Pulmonary rehabilitation to improve physical capacity, dyspnea and quality of life following pulmonary embolism (the PeRehab study): Study protocol for a two-centre randomized controlled trial.

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Study protocol

Keywords: Pulmonary embolism, rehabilitation, dyspnea, exercise capacity, quality of life

Posted Date: June 16th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-24003/v1

Version of Record: A version of this preprint was published on January 6th, 2021. See the published version at https://doi.org/10.1186/s13063-020-04940-9.

Abstract

Background: Recently, a large group of patients with persistent dyspnea, poor physical capacity and reduced health-related quality of life (HRQoL) following pulmonary embolism (PE) has been identified and clustered under the name “post pulmonary embolism syndrome” (PPS). These patients seem good candidates for pulmonary rehabilitation. The aim of the study is to explore whether a pulmonary rehabilitation program can improve physical capacity, dyspnea and HRQoL in PPS patients.

Methods: A two-centre randomized controlled trial (RCT) is being performed at Østfold Hospital and Akershus University Hospital in Norway. Patients with PPS are 1:1 randomized into an intervention or a control group. The intervention consists of a supervised, outpatient rehabilitation program twice weekly (1 hour) for 8 weeks provided by experienced physiotherapists. The intervention involves individually adapted exercises based on existing pulmonary rehabilitation programs (relaxation, interval and resistance training), and an educational session including topics such as normal anatomy and physiology of the respiratory and circulatory system, information on PE/PPS, breathing strategies, and benefits of exercise/physical activity. Patients randomized to the control group receive usual care without specific instructions to exercise.

Participants in the intervention and control groups will be compared based on assessments conducted at baseline, 12 weeks and 36 weeks after inclusion using the incremental shuttle walk test (primary outcome) and endurance shuttle walk test (exercise capacity), Sensewear activity monitor (daily physical activity), the Modified Medical Research Council scale, the Shortness of Breath questionnaire (dyspnea), and EQ-5D-5L and the Pulmonary Embolism Quality of Life Questionnaire (HRQoL).

Recruitment of 190 patients is currently ongoing.

Discussion: Results from this study may provide a currently untreated group of PPS patients with an effective treatment resulting in reduced symptoms of dyspnea, improved exercise capacity and better HRQoL following PE.

Trial registration: NCT03405480, Clinical Trials (registered prospectively.

Protocol version 1 (from original protocol September 2017).

The study protocol has been reported in accordance with the Standard Protocol Items: Recommendations for Clinical Interventional Trials (SPIRIT) guidelines (Additional file 1).

Background

Pulmonary embolism (PE) occurs when an emboli blocks a pulmonary artery resulting in acute symptoms, such as dyspnea and chest pain, which usually subside gradually with the majority of patients regaining normal function within 3-6 months (1). However, long-term complications following PE

can include recurrent venous thromboembolism (VTE), bleeding, and chronic thromboembolic pulmonary hypertension (CTEPH) (2, 3).

Several studies have shown that up to 50% of patients complain of various grades of persistent unexplained dyspnea many years after the diagnosis of PE (4, 5). Furthermore, patients who reported dyspnea had reduced exercise capacity as measured by the 6-minute walk test (6MWT) compared to patients with no dyspnea (6). Additionally, those suffering from persistent dyspnea had impaired health-related quality of life (HRQoL) compared to both the normative population and those without dyspnea (4). These findings have recently been confirmed by a prospective study showing that half of PE patients have exercise limitation at 1 year post-PE which negatively influences walking distance and reduces HRQoL (7). Some of these patients have persistent pathological findings, such as right ventricular dysfunction, pulmonary hypertension, or residual perfusion defects causing dead space ventilation, which may explain, at least in part, the persistent symptoms. The majority of patients, however, have no detectable cardiopulmonary sequel and merely suffers from deconditioning. Foregoing research has led to recognition of patients with the so-called “post-PE syndrome” (PPS), as defined as new or progressive dyspnea, exercise intolerance and/or diminished functional status following PE without an apparent non-PE alternative explanation (8). Guidelines provide clear recommendations for the management of CTEPH, the most severe presentation of PPS affecting about 4% of the patients following PE (2). Studies focusing on adequate treatment of other PPS presentations to improve functionality and decrease symptoms are, however, mostly unavailable and guidelines make no mention of this large patient group. Because it is likely that physical deconditioning may be responsible for at least a part of the disease burden, it has been hypothesized that patients with PPS may benefit from pulmonary rehabilitation (7, 9).

Pulmonary rehabilitation is a core component in the management of chronic lung disease and is mostly utilized by patients with chronic obstructive pulmonary disease (COPD). Programs typically consist of patient-tailored therapies such as exercise training, education, and behavioral change, based on a thorough assessment of the patient, with the goal of improving physical and psychological condition and promoting long-term adherence to health-enhancing behaviors (10). Rehabilitation is a cost-effective intervention and has demonstrated a reduction in respiratory symptoms such as the perception of dyspnea, improved physical function and HRQoL in patients with COPD, as well as reducing hospital admissions and improving mortality rates (10). Recently there has been an increased focus on the benefits of rehabilitation for other types of patients experiencing similar respiratory symptoms and reduced exercise capacity, such as lung cancer, pulmonary hypertension and cystic fibrosis (10). Moreover, a study in 2016 investigated the feasibility of a breathlessness rehabilitation program for patients with both respiratory and cardiac disease suggesting that rehabilitation should be focused on the symptoms and limitations that patients experience rather than traditional disease-focused rehabilitation (11).

To our knowledge, there are only two studies that have addressed the effect and safety of rehabilitation and exercise after PE or DVT. One retrospective study evaluated the safety of rehabilitation after PE, showing that it is safe to start to exercise following PE (12). One small randomized controlled trial (RCT)

objectively measured effect of exercise and behavioral weight loss after VTE demonstrating that early initiation of exercise was safe and resulted in improvements in physical activity and fitness (13). Both studies pointed out the need for large prospective RCTs. Furthermore, a recently completed study randomized patients with newly diagnosed PE, regardless of the presence of persistent dyspnea, to a home-based training program or a control group (14). This study concluded that home-based exercise training and nurse consultations did not improve exercise capacity or symptoms of dyspnea following PE. However, this study included all PE patients, rather than those with PPS, including patients who had recently been diagnosed with PE rather than at the long term, where a spontaneous improvement in symptoms can be expected from the natural course of the disease. No current studies have provided rehabilitation to patients suffering with PPS. Previous research has indicated that the HRQoL impairment in patients with PPS is driven by reduced physical capacity (4) suggesting a possible receptivity for an intervention such as pulmonary rehabilitation, including exercise training, in order to reduce breathing discomfort and improve HRQoL and exercise capacity.

The aim of this study is to explore the effect of pulmonary rehabilitation on exercise capacity, dyspnea and HRQoL in patients with PPS.

Hypothesis

The primary hypothesis is that a structured, outpatient, hospital-based, 8 weeks pulmonary rehabilitation program will lead to increased exercise capacity, less symptoms of dyspnea and improvements in HRQoL in patients with PPS as compared to a control group receiving no active intervention.

Methods And Design

Study design

A two-centre RCT is being performed at the outpatient departments of Østfold Hospital Trust (ØHT) and Akershus University Hospital (AHUS) in Norway. Patients with PPS are 1:1 randomized (using sealed envelopes) into 2 arms; an intervention arm and a control arm. In addition, a group of patients with no PPS following PE will be examined at baseline to compare patients with and without persistent dyspnea after PE in terms of exercise capacity, daily physical activity, dyspnea and HRQoL.

The primary study objective is to explore the short-term changes in exercise capacity from baseline to 12 weeks after inclusion between groups as measured by the incremental shuttle walk test (ISWT). The secondary objectives are to explore the long term effect of the rehabilitation program on exercise capacity 36 weeks after inclusion between groups (ISWT) as well as changes in exercise endurance (ESWT), subjective symptoms of dyspnea, daily physical activity levels and HRQoL from baseline to 12 and 36 weeks after inclusion.

Figure 1: Study design

Eligibility criteria

Patients diagnosed and treated for PE 6 months to 6 years previously at ØHT or AHUS are identified from ØHT's Thrombosis registry (TROLL registry – NSD 28435/3/LMR) (ØHT only) or via ICD-10 discharge codes (AHUS). Patients are invited to participate by postal mail.

Inclusion criteria include: age 18-75 years, objectively diagnosed symptomatic PE (greater than isolated sub-segmental PE) by CTPA 6 months to 6 years prior to inclusion to the study, persistent dyspnea defined as modified Medical Research Council (mMRC) breathlessness scale grade $\geq$ 1 that had appeared or worsened after the diagnosis of PE, and the ability to provide written informed consent.

Exclusion criteria include: pulmonary diseases (such as COPD GOLD $\geq$2 or restrictive pulmonary diseases, lung cancer or pleural disease), heart failure, CTEPH, significant valvular heart disease, patients with a condition that would interfere with the ability to comply with the study protocol or to give informed consent (e.g. history of drug abuse, excessive alcohol beverage consumption, cognitive dysfunction, or severe psychiatric disease), active malignancy or recurrent, metastatic or inoperable disease, life expectancy less than 3 months, and pregnancy.

Blinding

The investigators performing the walking tests at follow-up are blinded to the patients' group allocation.

Intervention

Rehabilitation group
Patients in the intervention group are allocated to a basic pulmonary rehabilitation program consisting of a supervised, outpatient exercise program for 1 hour twice weekly for 8 weeks. Experienced physiotherapists construct an individually adapted exercise program based on existing pulmonary rehabilitation programs (combining relaxation, interval training at moderate intensity measured with the Borg scale, and resistance training), and an educational session provided by a doctor and a physiotherapist. The educational session includes topics, such as normal anatomy and physiology of the respiratory and circulatory system, information on PE and PPS, breathing strategies, and benefits of exercise/physical activity. Training attendance is documented and patients will be given a simple home-based exercise program, consisting of resistance exercises that can be performed without equipment, to be performed once to twice weekly during the intervention period.

Control group

Patients randomised to the control group will receive usual care without specific instructions to exercise (no active intervention).

Outcome measures

Primary outcome measure

The primary endpoint of the study is improvement in physical capacity as measured by the ISWT. This walking test has been developed to assess exercise capacity and is valid, reliable, and responsive in a number of study populations, including patients with cardiac and respiratory diseases (15). The patient walks between two shuttles along a 9 meter track in a tempo guided by audible sounds which increase in speed every minute for a maximum of 12 minutes. The test ends when the patient cannot manage to keep the correct speed or has to stop because of symptoms (such as dyspnea or fatigue). Standardised instructions will be provided before the test commences. In order to exclude a learning effect, the ISWT is performed twice at baseline with at least 15 minutes between tests. Peripheral oxygen saturation is registered and patients will report their subjective experience of dyspnea during exertion using the Borg scale before and immediately after the test (16). The Borg scale is commonly used for assessing perceived exertion during field walk tests. The minimal clinical important difference (MCID) for the ISWT is 70 meters in patients with cardiac disease and 48 meters in patients with COPD (17, 18).

Secondary outcome measures

Endurance Shuttle Walk Test

The endurance shuttle walk test (ESWT) is a derivative of the ISWT. The patient walks between two shuttles along a 9 meter track at a predefined speed, usually at 85% of the maximum speed derived from the ISWT. The test ends when the patient cannot continue because of symptoms (such as dyspnea or fatigue) or for a maximum of 20 minutes (test completion). The outcome of the ESWT is usually reported as time (minutes and seconds), although in some studies the distance completed (meters) has been used. Studies suggest that the ESWT is more sensitive to change after rehabilitation when compared to the 6MWT and ISWT (19, 20). However, compared to our primary endpoint (ISWT), there is less evidence on using the ESWT and there are no reference values for the PPS population. The MCID for the ESWT has been demonstrated to be 174 – 279 seconds in COPD after pulmonary rehabilitation (21).

Modified MRC dyspnea scale

The mMRC scale is a widely used tool for evaluating the limitation of activities due to dyspnea. This short questionnaire consists of five statements describing the patient`s respiratory disability, ranging from 0 (“not troubled by breathlessness except on strenuous exercise”) to 4 (“too breathless to leave the house or breathless when dressing or undressing”). The MCID for the mMRC is 0.5 points (22).

The Shortness of Breath Questionnaire

The Shortness of Breath Questionnaire (SOBQ) is a patient-reported outcome measure which assesses subjective symptoms of dyspnea associated with activities of daily living (ADL). The SOBQ includes 24 items and each is scored on a scale from 0 (“not at all”) to 5 (“maximal/unable to do because of breathlessness”). Total scores range from 0 to 120 with a higher score indicating a higher degree of dyspnea.

Sensewear activity monitor

Daily physical activity is measured using a Sensewear activity monitor. The participants will wear the monitor for 1 week before and 1 week after the intervention period to investigate whether the intervention results in a change in daily physical activity or not by measuring number of steps taken per day and time spent in different activity intensities. Sensewear is a multisensor activity monitor combining a triaxial accelerometer and is shown to be a reliable and valid tool for measuring physical activity in people with respiratory disease (23, 24).

EQ-5D-5L

The EQ-5D-5L has been developed by the Euroqol Group as a patient-reported outcome measure to assess generic health status and HRQoL in 5 different dimensions; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 possible answers ranging from 1 to 5 with a higher score indicating worse possible state, and these scores can be aggregated to a utility score on a 0–1 scale using a tariff of preferences derived from a general population (25). In addition, the patient subjectively scores their general HRQoL on a visual analogue scale from 0 (“worst imaginable state of health”) to 100 (“best imaginable state of health”).

Pulmonary Embolism Quality of Life Questionnaire

The Pulmonary Embolism Quality of Life Questionnaire (PEmb-QoL) is a disease-specific patient-reported outcome measure to assess HRQoL following PE (26). The PEmb-QoL has 40 items over 6 domains, which assess symptom frequency, the time of day when complaints are at their worst, as well as the effect of pulmonary-specific symptoms on ADL and work-related problems. Scores for each domain range from 0 to 100 with the average score of all six domains being used to calculate the total score. A lower score indicates better HRQoL. The MCID for the PEmb-QoL is 15 points (27).

The Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a patient-reported outcome measure assessing symptoms of depression and anxiety. The HADS provides a total score with a 0 – 42 range with a higher score indicating that the patient is more symptomatic. Scores of ≥19 points indicate symptoms corresponding to cases of anxiety and depression, whilst scores between 15 and 18 points suggest possible symptoms of anxiety and depression. It is also possible to calculate a score for anxiety or depression only (range 0 – 21 points). Scores of ≥11 points indicate symptoms that can be compatible with anxiety/depression, and 8 – 10 points suggest possible symptoms of anxiety/depression. The MCID for the HADS has been suggested to be a reduction in 1.3 to 1.8 points in COPD patients undergoing pulmonary rehabilitation (28).

Data collection

All outcome measures are completed at baseline, 12 and 36 weeks after inclusion (Figure 1). In addition, a complete baseline evaluation is performed on all participants including a full history and medical examination, routine blood tests and biobanking (10 ml EDTA plasma, 10 ml citrated plasma, 10 ml

serum and 10 ml in paxgene), ventilation and perfusion scintigraphy, pulmonary function test (including spirometry, whole body plethysmography, carbon monoxide diffusing capacity of the lung) and transthoracic echocardiography. In addition, cardiac magnetic resonance imaging is performed on 50 participants without PPS, and 50 participants with PPS before and after rehabilitation. Finally, patients will be asked to complete questions on self-reported physical activity and exercise habits.

Data are stored in the secure research server at ØHT to which only the project investigators have access.

Data management and analysis

The results will be analyzed according to the intention-to-treat principle. Baseline characteristics will be described by mean and standard deviation, median and interquartile range or number and proportions as appropriate. The effect of the intervention on the primary outcome (ISWT) will be assessed by comparing the change in exercise capacity after 12 weeks. The primary analysis based on the baseline data and data after 12 weeks will be conducted as a linear regression. The subsequent analysis, which will include data after 36 weeks, will have three measurements per individual to assess the short term and long term effect of the intervention, and will therefore be analyzed using a linear mixed model. This variant of multiple linear regression allows for addressing such correlations as well as adjusting for possible confounders such as age, body mass index, sex, and treatment centre. HRQoL, general activity and the mMRC breathlessness scale will be compared between the 2 groups at 12 weeks using appropriate statistical tests depending on the normality of data. In addition, the model will also account for missing values.

Sample size calculation

There is currently no data on the physical capacity of PPS patients as measured by ISWT. Therefore, in concurrence with the Danish study that was ongoing when we designed our protocol (29) we have based our sample size calculations on the mean improvement in ISWT previously reported in patients with cardiac and respiratory disease. Rolving et al assumed that the achieved difference will be around 70 meters, i.e. comparable to cardiac patients. Based on 6MWT results from a previous study in patients with PPS (6), patients walked between 413 to 480 meters on 6MWT, which is closer to the cardiac population. Therefore, we assume a baseline ISWT for PE patients to be 390 meters.

Based on calculations, our clinical experience, and on previous findings, an improvement of 60 meters or more on the ISWT will be considered as being of clinical relevance. Given these assumptions, a required sample size to test for that effect size with a type 1 error of 5% and a type 2 error of 20%, 86 patients are needed in each study arm. By adding 10% attrition, the required sample size will be a total of 190 patients.

Discussion

This study is understood to be the first study exploring the effect of structured pulmonary rehabilitation on exercise capacity in patients with PPS. Results from this study may therefore increase the knowledge regarding the management of persistent dyspnea in this patient group as well as providing a currently untreated group of patients with a treatment potentially resulting in reduced chronic symptoms following PE. In comparison to previous studies, patients with chronic, persistent dyspnea from six months post-PE are included in the present study in whom no spontaneous improvement may be expected. The ISWT is validated, commonly used in clinical practice and was the chosen primary outcome for the study by Rolving et al (29). Thus, the ISWT was chosen as the primary endpoint in the present study to enable generalization to clinical practice as well as comparison to the findings by Rolving et al.

Of note, the term “post-PE syndrome” is still not clearly defined. However, in the present study we have chosen to adopt the suggested definition describing the long term sequelae of PE including chronic thromboembolic disease, CTEPH, right ventricular impairment and/or persistent unexplained dyspnea.

Results from this study may have clinical significance by increasing the understanding of the background, assessment, treatment and prevention of PPS, and may change treatment standards in this patient group. The study may also increase the awareness of pulmonary rehabilitation being a feasible treatment for patients with respiratory symptoms similar to COPD and other well documented respiratory diseases.

Data monitoring

The study will be monitored by the research department at ØHT. Any adverse effects will be reported.

Trial status

The trial is currently ongoing and recruitment began in January 2018 at ØHT and in August 2019 at AHUS. Recruitment is expected to be complete in late 2020 – early 2021.

Protocol version 1 (original protocol September 2017).

Abbreviations

VTE Venous thromboembolism

DVT Deep vein thrombosis

PE Pulmonary embolism

CTEPH Chronic thromboembolic pulmonary hypertension

6MWT Six minute walking test

HRQoL Health-related quality of life

PPS Post pulmonary embolism syndrome

COPD Chronic obstructive pulmonary disease

RCT Randomized controlled trial

ØHT Østfold Hospital Trust

AHUS Akershus University Hospital

ISWT Incremental shuttle walk test

mMRC Modified Medical Research Council breathlessness scale

MCID Minimal clinical important difference

ESWT Endurance shuttle walk test

SOBQ Shortness of Breath Questionnaire

ADL Activities of daily living

EQ-5D-5L Five level EQ-5D version

Pemb-QoL Pulmonary Embolism Quality of Life Questionnaire

HADS Hospital Anxiety and Depression Scale

Declarations

Ethical approval and consent to participate

The choice of study design and methods are based on a solid rationale and international recommendations. Patients will be informed about the study including the design, examinations, intervention, and anticipated benefits. Written informed consent will be obtained from all participants prior to clinical procedures. Patients who decline participation will be managed according to best current practice. The study is registered in Clinical Trials (NCT03405480). The protocol, including the patient information and consent form, is approved by the Regional Committee for Medical and Health Research Ethics (2017/1940/REK South-East D). See additional file.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable, no datasets are included in this study protocol.

Competing interests

The authors declare that they have no competing interests.

Funding

This study is funded by ØHT. The funding body's role is to contribute and support the design of the study, the collection, analysis, and interpretation of data, and several authors from ØHT are involved in writing the manuscript.

Authors' contributions

SHP PhD fellow and main investigator I. Participated in planning and conduction of study.

ØJ PhD fellow and main investigator II. Participated in planning and conduction of study.

HHJ Main supervisor for PhD fellow (SHP). Participated in planning and conduction of study.

JG PhD fellow and main investigator III. Participated in planning and conduction of the study.

KSta. Co-supervisor for PhD fellow (ØJ). Participated in planning of study.

KSte. Co-supervisor for PhD fellow (ØJ). Participated in planning of study.

MAS. Co-supervisor for PhD fellow (SHP). Participated in planning of study.

RH Statistician. Participated in planning of study (analysis).

MT Member of the steering committee. Participated in planning of study.

EK Member of the steering committee. Participated in planning of study.

WG Main and co-supervisor for PhD fellows (ØJ og SHP). Participated in planning and conduction of study.

All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Huisman MV, Barco S, Cannegieter SC, Le Gal G, Konstantinides SV, Reitsma PH, et al. Pulmonary embolism. Nature reviews Disease primers. 2018;4:18028.
2. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). European heart journal. 2019;41(4):543-603.
3. Klok FA, Zondag W, van Kralingen KW, van Dijk AP, Tamsma JT, Heyning FH, et al. Patient outcomes after acute pulmonary embolism. A pooled survival analysis of different adverse events. American journal of respiratory and critical care medicine. 2010;181(5):501-6.
4. Tavoly M, Utne KK, Jelsness-Jorgensen LP, Wik HS, Klok FA, Sandset PM, et al. Health-related quality of life after pulmonary embolism: a cross-sectional study. BMJ open. 2016;6(11):e013086.
5. Klok FA, Tijmensen JE, Haeck ML, van Kralingen KW, Huisman MV. Persistent dyspnea complaints at long-term follow-up after an episode of acute pulmonary embolism: results of a questionnaire. European journal of internal medicine. 2008;19(8):625-9.
6. Ghanima W, Wik HS, Tavoly M, Enden T, Jelsness-Jorgensen LP. Late consequences of venous thromboembolism: Measuring quality of life after deep vein thrombosis and pulmonary embolism. Thrombosis research. 2018;164:170-6.
7. Kahn SR, Hirsch AM, Akaberi A, Hernandez P, Anderson DR, Wells PS, et al. Functional and Exercise Limitations After a First Episode of Pulmonary Embolism: Results of the ELOPE Prospective Cohort Study. Chest. 2017;151(5):1058-68.
8. Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood reviews. 2014;28(6):221-6.
9. Klok FA, Barco S. Follow-up after acute Pulmonary Embolism. Hamostaseologie. 2018;38(1):22-32.
10. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. American journal of respiratory and critical care medicine. 2013;188(8):e13-64.
11. Man WD, Chowdhury F, Taylor RS, Evans RA, Doherty P, Singh SJ, et al. Building consensus for provision of breathlessness rehabilitation for patients with chronic obstructive pulmonary disease and chronic heart failure. Chronic respiratory disease. 2016;13(3):229-39.
12. Noack F, Schmidt B, Amoury M, Stoevesandt D, Gielen S, Pflaumbaum B, et al. Feasibility and safety of rehabilitation after venous thromboembolism. Vascular health and risk management. 2015;11:397-401.
13. Lakoski SG, Savage PD, Berkman AM, Penalosa L, Crocker A, Ades PA, et al. The safety and efficacy of early-initiation exercise training after acute venous thromboembolism: a randomized clinical trial. Journal of thrombosis and haemostasis : JTH. 2015;13(7):1238-44.

14. Rolving N, Brocki BC, Bloch-Nielsen JR, Larsen TB, Jensen FL, Mikkelsen HR, et al. Effect of a Physiotherapist-Guided Home-Based Exercise Intervention on Physical Capacity and Patient-Reported Outcomes Among Patients With Acute Pulmonary Embolism: A Randomized Clinical Trial. JAMA network open. 2020;3(2):e200064.
15. Parreira VF, Janaudis-Ferreira T, Evans RA, Mathur S, Goldstein RS, Brooks D. Measurement properties of the incremental shuttle walk test. a systematic review. Chest. 2014;145(6):1357-69.
16. Borg G, Linderholm H. Exercise performance and perceived exertion in patients with coronary insufficiency, arterial hypertension and vasoregulatory asthenia. Acta medica Scandinavica. 1970;187(1-2):17-26.
17. Houchen-Wolloff L, Boyce S, Singh S. The minimum clinically important improvement in the incremental shuttle walk test following cardiac rehabilitation. European journal of preventive cardiology. 2015;22(8):972-8.
18. Singh SJ, Jones PW, Evans R, Morgan MD. Minimum clinically important improvement for the incremental shuttle walking test. Thorax. 2008;63(9):775-7.
19. Revill SM, Morgan MD, Singh SJ, Williams J, Hardman AE. The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. Thorax. 1999;54(3):213-22.
20. Eaton T, Young P, Nicol K, Kolbe J. The endurance shuttle walking test: a responsive measure in pulmonary rehabilitation for COPD patients. Chronic respiratory disease. 2006;3(1):3-9.
21. Zatloukal J, Ward S, Houchen-Wolloff L, Harvey-Dunstan T, Singh S. The minimal important difference for the endurance shuttle walk test in individuals with chronic obstructive pulmonary disease following a course of pulmonary rehabilitation. Chronic respiratory disease. 2019;16:1479973119853828.
22. Araújo Oliveira AL, Andrade L, Marques A. Minimal clinically important difference and predictive validity of the mMRC and mBorg in acute exacerbations of COPD. European Respiratory Journal. 2017;50(suppl 61):PA4705.
23. Vooijs M, Alpay LL, Snoeck-Stroband JB, Beerthuizen T, Siemonsma PC, Abbink JJ, et al. Validity and usability of low-cost accelerometers for internet-based self-monitoring of physical activity in patients with chronic obstructive pulmonary disease. Interactive journal of medical research. 2014;3(4):e14.
24. Farooqi N, Slinde F, Haglin L, Sandstrom T. Validation of SenseWear Armband and ActiHeart monitors for assessments of daily energy expenditure in free-living women with chronic obstructive pulmonary disease. Physiological reports. 2013;1(6):e00150.
25. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2011;20(10):1727-36.
26. Klok FA, Cohn DM, Middeldorp S, Scharloo M, Buller HR, van Kralingen KW, et al. Quality of life after pulmonary embolism: validation of the PEmb-QoL Questionnaire. Journal of thrombosis and haemostasis : JTH. 2010;8(3):523-32.

27. Akaberi A, Klok FA, Cohn DM, Hirsch A, Granton J, Kahn SR. Determining the minimal clinically important difference for the PEmbQoL questionnaire, a measure of pulmonary embolism-specific quality of life. Journal of thrombosis and haemostasis : JTH. 2018;16(12):2454-61.
28. Smid DE, Franssen FM, Houben-Wilke S, Vanfleteren LE, Janssen DJ, Wouters EF, et al. Responsiveness and MCID Estimates for CAT, CCQ, and HADS in Patients With COPD Undergoing Pulmonary Rehabilitation: A Prospective Analysis. Journal of the American Medical Directors Association. 2017;18(1):53-8.
29. Rolving N, Brocki BC, Mikkelsen HR, Ravn P, Bloch-Nielsen JR, Frost L. Does an 8-week home-based exercise program affect physical capacity, quality of life, sick leave, and use of psychotropic drugs in patients with pulmonary embolism? Study protocol for a multicenter randomized clinical trial. Trials. 2017;18(1):245.

Figures

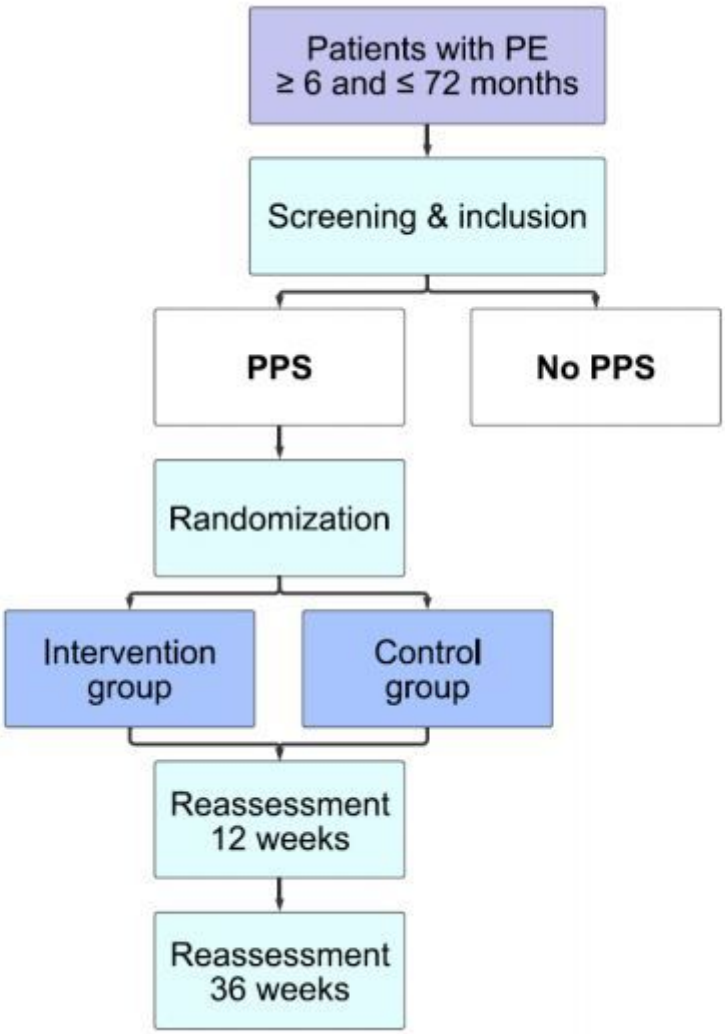
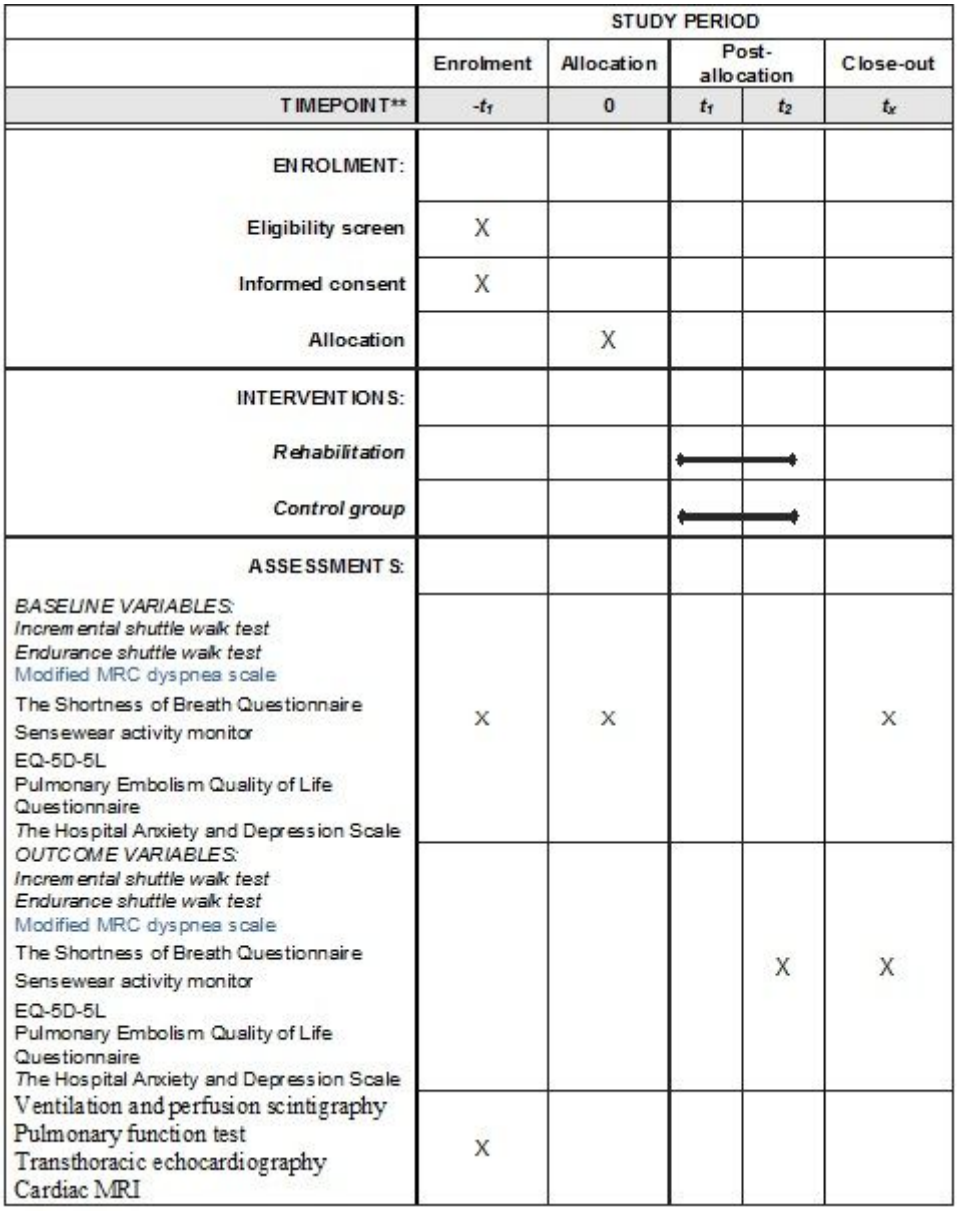


Figure 1

Study design



	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT**	$-t_1$	0	t_1	t_2	t_x
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Rehabilitation			←	→	
Control group			←	→	
ASSESSMENTS:					
BASELINE VARIABLES: *Incremental shuttle walk test* *Endurance shuttle walk test* Modified MRC dyspnea scale The Shortness of Breath Questionnaire Sensewear activity monitor EQ-5D-5L Pulmonary Embolism Quality of Life Questionnaire *The Hospital Anxiety and Depression Scale*	X	X			X
OUTCOME VARIABLES: *Incremental shuttle walk test* *Endurance shuttle walk test* Modified MRC dyspnea scale The Shortness of Breath Questionnaire Sensewear activity monitor EQ-5D-5L Pulmonary Embolism Quality of Life Questionnaire *The Hospital Anxiety and Depression Scale*				X	X
Ventilation and perfusion scintigraphy Pulmonary function test Transthoracic echocardiography Cardiac MRI	X				

Figure 2

Schedule of enrolment, interventions, and assessments

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SpiritchecklistPErehab2HaukelandParkeretal.docx
- PerehabfinancialsupportEnglishtranslation.docx