BMJ Open

The Pulmonary Hypertension And Home-Based (PHAHB) Exercise Intervention: Protocol for a Feasibility Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045460
Article Type:	Protocol
Date Submitted by the Author:	01-Oct-2020
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Keywords:	REHABILITATION MEDICINE, SPORTS MEDICINE, Respiratory physiology < THORACIC MEDICINE

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PHAHB Intervention Protocol

The Pulmonary Hypertension And Home-Based (PHAHB) Exercise Intervention: Protocol for a Feasibility Trial

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Word Count: 3852

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ABSTRACT

Introduction: Novel therapies for pulmonary hypertension (PH) have improved survival and slowed disease progression. However, patients still present with symptoms of exertional dyspnoea and fatigue, which impacts their ability to perform activities of daily living, reduces exercise tolerance and impairs their quality of life (QoL). Exercise training has shown to be safe and effective at enhancing QoL and physical function in PH patients, yet it remains an under-utilized adjunct therapy. Most exercise training for PH patients has been offered through hospital-based programmes. Home-based exercise programmes provide an alternative model that has the potential to increase the availability and accessibility of exercise training as an adjunct therapy in PH. The purpose of this study is to investigate the feasibility, acceptability, utility and safety of a novel remotely supervised home-based PH exercise programme. **Methods:** Single arm intervention with a pre/post comparisons design and a follow up maintenance phase will be employed. Eligible participants (n= 25) will be recruited from the Mater Misericordiae University Hospital PH Unit. Participants will undergo a 10-week remote home-based exercise program, with induction training, support materials, telecommunication support and health coaching sessions. The primary outcome measures are feasibility, acceptability, utility and safety of the intervention. Secondary outcomes will include the impact of the intervention on exercise capacity, physical activity levels, strength, health-related quality of life and exercise self-efficacy, assessed at baseline, 10 weeks (post intervention) and 20 weeks (follow up). **Ethics and dissemination:** Ethics approval has been obtained from the Mater Misericordiae Institutional Review Board REF:1/378/2032 and Dublin City University Research Ethics DCUREC/2018/246. A manuscript of the results will be submitted to a peer-reviewed journal and results will be presented at conferences, community and consumer forums and hospital

research conferences. Trial Registration: ISRCTN Registry: ISRCTN83783446.Protocol version. 2.0.

Keywords: Pulmonary Hypertension, exercise rehabilitation, physical activity, home-based, remote delivery, wearable technology, health coaching.

Strengths and limitations of this study

- This is the first study to assess the feasibility, utility and acceptability of a novel distance-based exercise intervention for PH patients
- The intervention is pragmatic and scalable and could be integrated into existing healthcare pathways.
- As PH is a rare disease with a small population size within Ireland, there is a lack of a usual care control group which is a limitation of the study.

INTRODUCTION

Despite earlier diagnosis and improved pharmaceutical therapies, many PH participants continue to experience exertional symptoms of dyspnoea and fatigue, which leads to a reduction in functional capacity and in turn, quality of life (QoL). Consequently, there is greater recognition for a more holistic approach to PH treatment beyond pharmacological therapies[1].

Exercise rehabilitation and physical activity (PA) interventions have continuously demonstrated effectiveness as adjuvant therapies for improving exercise capacity and QoL in a spectrum of cardio-pulmonary disorders[2-4]. Although research investigating exercise in PH is an emerging field of study, the body of evidence continues to grow. Recent systematic reviews and meta-analyses have reported improvements in exercise capacity and QoL in PH[6-

11], which has prompted a renewed focus on exercise training and pulmonary rehabilitation for PH patients.

In 2015, the European Society of Cardiology /European Respiratory Society published the first guidelines, stating that exercise training should be implemented by specialist PH centres as an adjunct to medical therapy for stable PH participants[12]. Currently, the optimal mode, intensity, and duration of the training and the characteristics of participants most likely to benefit from exercise training remains unknown[13].To date, the Hiedelberg program in Germany remains the gold standard exercise program in PH. It involves an intensive 3-week in-patient induction phase, with a continued multimodality, monitored outpatient period[14]. Despite the proven beneficial outcomes of this program, it is deemed resource intensive to operate and roll out.

An alternative and pragmatic approach, found to be as effective as a supervised exercise programme in cardiac rehabilitation, is a home-based model[15]. Home-based interventions provide solutions to common barriers to participation in centre-based programs such as access and transport issues, and are less expensive[16]. Further, older adults and patient populations express a preference for unsupervised, self-paced, low-moderate intensity PA, specifically walking[17-18]. Home-based interventions have not been studied extensively in PH. Through the use of telehealth, distance-based programmes could potentially offer an alternative mode of delivery for exercise training to increase adherence, availability and affordability for PH patients.

Previous exercise interventions in PH have not included strategies to maximise adherence. An evidence-based approach to implement lifestyle changes requires the

implementation of health behaviour change strategies grounded in health behaviour change theory[19]. Evidence-based behaviour change techniques (BCT's) can be used to improve intervention effectiveness[20]. For example, the combination of the following BCT's: self-monitoring; goal setting; providing feedback on performance; and, review of behaviour goals, is associated with increased intervention effectiveness in PA interventions[21]. Interventions that meet the support needs and offer opportunities for self-monitoring have been found to be effective for improving PA in other chronic disease groups[22]. Wearable technology holds great potential as an easy to use, low cost self-monitoring tool with feedback[23] and are perceived as acceptable and useful for individuals with chronic diseases[24]. Furthermore, telecommunication allows for real-time verbal and visual interaction between patients and clinicians.

The primary aim of this study is to assess the feasibility, acceptability, utility and safety of a novel home-based exercise training programme for PH patients. BCT's will be integrated in the intervention through wearable technology devices, the use of print and electronic materials and health coaching and support calls. The secondary aim is to examine the impact of the intervention on exercise capacity, physical activity levels, strength, health-related QoL and exercise self-efficacy.

METHODS AND ANALYSIS

Study Design

The study will employ a single group pre-post-intervention design with a follow up maintenance phase. The purpose of the maintenance phase is to asses if the intervention facilitates the adoption of independent exercise in participants when support is removed. The study will adhere to the Standard Protocol Items: Recommendations for Interventional Trials

Reporting Template (SPIRIT)[25]. Participants will complete assessments at baseline (T1), after the 10- week intervention (T2) and at 20-weeks follow up (T3).

Eligibility Criteria

Inclusion criteria are male or female > 18 years, with a diagnosis of PH by right heart catheterisation showing baseline mean pulmonary arterial pressure ≥25 mm Hg, pulmonary vascular resistance ≥240 dyn s cm^{-5}, pulmonary capillary wedge pressure ≤15 mmHg and receiving optimized conventional PH therapy. Participants must be clinically stable with no medication changes in the 2 months prior to enrolment.

Exclusion criteria include PH of any cause other than outlined in the inclusion criteria such as PH from left heart disease or lung disease/hypoxia, pregnancy, signs of right heart decompensation, acute infection and pyrexia, change in disease-targeted therapy within the last 2 months, scheduled to receive an investigational drug during the course of the study, FEV1/FVC <0.5, total lung capacity <70% of the normal value, active liver disease, porphyria, elevations of serum transaminases >3 x upper limit of normal (ULN), bilirubin >1.5 x ULN, haemoglobin concentration <75% of the lower limit of normal, systolic blood pressure <85 mmHg, active myocarditis, unstable angina pectoris, exercise induced ventricular arrhythmias, decompensated heart failure, hypertrophic obstructive cardiomyopathy or impaired left ventricular function.

Participant Recruitment

Participants will be recruited from the Pulmonary Hypertension Unit at the Mater Misericordiae University Hospital, Dublin, Ireland. Eligible participants will be invited to participate during their routine 3-6-month clinic visit. They will be given a verbal explanation

of the study and provided with a participation information sheet by their PH Specialist (SG/BMC) or a member of their team. After receiving the information, potential participants will have the option to speak on the day to a member of the research team or to receive a follow-up phone call within 1-2 days. Participants will have the opportunity to ask questions and will have time to consider their participation. Written consent will be obtained by mail.

Sample Size

A key objective of this feasibility study is to collate primary outcome measures to help inform sample size calculations for future outcome trials. Pilot study sample size typically ranges from 24 to 50[26-28]. We estimate a target sample size of 25 to be sufficient for this feasibility study[27].

Procedure

Participants will complete all assessments, induction training and exercise training in their own home and will maintain contact with researchers via telecommunication technologies (phone, videoconferencing and email). Following consent, a baseline assessment will be conducted (see Table 1) and participants will be provided with an accelerometer to record their activity for the following week, along with a prepaid postage envelope to return device. The assessment procedure will be repeated at T2 (10-weeks) and T3 (20-weeks).

Participants will be provided with a home exercise bike (NordicTrack GX 2.7U), a wearable tracker watch (The Fibit Charge 3), pulse oximeter (SafeHeart SpO_2 monitor), real time single lead ECG/HR/respiratory rate monitor (Frontier X), blood pressure monitor (Beurer BM44), exercise manual, exercise diary and access to online videos. The exercise manual offers a comprehensive, patient-friendly resource detailing; 1) general information about the trial; 2)

useful links and contacts; 3) background information on PH; 4) education regarding exercise safety and the benefits of physical activity; 5) workbook style sections on motivation, goal setting, overcoming barriers and psychosocial support; 6) managing breathlessness; 7) exercise intensity and limits; 8) guided home exercises with written and visual details and advice on progression; and 9) advice on pacing and energy conservation. Online videos will provide a visual demonstration of each exercise. Participants will be provided with an exercise diary as a tool to record their activity and effort.

The 10-week intervention consists of the following components: Three 60-90 min induction sessions (over week 1 and 2), up to five 30-min support health coaching sessions (at week 2, 3, 5, 7, 9) and 3-5 weekly home-based exercise sessions. The intervention will end prior to T2 assessment. Participants will continue to have access to the exercise manual, bike and Fitbit between T2 and T3, the maintenance phase.

Induction Training

Induction training is a key component to ensure patients are confident to exercise at home and understand the appropriate exercise intensity and how to exercise safely.1:1 induction sessions will take place via video conferencing. Participants will be encouraged to involve a family member, friend or carer in the induction training. The sessions will focus on the following topics:

Session 1 - Introduction; Education on PH and benefits of PA for PH. Familiarisation with intervention materials/equipment and self-monitoring.

Session 2 - Exercise Safety and Exercise Demonstration; The session will focus on recognizing exercise limits, warning signs, and managing exercise intensity. Visual demonstrations of breathing techniques and aerobic, strength and respiratory training will be provided, with the

opportunity for behavioural practice during the session to check technique and instil confidence.

Session 3 - Recap; Exercise demonstrations and key safety points will be reviewed. Any issues regarding intervention materials/equipment will be addressed and participant goals will be reviewed, alongside additional tips for family/friend support and motivation.

Health Coaching Sessions

During the intervention, participants will receive up to five 30 min formal health coaching sessions via videoconferencing. These sessions will use BCTs to improve exercise adherence, motivate and provide support. Over the 5 sessions the topics will include; benefits of exercise, goal setting, action planning , self-monitoring, identification and management of barriers to exercise, problem solving and feedback on behaviour, with the option for participants to complete formal paperwork in the intervention manual. If required, additional support will be available outside of scheduled sessions.

Participants will be asked to wear the Fitbit Charge 3 daily during the 10-weeks. The Fitbit data will be used to guide individually tailored goals, assess adherence to exercise and overall daily PA and as tool to provide feedback to the researcher and participants.

Exercise Program

Participants will complete a 10-week individualised, home-based exercise programme. The programme will be prescribed using the FITT principle (Frequency, Intensity, Time and Type) and will employ a multimodal approach that integrates aerobic, resistance and respiratory training. The goals for each component are outlined in the sections below. These are aspirational goals that may not be realistic for all participants. Exercise prescription will

be individualized based on their baseline PA levels, 6 min walk test distance (6MWD) and physical capabilities. The modified Borg rating of perceived exertion (RPE) scale[29] will be used to help prescribe exercise intensity. The RPE scale is a psychophysiological measurement that translates physical stimuli to a psychological construct of perceived exertion and has been validated in other clinical groups[30].Participants will aim to achieve an RPE of 3 (moderate) initially. Based on individual progress an RPE of 4 (somewhat hard) may be advised for some participants.

All participants exercise program will include:

Aerobic Training; Participants will initially aim will be to undertake a minimum of 10 min of structured aerobic exercise involving walking, cycling or a combination on ≥3 d/week. Participants will be allowed to perform this exercise in a single bout, or accumulate it in bouts of at least 5 min in duration. The duration will be progressively increased, with the goal of accumulating ≥30 min on ≥5 d/week.

Resistance Training; Participants will initially undertake resistance training on 2 d/week, involving a single set of 6-8 repetitions of upper and lower extremity and whole body exercises. Training volume will progressively increase with the goal of completing 2-3 sets of 10-12 reps of 4-6 exercises on three non-consecutive days. Participants will use pursed lip breathing to help airways stay open during exhalation. Bodyweight resistance will be used initially and based on individual ability, tera bands, water bottles or light dumbbells will be introduced.

Respiratory Training; Participants will initially perform 10 min of respiratory training at least twice a week, involving a combination of stretching, breathing techniques (e.g., pursed lip, diaphragmic and slow breathing), yoga, and respiratory muscle strengthening exercises. Training volume will progressively increase with the goal of completing 15/20 min of accumulated respiratory training on ≥3 d/week.

Participants will wear a Frontier X device (receiver attached to a strap place around the chest) during all exercise sessions. The first 2 weeks will be monitored by researchers and then periodically monitored. This will allow access to real time ECG, heart rate (HR), respiratory rate and cadence. Oxygen saturation will be monitored and participants will be instructed to stop exercising if the SpO_2 value drops below 88%, as per guidelines[31]. Participants will document any adverse events and report to the research team immediately.

Study Outcome Measures

Outcome assessments will take place at baseline (T1), after the 10-week intervention (T2) and at 20-weeks follow up (T3). Semi-structured interviews will be conducted at T2 to assess patient's perspective on program acceptability and feasibility and at T3 to assess the follow up phase. Table 1 outline the timepoints of the outcomes.

Table 1: Study outcome measures and time points

	Timepoint		
Assessments	**Baseline (T1)**	**Post-Intervention (T2)**	**Follow-up (T3)**
Written informed consent & eligibility	X		
Demographics	X		
Medical history	X		
WHO functional class	X	X	X
Concomitant medication	X	X	X
Adverse events	X	X	X
Exercise capacity (6-MWT), Borg Dyspnea Index	X	X	X

Muscle strength (Sit to Stand)	X	X	X
Physical activity (ActivPAL Micro)	X	X	X
Quality of life (CAMPHOR & SF-36)	X	X	X
Fear of exercise (Tampa Scale)	X	X	X
Psychological constructs	X	X	X
Intervention debrief questionnaires/ semi-structed interviews		X	X

Primary Outcomes

Primary outcome is the feasibility, acceptability, utility and safety of the intervention. Feasibility of the intervention will be assessed by (i) participant recruitment (enrolment as a proportion of eligible patients) and retention (proportion that completed all assessments); (ii) engagement with the intervention measured according to attendance at induction sessions and health coaching sessions and adherence, defined as the percentage of home-based exercise sessions recorded by participants who complete the intervention assessed via log books and weekly calls) and (iii) Implementation process and fidelity of the intervention captured through observation and detailed field notes. Researchers will note the feasibility of the trial protocols including the outcome assessment and any additional information on patient interactions or response during the intervention.

Acceptability and utility of the intervention will be assessed through self-report questionnaires and semi-structured interview. At T2 participants will be asked to complete a self-report questionnaire, assessing perceptions of intervention appropriateness, effectiveness, quality, accessibility/usability, intrusiveness, and overall enjoyment and attitude towards the intervention.

Semi-structured interviews will probe the elements outlined in the self-report questionnaire and will include perceptions of intervention practicality, i.e., participants' ability to undertake the prescribed activities and to accommodate the intervention within normal daily-life activities. Participants will be asked to highlight barriers to participation and offer suggestions for improvement and implementation. Interviews will be conducted via telephone and will be audio-recorded and transcribed. Interviews at T3 will assess the 10 weeks maintenance period.

Safety (patient reported adverse events directly related to participation in the exercise intervention) will be assessed during support calls and participants will be instructed to inform researchers immediately of any adverse advents in the time between calls.

Secondary Outcomes

Exercise capacity: Assessed using the 6 min walk test (6MWT). The test will be administered according to the European Respiratory Society Guidelines[32] and will be conducted at each participants home using detailed step by step video and written instructions and remotely supervised via phone/teleconferencing by a researcher (CMC). A family member/friend will assist with conducting the test, including measuring blood pressure and SpO_2 with guidance from the researcher before and after the test. Subjective symptoms (RPE and dyspnoea- Borg Dyspnoea Scale 0-10) will be recorded before and after the test. The Frontier X chest worn monitor will be worn during the test to provide real time feedback. The assistant will ask the participant to call out their SpO_2 and HR at each min of the test. Standard encouragement will be delivered by the assistant, with researcher prompting, if needed. The study participants are very familiar with the 6MWT.

Muscular strength: Lower body muscle strength will be assessed using the 30 sec sit-to-stand test (STS) from a seat height of 40-45 cm. The STS is a commonly used field-based measure of functional lower limb muscle strength, particularly in clinical and elderly populations. The test will be conducted in each participant's home via teleconference. A researcher (CMC) will provide a demonstration, time the test, and count the repetitions. Each participant will perform two trials separated by 5 min, with the best score being recorded.

Physical activity behaviour: ActivPAL^3 micro activity monitors (PAL Technologies Ltd. Glasgow, Scotland) will be used to assess free living activity behaviour. The device samples at 20Hz for 15 sec epochs and measures bodily accelerations using triaxial accelerometer. An inbuilt inclinometer measures thigh inclination. Proprietary algorithms classifies activities into sitting/lying time, standing time, stepping time, step count and activity counts. Participants will be mailed the accelerometer together with detailed wear instruction and provided with a prepaid postage envelope to return the device. They will be instructed to wear the device on the anterior aspect of their right thigh continuously for 7 days, except during water immersion activities (i.e., swimming and bathing). The ActivPAL is a valid and reliable measure of activity and sedentary behaviour[33-34].

Psychological Outcomes and Mediators

Quality of life: The Medical Outcomes Study Short-Form 36-Item Survey (SF-36) is a well-validated, generic questionnaire[35] consisting of physical functioning, physical role functioning, bodily pain, and general health and the four mental subscales of vitality, social functioning, emotional role functioning and mental health. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)[36] was designed as a disease-specific health-

related QoL measure for PH patients. It is widely used as a clinical and research tool in PH. It is made up of 3 main dimensions which assess symptoms (25 items) functioning (15 items) and quality life (25 items).

Fatigue: The Fatigue Severity Scale (FSS)[37] measures the patient's perception of the influence of fatigue on physical and social functioning through responses to nine different physical and social functioning situations. The FSS is a valid tool for assessing fatigue across various health conditions[38].

Self-regulatory self-efficacy for exercise: Assessed using a modified 11-item scale[39-40], which provide information on task, scheduling and recovery self-efficacy. Questions begin with the stem "*How confident are you that you can…*" and include items such as "*plan exercise sessions that will be at least moderately difficult (e.g. have you breathing a little hard, your heart rate increases)?*". Participants rate their confidence on a Likert scale from 0 (not confident at all) to 10 (very confident), with a higher score indicating greater self-efficacy for exercise (Cronbach alpha, α =.951).

Intentions to exercise: Two items will measure intention to engage in moderate intensity physical activity for 150 min per week in the next 10 weeks, based on previously established measures[41].

Outcome expectations: Ten-items will assess outcome expectations. Five-items are derived from the validated exercise pros subscale[42] and 5-items to asses outcomes on symptoms associated with PH.

Social support: Social support for exercise from family and friends scale[43] uses a 10-item scale assessing support from family and 10 items reflecting support from friends. Responses will be recorded on a Likert scale of 1-5, with higher scores representing greater social support. (Cronbach alpha, family α =.926, friends α =921).

Data Management

The trial will be overseen by the trial management group, consisting the principal investigator, the trial-coordinator and health coach. They will meet every 4 weeks and will oversee all aspects of the conduct of the trial including performing safety oversight activities. Individual data will be de-identified, coded and entered. Each participant, after providing consent, will be assigned a personal identification code (PIC), which will be used on all case report forms and in all electronic databases. Quantitative data will be double data entered, and data validation will take place according to the procedures set out in the data management plan and data validation plan. Prior to any statistical analysis, all variables will be checked for missing, impossible and improbable values. Impossible and improbable values will be defined by clinical opinion and will include values that are outside three standard deviations of the mean value.

Statistical Analysis

Statistical analysis of quantitative data will be performed using SPSS Version 24. Prior to statistical analysis, the Shapiro-Wilks test will be applied to check for normality. Continuous variables will be reported as mean (range), mean (standard deviation) or median and inter-quartile range, depending on distribution, and categorical variables as frequency (%). Descriptive analyses will be undertaken to summarise participant characteristics and the quantitative data of the intervention feasibility, acceptability and utility. Qualitative data from post trial interviews and researcher field notes will be analyzed using inductive thematic analysis to identity common themes[44]. A one-way ANOVA with repeated measures will be

used to compare the mean differences in secondary outcome variables between baseline(T1), 10 weeks(T2) and 20 weeks (T3).

Patient and Public Involvement

Formative qualitative research took place with PH patients during intervention development stages. Semi structured 1:1 phone interviews (N=20) were conducted providing insight into patient barriers and motivators to PA, current PA levels, past experience and personal preferences on components of an exercise programme. The findings fed into the design of the intervention along with PH clinician input. A patient representative provided opinions on the study protocol, patient-facing documentation (e.g. Participants Information Sheet) and intervention material (e.g. exercise manual) to ensure it was patient friendly.

Discussion

The promise of exercise training in the treatment and management of PH has gained significant interest over the past two decades. The observed positive effects of exercise programs on patients' exercise capacity, functional capacity and QoL[44] make a strong argument for the inclusion of exercise as an adjunctive therapy for stable PH patients[46]. Considering that structured and resource-intensive hospital-based exercise programs are unlikely to be scalable, it is an opportune time to assess the efficacy, safety and impact of home-based programs as an alternative mode of delivery for PH patients.

A home-based exercise program may eliminate many of the barriers associated with in-patients or out-patients setting such as transportation issues, location, long wait periods for availability and further accessibility for patients. A recent review of exercise interventions in PH by Ozemek and colleagues[46] highlighted the need for inclusion of home exercise programs to allow patients achieve the optimal 5 to 6 days of structured exercise.

This study will utilise a remote delivery for exercise training with the use of telehealth methods, wearable technology, performance feedback and behavioural support to deliver and monitor the intervention. The aim is to eliminate the burden on patients to attend several times per week to an outpatient clinic, accommodate resource availability, make the program achievable in a 'real world' setting and improve the reach beyond the traditional healthcare facilities. The follow-up post intervention (T3) phase will provide insight into whether behavioural support is necessary in order for PH patients to remain physically active. PH is considered a rare disease and with support centralised, remote services, which include assessment of patient progress are required. Remote assessment of outcomes may remove threats to external validity and evaluation of the feasibility of such assessment will address the goals of implementation science to close the research-to-practice gap and support implementation and scale up of evidence-based interventions[47].

To our knowledge, this will be the first study to employ the use of evidence-based BCTs to examine the feasibility, utility and efficacy of a remote home-based approach to exercise training for medically stable PH patients. The secondary aims of this study are to evaluate whether this approach leads to improvement in selected indices of physical and psychological health.

Conclusion

PH is a rare, debilitating condition with most clinics centralized and limited community resources available. Telehealth holds significant potential to meet the growing support for exercise training to be included as an add-on therapy by offering remote training and support, which is key to long-term implementation of exercise training for the PH population. It provides a service that is more accessible and may potentially offer a more affordable enhanced level of care. Our current understanding is limited with regards the acceptability, feasibility

and utility of a home-program for stable PH patients. This study will help gain a valuable insight into this gap in knowledge.

References

1. Gaine S, McLaughlin V. Pulmonary arterial hypertension: tailoring treatment to risk in the current era. *Eur Respir Rev*. 2017;26(146):170095. doi:10.1183/16000617.0095-2017.

2. Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev*. 2014;2014(4):CD003331. doi:10.1002/14651858.CD003331.pub4.

3. Buys R, Avila A, Cornelissen VA. Exercise training improves physical fitness in patients with pulmonary arterial hypertension: a systematic review and meta-analysis of controlled trials. *BMC Pulm Med*. 2015;15:40. doi:10.1186/s12890-015-0031-1.

4. Langer D, Hendriks E, Burtin C, et al. A clinical practice guideline for physiotherapists treating patients with chronic obstructive pulmonary disease based on a systematic review of available evidence. *Clin Rehabil*. 2009;23(5):445-462. doi:10.1177/0269215509103507.

5. Vanhees L, Rauch B, Piepoli M, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular disease (Part III). *Eur J Prev Cardiol*. 2012;19(6):1333-1356. doi:10.1177/2047487312437063.

6. Morris NR, Kermeen FD, Holland AE. Exercise-based rehabilitation programmes for pulmonary hypertension. *Cochrane Database Syst Rev*. 2017;1(1):CD011285.. doi:10.1002/14651858.CD011285.pub2.

7. Dalla Vecchia LA, Bussotti M. Exercise training in pulmonary arterial hypertension. *J Thorac Dis*. 2018;10(1):508-521. doi:10.21037/jtd.2018.01.90.

8. Babu AS, Padmakumar R, Maiya AG, Mohapatra AK, et al . Effects of Exercise Training on Exercise Capacity in Pulmonary Arterial Hypertension: A Systematic Review of Clinical Trials. *Heart Lung Circ*. 2016;25(4):333-341. doi:10.1016/j.hlc.2015.10.01.

9. Yuan P, Yuan XT, Sun XY, et al. Exercise training for pulmonary hypertension: a systematic review and meta-analysis. *Int J Cardiol*. 2015;178:142-146. doi:10.1016/j.ijcard.2014.10.161.

10. Pandey A, Garg S, Khunger M, et al. Efficacy and Safety of Exercise Training in Chronic Pulmonary Hypertension: Systematic Review and Meta-Analysis. *Circ Heart Fail*. 2015;8(6):1032-1043. doi:10.1161/CIRCHEARTFAILURE.115.00.

11. Benjamin N, Marra AM, Eichstaedt C, Grünig E. Exercise Training and Rehabilitation in Pulmonary Hypertension. *Heart Fail Clin*. 2018;14(3):425-430. doi:10.1016/j.hfc.2018.03.008.

12. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). *Eur Respir J*. 2015;46(4):903-975. doi:10.1183/13993003.01032-2015.

13. Galiè N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D60-D72. doi:10.1016/j.jacc.2013.10.031.

14. Mereles D, Ehlken N, Kreuscher S, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation*. 2006;114(14):1482-1489. doi:10.1161/CIRCULATIONAHA.106.618397.

15. Buckingham SA, Taylor RS, Jolly K, et al. Home-based versus centre-based cardiac rehabilitation: abridged Cochrane systematic review and meta-analysis. *Open Heart*. 2016;3(2):e000463. doi:10.1136/openhrt-2016-000463.

16. Hardcastle SJ, & Cohen PA. Effective physical activity promotion to survivors of cancer is likely to be home based and to require oncologist participation. *J Clin Oncol* 2017;35:3635-3637. doi: 10.1200/JCO.2017.74.6032.

17. Maxwell-Smith C, Zeps N, Hagger MS, et al. Barriers to physical activity participation in colorectal cancer survivors at high risk of cardiovascular disease. *Psycho-oncology* 2017;26:808-814. doi:10.1002/pon.4234.

18. Artinian NT, Fletcher GF, Mozaffarian D, et al. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122(4):406-441. doi:10.1161/CIR.0b013e3181e8edf1.

19. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci*. 2011;6:42. Published 2011 Apr 23. doi:10.1186/1748-5908-6-42.

20. Samdal GB, Eide GE, Barth T, Williams G, Meland E. Effective behaviour change techniques for physical activity and healthy eating in overweight and obese adults; systematic review and meta-regression analyses. *Int J Behav Nutr Phys Act*. 2017;14(1):42. Published 2017 Mar 28. doi:10.1186/s12966-017-0494-y.

21. Artinian NT, Fletcher GF, Mozaffarian D, et al. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122(4):406-441. doi:10.1161/CIR.0b013e3181e8edf1.

22. Lahart I, Metsios G, Nevill AM, et al. Randomised controlled trial of a home-based physical activity intervention in breast cancer survivors. *BMC Cancer* 2016*;* 16:234-247. doi: 10.1186/s12885-016-2258-5.

23. Hardcastle SJ, Hince D, Jiménez-Castuera R*, et al.* Promoting physical activity in regional and remote cancer survivors (PPARCS) using wearables and health coaching: randomised controlled trial protocol *BMJOpen* 2019;**9:**e028369. doi: 10.1136/bmjopen-2018-028369.

24. Mercer K, Giangregorio L, Schneider E, et al. Acceptance of commercially available wearable activity trackers among adults aged over 50 and with chronic illness: a mixed-methods evaluation. *JMIR Mhealth Uhealth* 2016;4: e7. doi:10.2196/mhealth.4225.

25. Chan A, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: Defining standard protocol items for clinical trials. *Annals of Internal Medicine* 2013*;*158:200-207.

26. Browne RH. On the use of a pilot sample for sample size determination. *Stat Med*. 1995;14(17):1933-1940. doi:10.1002/sim.4780141709.

27. Julious SA: Sample size of 12 per group rule of thumb for a pilot study. *Pharm Stat*. 2005, 4 (4): 287-291. 10.1002/pst.185.

28. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *J Clin Epidemiol*. 2012;65(3):301-308. doi:10.1016/j.jclinepi.2011.07.011.

29. Foster C, Florhaug JA, Franklin J, et al. A new approach to monitoring exercise training. *J Strength Cond Res*. 2001;15(1):109-115.

30. Rosales W, Cofré C, Alejandra C, et al. Validación de la escala de Borg en personas con diabetes mellitus tipo 2 [Validation of the Borg scale in participants with type 2 diabetes mellitus]. *Rev Med Chil*. 2016;144(9):1159-1163. doi:10.4067/S0034-98872016000900009.

31. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188(8):e13-e64. doi:10.1164/rccm.201309-1634ST.

32. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J*. 2014;44(6):1428-1446. doi:10.1183/09031936.00150314.

33. Harrington DM, Welk GJ, Donnelly AE. Validation of MET estimates and step measurement using the ActivPAL physical activity logger. *J Sports Sci*. 2011;29(6):627-633. doi:10.1080/02640414.2010.549499.

34. Kozey-Keadle S, Libertine A, Lyden K, et al. Validation of wearable monitors for assessing sedentary behavior. *Med Sci Sports Exerc*. 2011;43(8):1561-1567. doi:10.1249/MSS.0b013e31820ce174.

35. Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.

36. McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. *Qual Life Res*. 2006;15(1):103-115. doi:10.1007/s11136-005-3513-4.

37. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The Fatigue Severity Scale: Application to Patients With Multiple Sclerosis and Systemic Lupus Erythematosus. *Arch Neurol.* 1989;46(10):1121–1123. doi:10.1001/archneur.1989.00520460115022.

38. Schentag CT, Cichon J, MacKinnon A, Gladman DD, Urowitz MB. Validation and normative data for the 0–10 point scale version of the fatigue severity scale (FSS) [abstract]. *Arthritis Rheum* 2000; **43** Suppl: S177.

39. Luszczynska, A., & Sutton, S. (2006). Physical activity after cardiac rehabilitation: Evidence that different types of self-efficacy are important in maintainers and relapsers. *Rehabilitation Psychology, 51*(4), 314–321.doi. 10.1037/0090-5550.51.4.314.

40. Shields CA, Brawley LR. Preferring proxy-agency: impact on self-efficacy for exercise. J Health Psychol. 2006 Nov;11(6):904-14. doi: 10.1177/1359105306069092. PMID: 17035262.

41. Ajzen I, Brown TC, & Carvajal F. Explaining the discrepancy between intentions and actions: The case of hypothetical bias in contingent valuation. *Pers Soc Psychol Bull* 2004;30:1108-1121. doi:10.1177/0146167204264079.

42. Plotnikoff RC, Blanchard CM, Hotz SB, et al. Validation of the decisional balance scales in the exercise domain from the transtheoretical model: A longitudinal test. *Meas Phys Educ Exerc Sci* 2001;5:191-206. doi:10.1207/S15327841MPEE0504_01.

43. Sallis JF, Grossman RM, Pinski RB, Patterson TL, Nader PR. The development of scales to measure social support for diet and exercise behaviors. *Prev Med*. 1987;16(6):825-836. doi:10.1016/0091-7435(87)90022-3.

44. Virginia Braun & Victoria Clarke. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006;3:2, 77-101. doi: 10.1191/1478088706qp063oa.

45. Dalla Vecchia LA, Bussotti M. Exercise training in pulmonary arterial hypertension. *J Thorac Dis*. 2018;10(1):508-521. doi:10.21037/jtd.2018.01.90.

46. Ozemek C, Berry MJ, Arena R. A Review of Exercise Interventions in Pulmonary Arterial Hypertension and Recommendations for Rehabilitation Programing. *J Cardiopulm Rehabil Prev*. 2019;39(3):138-145. doi:10.1097/HCR.0000000000000402.

47. Eccles MP, Armstrong D, Baker R, et al. An implementation research agenda. *Implement Sci*. 2009;4:18. Published 2009 Apr 7. doi:10.1186/1748-5908-4-18.

Contributors: CMC led the study conceptualisation, development of intervention content and writing of the protocol. BK, SH, NM contributed to the study design, implementation methods and refinement of the study protocol. All authors edited the manuscript.

Funding: This work was supported by Actelion Pharmaceutical Company. The funding body had no role in the study design and data collection, analysis and interpretation of data.

Table 1: Study outcome measures and time points

	Timepoint		
Assessments	**Baseline (T1)**	**Post-Intervention (T2)**	**Follow-up (T3)**
Written informed consent & eligibility	X		
Demographics	X		
Medical history	X		
WHO functional class	X	X	X
Concomitant medication	X	X	X
Adverse events	X	X	X
Exercise capacity (6-MWT), Borg Dyspnea Index	X	X	X
Muscle strength (Sit to Stand)	X	X	X
Physical activity (ActivPAL Micro)	X	X	X
Quality of life (CAMPHOR & SF-36)	X	X	X
Fear of exercise (Tampa Scale)	X	X	X
Psychological constructs	X	X	X
Intervention debrief questionnaires/ semi-structed interviews		X	X

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(Page 1)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(Page 2)**
	2b	All items from the World Health Organization Trial Registration Data Set **(Page 2)**
Protocol version	3	Date and version identifier **(Page 2)**
Funding	4	Sources and types of financial, material, and other support **(Page 23)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (**Title page and Page 23)**
	5b	Name and contact information for the trial sponsor **(Page 23)**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **(Page 23**)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **(Page 23)**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **(Pages 3-5**)
	6b	Explanation for choice of comparators **(Page 7)**
Objectives	7	Specific objectives or hypotheses **(Page 5)**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **(Page 5)**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) (and list of countries where data will be collected. Reference to where list of study sites can be obtained **(Page 7)**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **(6)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(Page 7-11)**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (**N/A)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **(Page 8-10)**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **(Page 6)**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **(Page 5, & Page 11-15)**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **(table 1)**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **(Page 7)**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **(Page 6)**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. (To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(N/A)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are **(N/A)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(N/A)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(N/A)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(N/A)**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(Page 11-15)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **(Page 7)**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **(Page 16)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **(Page 16)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(Page 16)**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **(Page 16)**

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **(Page 16)**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **(N/A)**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **(Page 13)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **(Page 16)**

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **(Page 2)**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **(Page 16)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **(Page 7)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **(N/A)**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **(Page 16)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(Page 23)**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **(Page 23)**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(N/A)**

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **(Page 2)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(Page 23)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **(Page 2)**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **(Appendix A)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(N/A)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The Pulmonary Hypertension And Home-Based (PHAHB) Exercise Intervention: Protocol for a Feasibility Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045460.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Feb-2021
Complete List of Authors:	McCormack, Ciara; Dublin City University, School of Health and Human Performance Kehoe, Brona; Waterford Institute of Technology, Department of Sport & Exercise Science Hardcastle, Sarah; Dublin City University, School of Health and Human Performance; University of Notre Dame, Fremantle, Western Australia, Institute for Health Research McCaffrey, Noel; ExWell Medical McCarren, Andrew; Insight Centre for Data Analytics, Dublin City University, Dublin, Ireland Gaine, Sean; Mater Misericordiae University Hospital, Respiratory Department McCullagh, Brian; Mater Misericordiae University Hospital, Respiratory Department Moyna, Niall; Dublin City University, School of Health & Human performance
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Respiratory medicine, Sports and exercise medicine, Rehabilitation medicine
Keywords:	REHABILITATION MEDICINE, SPORTS MEDICINE, Respiratory physiology < THORACIC MEDICINE, Rehabilitation medicine < INTERNAL MEDICINE

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PHAHB Intervention Protocol

The Pulmonary Hypertension And Home-Based (PHAHB) Exercise Intervention: Protocol for a Feasibility Study

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PHAHB Intervention Protocol

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Word Count: 3998

ABSTRACT

Introduction: Novel therapies for pulmonary hypertension (PH) have improved survival and slowed disease progression. However, patients still present with symptoms of exertional dyspnoea and fatigue, which impacts their ability to perform activities of daily living, reduces exercise tolerance and impairs their quality of life (QoL). Exercise training has shown to be safe and effective at enhancing QoL and physical function in PH patients, yet it remains an under-utilized adjunct therapy. Most exercise training for PH patients has been offered through hospital-based programmes. Home-based exercise programmes provide an alternative model that has the potential to increase the availability and accessibility of exercise training as an adjunct therapy in PH. The purpose of this study is to investigate the feasibility, acceptability, utility and safety of a novel remotely supervised home-based PH exercise programme.

Methods: Single arm intervention with a pre/post comparisons design and a follow up maintenance phase will be employed. Eligible participants (n= 25) will be recruited from the Mater Misericordiae University Hospital PH Unit. Participants will undergo a 10-week home-based exercise program, with induction training, support materials, telecommunication support and health coaching sessions followed by a 10-week maintenance phase. The primary outcomes are feasibility, acceptability, utility and safety of the intervention. Secondary outcomes will include the impact of the intervention on exercise capacity, physical activity, strength, health-related quality of life and exercise self-efficacy. **Ethics and dissemination:** Ethics approval has been obtained from the Mater Misericordiae Institutional Review Board REF:1/378/2032 and Dublin City University Research Ethics DCUREC/2018/246. A manuscript of the results will be submitted to a peer-reviewed journal and results will be presented at conferences, community and consumer forums and hospital research conferences. Trial Registration: ISRCTN Registry: ISRCTN83783446.Protocol version. 2.0.

Keywords: Pulmonary Hypertension, exercise rehabilitation, physical activity, exercise training, home-based, remote delivery, wearable technology, health coaching.

Strengths and limitations of this study

- This is the first study to assess the feasibility, utility, safety and acceptability of a novel distance-based exercise intervention for PH patients

- The intervention is pragmatic and scalable and could be integrated into existing healthcare pathways.
- As PH is a rare disease with a small population size within Ireland, there is a lack of a usual care control group which is a limitation of the study.

PHAHB Intervention Protocol

INTRODUCTION

Despite earlier diagnosis and improved pharmaceutical therapies, many PH participants continue to experience exertional symptoms of dyspnoea and fatigue, which leads to a reduction in functional capacity and in turn, quality of life (QoL). Consequently, there is greater recognition for a more holistic approach to PH treatment beyond pharmacological therapies[1].

Exercise rehabilitation and physical activity (PA) interventions have continuously demonstrated effectiveness as adjuvant therapies for improving exercise capacity and QoL in a spectrum of cardio-pulmonary disorders[2-5]. Although research investigating exercise in PH is an emerging field of study, the body of evidence regarding its efficacy continues to grow. Recent systematic reviews and meta-analyses have reported improvements in exercise capacity and QoL in PH [6-11], which has prompted a renewed focus on exercise training and pulmonary rehabilitation for PH patients.

In the 2015, the European Society of Cardiology /European Respiratory Society published guidelines for the diagnosis and treatment of pulmonary hypertension, it was recommended that exercise training should be implemented by specialist PH centres as an adjunct to medical therapy for stable PH participants [12]. Currently, the optimal mode, intensity, and duration of exercise training, and the characteristics of participants most likely to benefit from exercise training are poorly understood [13]. To date, the centre-based Hiedelberg rehabilitation program remains the gold standard exercise program in PH. It involves an intensive 3-week in-patient induction phase, with a continued multimodality,

monitored outpatient period [14]. Despite improvements in exercise capacity, muscle function, QoL and pulmonary haemodynamics, the initial in-patient phase is resource intensive to operate and roll out [15].

An alternative and pragmatic approach, found to be as effective as a supervised exercise programme in cardiac rehabilitation, is a home-based model of delivery [16]. Home-based interventions also provide solutions to common barriers to participation in centre-based programs such as access and transport issues, and are less expensive [17]. Further, patient populations express a preference for unsupervised, self-paced, low-moderate intensity PA, specifically walking [18-19]. Through the use of telehealth, distance-based programmes could potentially offer an alternative mode of delivery for exercise training to increase adherence, availability and affordability for PH patients.

Although the few studies examining the beneficial effects of home-based exercise training in PH are promising [20-21] none included strategies to maximise adherence. An evidence-based approach to implement lifestyle changes requires the implementation of health behaviour change strategies grounded in behaviour change theory [22]. Evidence-based behaviour change techniques (BCT's) can be used to improve intervention effectiveness [23]. For example, the combination of the following BCT's: self-monitoring; goal setting; providing feedback on performance; and, review of behaviour goals, is associated with increased intervention effectiveness in PA interventions [24]. Interventions that meet the support needs and offer opportunities for self-monitoring have been found to be effective for improving PA in other chronic disease groups[25]. Wearable technology holds great potential as an easy to

use, low cost self-monitoring tool with continuous feedback [26] and are perceived as acceptable and useful for individuals with chronic diseases [27]. Through the use of telehealth, distance-based programmes could potentially offer an alternative mode of delivery for exercise training to increase adherence, availability and affordability for PH patients. The aim of this study is to assess the feasibility, acceptability, utility and safety of a novel home-based exercise training programme for PH patients.

METHODS AND ANALYSIS

Study Design

The study will employ a single group pre-post-intervention design with a follow up maintenance phase. The purpose of the maintenance phase is to assess if the intervention facilitates the adoption of independent exercise in participants when formal support is removed. The study will adhere to the Standard Protocol Items: Recommendations for Interventional Trials Reporting Template (SPIRIT)[28]. Participants will complete assessments at baseline (T1), after the 10-week intervention (T2) and at 20-weeks follow up (T3).

Eligibility Criteria

Inclusion criteria are male or female > 18 years, with a diagnosis of PH (WHO Groups I and IV) by right heart catheterisation showing baseline mean pulmonary arterial pressure ≥25 mm Hg, pulmonary vascular resistance ≥240 dyne s cm^{-5}, pulmonary capillary wedge pressure ≤15 mmHg and receiving optimized conventional PH therapy. Participants must be clinically stable with no medication changes in the 2 months prior to enrolment.

Exclusion criteria include PH of any cause other than outlined in the inclusion criteria such as PH from left heart disease or lung disease/hypoxia (WHO Groups II and III) , pregnancy, signs of right heart decompensation, acute infection and pyrexia, change in disease-targeted therapy within the last 2-months, scheduled to receive an investigational drug during the course of the study, FEV1/FVC <0.5, total lung capacity <70% of the normal value, active liver disease, porphyria, elevations of serum transaminases >3 x upper limit of normal (ULN), bilirubin >1.5 x ULN, haemoglobin concentration <75% of the lower limit of normal, systolic blood pressure <85 mmHg, active myocarditis, unstable angina pectoris, exercise induced ventricular arrhythmias, decompensated heart failure, hypertrophic obstructive cardiomyopathy or impaired left ventricular function.

Participant Recruitment

Participants will be recruited from the Pulmonary Hypertension Unit at the Mater Misericordiae University Hospital, Dublin, Ireland. Eligible participants will be invited to participate during their routine 3-6 month clinic visit. They will be given a verbal explanation of the study and provided with an information sheet by their PH Specialist (SG/BMC) or a member of their clinical team. After receiving the information, potential participants will have the option to speak on the day to a member of the research team or to receive a follow-up phone call within 1-2 days. Participants will have the opportunity to ask questions and will have time to consider their participation. Written consent will be obtained by mail.

Sample Size

Pilot study sample size typically ranges from 24 to 50[29-31]. We estimate a target sample size of 25 to be sufficient for this feasibility study [30].

Primary Outcomes

Feasibility: Assessed by participant recruitment (enrolment as a proportion of eligible participants) and retention (proportion that completed all assessments); (ii) engagement with the intervention measured according to attendance at induction sessions and health coaching sessions and adherence, defined as the percentage of home-based exercise sessions recorded by participants who complete the intervention assessed via log books and weekly calls) and (iii) by examining delivery as intended (as per protocol) and health coach perceptions concerning how patients' received the intervention components. This will be captured immediately after each session in order to keep a record of how delivery was received in relation to the planned delivery (e.g., if a participants required extra time or further support following the induction training session).

Acceptability and utility: Assessed through self-report questionnaires completed at T2 and interviews. The questionnaire will assess participant perceptions of intervention appropriateness, effectiveness, quality, accessibility/usability, intrusiveness, and overall enjoyment and attitude towards the intervention. Semi-structured interviews with a sub-set of participants (~ n=12) will be conducted within 2-weeks of completing the T2 assessment. The interviews will further explore acceptability and utility of the intervention including perceptions concerning exercise prescription, adherence to different components of the intervention, in addition to the facilitating and hindering factors to participation. Participants

will also be asked to offer suggestions for improvement and implementation. Interviews will be conducted via telephone or online platforms (i.e., Zoom) and will be audio-recorded and transcribed.

Safety: Participants will be instructed to inform researchers immediately of any adverse advent. In addition, participants will be questioned about adverse events directly related to participation in the exercise intervention during a bi-weekly support call.

Secondary Outcomes

Exercise capacity: Assessed using the 6-min walk test (6MWT). The test will be administered according to the European Respiratory Society Guidelines [32] and will be conducted at home using detailed step-by-step video and written instructions and remotely supervised via phone/teleconferencing by a researcher (CMC). A family member/friend will assist with conducting the test, including measuring blood pressure and SpO_2 with guidance from the researcher before and after the test. Subjective symptoms (RPE and dyspnoea- Borg Dyspnoea Scale 0-10) will be recorded before and after the test. The Frontier X chest worn monitor will be worn during the test to provide real-time feedback. The assistant will ask the participant to call out their SpO_2 and HR at each minute of the test. Standard encouragement will be delivered by the assistant, with researcher prompting, if needed.

Muscular strength*:* Lower body muscle strength will be assessed using the 30-sec sit-to-stand test (STS) from a seat height of 40-45 cm. The STS is a commonly used field-based measure

of functional lower limb muscle strength, particularly in clinical and elderly populations. The test will be conducted in each participant's home via teleconference. A researcher (CMC) will provide a demonstration, time the test, and count the repetitions. Each participant will perform two trials separated by 5-min, with the best score being recorded.

Physical activity behaviour: ActivPAL^3 micro activity monitors (PAL Technologies Ltd. Glasgow, Scotland) will be used to assess free living activity behaviour. The device samples at 20Hz for 15-sec epochs and measures bodily accelerations using triaxial accelerometer. An inbuilt inclinometer measures thigh inclination. Proprietary algorithms classifies activities into sitting/lying time, standing time, stepping time, step count and activity counts. Participants will be mailed the accelerometer together with detailed wear instruction and provided with a prepaid postage envelope to return the device. They will be instructed to wear the device on the anterior aspect of their right thigh continuously for 7-days, except during water immersion activities (i.e., swimming and bathing). The ActivPAL is a valid and reliable measure of activity and sedentary behaviour [33-34].

Psychological Outcomes and Mediators

Quality of life: The Medical Outcomes Study Short-Form 36-Item Survey (SF-36) is a well-validated, generic questionnaire [35] consisting of physical functioning, physical role functioning, bodily pain, and general health and the four mental subscales of vitality, social functioning, emotional role functioning and mental health. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)[36] was designed as a disease-specific health-

related QoL measure for PH patients. It is widely used as a clinical and research tool in PH. It is made up of three dimensions which assess symptoms (25 items) functioning (15 items) and quality life (25 items).

Fatigue: The Fatigue Severity Scale (FSS)[37] measures the patient's perception of the influence of fatigue on physical and social functioning through responses to nine different physical and social functioning situations. The FSS is a valid tool for assessing fatigue across various health conditions[38].

Self-regulatory self-efficacy for exercise: Assessed using a modified 11-item scale[39-40], which provide information on task, scheduling and recovery self-efficacy. Questions begin with the stem "*How confident are you that you can…*" and include items such as "*plan exercise sessions that will be at least moderately difficult (e.g. have you breathing a little hard, your heart rate increases)?*". Participants rate their confidence on a 0-10 Likert scale, with a higher score indicating greater self-efficacy for exercise (Cronbach alpha, α =.951).

Intentions to exercise: Two items will measure intention to engage in moderate-intensity physical activity for 150-min/week in the next 10-weeks, based on previously established measures[41].

Outcome expectations: Ten-items will assess outcome expectations. Five-items are derived from the validated exercise pros subscale [42] and 5-items to assess outcomes related to common symptoms reported in PH, 'such as breathlessness' [43].

Social support: Social support for exercise from family and friends scale[44] uses a 20-item scale to assess support from family and friends respectively. Responses will be recorded on a

Likert scale of 1-5, with higher scores representing greater social support. (Cronbach alpha, family α =.926, friends α =921).

Outcome assessments will take place at baseline (T1), after the 10-week intervention (T2) and at 20-weeks follow up (T3). Semi-structured interviews will be conducted at T2 to assess patient's perspective on program acceptability and feasibility and at T3 to assess the follow up phase. Table 1 outlines the timeline of the assessments.

Procedure

Participants will complete all assessments, induction training and exercise training in their own home and will maintain in contact with researchers via telecommunication technologies (phone, videoconferencing and email). Following consent, a baseline assessment will be conducted (see Table 1) and participants will be provided with an accelerometer to record their activity for the following week, along with a prepaid postage envelope to return device. The assessment procedure will be repeated at T2 (10-weeks) and T3 (20-weeks).

Participants will be provided with a home exercise bike (NordicTrack GX 2.7U), a wearable tracker watch (The Fibit Charge 3), pulse oximeter (SafeHeart SpO_2 monitor), real time single lead ECG/HR/respiratory rate monitor (Frontier X), blood pressure monitor (Beurer BM44), a TheraBand, exercise manual, exercise diary and access to online videos. The exercise manual was partly based on the design of previous PA intervention in chronic disease - PPARCS [26] and WATTAP [45] trials and also our formative research with PH patients. The formative research highlighted the lack of understanding of the benefits of exercise, the importance of self-regulation strategies to support motivation and exercise engagement and the desire for

visual picture and instruction of exercise. Concerns of breathlessness and energy management were also evident in interviews with PH patients and integrated into the exercise manual. The manual offers a comprehensive, patient-friendly resource detailing; 1) general information about the study; 2) useful links and contacts; 3) background information on PH; 4) education regarding exercise safety and the benefits of physical activity; 5) workbook style sections on motivation, goal setting, overcoming barriers and psychosocial support; 6) managing breathlessness; 7) exercise intensity and limits; 8) guided home exercises with written and visual details and advice on progression; and 9) advice on pacing and energy conservation. Participants will receive video clips of a qualified exercise specialist performing the exercises. Participants will be encouraged to refer to the video to ensure adherence to correct technique. Online videos will provide a visual demonstration of each exercise. Participants will be provided with an exercise diary as a tool to record their activity and effort. BCTs will be integrated in the intervention through wearable technology devices, the use of print and visual materials and health coaching and support calls.

The 10-week intervention consists of the following components: Three 60-90 min induction sessions (week 0 and 1), up to five 30-min support health coaching sessions (at week 2, 3, 5, 7, 9) and 3-5 weekly home-based exercise sessions. The intervention will end prior to T2 assessment. Participants will continue to have access to the exercise manual, bike and Fitbit during the maintenance phase.

Induction Training

Induction training (1:1), via video conferencing, is a key component to ensure patients are confident to exercise at home and understand the appropriate exercise intensity and how to exercise safely. Participants will be encouraged to involve a family member, friend or carer in the induction training. The sessions will focus on the following topics:

Session 1 - Introduction; Education on PH and benefits of PA for PH. Familiarisation with intervention materials/equipment and self-monitoring.

Session 2 - Exercise Safety and Exercise Demonstration; The session will focus on recognizing exercise limits, warning signs, and managing exercise intensity. Visual demonstrations of breathing techniques and aerobic, strength, and respiratory training will be provided, with the opportunity for behavioural practice during the session to check technique and instil confidence.

Session 3 - Recap; Exercise demonstrations and key safety points will be reviewed. Any issues regarding intervention materials/equipment will be addressed and participant goals will be reviewed, alongside additional tips for family/friend support and motivation.

Health Coaching Sessions

The health coaching sessions (via videoconferencing) will use BCTs to foster exercise adherence, motivate and provide support. Over the 5 sessions the topics will include; benefits of exercise, goal setting, action planning , self-monitoring, identification and management of barriers to exercise, problem solving and feedback on behaviour, with the option for

participants to complete formal paperwork in the intervention manual. If required, additional support will be available outside of scheduled sessions.

Participants will be encouraged to wear the Fitbit Charge 3 daily during the intervention. The Fitbit data will be used to guide individually tailored goals, assess adherence to exercise and overall daily PA and as tool to provide feedback to the researcher and participants.

Exercise Program

Participants will complete a 10-week individualised, home-based exercise programme. The programme will be prescribed using the FITT principle (Frequency, Intensity, Time and Type) and will employ a multimodal approach that integrates aerobic, resistance and respiratory training. The goals for each component are outlined in the sections below. These are aspirational goals that may not be realistic for all participants. Exercise prescription will be individualized based on their baseline PA levels, 6-min walk test distance (6MWD) and physical capabilities. The modified Borg rating of perceived exertion (RPE) scale[46] will be used to help prescribe exercise intensity. The RPE scale is a psychophysiological measurement that translates physical stimuli to a psychological construct of perceived exertion and has been validated in other clinical groups[47].Participants will aim to achieve an RPE of 3 (moderate) initially. Based on individual progress an RPE of 4 (somewhat hard) may be advised for some participants. The exercise program will include:

Aerobic Training; Participants will initially aim will be to undertake a minimum of 10-min of structured aerobic exercise involving walking, cycling or a combination on ≥3 d/week. Participants will be allowed to perform this exercise in a single bout, or accumulate it in bouts

of at least 5-min in duration. The duration will be progressively increased, with the goal of accumulating ≥30 min on ≥5 d/week.

Resistance Training; Participants will initially undertake resistance training on 2 d/week, involving a single set of 6-8 repetitions of upper and lower extremity and whole body exercises. Training volume will progressively increase with the goal of completing 2-3 sets of 10-12 reps of 4-6 exercises on three non-consecutive days. Participants will use pursed lip breathing to help airways stay open during exhalation. Bodyweight resistance will be used initially and based on individual ability, TheraBand's, water bottles or light dumbbells will be introduced.

Respiratory Training; Participants will initially perform 10-min of respiratory training at least twice a week, involving a combination of stretching, breathing techniques (e.g., pursed lip, diaphragmic and slow breathing), and respiratory muscle strengthening exercises. Training volume will progressively increase with the goal of completing 15/20 min of accumulated respiratory training on ≥3 d/week. Participants can progress to use a TheraBand to complete respiratory training.

Participants will wear a Frontier X device (receiver attached to a strap place around the chest) during exercise sessions. The first 2-weeks will be monitored by researchers and then periodically monitored. This will allow access to real time ECG, heart rate (HR), respiratory rate and cadence. Oxygen saturation will be monitored and participants will be instructed to stop exercising if the SpO_2 value drops below 88%, as per guidelines[48]. Participants will document any adverse events and report to the research team immediately.

Data Management

The trial will be overseen by the trial management group, consisting the principal investigator, the trial-coordinator and health coach. They will meet every 4-weeks and will oversee all aspects of the conduct of the trial including performing safety oversight activities. Individual data will be de-identified, coded and entered. Each participant will be assigned a personal identification code (PIC), which will be used on all case report forms and in all electronic databases. Prior to any statistical analysis, all variables will be checked for missing, impossible and improbable values. Impossible and improbable values will be defined by clinical opinion and will include values that are outside three standard deviations of the mean value.

Statistical Analysis

Statistical analysis of quantitative data will be performed using SPSS Version 24. Prior to statistical analysis, the Shapiro-Wilks test will be applied to check for normality. Continuous variables will be reported as mean (range), mean (standard deviation) or median and inter-quartile range, depending on distribution, and categorical variables as frequency (%). Descriptive analyses will be undertaken to summarise participant characteristics and the quantitative data of the intervention feasibility, acceptability and utility. Qualitative data from post-trial interviews and researcher field notes will be analyzed using inductive thematic analysis to identity common themes[49]. A linear mixed model analysis (MMA) will be used to examine the impact of time in this study . A MMA is a suitable approach to modelling time series data which contains repeated measures [50]. The MMA does not require complete data

sets and does not exclude participants with missing data [51]. Furthermore, MMA has less stringent assumptions than other repeated measures models (such as analysis of variance) and also exhibits increased power to detect treatment effects. The data will adjust for confounding variables, such as age, baseline line fitness, gender and PH group.

Patient and Public Involvement

Formative qualitative research took place with PH patients during intervention development stages. Semi-structured phone interviews (N=19) were conducted providing insight into patient barriers and motivators to PA, and exercise preferences. The findings fed into the design of the intervention along with PH clinician input. A patient representative provided opinions on the study protocol, patient-facing documentation (e.g., Participants Information Sheet) and intervention material (e.g., exercise manual) to ensure it was patient friendly.

Discussion

The promise of exercise training in the treatment and management of PH has gained significant interest over the past two decades. The observed positive effects of exercise programs on patients' exercise capacity, functional capacity and QoL[52] make a strong argument for the inclusion of exercise as an adjunctive therapy for stable PH patients[53]. Considering that structured and resource-intensive hospital-based exercise programs are unlikely to be scalable, it is an opportune time to assess the efficacy, safety and impact of home-based programs as an alternative mode of delivery for PH patients.

A home-based exercise program may eliminate many of the barriers associated with in-patients or out-patients setting such as transportation issues, location, long wait periods for availability and accessibility for patients. A recent review of exercise interventions in PH by Ozemek and colleagues [53] highlighted the need for inclusion of home exercise programs to allow patients achieve the optimal 5 to 6 days of structured exercise.

This study will utilise a remote delivery for exercise training with the use of telehealth methods, wearable technology, performance feedback and behavioural support to deliver and monitor the intervention. The aim is to eliminate the burden on patients to attend several times per week to an outpatient clinic, accommodate resource availability, make the program achievable in a 'real world' setting and improve the reach beyond the traditional healthcare facilities. The follow-up post intervention (T3) phase will provide insight into whether behavioural support is necessary in order for PH patients to remain physically active. Furthermore, it will allow us to assess resource needs in future home-based exercise programmes such as the provision of specific exercise equipment and the use of ubiquitous, low cost devices to monitor activity and safety (e.g. bike, wearable activity tracker). PH is considered a rare disease and with support centralised, remote services, which include assessment of patient progress are required. Remote assessment of outcomes may remove threats to external validity and evaluation of the feasibility of such assessment will address the goals of implementation science to close the research-to-practice gap and support implementation and scale up of evidence-based interventions[54].

To our knowledge, this will be the first study to employ the use of evidence-based BCTs to examine the feasibility, utility and efficacy of a remote home-based approach to exercise

training for medically stable PH patients. The secondary aims of this study are to evaluate whether this approach leads to improvement in selected indices of physical and psychological health.

PH is a rare, debilitating condition with most clinics centralized and limited community resources available. Telehealth holds significant potential to meet the growing support for exercise training to be included as an adjunct therapy by offering remote training and support, which is key to long-term implementation of exercise training for the PH population. It provides a service that is more accessible and may potentially offer a more affordable enhanced level of care. Our current understanding is limited concerning the acceptability, feasibility and utility of a home-program for stable PH patients. This study will help gain a valuable insight into this gap in knowledge.

Ethics and dissemination: Ethics approval has been obtained from the Mater Misericordiae Institutional Review Board REF:1/378/2032 and Dublin City University Research Ethics DCUREC/2018/246. A manuscript of the results will be submitted to a peer-reviewed journal and results will be presented at conferences, community and consumer forums and hospital research conferences. Trial Registration: ISRCTN Registry: ISRCTN83783446.Protocol version. 2.0

References

1. Gaine S, McLaughlin V. Pulmonary arterial hypertension: tailoring treatment to risk in the current era. *Eur Respir Rev*. 2017;26(146):170095. doi:10.1183/16000617.0095-2017.
2. Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev*. 2014;2014(4):CD003331. doi:10.1002/14651858.CD003331.pub4.
3. Buys R, Avila A, Cornelissen VA. Exercise training improves physical fitness in patients with pulmonary arterial hypertension: a systematic review and meta-analysis of controlled trials. *BMC Pulm Med*. 2015;15:40. doi:10.1186/s12890-015-0031-1.
4. Langer D, Hendriks E, Burtin C, et al. A clinical practice guideline for physiotherapists treating patients with chronic obstructive pulmonary disease based on a systematic review of available evidence. *Clin Rehabil*. 2009;23(5):445-462. doi:10.1177/0269215509103507.
5. Vanhees L, Rauch B, Piepoli M, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular disease (Part III). *Eur J Prev Cardiol*. 2012;19(6):1333-1356. doi:10.1177/2047487312437063.
6. Morris NR, Kermeen FD, Holland AE. Exercise-based rehabilitation programmes for pulmonary hypertension. *Cochrane Database Syst Rev*. 2017;1(1):CD011285.. doi:10.1002/14651858.CD011285.pub2.
7. Dalla Vecchia LA, Bussotti M. Exercise training in pulmonary arterial hypertension. *J Thorac Dis*. 2018;10(1):508-521. doi:10.21037/jtd.2018.01.90.
8. Babu AS, Padmakumar R, Maiya AG, Mohapatra AK, et al . Effects of Exercise Training on Exercise Capacity in Pulmonary Arterial Hypertension: A Systematic

Review of Clinical Trials. *Heart Lung Circ*. 2016;25(4):333-341. doi:10.1016/j.hlc.2015.10.01.

9. Yuan P, Yuan XT, Sun XY, et al. Exercise training for pulmonary hypertension: a systematic review and meta-analysis. *Int J Cardiol*. 2015;178:142-146. doi:10.1016/j.ijcard.2014.10.161.
10. Pandey A, Garg S, Khunger M, et al. Efficacy and Safety of Exercise Training in Chronic Pulmonary Hypertension: Systematic Review and Meta-Analysis. *Circ Heart Fail*. 2015;8(6):1032-1043. doi:10.1161/CIRCHEARTFAILURE.115.00.
11. Benjamin N, Marra AM, Eichstaedt C, Grünig E. Exercise Training and Rehabilitation in Pulmonary Hypertension. *Heart Fail Clin*. 2018;14(3):425-430. doi:10.1016/j.hfc.2018.03.008.
12. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). *Eur Respir J*. 2015;46(4):903-975. doi:10.1183/13993003.01032-2015.
13. Galiè N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D60-D72. doi:10.1016/j.jacc.2013.10.031.
14. Mereles D, Ehlken N, Kreuscher S, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation*. 2006;114(14):1482-1489. doi:10.1161/CIRCULATIONAHA.106.618397.
15. Babu AS, Padmakumar R, Maiya AG, et al. Letter by Babu et al Regarding Article, "Advances in Therapeutic Interventions for Patients With Pulmonary Arterial

Hypertension". *Circulation*. 2015;132(12):e153. doi: 10.1161/CIRCULATIONAHA.114.014978.

16. Buckingham SA, Taylor RS, Jolly K, et al. Home-based versus centre-based cardiac rehabilitation: abridged Cochrane systematic review and meta-analysis. *Open Heart*. 2016;3(2):e000463. doi:10.1136/openhrt-2016-000463.
17. Hardcastle SJ, & Cohen PA. Effective physical activity promotion to survivors of cancer is likely to be home based and to require oncologist participation. *J Clin Oncol* 2017;35:3635-3637. doi: 10.1200/JCO.2017.74.6032.
18. Maxwell-Smith C, Zeps N, Hagger MS, et al. Barriers to physical activity participation in colorectal cancer survivors at high risk of cardiovascular disease. *Psycho-oncology* 2017;26:808-814. doi:10.1002/pon.4234.
19. Artinian NT, Fletcher GF, Mozaffarian D, et al. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122(4):406-441. doi:10.1161/CIR.0b013e3181e8edf1.
20. Karapolat H, Çınar ME, Tanıgör G, et al. Effects of cardiopulmonary rehabilitation on pulmonary arterial hypertension: A prospective, randomized study. *Turk J Phys Med Rehabil*. 2019;65(3):278-286. doi: 10.5606/tftrd.2019.2758.
21. Babu AS, Padmakumar R, Nayak K,et al. Effects of home-based exercise training on functional outcomes and quality of life in patients with pulmonary hypertension: A randomized clinical trial. *Indian Heart J.* 2019;71(2):161-165. doi:10.1016/j.ihj.2019.03.002
22. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci*. 2011;6:42. Published 2011 Apr 23. doi:10.1186/1748-5908-6-42.

23. Samdal GB, Eide GE, Barth T, Williams G, Meland E. Effective behaviour change techniques for physical activity and healthy eating in overweight and obese adults; systematic review and meta-regression analyses. *Int J Behav Nutr Phys Act*. 2017;14(1):42. Published 2017 Mar 28. doi:10.1186/s12966-017-0494-y.

24. Artinian NT, Fletcher GF, Mozaffarian D, et al. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122(4):406-441. doi:10.1161/CIR.0b013e3181e8edf1.

25. Lahart I, Metsios G, Nevill AM, et al. Randomised controlled trial of a home-based physical activity intervention in breast cancer survivors. *BMC Cancer* 2016*;* 16:234-247. doi: 10.1186/s12885-016-2258-5.

26. Hardcastle SJ, Hince D, Jiménez-Castuera R*, et al.,* Promoting physical activity in regional and remote cancer survivors (PPARCS) using wearables and health coaching: randomised controlled trial protocol *BMJOpen* 2019;**9:**e028369. doi: 10.1136/bmjopen-2018-028369.

27. Mercer K, Giangregorio L, Schneider E, et al. Acceptance of commercially available wearable activity trackers among adults aged over 50 and with chronic illness: a mixed-methods evaluation. *JMIR Mhealth Uhealth* 2016;4: e7. doi:10.2196/mhealth.4225.

28. Chan A, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: Defining standard protocol items for clinical trials. *Annals of Internal Medicine* 2013*;*158:200-207.

29. Browne RH. On the use of a pilot sample for sample size determination. *Stat Med*. 1995;14(17):1933-1940. doi:10.1002/sim.4780141709.

30. Julious SA: Sample size of 12 per group rule of thumb for a pilot study. *Pharm Stat*. 2005, 4 (4): 287-291. 10.1002/pst.185.

31. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *J Clin Epidemiol*. 2012;65(3):301-308. doi:10.1016/j.jclinepi.2011.07.011.

32. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J*. 2014;44(6):1428-1446. doi:10.1183/09031936.00150314.

33. Harrington DM, Welk GJ, Donnelly AE. Validation of MET estimates and step measurement using the ActivPAL physical activity logger. *J Sports Sci*. 2011;29(6):627-633. doi:10.1080/02640414.2010.549499.

34. Kozey-Keadle S, Libertine A, Lyden K, et al. Validation of wearable monitors for assessing sedentary behavior. *Med Sci Sports Exerc*. 2011;43(8):1561-1567. doi:10.1249/MSS.0b013e31820ce174.

35. Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.

36. McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. *Qual Life Res*. 2006;15(1):103-115. doi:10.1007/s11136-005-3513-4.

37. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The Fatigue Severity Scale: Application to Patients With Multiple Sclerosis and Systemic Lupus Erythematosus. *Arch Neurol.* 1989;46(10):1121–1123. doi:10.1001/archneur.1989.00520460115022.

38. Schentag CT, Cichon J, MacKinnon A, Gladman DD, Urowitz MB. Validation and normative data for the 0–10 point scale version of the fatigue severity scale (FSS) [abstract]. *Arthritis Rheum* 2000; **43** Suppl: S177.

39. Luszczynska, A., & Sutton, S. (2006). Physical activity after cardiac rehabilitation: Evidence that different types of self-efficacy are important in maintainers and relapsers. *Rehabilitation Psychology, 51*(4), 314–321.doi. 10.1037/0090-5550.51.4.314.

40. Shields CA, Brawley LR. Preferring proxy-agency: impact on self-efficacy for exercise. J Health Psychol. 2006 Nov;11(6):904-14. doi: 10.1177/1359105306069092. PMID: 17035262.

41. Ajzen I, Brown TC, & Carvajal F. Explaining the discrepancy between intentions and actions: The case of hypothetical bias in contingent valuation. *Pers Soc Psychol Bull* 2004;30:1108-1121. doi:10.1177/0146167204264079.

42. Plotnikoff RC, Blanchard CM, Hotz SB, et al. Validation of the decisional balance scales in the exercise domain from the transtheoretical model: A longitudinal test. *Meas Phys Educ Exerc Sci* 2001;5:191-206. doi:10.1207/S15327841MPEE0504_01.

43. Yorke J, Deaton C, Campbell M, et al. Symptom severity and its effect on health-related quality of life over time in patients with pulmonary hypertension: a multisite longitudinal cohort study. *BMJ Open Respiratory Research.* 2018;**5:**e000263. doi: 10.1136/bmjresp-2017-000263.

44. Sallis JF, Grossman RM, Pinski RB, Patterson TL, Nader PR. The development of scales to measure social support for diet and exercise behaviors. *Prev Med.* 1987;16(6):825-836. doi:10.1016/0091-7435(87)90022-3.

45. Maxwell-Smith C, Cohen PA, Platell C, et al. Wearable Activity Technology And Action-Planning (WATAAP) to promote physical activity in cancer survivors:

Randomised controlled trial protocol. *Int J Clin Health Psychol*. 2018;18(2):124-132. doi:10.1016/j.ijchp.2018.03.003.

46. Foster C, Florhaug JA, Franklin J, et al. A new approach to monitoring exercise training. *J Strength Cond Res*. 2001;15(1):109-115.
47. Rosales W, Cofré C, Alejandra C, et al. Validación de la escala de Borg en personas con diabetes mellitus tipo 2 [Validation of the Borg scale in participants with type 2 diabetes mellitus]. *Rev Med Chil*. 2016;144(9):1159-1163. doi:10.4067/S0034-98872016000900009.
48. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188(8):e13-e64. doi:10.1164/rccm.201309-1634ST.
49. Braun V, & Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006;3:2, 77-101. doi: 10.1191/1478088706qp063oa.
50. Haapalainen E, Laurinen P, Siirtola P, et al. Exercise energy expenditure estimation based on acceleration data using the linear mixed model. *IEEE International Conference on Information Reuse and Integration*. 2008: 131–136
51. Armstrong R. A. Recommendations for analysis of repeated-measures designs: Testing and correcting for sphericity and use of manova and mixed model analysis. *Ophthalmic and Physiological Optics*. 2017: *37*(5), 585–593.
52. Dalla Vecchia LA, Bussotti M. Exercise training in pulmonary arterial hypertension. *J Thorac Dis*. 2018;10(1):508-521. doi:10.21037/jtd.2018.01.90.
53. Ozemek C, Berry MJ, Arena R. A Review of Exercise Interventions in Pulmonary Arterial Hypertension and Recommendations for Rehabilitation Programming. *J*

Cardiopulm Rehabil Prev. 2019;39(3):138-145. doi:10.1097/HCR.0000000000000402

54. Eccles MP, Armstrong D, Baker R, et al. An implementation research agenda. *Implement Sci*. 2009;4:18. Published 2009 Apr 7. doi:10.1186/1748-5908-4-18.

Contributors: CMC, BK, SJH, NMC, SG, BMC, and NM were involved in study conceptualisation, development of intervention content and writing of the protocol. AMC provided guidance on the statistical analysis. CMC led the writing of the manuscript and all authors edited and reviewed the manuscript.

Funding: This work was supported by Janssen Sciences Ireland UC. The funding body had no role in the study design and data collection, analysis and interpretation of data.

Competing interest statement: None declared.

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612 Table 1: Study outcome measures and time points

	Time		
Assessments	**Baseline (T1)**	**Post-Intervention (T2)**	**Follow-up (T3)**
Written informed consent & eligibility	X		
Demographics	X		
Medical history	X		
WHO functional class	X	X	X
Concomitant medication	X	X	X
Adverse events	X	X	X
Exercise capacity (6-MWT), Borg Dyspnea Index	X	X	X
Muscle strength (Sit to Stand)	X	X	X
Physical activity (ActivPAL Micro)	X	X	X
Quality of life (CAMPHOR & SF-36)	X	X	X

PHAHB Intervention Protocol

Psychological constructs	X	X	X
Intervention debrief questionnaires/ semi-structed interviews		X	X

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(Page 1)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(Page 3)**
	2b	All items from the World Health Organization Trial Registration Data Set **(Page 3)**
Protocol version	3	Date and version identifier **(Page 3)**
Funding	4	Sources and types of financial, material, and other support **(Page 29)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (**Title page and Page 29)**
	5b	Name and contact information for the trial sponsor **(Page 29)**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **(Page 29**)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **(Page 29)**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **(Pages 5-7**)
	6b	Explanation for choice of comparators **(Page 9)**
Objectives	7	Specific objectives or hypotheses **(Page 7)**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **(Page 7)**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) (and list of countries where data will be collected. Reference to where list of study sites can be obtained **(Page 8)**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **(7)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(Page 13-17)**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (**N/A)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **(Page 13-17)**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **(Page 8)**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **(Page 7 & 9-13)**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **(table 1)**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **(Page 9)**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **(Page 8)**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. (To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(N/A)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are **(N/A)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(N/A)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(N/A)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(N/A)**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(Page9-13)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **(Page 13)**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **(Page 18)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **(Page 18)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(Page 18)**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **(Page 18)**

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **(Page 18)**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **(N/A)**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **(Page 10)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **(Page 18)**

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **(Page 3)**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **(Page 18)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **(Page 8)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **(N/A)**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **(Page 18)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(Page 29)**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **(Page 18)**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(N/A)**

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **(Page 3)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(Page 29)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **(Page 3)**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **(Appendix A)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(N/A)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The Pulmonary Hypertension And Home-Based (PHAHB) Exercise Intervention: Protocol for a Feasibility Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045460.R2
Article Type:	Protocol
Date Submitted by the Author:	30-Mar-2021
Complete List of Authors:	McCormack, Ciara; Dublin City University, School of Health and Human Performance Kehoe, Brona; Waterford Institute of Technology, Department of Sport & Exercise Science Hardcastle, Sarah; Dublin City University, School of Health and Human Performance; University of Notre Dame, Fremantle, Western Australia, Institute for Health Research McCaffrey, Noel; ExWell Medical McCarren, Andrew; Insight Centre for Data Analytics, Dublin City University, Dublin, Ireland Gaine, Sean; Mater Misericordiae University Hospital, Respiratory Department McCullagh, Brian; Mater Misericordiae University Hospital, Respiratory Department Moyna, Niall; Dublin City University, School of Health & Human performance
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Respiratory medicine, Sports and exercise medicine, Rehabilitation medicine
Keywords:	REHABILITATION MEDICINE, SPORTS MEDICINE, Respiratory physiology < THORACIC MEDICINE, Rehabilitation medicine < INTERNAL MEDICINE

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PHAHB Intervention Feasibility Study Protocol

The Pulmonary Hypertension and Home-Based (PHAHB) Exercise Intervention: Protocol for a Feasibility Study

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PHAHB Intervention Feasibility Study Protocol

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Word Count: 4016

PHAHB Intervention Feasibility Study Protocol

ABSTRACT

Introduction: Novel therapies for pulmonary hypertension (PH) have improved survival and slowed disease progression. However, patients still present with symptoms of exertional dyspnoea and fatigue, which impacts their ability to perform activities of daily living, reduces exercise tolerance and impairs their quality of life (QoL). Exercise training has shown to be safe and effective at enhancing QoL and physical function in PH patients, yet it remains an under-utilized adjunct therapy. Most exercise training for PH patients has been offered through hospital-based programmes. Home-based exercise programmes provide an alternative model that has the potential to increase the availability and accessibility of exercise training as an adjunct therapy in PH. The purpose of this study is to investigate the feasibility, acceptability, utility and safety of a novel remotely supervised home-based PH exercise programme. **Methods:** Single arm intervention with a pre/post comparisons design and a follow up maintenance phase will be employed. Eligible participants (n= 25) will be recruited from the Mater Misericordiae University Hospital PH Unit. Participants will undergo a 10-week home-based exercise programme, with induction training, support materials, telecommunication support and health coaching sessions followed by a 10-week maintenance phase. The primary outcomes are feasibility, acceptability, utility and safety of the intervention. Secondary outcomes will include the impact of the intervention on exercise capacity, physical activity, strength, health-related quality of life and exercise self-efficacy. **Ethics and dissemination:** Ethics approval has been obtained from the Mater Misericordiae

Institutional Review Board REF:1/378/2032 and Dublin City University Research Ethics DCUREC/2018/246. A manuscript of the results will be submitted to a peer-reviewed journal and results will be presented at conferences, community and consumer forums and hospital research conferences. Trial Registration: ISRCTN Registry: ISRCTN83783446.Protocol version. 2.0.

Keywords: Pulmonary Hypertension, exercise rehabilitation, physical activity, exercise training, home-based, remote delivery, wearable technology, health coaching.

Strengths and limitations of this study

- This is the first study to assess the feasibility, utility, safety and acceptability of a novel distance-based exercise intervention for PH patients
- The intervention is pragmatic and scalable and could be integrated into existing healthcare pathways
- As PH is a rare disease with a small population size within Ireland, there is a lack of a usual care control group which is a limitation of the study

INTRODUCTION

Despite earlier diagnosis and improved pharmaceutical therapies, many PH participants continue to experience exertional symptoms of dyspnoea and fatigue, which leads to a reduction in functional capacity and in turn, QoL. Consequently, there is greater recognition for a more holistic approach to PH treatment beyond pharmacological therapies[1].

Exercise rehabilitation and physical activity (PA) interventions have continuously demonstrated effectiveness as adjuvant therapies for improving exercise capacity and QoL in a spectrum of cardio-pulmonary disorders[2-5]. Although research investigating exercise in PH is an emerging field of study, the body of evidence regarding its efficacy continues to grow. Recent systematic reviews and meta-analyses have reported improvements in exercise capacity and QoL in PH [6-11], which has prompted a renewed focus on exercise training and pulmonary rehabilitation for PH patients.

In the 2015, the European Society of Cardiology /European Respiratory Society recommended that exercise training should be implemented by specialist PH centres as an adjunct to medical therapy for stable PH participants [12]. Currently, the optimal mode, intensity, and duration of exercise training, and the characteristics of participants most likely to benefit from exercise training are poorly understood [13]. To date, the centre-based Heidelberg rehabilitation programme remains the gold standard exercise programme in PH. It involves an intensive 3-week in-patient induction phase, with a continued multimodality, monitored outpatient period [14]. Despite improvements in exercise capacity, muscle function,

QoL and pulmonary haemodynamics, the initial in-patient phase is resource intensive to operate and roll out [15].

An alternative and pragmatic approach, found to be as effective as a supervised exercise programme in cardiac rehabilitation, is a home-based model of delivery [16]. Home-based interventions also provide solutions to common barriers to participation in centre-based programmes such as access and transport issues, and are less expensive [17]. Further, patient populations, including PH [18] express a preference for unsupervised, self-paced, low-moderate intensity PA, specifically walking [19-20]. Through the use of telehealth, distance-based programmes could potentially offer an alternative mode of delivery for exercise training to increase adherence, availability and affordability for PH patients.

Although the few studies examining the beneficial effects of home-based exercise training in PH are promising [21-22] none included strategies to maximise adherence. An evidence-based approach to implement lifestyle changes requires the implementation of health behaviour change strategies grounded in behaviour change theory [23]. Evidence-based behaviour change techniques (BCT's) can be used to improve intervention effectiveness [24]. For example, the combination of the following BCT's: self-monitoring; goal setting; providing feedback on performance; and, review of behaviour goals, is associated with increased intervention effectiveness in PA interventions [25]. Interventions that meet the support needs and offer opportunities for self-monitoring have been found to be effective for improving PA in other chronic disease groups [26]. Wearable technology holds great potential as an easy to use, low cost self-monitoring tool with continuous feedback [27] and are perceived as

acceptable and useful for individuals with chronic diseases [28]. Through the use of telehealth, distance-based programmes could potentially offer an alternative mode of delivery for exercise training to increase adherence, availability and affordability for PH patients. The aim of this study is to assess the feasibility, acceptability, utility and safety of a novel home-based exercise training programme for PH patients.

METHODS AND ANALYSIS

Study Design

The study will employ a single group pre-post-intervention design with a follow-up maintenance phase. The purpose of the maintenance phase is to assess if the intervention facilitates the adoption of independent exercise in participants when formal support is removed. The study will adhere to the Standard Protocol Items: Recommendations for Interventional Trials Reporting Template (SPIRIT)[29]. Participants will complete assessments at baseline (T1), after the 10-week intervention (T2) and at 20-weeks follow up (T3).

Eligibility Criteria

Inclusion criteria are male or female > 18 years, with a diagnosis of PH (WHO Groups I and IV) by right heart catheterisation showing baseline mean pulmonary arterial pressure ≥25 mm Hg, pulmonary vascular resistance ≥240 dyne s cm^{-5}, pulmonary capillary wedge pressure ≤15 mmHg and receiving optimized conventional PH therapy. Participants must be clinically stable with no medication changes in the 2 months prior to enrolment.

Exclusion criteria include PH of any cause other than outlined in the inclusion criteria such as PH from left heart disease or lung disease/hypoxia (WHO Groups II and III), pregnancy, signs of right heart decompensation, acute infection and pyrexia, change in disease-targeted therapy within the last 2-months, scheduled to receive an investigational drug during the course of the study, FEV1/FVC <0.5, total lung capacity <70% of the normal value, active liver disease, porphyria, elevations of serum transaminases >3 x upper limit of normal (ULN), bilirubin >1.5 x ULN, haemoglobin concentration <75% of the lower limit of normal, systolic blood pressure <85 mmHg, active myocarditis, unstable angina pectoris, exercise induced ventricular arrhythmias, decompensated heart failure, hypertrophic obstructive cardiomyopathy or impaired left ventricular function.

Participant Recruitment

Participants will be recruited from the Pulmonary Hypertension Unit at the Mater Misericordiae University Hospital, Dublin, Ireland. Eligible participants will be invited to participate during their routine 3-6-month clinic visit. They will be given a verbal explanation of the study and provided with an information sheet by their PH Specialist (SG/BMC) or a member of their clinical team. After receiving the information, potential participants will have the option to speak on the day to a member of the research team or to receive a follow-up phone call within 1-2 days. Participants will have the opportunity to ask questions and will have time to consider their participation. Written consent will be obtained by mail.

Sample Size

Pilot study sample size typically ranges from 24 to 50 [30-32]. We estimate a target sample size of 25 to be sufficient for this feasibility study [31].

Primary Outcomes

Feasibility: Assessed by participant recruitment (enrolment as a proportion of eligible participants) and retention (proportion that completed all assessments); (ii) engagement with the intervention measured according to attendance at induction sessions and health coaching sessions and adherence, defined as the percentage of home-based exercise sessions recorded by participants who complete the intervention assessed via log books and weekly calls) and (iii) by examining delivery as intended (as per protocol) and health coach perceptions concerning how patients' received the intervention components. This will be captured immediately after each session in order to keep a record of how delivery was received in relation to the planned delivery (e.g., if a participants required extra time or further support following the induction training session).

Acceptability and utility: Assessed through self-report questionnaires completed at T2 and interviews. The questionnaire will assess participant perceptions of intervention appropriateness, effectiveness, quality, accessibility/usability, intrusiveness, and overall enjoyment and attitude towards the intervention. Semi-structured interviews with a sub-set of participants (~ n=12) will be conducted within 2-weeks of completing the T2 assessment. The interviews will further explore acceptability and utility of the intervention including perceptions concerning exercise prescription, adherence to different components of the intervention, in addition to the facilitating and hindering factors to participation. Participants

will also be asked to offer suggestions for improvement and implementation. Interviews will be conducted via telephone or online platforms (i.e., Zoom) and will be audio-recorded and transcribed.

Safety: Participants will be instructed to inform researchers immediately of any adverse advent. In addition, participants will be questioned about adverse events directly related to participation in the exercise intervention during a bi-weekly support call.

Secondary Outcomes

Exercise capacity: Assessed using the 6-min walk test (6MWT). The test will be administered according to the European Respiratory Society/ American Thoracic Society technical standard Guidelines [33] and will be conducted at home using detailed step-by-step video and written instructions and remotely supervised via phone/teleconferencing by a researcher (CMC). A family member/friend will assist with conducting the test, including measuring blood pressure and SpO_2 with guidance from the researcher before and after the test. The Frontier X heart rate monitor will be worn during the test to provide real-time feedback. The assistant will ask the participant to call out their SpO_2 and HR at each minute of the test. Subjective symptoms of dyspnoea and fatigue will be recorded using the Modified Borg Scale (0-10) [34] before and after the test. Standard encouragement will be delivered by the assistant, with researcher prompting, if needed.

Muscular strength: Lower body muscle strength will be assessed using the 30-sec sit-to-stand test (STS) from a seat height of 40-45 cm. The STS is a commonly used field-based measure of functional lower limb muscle strength, particularly in clinical and elderly populations. The test will be conducted in each participant's home via teleconference. A researcher (CMC) will provide a demonstration, time the test, and count the repetitions. Each participant will perform two trials separated by 5-min, with the best score being recorded.

Physical activity behaviour: ActivPAL^3 micro activity monitors (PAL Technologies Ltd. Glasgow, Scotland) will be used to assess free living activity behaviour. The device samples at 20Hz for 15-sec epochs and measures bodily accelerations using triaxial accelerometer. An inbuilt inclinometer measures thigh inclination. Proprietary algorithms classifies activities into sitting/lying time, standing time, stepping time, step count and activity counts. Participants will be mailed the accelerometer together with detailed wear instruction and provided with a prepaid postage envelope to return the device. They will be instructed to wear the device on the anterior aspect of their right thigh continuously for 7-days, except during water immersion activities (i.e., swimming and bathing). The ActivPAL is a valid and reliable measure of activity and sedentary behaviour [35-36].

Psychological Outcomes and Mediators

Quality of life: The Medical Outcomes Study Short-Form 36-Item Survey (SF-36) is a well-validated, generic questionnaire [37] consisting of physical functioning, physical role functioning, bodily pain, and general health and the four mental subscales of vitality, social

functioning, emotional role functioning and mental health. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)[38] was designed as a disease-specific health-related QoL measure for PH patients. It is widely used as a clinical and research tool in PH and assess symptoms (25 items) functioning (15 items) and quality life (25 items).

Fatigue: The Fatigue Severity Scale (FSS)[39] measures the patient's perception of the influence of fatigue on physical and social functioning through responses to nine different physical and social functioning situations. The FSS is a valid tool for assessing fatigue across various health conditions[40].

Self-regulatory self-efficacy for exercise: Assessed using a modified 11-item scale [41-42], which provide information on task, scheduling and recovery self-efficacy. Questions begin with the stem "*How confident are you that you can…*" and include items such as "*plan exercise sessions that will be at least moderately difficult (e.g. have you breathing a little hard, your heart rate increases)?*". Participants rate their confidence on a 0-10 Likert scale, with a higher score indicating greater self-efficacy for exercise (Cronbach alpha, α =.951).

Intentions to exercise: Two items will measure intention to engage in moderate-intensity physical activity for 150-min/week in the next 10-weeks, based on previously established measures[43].

Outcome expectations: Ten-items will assess outcome expectations. Five-items are derived from the validated exercise pros subscale [44] and 5-items to assess outcomes related to common symptoms reported in PH, 'such as breathlessness' [45].

Social support: Social support for exercise from family and friends scale [46] uses a 20-item scale to assess support from family and friends respectively. Responses will be recorded on a

Likert scale of 1-5, with higher scores representing greater social support. (Cronbach alpha, family α =.926, friends α =921).

Outcome assessments will take place at baseline (T1), after the 10-week intervention (T2) and at 20-weeks follow up (T3). Semi-structured interviews will be conducted at T2 to assess patient's perspective on programme acceptability and feasibility and at T3 to assess the follow up phase. Table 1 outlines the timeline of the assessments.

Procedure

Participants will complete all assessments, induction training and exercise training in their own home and will maintain in contact with researchers via telecommunication technologies (phone, videoconferencing and email). Following consent, a baseline assessment will be conducted (see Table 1) and participants will be provided with an accelerometer to record their activity for the following week. The assessment procedure will be repeated at T2 (10-weeks) and T3 (20-weeks).

Participants will be provided with a home exercise bike (NordicTrack GX 2.7U), a wearable tracker watch (The Fitbit Charge 3), pulse oximeter (SafeHeart SpO_2 monitor), real time single lead ECG/HR/respiratory rate monitor (Frontier X), blood pressure monitor (Beurer BM44), a TheraBand, exercise manual, exercise diary and access to online videos. The exercise manual was partly based on the design of previous PA intervention in chronic disease - PPARCS [27] and WATTAP [47] trials and also our formative research with PH patients. The formative research highlighted the lack of understanding of the benefits of exercise, the importance of self-regulation strategies to support motivation and exercise engagement and the desire for

visual picture and instruction of exercise. Concerns of breathlessness and energy management were also evident in interviews with PH patients and integrated into the exercise manual. The manual offers a comprehensive, patient-friendly resource detailing; 1) general information about the study; 2) useful links and contacts; 3) background information on PH; 4) education regarding exercise safety and the benefits of physical activity; 5) workbook style sections on motivation, goal setting, overcoming barriers and psychosocial support; 6) managing breathlessness; 7) exercise intensity and limits; 8) guided home exercises with written and visual details and advice on progression; and 9) advice on pacing and energy conservation. Participants will receive video clips of a qualified exercise specialist performing the exercises. Participants will be encouraged to refer to the video to ensure adherence to correct technique. Online videos will provide a visual demonstration of each exercise. Participants will be provided with an exercise diary as a tool to record their activity and effort perception. BCTs will be integrated in the intervention through wearable technology devices, the use of print and visual materials and health coaching and support calls.

The 10-week intervention consists of the following components: Three 60-90 min induction sessions (week 0 and 1), up to five 30-min support health coaching sessions (at week 2, 3, 5, 7, 9) and 3-5 weekly home-based exercise sessions. The intervention will end prior to T2 assessment. Participants will continue to have access to the exercise manual, bike and Fitbit during the maintenance phase.

Induction Training

Induction training (1:1), via video conferencing, is a key component to ensure patients are confident to exercise at home and understand the appropriate exercise intensity and how to exercise safely. Participants will be encouraged to involve a family member, friend or carer in the induction training. The sessions will focus on the following topics:

Session 1 - Introduction; Education on PH and benefits of PA for PH. Familiarisation with intervention materials/equipment and self-monitoring.

Session 2 - Exercise Safety and Exercise Demonstration; The session will focus on recognizing exercise limits, warning signs, and managing exercise intensity. Visual demonstrations of breathing techniques and aerobic, strength, and respiratory training will be provided, with the opportunity for behavioural practice during the session to check technique and instil confidence.

Session 3 - Recap; Exercise demonstrations and key safety points will be reviewed. Any issues regarding intervention materials/equipment will be addressed and participant goals will be reviewed, alongside additional tips for family/friend support and motivation.

Health Coaching Sessions

The health coaching sessions (via videoconferencing) will use BCTs to foster exercise adherence, motivate and provide support. Over the 5 sessions the topics will include; benefits of exercise, goal setting, action planning , self-monitoring, identification and management of barriers to exercise, problem solving and feedback on behaviour, with the option for

participants to complete formal paperwork in the intervention manual. If required, additional support will be available outside of scheduled sessions.

Participants will be encouraged to wear the Fitbit Charge 3 daily during the intervention. The Fitbit data will be used to guide individually tailored goals, assess adherence to exercise and overall daily PA and as tool to provide feedback to the researcher and participants.

Exercise Programme

Participants will complete a 10-week individualised, home-based exercise programme. The programme will be prescribed using the FITT principle (Frequency, Intensity, Time and Type) and will employ a multimodal approach that integrates aerobic, resistance and respiratory training. The goals for each component are outlined in the sections below. These are aspirational goals that may not be realistic for all participants. Exercise prescription will be individualized based on their baseline PA levels, 6-min walk test distance (6MWD) and physical capabilities. The modified Borg rating of perceived exertion (RPE) scale [48] will be used to help prescribe exercise intensity. The RPE scale is a psychophysiological measurement that translates physical stimuli to a psychological construct of perceived exertion and has been validated in other clinical groups [49]. Participants will aim to achieve an RPE of 3 (moderate) initially. Based on individual progress an RPE of 4 (somewhat hard) may be advised for some participants. The exercise programme will include:

Aerobic Training; Participants will initially aim to undertake a minimum of 10-min of structured aerobic exercise involving walking, cycling or a combination on ≥3 d/week. Participants will be allowed to perform this exercise in a single bout, or accumulate it in bouts

of at least 5-min in duration. The duration will be progressively increased, with the goal of accumulating ≥30 min on ≥5 d/week.

Resistance Training; Participants will initially undertake resistance training on 2 d/week, involving a single set of 6-8 repetitions of upper and lower extremity and whole body exercises. Training volume will progressively increase with the goal of completing 2-3 sets of 10-12 reps of 4-6 exercises on three non-consecutive days. Participants will use pursed lip breathing to help airways stay open during exhalation. Bodyweight resistance will be used initially and based on individual ability, TheraBands, water bottles or light dumbbells will be introduced.

Respiratory Training; Participants will initially perform 10-min of respiratory training at least twice a week, which will follow the protocol established by the Heidelberg PH research group [50]. This involves a combination breathing techniques (e.g., pursed lip, diaphragmic and slow breathing) emphasising control over their rate of inspiration to expiration and to strengthen the diaphragm , stretching of the chest and thoracic muscles (e.g., cat-to-cow) and respiratory muscle strengthening exercises. Training volume will progressively increase with the goal of completing 15/20 min of accumulated respiratory training on ≥3 d/week. The intensity of the respiratory muscle strengthening exercises can be progressed using a TheraBand.

Participants will wear a Frontier X device (receiver attached to a strap place around the chest) during exercise sessions. The first 2-weeks will be monitored by researchers and then periodically monitored. This will allow access to real time ECG, heart rate (HR), respiratory rate and cadence. Oxygen saturation will be monitored and participants will be instructed to stop exercising if the SpO_2 value drops below 88%, as per guidelines[51]. Participants will document any adverse events and report to the research team immediately.

Data Management and Timeline

The trial will be overseen by the trial management group, consisting the principal investigator, the trial-coordinator and health coach. They will meet every 4-weeks and will oversee all aspects of the conduct of the trial including performing safety oversight activities. Individual data will be de-identified, coded and entered. Each participant will be assigned a personal identification code (PIC), which will be used on all case report forms and in all electronic databases. Prior to any statistical analysis, all variables will be checked for missing, impossible and improbable values. Impossible and improbable values will be defined by clinical opinion and will include values that are outside three standard deviations of the mean value. Study recruitment began at the end of September 2020 and the study is expected to be completed in July 2021.

Statistical Analysis

Statistical analysis of quantitative data will be performed using SPSS Version 24. Prior to statistical analysis, the Shapiro-Wilks test will be applied to check for normality. Continuous variables will be reported as mean (range), mean (standard deviation) or median and inter-quartile range, depending on distribution, and categorical variables as frequency (%). Descriptive analyses will be undertaken to summarise participant characteristics and the quantitative data of the intervention feasibility, acceptability and utility. Qualitative data from post-trial interviews and researcher field notes will be analyzed using inductive thematic analysis to identity common themes[52]. A linear mixed model analysis (MMA) will be used

to examine the impact of time in this study . A MMA is a suitable approach to modelling time series data which contains repeated measures [53]. The MMA does not require complete data sets and does not exclude participants with missing data [54]. Furthermore, MMA has less stringent assumptions than other repeated measures models (such as analysis of variance) and also exhibits increased power to detect treatment effects. The data will adjust for confounding variables, such as age, baseline line fitness, gender and PH group.

Patient and Public Involvement

Formative qualitative research took place with PH patients during the intervention development stages. Semi-structured phone interviews (N=19) were conducted providing insight into patient barriers and motivators to PA, and exercise preferences. The findings fed into the design of the intervention along with PH clinician input. A patient representative provided opinions on the study protocol, patient-facing documentation (e.g., participants information sheet) and intervention material (e.g., exercise manual) to ensure it was patient friendly.

Discussion

The promise of exercise training in the treatment and management of PH has gained significant interest over the past two decades. The observed positive effects of exercise programmes on patients' exercise capacity, functional capacity and QoL[55] make a strong argument for the inclusion of exercise as an adjunctive therapy for stable PH patients[56]. Considering that structured and resource-intensive hospital-based exercise programmes are unlikely to be scalable, it is an opportune time to assess the efficacy, safety and impact of home-based programmes as an alternative mode of delivery for PH patients.

A home-based exercise programme may eliminate many of the barriers associated with in-patients or out-patients setting such as transportation issues, location, long wait periods for availability and accessibility for patients. A recent review of exercise interventions in PH by Ozemek and colleagues [56] highlighted the need for inclusion of home exercise programmes to allow patients achieve the optimal 5 to 6 days of structured exercise.

This study will utilise a remote delivery for exercise training with the use of telehealth methods, wearable technology, performance feedback and behavioural support to deliver and monitor the intervention. The aim is to eliminate the burden on patients to attend several times per week to an outpatient clinic, accommodate resource availability, make the programme achievable in a 'real world' setting and improve the reach beyond the traditional healthcare facilities. The follow-up post intervention (T3) phase will provide insight into whether behavioural support is necessary in order for PH patients to remain physically active. Furthermore, it will allow us to assess resource needs in future home-based exercise programmes such as the provision of specific exercise equipment and the use of ubiquitous, low cost devices to monitor activity and safety (e.g. bike, wearable activity tracker). Remote assessment of outcomes may remove threats to external validity and evaluation of the feasibility of such assessment will address the goals of implementation science to close the research-to-practice gap and support implementation and scale up of evidence-based interventions[57].

To our knowledge, this will be the first study to employ the use of evidence-based BCTs to examine the feasibility, utility and efficacy of a remote home-based approach to exercise training for medically stable PH patients. The secondary aims of this study are to evaluate

whether this approach leads to improvement in selected indices of physical and psychological health.

PH is a rare, debilitating condition with most clinics centralized and limited community resources available. Telehealth holds significant potential to meet the growing support for exercise training to be included as an adjunct therapy by offering remote training and support, which is key to long-term implementation of exercise training for the PH population. It provides a service that is more accessible and may potentially offer a more affordable enhanced level of care. Our current understanding is limited concerning the acceptability, feasibility and utility of a home-based programme for stable PH patients. This study will help gain a valuable insight into this gap in knowledge.

Ethics and dissemination: Ethics approval has been obtained from the Mater Misericordiae Institutional Review Board REF:1/378/2032 and Dublin City University Research Ethics DCUREC/2018/246. A manuscript of the results will be submitted to a peer-reviewed journal and results will be presented at conferences, community and consumer forums and hospital research conferences. Trial Registration: ISRCTN Registry: ISRCTN83783446.Protocol version. 2.0

References

1. Gaine S, McLaughlin V. Pulmonary arterial hypertension: tailoring treatment to risk in the current era. *Eur Respir Rev*. 2017;26(146):170095. doi:10.1183/16000617.0095-2017.
2. Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev*. 2014;2014(4):CD003331. doi:10.1002/14651858.CD003331.pub4.
3. Buys R, Avila A, Cornelissen VA. Exercise training improves physical fitness in patients with pulmonary arterial hypertension: a systematic review and meta-analysis of controlled trials. *BMC Pulm Med*. 2015;15:40. doi:10.1186/s12890-015-0031-1.
4. Langer D, Hendriks E, Burtin C, et al. A clinical practice guideline for physiotherapists treating patients with chronic obstructive pulmonary disease based on a systematic review of available evidence. *Clin Rehabil*. 2009;23(5):445-462. doi:10.1177/0269215509103507.
5. Vanhees L, Rauch B, Piepoli M, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular disease (Part III). *Eur J Prev Cardiol*. 2012;19(6):1333-1356. doi:10.1177/2047487312437063.
6. Morris NR, Kermeen FD, Holland AE. Exercise-based rehabilitation programmes for pulmonary hypertension. *Cochrane Database Syst Rev*. 2017;1(1):CD011285.. doi:10.1002/14651858.CD011285.pub2.
7. Dalla Vecchia LA, Bussotti M. Exercise training in pulmonary arterial hypertension. *J Thorac Dis*. 2018;10(1):508-521. doi:10.21037/jtd.2018.01.90.
8. Babu AS, Padmakumar R, Maiya AG, Mohapatra AK, et al . Effects of Exercise Training on Exercise Capacity in Pulmonary Arterial Hypertension: A Systematic

Review of Clinical Trials. *Heart Lung Circ*. 2016;25(4):333-341. doi:10.1016/j.hlc.2015.10.01.

9. Yuan P, Yuan XT, Sun XY, et al. Exercise training for pulmonary hypertension: a systematic review and meta-analysis. *Int J Cardiol*. 2015;178:142-146. doi:10.1016/j.ijcard.2014.10.161.
10. Pandey A, Garg S, Khunger M, et al. Efficacy and Safety of Exercise Training in Chronic Pulmonary Hypertension: Systematic Review and Meta-Analysis. *Circ Heart Fail*. 2015;8(6):1032-1043. doi:10.1161/CIRCHEARTFAILURE.115.00.
11. Benjamin N, Marra AM, Eichstaedt C, Grünig E. Exercise Training and Rehabilitation in Pulmonary Hypertension. *Heart Fail Clin*. 2018;14(3):425-430. doi:10.1016/j.hfc.2018.03.008.
12. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). *Eur Respir J*. 2015;46(4):903-975. doi:10.1183/13993003.01032-2015.
13. Galiè N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D60-D72. doi:10.1016/j.jacc.2013.10.031.
14. Mereles D, Ehlken N, Kreuscher S, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation*. 2006;114(14):1482-1489. doi:10.1161/CIRCULATIONAHA.106.618397.
15. Babu AS, Padmakumar R, Maiya AG, et al. Letter by Babu et al Regarding Article, "Advances in Therapeutic Interventions for Patients With Pulmonary Arterial

Hypertension". *Circulation*. 2015;132(12):e153. doi: 10.1161/CIRCULATIONAHA.114.014978.

16. Buckingham SA, Taylor RS, Jolly K, et al. Home-based versus centre-based cardiac rehabilitation: abridged Cochrane systematic review and meta-analysis. *Open Heart*. 2016;3(2):e000463. doi:10.1136/openhrt-2016-000463.
17. Hardcastle SJ, & Cohen PA. Effective physical activity promotion to survivors of cancer is likely to be home based and to require oncologist participation. *J Clin Oncol* 2017;35:3635-3637. doi: 10.1200/JCO.2017.74.6032.
18. Chia KSW, Brown K, Kotlyar E, et al.. 'Tired, afraid, breathless … .' An international survey of the exercise experience for people living with pulmonary hypertension. *Pulm Circ*. 2020 Nov 16;10(4):2045894020968023. doi: 10.1177/2045894020968023.
19. Maxwell-Smith C, Zeps N, Hagger MS, et al. Barriers to physical activity participation in colorectal cancer survivors at high risk of cardiovascular disease. *Psycho-oncology* 2017;26:808-814. doi:10.1002/pon.4234.
20. Artinian NT, Fletcher GF, Mozaffarian D, et al. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122(4):406-441. doi:10.1161/CIR.0b013e3181e8edf1.
21. Karapolat H, Çınar ME, Tanıgör G, et al. Effects of cardiopulmonary rehabilitation on pulmonary arterial hypertension: A prospective, randomized study. *Turk J Phys Med Rehabil*. 2019;65(3):278-286. doi: 10.5606/tftrd.2019.2758.
22. Babu AS, Padmakumar R, Nayak K,et al. Effects of home-based exercise training on functional outcomes and quality of life in patients with pulmonary hypertension: A randomized clinical trial. *Indian Heart J*. 2019;71(2):161-165. doi:10.1016/j.ihj.2019.03.002.

23. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci*. 2011;6:42. Published 2011 Apr 23. doi:10.1186/1748-5908-6-42.

24. Samdal GB, Eide GE, Barth T, Williams G, Meland E. Effective behaviour change techniques for physical activity and healthy eating in overweight and obese adults; systematic review and meta-regression analyses. *Int J Behav Nutr Phys Act*. 2017;14(1):42. Published 2017 Mar 28. doi:10.1186/s12966-017-0494-y.

25. Artinian NT, Fletcher GF, Mozaffarian D, et al. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122(4):406-441. doi:10.1161/CIR.0b013e3181e8edf1.

26. Lahart I, Metsios G, Nevill AM, et al. Randomised controlled trial of a home-based physical activity intervention in breast cancer survivors. *BMC Cancer* 2016*;* 16:234-247. doi: 10.1186/s12885-016-2258-5.

27. Hardcastle SJ, Hince D, Jiménez-Castuera R*, et al.,* Promoting physical activity in regional and remote cancer survivors (PPARCS) using wearables and health coaching: randomised controlled trial protocol *BMJOpen* 2019;**9:**e028369. doi: 10.1136/bmjopen-2018-028369.

28. Mercer K, Giangregorio L, Schneider E, et al. Acceptance of commercially available wearable activity trackers among adults aged over 50 and with chronic illness: a mixed-methods evaluation. *JMIR Mhealth Uhealth* 2016;4: e7. doi:10.2196/mhealth.4225.

29. Chan A, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: Defining standard protocol items for clinical trials. *Annals of Internal Medicine* 2013*;*158:200-207.

30. Browne RH. On the use of a pilot sample for sample size determination. *Stat Med*. 1995;14(17):1933-1940. doi:10.1002/sim.4780141709.

31. Julious SA: Sample size of 12 per group rule of thumb for a pilot study. *Pharm Stat*. 2005, 4 (4): 287-291. 10.1002/pst.185.

32. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *J Clin Epidemiol*. 2012;65(3):301-308. doi:10.1016/j.jclinepi.2011.07.011.

33. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J*. 2014;44(6):1428-1446. doi:10.1183/09031936.00150314.

34. Borg, G. A. V. (1982). Psychophysical bases of perceived exertion. *Medicine & Science in Sports & Exercise.* 1982;*14*(5):377–381. doi.10.1249/00005768-198205000-0001.

35. Harrington DM, Welk GJ, Donnelly AE. Validation of MET estimates and step measurement using the ActivPAL physical activity logger. *J Sports Sci*. 2011;29(6):627-633. doi:10.1080/02640414.2010.549499.

36. Kozey-Keadle S, Libertine A, Lyden K, et al. Validation of wearable monitors for assessing sedentary behavior. *Med Sci Sports Exerc*. 2011;43(8):1561-1567. doi:10.1249/MSS.0b013e31820ce174.

37. Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.

38. McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related

quality of life and quality of life for patients with pulmonary hypertension. *Qual Life Res*. 2006;15(1):103-115. doi:10.1007/s11136-005-3513-4.

39. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The Fatigue Severity Scale: Application to Patients With Multiple Sclerosis and Systemic Lupus Erythematosus. *Arch Neurol.* 1989;46(10):1121–1123. doi:10.1001/archneur.1989.00520460115022.
40. Schentag CT, Cichon J, MacKinnon A, Gladman DD, Urowitz MB. Validation and normative data for the 0–10 point scale version of the fatigue severity scale (FSS) [abstract]. *Arthritis Rheum* 2000; **43** Suppl: S177.
41. Luszczynska, A., & Sutton, S. (2006). Physical activity after cardiac rehabilitation: Evidence that different types of self-efficacy are important in maintainers and relapsers. *Rehabilitation Psychology, 51*(4), 314–321.doi. 10.1037/0090-5550.51.4.314.
42. Shields CA, Brawley LR. Preferring proxy-agency: impact on self-efficacy for exercise. J Health Psychol. 2006 Nov;11(6):904-14. doi: 10.1177/1359105306069092. PMID: 17035262.
43. Ajzen I, Brown TC, & Carvajal F. Explaining the discrepancy between intentions and actions: The case of hypothetical bias in contingent valuation. *Pers Soc Psychol Bull* 2004;30:1108-1121. doi:10.1177/0146167204264079.
44. Plotnikoff RC, Blanchard CM, Hotz SB, et al. Validation of the decisional balance scales in the exercise domain from the transtheoretical model: A longitudinal test. *Meas Phys Educ Exerc Sci* 2001;5:191-206. doi:10.1207/S15327841MPEE0504_01.
45. Yorke J, Deaton C, Campbell M, et al. Symptom severity and its effect on health-related quality of life over time in patients with pulmonary hypertension: a multisite

longitudinal cohort study. *BMJ Open Respiratory Research.* 2018;**5:**e000263. doi: 10.1136/bmjresp-2017-000263.

46. Sallis JF, Grossman RM, Pinski RB, Patterson TL, Nader PR. The development of scales to measure social support for diet and exercise behaviors. *Prev Med*. 1987;16(6):825-836. doi:10.1016/0091-7435(87)90022-3.
47. Maxwell-Smith C, Cohen PA, Platell C, et al. Wearable Activity Technology And Action-Planning (WATAAP) to promote physical activity in cancer survivors: Randomised controlled trial protocol. *Int J Clin Health Psychol*. 2018;18(2):124-132. doi:10.1016/j.ijchp.2018.03.003.
48. Foster C, Florhaug JA, Franklin J, et al. A new approach to monitoring exercise training. *J Strength Cond Res*. 2001;15(1):109-115.
49. Rosales W, Cofré C, Alejandra C, et al. Validación de la escala de Borg en personas con diabetes mellitus tipo 2 [Validation of the Borg scale in participants with type 2 diabetes mellitus]. *Rev Med Chil*. 2016;144(9):1159-1163. doi:10.4067/S0034-98872016000900009.
50. Mereles D, Ehlken N, Kreuscher S, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension.*Circulation*.2006;114(14):1482-9.doi: 10.1161/CIRCULATIONAHA.106.618397.
51. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188(8):e13-e64. doi:10.1164/rccm.201309-1634ST.
52. Braun V, & Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006;3:2, 77-101. doi: 10.1191/1478088706qp063oa.

53. Haapalainen E, Laurinen P, Siirtola P, et al. Exercise energy expenditure estimation based on acceleration data using the linear mixed model. *IEEE International Conference on Information Reuse and Integration*. 2008: 131–136.

54. Armstrong R. A. Recommendations for analysis of repeated-measures designs: Testing and correcting for sphericity and use of manova and mixed model analysis. *Ophthalmic and Physiological Optics*. 2017: *37*(5), 585–593.

55. Dalla Vecchia LA, Bussotti M. Exercise training in pulmonary arterial hypertension. *J Thorac Dis*. 2018;10(1):508-521. doi:10.21037/jtd.2018.01.90.

56. Ozemek C, Berry MJ, Arena R. A Review of Exercise Interventions in Pulmonary Arterial Hypertension and Recommendations for Rehabilitation Programming. *J Cardiopulm Rehabil Prev*. 2019;39(3):138-145. doi:10.1097/HCR.0000000000000402.

57. Eccles MP, Armstrong D, Baker R, et al. An implementation research agenda. *Implement Sci*. 2009;4:18. Published 2009 Apr 7. doi:10.1186/1748-5908-4-18.

Contributors: CMC, BK, SJH, NMC, SG, BMC, and NM were involved in study conceptualisation, development of intervention content and writing of the protocol. AMC provided guidance on the statistical analysis. CMC led the writing of the manuscript and all authors edited and reviewed the manuscript.

Funding: This work was supported by Janssen Sciences Ireland UC. The funding body had no role in the study design and data collection, analysis and interpretation of data.

Competing interest statement: None declared.

Table 1: Study outcome measures and time points

	Time		
Assessments	**Baseline (T1)**	**Post-Intervention (T2)**	**Follow-up (T3)**
Written informed consent & eligibility	X		
Demographics	X		
Medical history	X		
WHO functional class	X	X	X

Concomitant medication	X	X	X
Adverse events	X	X	X
Exercise capacity (6-MWT)	X	X	X
Muscle strength (Sit to Stand)	X	X	X
Physical activity (ActivPAL Micro)	X	X	X
Quality of life (CAMPHOR & SF-36)	X	X	X
Psychological constructs	X	X	X
Intervention debrief questionnaires/ semi-structed interviews		X	X

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(Page 1)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(Page 3)**
	2b	All items from the World Health Organization Trial Registration Data Set **(Page 3)**
Protocol version	3	Date and version identifier **(Page 3)**
Funding	4	Sources and types of financial, material, and other support **(Page 29)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (**Title page and Page 29)**
	5b	Name and contact information for the trial sponsor **(Page 29)**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **(Page 29**)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **(Page 29)**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **(Pages 5-7**)
	6b	Explanation for choice of comparators **(Page 9)**
Objectives	7	Specific objectives or hypotheses **(Page 7)**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **(Page 7)**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) (and list of countries where data will be collected. Reference to where list of study sites can be obtained **(Page 8)**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **(7)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(Page 13-17)**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (**N/A)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **(Page 13-17)**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **(Page 8)**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **(Page 7 & 9-13)**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **(table 1)**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **(Page 9)**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **(Page 8)**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. (To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(N/A)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are **(N/A)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(N/A)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(N/A)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(N/A)**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(Page9-13)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **(Page 13)**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **(Page 18)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **(Page 18)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(Page 18)**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **(Page 18)**

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **(Page 18)**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **(N/A)**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **(Page 10)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **(Page 18)**

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **(Page 3)**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **(Page 18)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **(Page 8)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **(N/A)**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **(Page 18)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(Page 29)**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **(Page 18)**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(N/A)**

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **(Page 3)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(Page 29)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **(Page 3)**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **(Appendix A)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(N/A)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.