# Investigation of outpatient **PU**lmonary **RE**habilitation in patients suffering from post-**PE** syndrome: a randomized waitlist-controlled trial – the PURE-PE study

NCT: NCT04615130

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# Study Synopsis

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|---|---|
| **Title** | Investigation of outpatient **PU**lmonary **RE**habilitation in patients suffering from post-**PE** syndrome: a randomized waitlist-controlled trial |
| **Short title** | PURE-PE study |
| **NCT Number** | NCT04615130 |
| **Primary objective** | The primary objective of the study is to assess the effects of outpatient pulmonary rehabilitation (PR) in patients suffering from post-PE syndrome on exercise capacity measured by difference in 6-minute walk test (6MWT). |
| **Secondary objectives** | To assess the effect of outpatient PR on:<br>1. Maximal exercise capacity<br>2. Inspiratory muscle strength<br>3. Dyspnea<br>4. Functional limitations<br>5. Quality of life |
| **Study design** | This study is a multicenter, parallel, randomized waitlist-controlled trial that primarily focuses on the short-term benefit of outpatient PR on patients after acute PE.<br>Patients will be randomized into an intervention and a control cohort. The intervention cohort will receive 6 weeks of outpatient PR, while patients in the other treatment arm will serve as control. After completion of the randomized study, the second arm will undergo PR as well. After one year, a follow-up with regards to long-term benefit will be performed. |
| **Study population** | 1) Inclusion criteria<br>a. Post-PE syndrome diagnosed<br>b. Possibility of starting rehabilitation between 12 and 36 weeks after initial event of PE<br>2) Exclusion criteria<br>a. Chronic pulmonary diseases<br>b. Active cancer<br>c. Pregnancy<br>d. Myocardial infarction or cardiac surgery one year prior to inclusion<br>e. Congenital heart disease, congestive heart failure<br>f. History of stroke |

| | |
|---|---|
| | g. Any previous inpatient or outpatient PR |
| **Primary endpoint** | Difference in 6MWT (m) at baseline and after 6 weeks |
| **Secondary endpoints** | <u>Difference in exercise parameters</u><br>1. Difference in peak oxygen consumption (VO2/kg/min) measured with spiroergometry<br>2. Difference in maximal workload (Wmax) in cycle ergometer tests<br>3. Difference in one-repetition maximum for lower extremities<br>4. Difference in one-repetition maximum for upper extremities<br>5. Difference in maximal inspiratory muscle pressure (Pimax)<br>6. Difference in inspiratory muscle endurance (Tlim)<br><u>Difference in dyspnea parameters</u><br>7. Difference in dyspnea at rest and exertion measured with the Modified Medical Research Council Dyspnea Scale (mMRC) and BORG scale<br><u>Quality of life, functional limitations and others</u><br>8. Change in quality of life will be measured with the EQ-5D-5L<br>9. Change in functional limitations assessed with the PROMIS Physical function short form and the post-VTE functional status scale<br>10. Change in anxiety and depression measured with HADS |
| **Study start and duration** | We anticipate starting enrolment in June 2021. Based on our case number estimation we aim to include a total number of 48 patients over a period of 2 years. Follow-up will be performed one year after PR which will result in a total duration of 3 years. |

# BACKGROUND

Pulmonary embolism (PE) is an acute complication of venous thromboembolism (VTE), which is potentially life-threatening. The incidence of PE has increased over time, while its case fatality rate has declined [1, 2]. A significant proportion of survivors of acute PE are at risk of disabling long-term sequela, commonly referred to as the post-PE syndrome [3, 4]. The post-PE syndrome, with its most severe manifestation - chronic thromboembolic pulmonary hypertension (CTEPH) - is characterized by persistent dyspnea, chronic (cardiopulmonary) functional limitations and decreased quality of life. The incidence of the post-PE syndrome has been reported to reach up to 50%, and up to 4% of PE patients may manifest with CTEPH [5-7].

While many studies in PE survivors have focused on investigation of risk of recurrence, presence of residual thrombosis and right ventricular strain [8], only few studies examined persistent dyspnea and functional outcomes. Of note, reduced physical performance, assessed with the 6-min walk test (6MWT), has been reported in approximately half of all patients with PE, which again is associated with decreased health-related quality of life [9-11]. Similarly, patient-reported outcome measures have indicated acute decline in physical function after PE, which highlights the need for measures to improve functional deficits in patients with PE [12].

After acute myocardial infarction participation in a cardiopulmonary rehabilitation program is recommended to increase functional capacity and quality of life, and decrease cardiovascular mortality [13]. However, in patients with PE, evidence for rehabilitation is scarce and participation in rehabilitation programs after PE is not routine. One retrospective analysis and one prospective study proved feasibility and safety of inpatient pulmonary rehabilitation (PR) in PE survivors [14, 15], but no study

have evaluated the effect of outpatient PR in patients with PE so far. Only recently, a guideline for exercise training and rehabilitation was released for patients with chronic pulmonary hypertension, including CTEPH [16]. Whether a broader population of patients with PE and persisting symptoms and functional limitations would benefit from rehabilitation is unknown.

### Study rationale

Patients with PE may suffer from long-term consequences, including decreased functional capacity with chronic exercise limitations. Current guidelines suggest diagnostic workup to identify such patients with post-PE symptoms. However, if CTEPH could be excluded, no standardized treatment is available. Cardiopulmonary rehabilitation has been shown to be effective in a variety of cardiopulmonary diseases. But data on the benefits of PR in patients with PE are scarce, and no data about the effects of outpatient PR in PE patients are available so far.

## STUDY DESIGN

This study is a multicentric, academically sponsored, parallel, randomized waitlist-controlled trial that primarily focuses on the short-term benefit of outpatient PR on patients after acute PE. It is important to point out, that only the recruiting part of the study will be multicentric. The main study including intervention and study assessments will take place in one center only (Therme Wien Med).

All patients planning undergoing outpatient PR at the Therme Wien Med due to post-PE symptoms after acute PE are eligible and will be asked for inclusion. After inclusion, patients will be randomized into two treatment arms and will be equally allocated. One arm will receive 6 weeks of outpatient PR, while patients in the other

treatment arm will serve as control. After completion of the study, the second arm will undergo PR as well. PR will be performed according to the Austrian guidelines of outpatient PR. [17]

A follow-up will be performed one year after completion of PR and quality of life, functional limitations, dyspnea and long-term benefits will be assessed.

# PARTICIPANTS

## Eligibility criteria:

All patients above 18 years who get referred to the outpatient PR center are screened for inclusion and exclusion criteria. If patients fulfill all inclusion criteria and meet none of the exclusion criteria, patients are asked to consent into study inclusion. After written informed consent, patients will be randomized to the treatment or control arm.

## Inclusion criteria:

1. Post-PE syndrome (except patients previously diagnosed with CTEPH) diagnosed by any of the following:
   - **Post-PE functional impairment criteria**:
     - New or progressive dyspnea, exercise intolerance and/or diminished functional status following a diagnosis of acute symptomatic or incidental pulmonary embolism treated with effective therapeutic anticoagulation for at least 3 months

        - *Anticoagulation is considered effective if a direct oral anticoagulant (DOAC) or Vitamin K-Antagonist was used according to guidelines [18]*
    - No apparent non-PE related alternative explanation on echocardiography, pulmonary function testing and CPET, or other diagnostic testing

- **Post-PE Cardiac Impairment criteria**
    - Confirmed acute symptomatic or incidental pulmonary embolism treated with effective therapeutic anticoagulation for at least 3 months
    - Intermediate/high echocardiographic probability of pulmonary hypertension according to ESC criteria, defined as (newly developed if prior echocardiographic data are available) estimated peak regurgitation velocity >2.8 m/s, or ≤2.8 m/s associated with at least one of the following:
        - RVEDD >30 mm, or RVEDD/LVEDD >0.9
        - Hypokinesia of the RV free wall
        - Exertional dyspnoea corresponding to NYHA class II, III or IV
- **Chronic Thromboembolic Disease criteria**
    - Exertional dyspnoea of the NYHA class II, III or IV
    - Persistent thromboembolic material in pulmonary artery tree despite 3 months of adequate anticoagulant therapy
    - Normal mPAP at rest

2. Possibility of starting rehabilitation between 12 and 36 weeks after initial event of PE.

*Due to difficulties faced during the COVID-19 pandemic (i.e., very long waiting periods to get approval for undergoing rehabilitation, very long waiting lists at the rehabilitation unit to start rehabilitation), the decision was made to extend the inclusion period to up to 36 weeks after the acute PE event.*

## Exclusion criteria

- CTEPH diagnosis *
    - **Criteria**
        - At least one mismatched segmental perfusion defect demonstrated by ventilation/perfusion scanning after 3 months of adequate therapeutic anticoagulation
        - Resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg measured by invasive right heart catheterization
        - Pulmonary capillary wedge pressure ≤15 mmHg
- Chronic pulmonary diseases: COPD, interstitial lung diseases, asthma (only patients with severe asthma defined as a FEV1 ≤ 80% will be excluded), a statement on COVID-19 was amended due to the pandemic #
- Active cancer
    - Cancer is considered active, if any of the following applies:
        - has not received potentially curative cancer treatment; or
        - there is evidence that cancer treatment has not been curative (e.g. metastatic, progressive or recurrent disease); or
        - cancer treatment is ongoing. [19]
- Pregnancy
- Myocardial infarction or cardiac surgery one year prior to inclusion
- Congenital heart disease, congestive heart failure
- History of stroke

- Any previous inpatient or outpatient PR

* CTEPH patients will be excluded, because rehabilitation has been proven effective in those patients. [20]

# Patients with a history of moderate, severe, or critical COVID-19 as defined by the World Health Organization (WHO) [21] will be excluded from the study.

## Additional criteria that are absolute contraindications for pulmonary rehabilitation

- Acute and decompensated disease states with severe functional restrictions of various organ systems (e.g. heart, kidney and liver insufficiency, unstable angina pectoris, hemodynamically unstable arrhythmias, acute spinal cord injury, untreated hormonal disorders, acute psychological disorders)
- open tuberculosis
- active infectious diseases and acute inflammatory processes
- Stressful and time-consuming therapy that significantly impair the ability to rehabilitate (e.g. chemotherapy or radiation therapy after malignancy)
- Participants who are not sufficiently resilient due to physical or mental impairment and / or cannot be mobilized and therefore cannot actively use the rehabilitation facility
- lack of motivation for therapy
- massive incontinence
- drugs and alcohol addiction

### Settings and locations where the data is collected

Inclusion and randomization will be performed at the Outpatient Pulmonary Rehabilitation, Therme Wien Med. PR itself, all tests and performance measurements will also be carried out at the Therme Wien Med. Similarly, all data will be collected there.

## STUDY PROCEDURE

### Pre-Visit

Patients who get referred to outpatient PR will routinely visit the rehabilitation center to arrange a starting date. Here the patients will be screened for eligibility. If all inclusion and none of the exclusion criteria are met, the patient will be asked to participate in the study. After inclusion the patient will be randomized into the intervention or the control arm. Participants in the intervention group will undergo PR routinely. Patients in the control arm will arrange a starting date for their rehabilitation as well and a date for the 2-day baseline visit 6 weeks prior to their starting date of the rehabilitation will be set.

### Baseline visit

Note, baseline visit refers to the starting date of the rehabilitation in the intervention group and to the baseline visit in the control group 6 weeks prior to their starting date of the PR.

At baseline visit, referral site will be noted and a structured interview about the patient’s medical history will be performed. Information on the PE event including severity/anatomical extent, diagnostic method (CTPA, ventilation-perfusion lung

scanning, pulmonary angiography), unprovoked/provoked (recent surgery or trauma, immobilization, estrogen therapy, active cancer), admitted to intensive care unit, concurrent symptomatic DVT, known thrombophilic condition, previous venous thromboembolism, right ventricular strain in initial CT or echocardiography. Dyspnoe (mMRC, BORG), functional limitations (WHO functional class) will be recorded. Furthermore, age, weight, BMI, comorbidities (presented separately and combined using the Charlson Comorbidity Index), socioeconomic status will be assessed. A recent echocardiogram, which is obligatory for undergoing PR will be added to the chart.

## Baseline assessments

At baseline, assessments of cardiopulmonary exercise test (peak VO2), 6MWT, inspiratory muscle strength (Pimax, Tlim), maximal workload (Wmax), upper and lower extremity strength will be performed. Similarly, measurements of quality of life and functional limitations will be assessed. All measurements are further prescribed below.

Those assessment will be conducted within the first 2 days of starting rehabilitation in the intervention group and in the control group, assessments will be performed on 2 consecutive days 6 weeks prior to rehabilitation. On the first day of assessment spiroergometry to assess peak VO2 and Wmax will be performed. On the second day 6MWT, inspiratory muscle pressure assessment, and maximal upper and lower extremity strength will be measured. Between measurements patients will have at least half an hour to regenerate. Furthermore, it is ensured that there is at least 1 hour between 6MWT and assessment of lower extremity strength.

## End of study

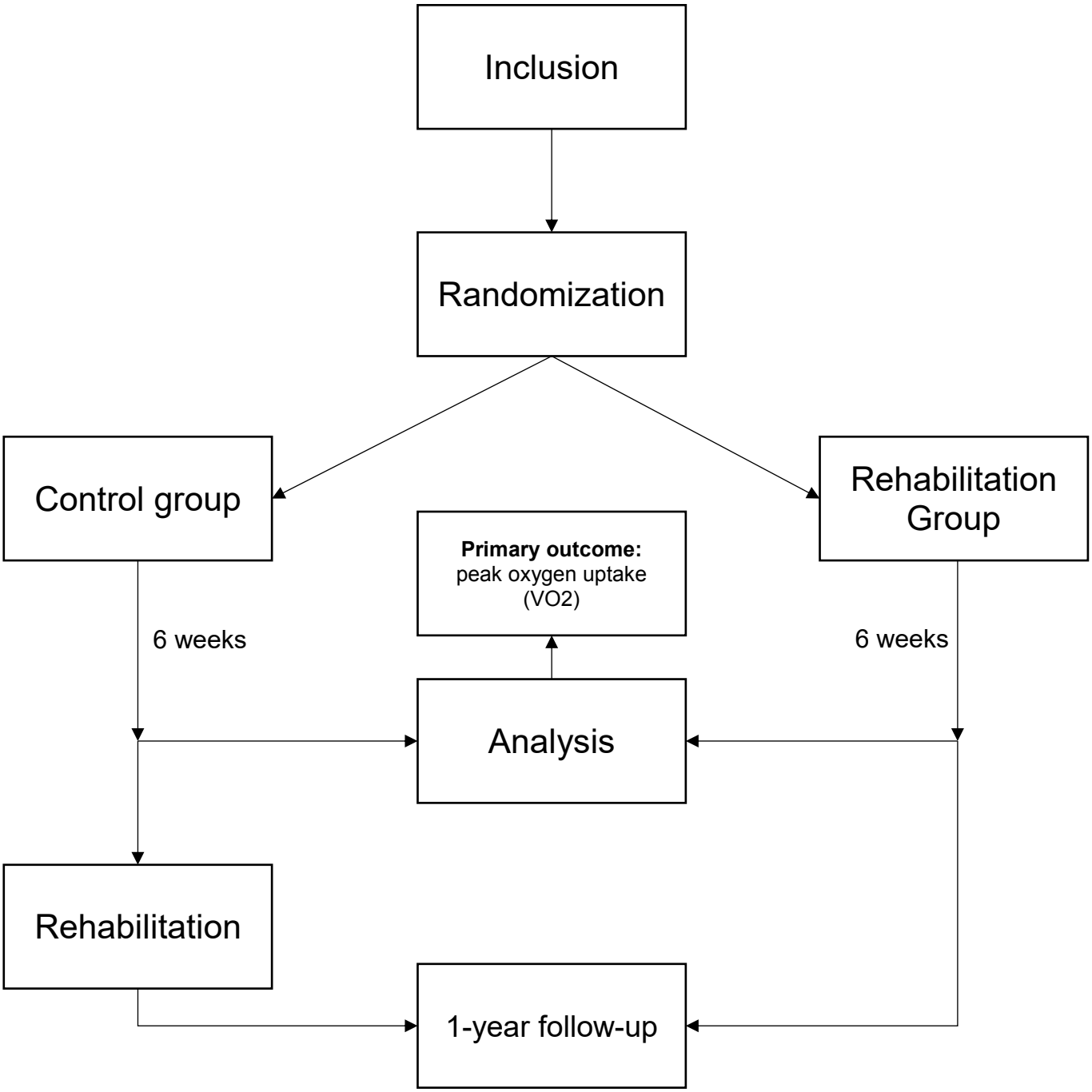
After 6 weeks - at the end of the study - all assessment, which were performed at baseline, will be repeated. Adverse events and complications including bleeding events, myocardial infarction, and unexpected hospital admissions will be recorded. Further, comments will be made in case any patient experienced a disease or an event that might potentially influence an outcome. To measure compliance, the number of completed sessions will be recorded.

## Follow-up study

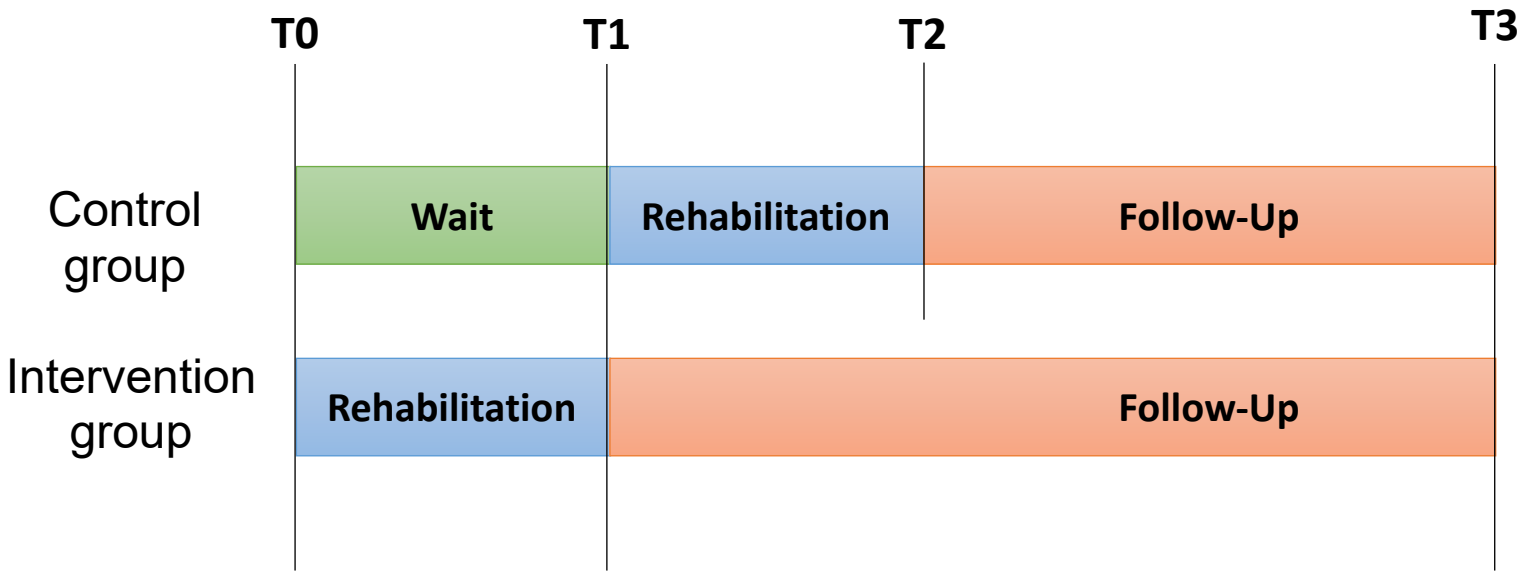
After completion of the primary randomized study, follow-up will be performed in a different study setting. Since we conduct a waitlist-controlled trial, the control group will undergo rehabilitation as well. Therefore, the whole study population will be followed up in a prospective cohort setting. One year after the completion of the outpatient PR, patients will be contacted via mail and phone and a follow-up will be performed with regards to quality of life, functional limitations, hospital admissions, smoking habits, recurrent events, comorbidities and medication.

Study flow charts

**Flow chart 1**




**Flow chart 2**




## INTERVENTION

Patients randomized to the treatment group will all undergo a multi-professional and individualized PR according to the Austrian guidelines for outpatient PR [17]. Three times a week for 3 to 4 hours, participants will complete endurance, strength and inspiratory muscle training over 6 weeks. Exercises were individually prescribed following a medical evaluation and an exercise tolerance test by the medical consultant of the program.

### Outpatient pulmonary rehabilitation program

Patients will undergo a comprehensive interdisciplinary and individualized rehabilitation program according to the Austrian guidelines for outpatient PR that has been described before in detail [17]. On three half days per week over a period of 6 weeks patients complete 60 rehabilitation sessions of 50 minutes each. Forty-six of the 60 sessions are training sessions only, which accounts for a net workout time of approximately 38 hours. The exercise sessions consisting of endurance, strength and

inspiratory muscle training will performed under supervision of medical staff, physiotherapists and sport scientists. Endurance training implements cycle ergometer exercises targeting a heart rate calculated by the Karvonen formula [22], strength training include 4-6 muscle groups including upper and lower extremity. All patients will receive inspiratory respiratory muscle training using a special training device (Eumedics -RESPIFIT S). Physiotherapy sessions focus on improvement of pulmonary problems, mobility and coordination. Additionally, the program consists of individualized patient education, which includes 4 disease- and medical treatment-specific sessions, 2 sessions focusing on nutritional counseling, and 4 psychologic sessions. If indicated further psycho-social counseling and smoking cessation sessions will be offered to all participants. Medical evaluation and assessments at admission and discharge of PR accounts for another 4 sessions.

# MEASUREMENTS

## All variables and measurements

| **Demographic data** | | | |
|---|---|---|---|
| ***Variable*** | ***Units/categories*** | ***Scale*** | ***Time points T*** |
| Age | Years | Metric | T0 |
| Gender | Female, male | Nominal | T0 |
| Weight | kg | Metric | T0, T1, T2, T3 |
| Height | cm | Metric | T0 |
| Smoking | Current, Former, Never | Nominal | T0, T3 |
| Education level | Hauptschule<br>Polytechnische Oberschule<br>Oberstufengymnasium/Matura<br>FH/Universität | Nominal | T0 |
| Marital status | Married<br>Single | Nominal | T0 |

| | | | |
|---|---|---|---|
| | Partnership<br>Widowed<br>Seperated | | |
| Job | Seeking employment<br>In Training<br>Employed<br>In pension<br>Self employed | Nominal | T0 |

| **PE characteristics** | | | |
|---|---|---|---|
| ***Variable*** | ***Units/categories*** | ***Scale*** | ***Time points T*** |
| Site of PE | Unilateral, Bilateral | Nominal | T0 |
| Location of PE | Central<br>Lobar<br>Segmental<br>Subsegmental | Nominal | T0 |
| DVT present at index event | Yes, No | Nominal | T0 |
| Triggering events | No event<br>Oestrogen use<br>Recent surgery<br>Long travel<br>Immobility | Nominal | T0 |

| **Exercise parameters** | ***Units/categories*** | ***Scale*** | ***Time points T*** |
|---|---|---|---|
| 6MWT | meter | Metric | T0, T1, T2 |
| ***Cardiopulmonary exercise testing*** | | | |
| Maximal workload | Watt | Metric | T0, T1, T2 |
| $VO_2$ max | ml $O_2$/min<br>ml $O_2$/min/kg | Metric | T0, T1, T2 |
| $CO_2$ max | ml $O_2$/min<br>ml $O_2$/min/kg | Metric | T0, T1, T2 |
| Ventilation equivalent $O_2$ | / | Metric | T0, T1, T2 |

| | | | |
|---|---|---|---|
| Ventilation equivalent $CO_2$ | / | Metric | T0, T1, T2 |
| Minute ventilation volume | ml | Metric | T0, T1, T2 |
| Tidal volume | ml/kg/min | Metric | T0, T1, T2 |
| Heart rate at rest | rate/min | Metric | T0, T1, T2 |
| Heart rate at maximal exertion | rate/min | Metric | T0, T1, T2 |
| Blood pressure at rest and maximal exertion | mmHg | Metric | T0, T1, T2 |
| Constant-work-rate test at 70% | min | Metric | T0, T1, T2 |
| BORG scale at rest and maximal exertion | 1-10 | Ordinal | T0, T1, T2 |
| **Other assessments** | | | |
| 1-MSTST | counts | Metric | T0, T1, T2 |
| Maximal inspiratory muscle pressure | mbar | Metric | T0, T1, T2 |
| Inspiratory muscle endurance | min | Metric | T0, T1, T2 |
| Lower extremity strength | kg | Metric | T0, T1, T2 |
| Upper extremity strength | kg | Metric | T0, T1, T2 |

| **Questionnaires and other outcomes** | | | |
|---|---|---|---|
| ***Questionnaire, Scales*** | | ***Scale*** | ***Time points T*** |
| 5-level EQ-5D version (EQ-5D-5L) | | Ordinal | T0, T1, T2, T3 |
| PEmb-QOL | | Ordinal | T0, T1, T2, T3 |
| PROMIS Short Form v2.0 – Physical Function 10a | | Ordinal | T0, T1, T2, T3 |
| Post-VTE functional status scale | | Ordinal | T0, T1, T2, T3 |
| Modified Medical Research Council (mMRC) scale | | Ordinal | T0, T1, T2, T3 |
| Hospital Anxiety and Depression Scale (HADS) | | Ordinal | T0, T1, T2, T3 |
| Fagerström-Questionnaire | | Ordinal | T0, T1, T2, T3 |
| **Other outcomes** | ***Units/categories*** | | |
| Adherence | Number of completed session | Metric | T1, T2 |

## The 6-minute walk test

The 6MWT is a simple frequently used method in cardiopulmonary studies, and a difference of 30.5 m between measurements is considered a minimal clinical important difference [23, 24]. Assessment of 6MWT will be performed on a 30 meter walking course according to the standardized protocol of the American Thoracic Society [25].

## Cardiopulmonary exercise testing

Peak exercise capacity is defined as “the maximum ability of the cardiovascular system to deliver oxygen to exercising skeletal muscle and of the exercising muscle to extract oxygen from the blood”. Consequently, exercise tolerance is determined by three factors: pulmonary gas exchange; cardiovascular performance, including the peripheral vascular tree; and skeletal muscle metabolism [26].

At maximal exercise, the Fick equation is expressed as follows:

$$Vo2max = (SVmax \times HRmax) \times (Cao2max - Cvo2max)$$

where SV is the stroke volume, HR is the heart rate, Cao2 is the arterial oxygen content, and Cvo2 is the mixed venous oxygen content.

Cardiopulmonary exercise will be performed with incremental testing according to protocol on a cycle ergometer. [26] Starting with 20W the patient will be challenged by increasing the workload by 10W each minute until he/her reached his/her maximal workload. The following measurements will be taken: Peak oxygen content (PVo2), ventilatory anaerobic threshold (VAT), maximum heart rate (HRmax), heart rate reserve (HRR), blood pressure (BP), ventilatory reserve (VR), respiratory rate (RR), minute ventilation/carbon dioxide output ratio (VE/Vco2) at VAT.

Reasons for termination, symptoms and complications will be noted and subjective assessment of effort will be assessed with the BORG scale.

## Maximal workload

A continuous and maximal escalating protocol will be used, comprised of an initial resting period for six minutes with the patient sitting on the cycle ergometer, followed by a four-minute warm-up of pedaling without any workload, and later, by the escalating phase with a maximum duration between eight and twelve minutes.

## Inspiratory muscle strength

Maximal inspiratory muscle strength (Pimax) in mbar and inspiratory muscle endurance (Tlim) in minutes will be measured with the training device Eumedics - RESPIFIT S.

## Upper and lower extremity strength

The maximal one-repetition maximum for upper and lower extremities will be measured and performed with a training machine. Maximal measurable weight with the machine will be 160 kg.

## Quality of life, functional limitations and anxiety

Quality of life will be measured with the EQ-5D-5L [27] and the PEmb-QoL [28]. Functional limitations will be assessed with the PROMIS Physical Function short form [29] and the post-VTE functional status scale. [30]

Anxiety and Depression will be assessed using Hospital Anxiety and Depression Scale (HADS) [31].[32]

Additionally, Fagerström-Test will be used to assess cigarette dependence of the participants and to assess effectiveness of smoking cessation session during rehabilitation. [33]

# ASSESSMENT OF SAFETY

The study does not intervene in the management of medical issues. As all physical assessments are routinely performed at the PR center as well management of medical issues which arise during the study will be handled as done during routine. However, everything will be recorded and presented to the safety board members.

The following events will be recorded and reported as a serious adverse event:

- Death
- Life-threatening (subject at immediate risk of death)
- Requires in-patient hospitalization*
- Persistent or significant disability or incapacity
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require a surgical intervention to prevent one of the outcomes listed in this definition.

*Any pre-scheduled procedures which requires hospitalization will not be reported as an SAE.

### Data and safety monitoring board (DSMB)

The board members will meet after 24 participants have undergone rehabilitation. Should safety issues arise that the DSMB feel compromises the trial and/or participant safety, then the committee will be convened to consider amending or stopping the trial.

The safety board members include:

Ass.-Prof. Dr. Karin Janata-Schwatczek – Department of Emergency Medicine, Medical University of Vienna, Vienna, Austria

Assoc. Prof. Priv. Doz. Dr. Jolanta Siller-Matula, PhD – Department of Medicine II, Clinical Division of Cardiology, Medical University Vienna, Vienna, Austria

PD Dr. Johannes Thaler, PhD – Department of Medicine I, Clinical Division of Haematology & Haemostaseology, Medical University Vienna, Vienna, Austria

## OUTCOMES

### Primary outcome:

The primary outcome is difference in 6MWT from baseline to 6 weeks.

For the intervention group, 6MWT will be assessed at admission (until 3rd training session) and discharge (last three training sessions). For the control group, 6MWT

will be assessed 6 weeks prior to their starting point of their PR and at the beginning of their outpatient PR.

## Secondary Outcomes:

Difference in exercise parameters:

1. Change in peak oxygen uptake (VO2/kg)
2. Difference in maximal workload (Wmax) on cycle ergometer test
3. Difference in one-repetition maximum for lower extremities
4. Difference in one-repetition maximum for upper extremities
5. Difference in maximal inspiratory muscle pressure (Pimax)
6. Difference in inspiratory muscle endurance (Tlim)

Dyspnea parameters

7. Difference in dyspnea at rest and exertion measured with the Modified Medical Research Council Dyspnea Scale (MMRC) and BORG scale

Quality of life, functional limitations and others

8. Change in quality of life will be measured with the EQ-5D-5L
9. Change in functional limitations will be assessed with the PROMIS Physical Function short form and the post-VTE functional status scale
10. Change in anxiety and depression measured with HADS

## Randomization

### Allocation sequence generation

Randomization will be performed using permuted block randomization with block sizes of 2 and 4 and a 1:1 ratio. The site, which refers the patient to PR, will be considered as a factor for stratification. Here 3 sites will be considered as a factor (AKH, Krankenhaus Hietzing, and all others). At the beginning of the study, generation of the random allocation sequence will be performed by Dr. Stephan Nopp using the web-based Randomizer software (Version 2.0.3 © Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz), which ensures that the sequence is hidden to all users.

### Allocation concealment

Enrolling and assigning the patients to the different treatment arms will be done by Dr. Ralf Harun Zwick, the head of the outpatient PR unit using the Randomizer software. By entering the participant's name into the randomization software, the program will automatically assign the participant to the different treatment groups. A unique study participant number and study group allocation will be given after entering the patients' basic information and eligibility criteria. Furthermore, the allocation concealment is ensured by the Randomizer software and the permuted block randomization.

### Implementation

Generation of the random allocation sequence will be performed by Dr. Stephan Nopp using the Randomizer Software. Enrolling and assigning the patients to the

different treatment arms will be done by Dr. Ralf Harun Zwick, the head of the outpatient PR unit.

Blinding

Patients will be kept uniformed about the different nature of the treatment arms and their allocation. The participants will be informed that they participate in a study with different time points on starting rehabilitation, but they will not know about the nature of the study arms and to which arm they got allocated to. On the site of the outpatient PR only Dr. Ralf Harun Zwick knows about the allocation of the patients. Assessments (e.g. spiroergometry, 6MWT) will be performed by the outpatient rehabilitation staff who will be blinded to the treatment arm of the participants. They will not be instructed about the nature of the ongoing study and especially not to which treatment arm the patients belong to. This is possible because the exercise measurements are part of the routine program which is completed by all patients undergoing PR at this center.

# STATISTICAL CONSIDERATIONS

## Sample Size

Sample size estimation was based on certain assumptions, including that a week 6 mean change from baseline 6MWD of at least 30.5 meters between treatment and control group would be considered a clinically meaningful change. This estimation was taken from a systematic review on minimal clinically important difference (MCID) of patients with cardiopulmonary disease. [24] Assumptions on standard deviations are based on a previously published article on rehabilitation by our group. [34]

A sample size of 20 in each group will have 80% power to detect a difference in means of 30.5m assuming that the Group 1 standard deviation, $\sigma_1$, is 40 and the Group 2 standard deviation, $\sigma_2$, is 20 (ratio of Group 2 to Group 1 standard deviation is 0.5) using a two group Satterthwaite t-test with a 0.05 two-sided significance level. To correct for a potential design effect, estimated sample size number will be multiplied by 1.2. This accounts for a **total sample size of 48 patients** for both treatment arms.

In addition, sample size estimation was performed for the main secondary endpoint change of VO2/peak oxygen consumption.

Data from the ELOPE-study reporting on PE patients showed a mean (SD) VO2 peak of 1,971.2 (663.3) mL/min or 23.3 (9.2) mL/kg/min at 1 year. Patients with functional limitations (VO2 peak < 80%), reached a VO2 peak of 18.9 (4.2) mL/kg/min. [9] Few data on clinically important difference in VO2 peak is available to date and no data on VO2 and MCID in PE patients exists. Therefore, MCID estimation are based on known results in different diseases. In severe COPD a change in 40 mL/min (0.5 mL/kg/min for an 80kg patient) is considered a meaningful change. Further, data on pulmonary arterial hypertension (PAH) patients show an increase in 1-1.5 mL/kg/min after rehabilitation. [35] Based on these data we estimate that a change in 2 mL/kg/min, which would approximately account for a 10% increase from the baseline VO2 value, would definitely be considered a meaningful change. [36] Standard deviation for sample size calculation was estimated based on previous studies. [9, 35, 36]

Therefore, with a sample size of **24 in each group** we should be able to detect a difference of 2 mL/kg/min peak VO2 assuming the intervention group standard deviation, $\sigma_1$, is 3 mL/kg/min and the control group standard deviation, $\sigma_2$, is 1.5

mL/kg/min (ratio of Group 2 to Group 1 standard deviation is 0.333) using a two group Satterthwaite t-test with a 0.05 two-sided significance level.

Final analysis will be conducted using Analysis of Covariance (ANCOVA) model using baseline as a covariate.

For all other secondary exercise parameter outcomes, no minimal important difference is known. However, the sample size of 48 patients will be big enough to detect at least a 10% increase of the baseline variable assuming that the control group will not or only slightly improve in performance on each assessment.

Sample size calculations were performed using nQuery 8 (Version 8.5.1.0, Statistical Solutions Ltd.)

## Analysis

In order to correct for the regression to the mean effect, statistical analysis for the primary outcome comparing peak VO2 between the two treatment arms will be performed using Analysis of Covariance (ANCOVA) model using baseline value as a covariate.

Both, intention-to-treat and per-protocol analysis, will be reported. Intention-to-treat analysis will be performed according to randomization. Per-protocol analysis will be performed with all participants completing at least 80% of the outpatient PR sessions in the intervention group. Sensitivity analysis will be performed adjusted for age and sex.

Similarly, all other exercise parameters, scores on functional limitation and quality of life scores will be assessed by comparing the mean difference in group A and group B using an ANCOVA with baseline value as a covariate.

Patient demographics, clinical characteristics, and follow-up data will be summarized as mean and standard deviation, median and 25th-75th percentile (i.e. interquartile range [IQR]), or frequencies and proportions, as appropriate.

Quality of life questionnaires will be analyzed in a blinded fashion.

# DATA HANDLING AND RECORD KEEPING

Electronic Case Reports Forms Data (eCRF) collection will be performed using a web-based system. Only trained research personnel will have authorization with an access password to enter and modify eCRFs. The web-based system functions with a secure server and backups will be done regularly. An audit trail will be implemented that will track who enters the data and when. All data queries, responses to queries and changes to the data will be captured in the eCRF.

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