analysis will be done in STATA, R 4.3.1 or SPSS 28 statistical software. The University of Leicester holds the relevant software licences.

Statistical methodology

Disposition of patients

Patient disposition will be presented with respect to trial completion status, reason for non-completion, protocol deviations, primary outcome data completeness and length of stay in the trial. Results will be tabulated and summarised over time by intervention arm. A CONSORT diagram will display the flow of patients through the trial (Figure 2).

Figure 2: CONSORT diagram



Demographic and baseline characteristics

Numbers (with percentages) for binary and categorical variables and means (and standard deviations), and medians (with lower and upper quartiles) for continuous variables will be presented. The stratification variable will be summarised by treatment arm in order to check the balance of the baseline characteristics and outcome measures prior to the study between the two randomised arms. Tests for differences between groups at baseline will be conducted using independent t-test, Wilcoxon test (Mann-Whitney), Kruskal-Wallis, and Chi-Squared depending on the type of data and distribution.

Comparison of losses to follow-up

The numbers (with percentages) of losses to follow-up, withdrawals and discontinuation of study treatment will be reported descriptively between the intervention and control arms. Any deaths (and their causes) will be reported separately.

Primary outcome analysis

Primary analysis of primary outcome

The primary statistical analyses will be an intention to treat (ITT) where the population consists of all randomised participants into the trial regardless of whether they received the intervention. The primary outcome is the change in ISWT from baseline following the 6-week pulmonary rehabilitation intervention compared to changes for the same time period of usual care.

A Generalized Linear Mixed Model (GLMM) will be used to model the repeated measures for ISWT distance over the intervention period. Independent variables in the model will be time point and group (pulmonary rehabilitation vs usual care). An interaction term, time point×group and a random intercept for subject will be included in the model. GLMMs will be fitted using the lmer function from the lme4 package in R. Analyses will be controlled for pre-existing characteristics (e.g., sex) which potentially differ between treatment and control group (statistically or in magnitude).

The primary analysis will report the changes in meters per group and the differences between the intervention (face to face or digital) compared to usual care. Statistical significance will be set at $p<0.05$ with 95% CI presented.

Secondary analysis of primary outcome

A per protocol analysis will be performed on all individuals that have complete data on the primary outcome (attend a baseline and discharge assessment) and that adhere to the intervention defined if they attended 75% of face-to-face sessions and attends the follow up appointment. A GLMM as previously described will be performed on this cohort. The n (%) achieving the MCID of 35m fpr the ISWT will be presented for each group (Table 2).

Secondary outcome analyses

Primary analysis of secondary outcomes

All secondary end-points (see earlier section) will be analysed using the modified intention-to-treat population, whereby participants are analysed in their allocated group regardless of whether they received the intervention, where data is available, and excluding those without primary outcome data.

Descriptive statistics of all the secondary outcomes will be presented by treatment arms and overall by assessment time points (i.e., by visit). Numbers (with percentages) for binary and categorical variables and means (and standard deviations), and medians (with lower and upper quartiles) for continuous variables will be presented. A GLMM as previously described will be performed on this cohort.

Secondary analysis of secondary outcomes

A per protocol analysis will be performed on all individuals that have complete data on the primary outcome (attend a baseline and discharge assessment) and that adhere to the intervention defined if they attended 75% of face-to-face sessions and attends the follow up appointment. A GLMM as previously described will be performed on this cohort. The n (%) achieving the available MIDs for secondary outcomes will be presented for each group (Table 2).

Table 2: Minimum (clinically) important differences for primary and secondary outcomes

Primary outcome	**MCID**
ISWT (m)	35 [1]
Secondary outcomes	**MID/MCID**
ESWT (sec)	147-279 [3]
Sit-to-stand (sec)	1.7 [4]
MRC scale	1 [5,6]
CCQ	0.4 [7]
CAT	2 [8]
HADS-Anxiety	2 [9,10]
HADS-Depression	2 [9,10]
EQ-5D-5L utility index	0.05 [11]
EQ-5D-5L visual analogue scale	7 [11]

Sensitivity analyses

There will be no sensitivity analyses carried out for any secondary outcome measures.

Changes to the planned analysis

All changes to the original planned analysis will be noted in the statistical report alongside the reasons and justifications.

Adverse event reporting

Any and all untoward events arising from the intervention that require further medical attention and/or hospitalisation will be recorded on an adverse events or serious adverse events log in the investigator site file and reported to the Sponsor. Adverse events will be explored and categorised as related or unrelated to the trial intervention. All adverse events will be listed including, seriousness, duration, relatedness, severity, action taken, outcome, and treatment arm and overall. Due to the nature of the trial, there are no formal stopping rules as problems that are detrimental to the participant are not anticipated.

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(10) Wynne Set al. The hospital anxiety and depression scale (HADS) in bronchiectasis: response to pulmonary rehabilitation (PR) and minimum clinically important difference (MCID). Chron Respir Dis. 2020; 17:1479973120933292.
(11) Nolan CM, Longworth L, Lord J, et al. The EQ-5D-5L health status questionnaire in COPD: validity, responsiveness and minimum important difference. Thorax 2016; 71:493–500.

Appendices

Appendix 1: Scheduled and attended pulmonary rehabilitation classes

Number of classes	**Total scheduled**	**Total attended**
Median [IQR]		
Frequency, n (%) *0* *1* *2* *3* *4* *5* *6* *7* *8* *9*[α] *10* *11* *12*[β] *13* *14* *15*		

[α]*minimum attendance for completion;* [β]*maximum number of attended classes*

Appendix 2: Demographic and baseline characteristics

Baseline characteristics	**Intervention**	**Control**	**Total**
Demographics			
Age (years)			
Sex, n (%): *Male* *Female*			
Lung health			
FEV_1 (L)			
FVC (L)			
FEV_1/FVC			
Smoking status, n (%): *Never smoked* *Current smoker* *Former smoker*			
Pack-years			
Biomass daily exposure, n (%) *Yes* *No*			
Biomass years exposed			
Times treated for TB			
Times treated for TB, n (%) *0* *1*			

2 *3* *4* *5*			
Abnormal chest x-ray, n (%) *Fibrosis* *Nodules* *Infiltrates* *Cavities* *Pleural effusion* *Masses (≥30mm diameter)* *Hilar adenopathy* *Mediastinal adenopathy*			
Respiratory-related treatments, n (%) *ICS* *LABA* *LAMA* *ICS/LABA* *SABA* *SAMA* *Anti-histamines* *Cough syrup* *Mucolytics* *Antibiotics*			
Known HIV status, n (%) *Yes – Positive* *Yes – Negative* *No*			
Comorbidities			
Comorbidities, n (%): *Cardiac disease* *Peripheral vascular disease* *Hypertension* *Diabetes* *Kidney disease* *Arthritis* *Mental health disorder* *Malignancy*			
Health status			
Height (m)			
Weight (kg)			
BMI (kg/m^2)			
Hospitalisations in last 12 months			
Hospitalisations in last 12 months, n (%) *0* *1* *2*			
MRC score			
MRC score, n (%) *2*			

3 *4* *5*			
CCQ score (symptoms)			
CCQ score (mental)			
CCQ score (functional)			
CCQ score (total)			
CAT score			
HADS Depression score			
HADS Depression, n (%) *Normal (0-7)* *Mild (8-10)* *Moderate (11-15)* *Severe (16-21)*			
HADS Anxiety score			
HADS Anxiety, n (%) *Normal (0-7)* *Mild (8-10)* *Moderate (11-15)* *Severe (16-21)*			
Socioeconomic status and health economics			
Employment status, n (%): *In paid work (employed)* *In paid work (self-employed)* *In unpaid work* *Not in work*			
Household income (soms/month), n (%): *Bound 1 (<5,700)* *Bound 2 (5,701-12,500)* *Bound 3 (12,501-19,500)* *Bound 4 (19,501-26,000)* *Bound 5 (26,001-33,000)* *Bound 6 (33,001-40,000)* *Bound 7 (40,001-47,000)* *Bound 8 (47,001-53,500)* *Bound 9 (53,501-60,500)* *Bound 10 (≥60,501)*			
Education level, n (%): *Under 9 years* *School (9 years)* *School (11 years)* *College* *University/Academy*			
EQ5D5L Mobility, n (%) *No problems* *Slight problems* *Moderate problems* *Severe problems* *Unable to*			
EQ5D5L Self-care, n (%)			

No problems *Slight problems* *Moderate problems* *Severe problems* *Unable to*			
EQ5D5L Usual activities, n (%) *No problems* *Slight problems* *Moderate problems* *Severe problems* *Unable to*			
EQ5D5L Pain/Discomfort, n (%) *No pain or discomfort* *Slight pain or discomfort* *Moderate pain or discomfort* *Severe pain or discomfort* *Extreme pain or discomfort*			
EQ5D5L Anxiety/Depression, n (%) *Not anxious or depressed* *Slightly anxious or depressed* *Moderately anxious or depressed* *Severely anxious or depressed* *Extremely anxious or depressed*			
EQ5D5L Visual Analogue Scale			
Physical measures			
Sit-to-stand (sec)			
ISWT (m)			
ESWT (sec)			

Appendix 3: Baseline work productivity and activity impairment characteristics

Baseline characteristics	**Intervention**	**Control**	**Total**
WPAI			
Currently employed (working for pay), n (%) *Yes*			
Lost hours work problem			
Lost hours work other			
Hours worked 7 days			
Problem affected 7 days			
Problem affected activity 7 days			
Lost hours not work problem			
Rely other members			
Percent work time missed health			
Percent impairment while working health			
Percent overall work impairment health			
Percent activity impairment health			

Appendix 4: Incremental shuttle walking test baseline performance indicators

Baseline characteristics	Intervention	Control	Total
ISWT conducted, n (%) *Yes* *No*[α]			
Best ISWT, n (%) *First test* *Second test* *Missing*			
Best ISWT			
ISWT (m)			
Start SpO2			
Start BORG breathlessness			
Start heart rate			
Start RPE			
Reason for termination, n (%) *Shortness of breath* *Leg fatigue* *Timing* *Unable to keep up* *Other*			
End SpO2			
End BORG breathlessness			
End heart rate			
End RPE			

Appendix 5: Changes in outcome measures between 0 and 6 weeks

Outcome variables	Intervention		Control	
	Pre	Post	Pre	Post
Weight (kg)				
BMI (kg/m^2)				
MRC score				
MRC score, n (%) *1* *2* *3* *4* *5*				
CCQ score (symptoms)				
CCQ score (mental)				
CCQ score (functional)				
CCQ score (total)				
CAT score				
HADS score (depression)				
HADS Depression, n (%) *Normal (0-7)* *Mild (8-10)* *Moderate (11-15)*				

Severe (16-21)				
HADS score (anxiety)				
HADS Anxiety, n (%) *Normal (0-7)* *Mild (8-10)* *Moderate (11-15)* *Severe (16-21)*				
EQ5D5L Mobility, n (%) *No problems* *Slight problems* *Moderate problems* *Severe problems* *Unable to*				
EQ5D5L Self-care, n (%) *No problems* *Slight problems* *Moderate problems* *Severe problems* *Unable to*				
EQ5D5L Usual activities, n (%) *No problems* *Slight problems* *Moderate problems* *Severe problems* *Unable to*				
EQ5D5L Pain/Discomfort, n (%) *No pain or discomfort* *Slight pain or discomfort* *Moderate pain or discomfort* *Severe pain or discomfort* *Extreme pain or discomfort*				
EQ5D5L Anxiety/Depression, n (%) *Not anxious or depressed* *Slightly anxious or depressed* *Moderately anxious or depressed* *Severely anxious or depressed* *Extremely anxious or depressed*				
EQ5D Visual Analogue Scale				
Sit-to-stand (sec)				
ISWT (m)				
ESWT (sec)				

Appendix 6: Changes in work productivity and activity impairment between 0 and 6 weeks

WPAI	**Intervention**		**Control**	
	Pre	**Post**	**Pre**	**Post**
Currently employed (working for pay), n (%) *Yes*				
Lost hours work problem				
Lost hours work other				

Hours worked 7 days				
Problem affected 7 days				
Problem affected activity 7 days				
Lost hours not work problem				
Rely other members				
Percent work time missed health				
Percent impairment while working health				
Percent overall work impairment health				
Percent activity impairment health				

Appendix 7: Incremental shuttle walking test performance indicators

	Intervention		**Control**	
	Pre	**Post**	**Pre**	**Post**
ISWT				
ISWT conducted, n (%) *Yes* *No*[α]				
Best ISWT, n (%) *First test* *Second test* *Missing*				
Best ISWT				
ISWT (m)				
Start SpO2				
Start BORG breathlessness, median [IQR]				
Start heart rate				
Start RPE, median [IQR]				
Reason for termination, n (%) *Shortness of breath* *Leg fatigue* *Timing* *Unable to keep up* *Other*				
End SpO2				
End BORG breathlessness, median [IQR]				
End heart rate				
End RPE, median [IQR]				

Appendix 8: Patient reported outcomes for weeks 0, 6 and 12

Outcome variables	**Intervention**			**Control**		
	Pre	**Post**	**Follow-up**	**Pre**	**Post**	**Follow-up**
MRC score						
MRC score, n (%) *1* *2* *3* *4*						

5						
CCQ score (symptoms)						
CCQ score (mental)						
CCQ score (functional)						
CCQ score (total)						
CAT score						
HADS score (depression)						
HADS Depression, n (%) *Normal (0-7)* *Mild (8-10)* *Moderate (11-15)* *Severe (16-21)*						
HADS score (anxiety)						
HADS Anxiety, n (%) *Normal (0-7)* *Mild (8-10)* *Moderate (11-15)* *Severe (16-21)*						
EQ5D5L Mobility, n (%) *No problems* *Slight problems* *Moderate problems* *Severe problems* *Unable to*						
EQ5D5L Self-care, n (%) *No problems* *Slight problems* *Moderate problems* *Severe problems* *Unable to*						
EQ5D5L Usual activities, n (%) *No problems* *Slight problems* *Moderate problems* *Severe problems* *Unable to*						
EQ5D5L Pain/Discomfort, n (%) *No pain or discomfort* *Slight pain or discomfort* *Moderate pain or discomfort* *Severe pain or discomfort* *Extreme pain or discomfort*						
EQ5D5L Anxiety/Depression, n (%) *Not anxious or depressed* *Slightly anxious or depressed* *Moderately anxious or depressed* *Severely anxious or depressed* *Extremely anxious or depressed*						
EQ5D Visual Analogue Scale						
Currently employed (working for pay), n (%)						

Yes						
Lost hours work problem						
Lost hours work other						
Hours worked 7 days						
Problem affected 7 days						
Problem affected activity 7 days						
Lost hours not work problem						
Rely other members						
Percent work time missed health						
Percent impairment while working health						
Percent overall work impairment health						
Percent activity impairment health						

Appendix 9: Prevalence of AEs and SAEs by relatedness and severity

Baseline characteristics	**Intervention**	**Control**	**Total**
Total AEs			
By severity *Mild* *Moderate* *Severe*			
Causality *Certain* *Probable* *Possible* *Conditional* *Assessable*			
Total SAEs			
Criteria *Death* *Life threatening* *Hospitalization* *Medically significant* *Not applicable*			
By severity *Mild* *Moderate* *Severe*			
Causality *Certain* *Probable* *Possible* *Conditional* *Assessable*			