PROTOCOL

Supervised Pulmonary Hypertension Exercise REhabilitation (SPHERe): a multi-centre randomised controlled trial

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Protocol Amendments:

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TRIAL SUMMARY

Trial Title	Supervised Pulmonary Hypertension Exercise Rehabilitation: a multicentre RCT
Sponsor ref. number	SPHERe/GM427119
Clinical Phase	Phase III
Trial Design	Multi-centre randomised controlled trial with embedded process evaluation and health economic evaluation
Trial Participants	Adults with pulmonary hypertension
Planned sample size	352 people randomly allocated to receive the SPHERe intervention or active control
Treatment Duration	Maximum 4 months post randomisation
Follow-up Duration	12 months post randomisation (5 years postal follow-up, outside trial)
Planned Trial Period	01 Jun 2019 to 31 Aug 2022 (39 months)
Objectives	To run a definitive multi-centre RCT testing the clinical and cost-effectiveness of SPHERe vs. best-practice usual care, including: 1. A pre-pilot to confirm feasibility, refine intervention delivery and manualised practitioner training, and prepare trial set-up at selected centres; 2. An internal pilot, with formative process evaluation, at a sample of out-patient centres to test recruitment and trial procedures; 3. A main trial with embedded process evaluation.
Outcomes **Primary** **Secondary**	Assessed at baseline, four months (post-randomisation) and 12 months Incremental shuttle walk test at four months 1. Six-minute walk test 2. Cambridge Pulmonary Hypertension Outcome Review 3. Hospital Anxiety and Depression Scale 4. Generalised self-efficacy scale 5. Fatigue Severity Scale 6. WHO functional class 7. Medication use 8. Time to clinical worsening 9. Hospital admissions 10. Adverse events 11. All-cause mortality 12. EQ-5D-5L 13. Health and care resource use
Qualitative objective	To explore and contextualise participant and practitioner experience, barriers and enablers, to inform interpretation of quantitative data and facilitate wider implementation
Qualitative outcomes	Semi-structured interviews with participants and practitioners

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
ACHD	Adult congenital heart disease
AE	Adverse Event
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CI	Chief Investigator
CONSORT	Consolidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CTU	Clinical Trials Unit
CTEP	Chronic thromboembolic pulmonary hypertension
DMC	Data Monitoring Committee
FSS	Fatigue severity scale
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
ISWT	Incremental shuttle walk test
NICE	National Institute for health and Care Excellence
MRC	Medical Research Council
PAH	Pulmonary Arterial Hypertension
PH	Pulmonary hypertension
PI	Principal investigator
PPI	Patient & Public Involvement
PPMO	Performance and Programme Management Office
QoL	Quality of Life
RCT	Randomised controlled trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
UHCW	University Hospitals Coventry & Warwickshire
WCTU	Warwick Clinical Trials Unit
6MWT	Six-minute walk test

1. BACKGROUND

1.1 Epidemiology and burden of the condition

Pulmonary hypertension (PH) is a debilitating long-term condition characterised by severe exercise intolerance [1]. Pulmonary arterial pressure is abnormally raised due to dysfunctional endothelial cells and vascular smooth muscle, leading to maladaptive pulmonary vascular remodelling and increased right ventricular afterload [2, 3]. Pulmonary and cardiovascular haemodynamics are progressively compromised, often during minimal physical exertion [4, 5]. Consequently, exertional dyspnoea, fatigue and syncope are the most common symptoms, impacting profoundly on quality of life (QoL), morbidity and mortality [6].

Guidance from the World Symposium on Pulmonary Hypertension [7] identified five distinct subgroups:

Group 1 - Pulmonary arterial hypertension (PAH)
Group 2 - PH due to left heart disease
Group 3 - PH due to lung diseases or hypoxia, or both
Group 4 - Chronic thromboembolic pulmonary hypertension (CTEPH)
Group 5 - PH with unclear multifactorial mechanisms.

Drug treatment and pulmonary endarterectomy may help people with PAH [8] and CTEPH [9], respectively, but benefit is often limited. For people with PH secondary to cardiac or pulmonary disease (groups 2 & 3), there are no specific treatments of proven benefit [10, 11].

1.2 Existing knowledge

There are many similarities between PH and conditions like chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF); indeed, they often co-exist [6]. For people living with these conditions, exercise rehabilitation is recommended by NICE [12], and the British Thoracic Society [13], supported by a considerable evidence base [14]. Exercise rehabilitation can improve fitness in these populations, and increase ability to 'self-manage', often reducing health and care utilisation [14, 15]. Thus, it is plausible, that exercise may also help people with PH groups 2 & 3 due to underlying cardiac and pulmonary disease [6, 11]. In PH, exercise rehabilitation appears to be safe and may help people with PAH and CTEPH, particularly when undertaken as an in-patient [3]. Recent recommendations support a conservative approach, under the supervision of appropriately skilled practitioners [16, 17]. However, exercise rehabilitation has not yet been adequately tested in PH groups 2 & 3, or in an out-patient setting in the UK [10, 11].

A 2017 Cochrane review of exercise rehabilitation for PH identified six RCTs (N=206 mainly people with PAH or CTEPH) with short follow-up (3-15 weeks) [18]. Low quality evidence showed that exercise rehabilitation programmes increased six-minute walk test (6MWT) distance by 60m, compared to usual care (95% CI 30m to 90m), without any serious adverse events [19]. The SF-36 physical component score improved by 4.63 points (95% CI 0.80 to 8.47), which the review authors did not consider clinically important. Updating this review, identified one further trial (n=40) with eight-week follow-up [20], two ongoing trials with published protocols [21, 22], and seven trial registry entries, testing exercise rehabilitation in PAH or CTEPH. Few studies have tested exercise rehabilitation for PH groups 2 & 3 [4, 23], and there is only one ongoing study according to trial

registries (extension of existing long-term recruitment trial using an in-patient intervention protocol [24]).

A 2018 review examined the specific components and reporting quality of exercise interventions in 19 RCTs and non-randomised studies [25]. The highest quality reporting and best outcomes came from two studies at one centre using a three-week residential exercise intervention prior to 12 weeks of home exercise [24, 26]. Distance on 6MWT improved at three weeks; 111m (95% CI 65m to 139m) and 41m (no 95% CI) respectively. These clinically important benefits were maintained at 15 weeks. Current data do not confirm the effectiveness, or safety, of out-patient/community outreach exercise rehabilitation, or report on any outcomes beyond 15 weeks. The exercise interventions were well described, but only one of 19 studies adequately described behavioural or motivational strategies aimed at improving exercise adherence and compliance.

Exercise training might increase the risk of serious adverse events for some people with PH, due to reduced cardiac output, arrhythmias, pulmonary venous congestion, and hypoxemia [5]. Historically, there has been a reluctance to provide exercise rehabilitation for this population [27], and many patients were advised against exercise, leading to heightened anxiety. As such, modifiable psychosocial variables such as depression, anxiety and/or fear of exercise should be addressed when treating PH, as they are equally important as physical factors at predicting health-related outcomes in people living with PAH and CTEPH [28, 29]. These modifiable factors are also likely to be relevant for people with PH groups 2, 3, or 5.

1.3 Hypothesis

We will run a multi-centre RCT to test if SPHERe, a programme of supervised exercise rehabilitation, with psychosocial and motivational support, can improve walking distance and QoL, compared to best practice usual care, in people with PH (particularly groups 2 & 3).
We hypothesise that the SPHERe intervention will improve clinical, and patient reported, outcomes when compared to best practice usual care.

1.4 Need for a trial

In-patient exercise rehabilitation may have a short-term benefit on exercise capacity in selected people with PAH or CTEPH. However, it is not known if these benefits extend to PH groups 2, 3, & 5, if exercise rehabilitation delivered in an NHS out-patient setting is effective or cost effective, or if there are any long-term health benefits or harms. Further, current exercise rehabilitation interventions for PH do not explicitly target modifiable psychosocial factors. To address these evidence gaps, a definitive RCT is required.

1.5 Ethical considerations

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation and University of Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with the General Data Protection Regulation.

Before enrolling people into the trial, each trial site will ensure that the local conduct of the trial has the agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not

be permitted to enrol people into the trial until written confirmation of R&D agreement is received by Warwick Clinical Trials Unit (WCTU).

Trial staff will ensure that participants' anonymity is maintained. Participant identifiable information will be stored securely on the electronic database and when in paper form, will be stored separately from CRFs using only that persons participant ID number. All documents will be stored securely and will only be accessed by trial staff and authorised personnel. The study will comply with relevant UK data protection legislation, which requires data to be pseudo-anonymised as soon as it is practical to do so.

Data will be collected on paper CRFs at assessments appointments, or entered directly into a secure online database provided by WCTU. Paper CRFs will be posted and stored on site at WCTU under locked conditions for the duration of the trial; these will be considered source documents for the study. Direct access to source data and documents will be granted to authorised representatives from the sponsor, host institutions and the regulatory authorities to permit trial related monitoring, audits and inspections.

All approaches to potential participants will come from clinical teams involved in their care and all individual data will be maintained within NHS sites until participants have agreed to provide the study team with their personal details.

Participants who are not fluent in written English will be eligible to take part. The primary outcome is a measure of exercise capacity which, unlike patient reported outcomes, does not require literacy; fluency in spoken English, however, is required for study entry. This group will, however, have problems reading study material. When confirming consent for those unable to read English, a second person will be present to ensure correct explanation. The CAMPHOR and the EQ-5D-5L questionnaires will be collected orally, where necessary, to ensure that those unable to read English are able to contribute participant reported outcomes to the study.

For adults lacking capacity to consent, e.g. people with PH secondary to Down's syndrome, but who are able to participate in the SPHERe intervention, we will seek advice from a personal consultee on whether they would wish to be included in our research study.

Historically there have been concerns that exercise might involve an element of risk for people with PH. Recent evidence, however, does not indicate any increased risk of death during exercise for people with PAH & CTEPH. Nevertheless, deaths will be closely monitored in all trial participants and these data presented to the DMC regularly. A robust safety reporting procedure will be in place to, in accordance with WCTU SOPs, to ensure participant safety and well-being are protected.

1.6 CONSORT

The trial will be reported in line with the CONSORT (Consolidated Standards *o*f *R*eporting *T*rials) statement (Lancet 2001, **357**: 1191-1194).

1.7 Assessment and management of risk

The exercise rehabilitation sessions with psychosocial and motivational support (intervention), and the single session of one-to-one advice on safe and effective lifestyle physical activity (control) are

current practice across the NHS for the management of severe cardiopulmonary disease (i.e CHF and COPD), including, incidentally, some people with PH. However, these are not routinely provided as a dedicated service for people with all forms of PH. Consequently, whilst the interventions generally reflect current standard practice, they may expose some trial participants to additional exercise related risk over and above standard care currently received. In keeping with WCTU SOPs, a risk assessment and monitoring plan will be implemented, focusing on ensuring safe exercise assessment and prescription in PH. Primarily this will involve undertaking appropriate pre-exercise screening (as per existing guidelines[13, 30]), application of existing exercise guidelines for CHF and severe COPD, and the provision of appropriately trained staff, suitable facilities, and comprehensive emergency equipment with thorough clinical procedures for use.

2. TRIAL DESIGN

2.1 Pre-pilot feasibility study

A small pre-pilot feasibility phase (n= 6-10) will be undertaken to complete development of intervention and trial materials, refine recruitment processes, pilot practitioner training, and confirm feasibility of intervention delivery. Over a three month period, the constituent parts of the SPHERe intervention will be tested with six to ten participants recruited from up to three centres. The purpose of the pre-pilot feasibility will be to refine and test intervention and control materials, including participant (see section 2.4.2.1) and practitioner manuals, and staff training procedures, and to commence preparation for trial set-up at selected centres. This will allow us to confirm the feasibility of all aspects of the trial and make final alterations prior to the internal pilot.

2.2 Trial summary and flow diagram

The SPHERe intervention will be produced and refined during a six-month development phase. A small pre-pilot feasibility phase will be undertaken to complete development, refine recruitment processes, pilot practitioner training, and confirm feasibility of intervention delivery. Subsequently, in an internal pilot at multiple sites, trial recruitment and retention will be confirmed. This will also provide provisional data on the fidelity of the intervention, its safety, and participant compliance and experiences. Finally, a multi-centre RCT with an embedded process evaluation will be conducted at up to 20 NHS out-patient exercise rehabilitation centres principally in the East and West Midlands.

Trial overview: Adults with PH will be identified by the clinical care team using multiple screening strategies, primarily via existing secondary care disease registers, out-patient clinic attendance, and hospital discharge data. Those with a formal PH diagnosis (European Society of Cardiology (ESC)/ European Respiratory Society(ERS)) [17], and confirmed trial eligibility will be invited to participate, and approached by clinical teams involved in their care.

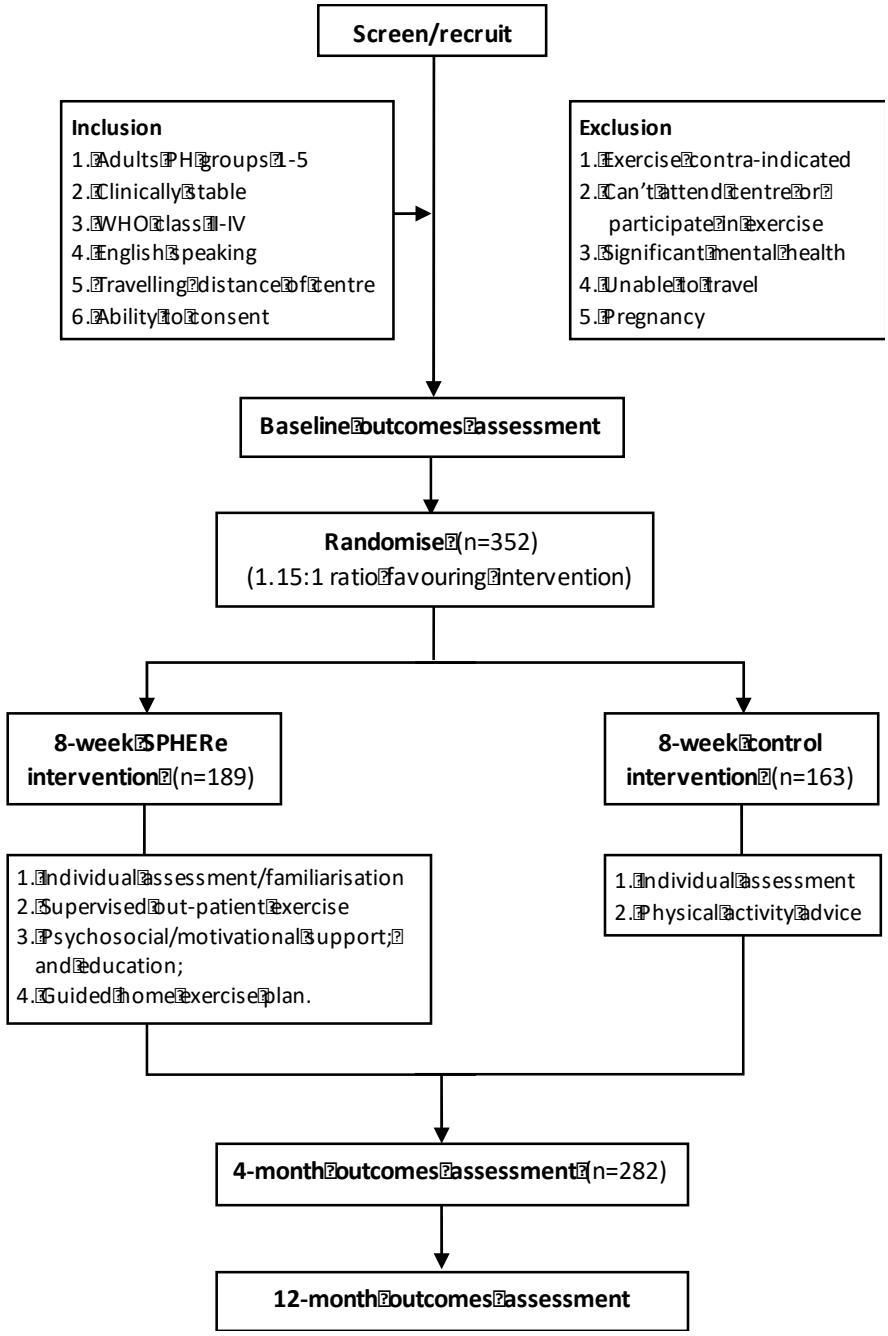
We aim to recruit 352 participants from between 10 and 20 treatment centres, who will be randomised to the SPHERe intervention or best practice usual care on a 1.15:1 basis using a computer-generated randomisation sequence, performed by minimisation, based on centre, PH group, and World Health Organisation (WHO) functional class.

Best practice usual care will consist of an individual practitioner appointment, with general advice on safe and effective physical activity.

The eight-week SPHERe intervention includes: 1) An hour long individual assessment and exercise familiarisation sessions; 2) twice-weekly supervised, out-patient exercise training; 3) weekly individual psychosocial and motivational support and education; and 4) a guided home exercise plan to complete once per week. Practitioners will be provided with a comprehensive trial manual and will be fully supported by the trial team.

Outcomes will be assessed at baseline, four months (post randomisation) and 12 months. The primary outcome will be incremental shuttle walk (ISWT) distance at four months. The ISWT is an externally paced assessment of maximal exercise capacity which is sensitive to treatment effect, predicts mortality, and has no ceiling effect in PH [31]. Secondary outcomes will include health related quality of life (HR-QoL), clinical worsening, and a health economic analysis.

Figure 1 Trial flow diagram



2.3 Aims and objectives

The aim of this trial is to assess the clinical and cost-effectiveness of supervised pulmonary hypertension exercise rehabilitation (SPHERe) compared to best-practice usual care for people with pulmonary hypertension.

2.3.1 Objectives

The objective of this trial is to run a definitive multi-centre RCT testing the clinical and cost-effectiveness of SPHERe vs. best-practice usual care, including:

1. A pre-pilot to confirm feasibility, refine intervention delivery and manualised practitioner training, and prepare trial set-up at selected centres;

2. An internal pilot, with formative process evaluation, at a sample of out-patient centres to test recruitment and trial procedures;
3. A main trial with embedded process evaluation.

2.4 Outcome measures

2.4.1 Efficacy

Primary Outcome:

Exercise capacity as determined by distance walked in the incremental shuttle walk test (ISWT) at four months. ISWT will be performed as per European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines [19]. The externally paced ISWT is a simple assessment of maximal exercise capacity and, in PH, is sensitive to treatment effect, predicts mortality, and has no ceiling effect [31].

Secondary outcomes:

1. Six-minute walk test (6MWT) distance: included as a secondary outcome measure of exercise capacity to allow inclusion of our data in meta-analyses, and performed as per guidelines [19].

2. Disease specific health-related quality of life (HR-QoL): Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) [32]. This is widely used as a clinical and research tool in PH, displaying good construct validity and reproducibility. It consists of a 25-item symptoms scale (scored 0–25), a 15-item functioning scale (scored 0–30) and a 25-item QoL scale (scored 0–25). For all scales, a low score indicates a better status [32].

3. Health utility: EQ-5D-5L [33]. A validated, generic HR-QoL measure consisting of five dimensions, each with five levels of response. Each combination of answers can be converted into a health utility score. It has good test-retest reliability, is simple to use, and gives a single preference based index value for health status that can be used for cost-effectiveness analysis.

4. Emotional well-being: Hospital Anxiety and Depression Scale (HADS) [34]. A 14-item questionnaire from which an anxiety and depression subscale can be derived. Sub-score values >5 points identify increased anxiety and/or depression; a total score >9 is pathological. Not used extensively in PH, but included as a well validated measure in clinical populations.

5. Generalised self-efficacy scale: a 10-item psychometric scale that is designed to assess optimistic self-beliefs to cope with a variety of difficult demands in life that are key targets of the behavioural component of the SPHERe intervention.

6. Fatigue: Fatigue Severity Scale (FSS) [35]. A nine-item questionnaire validated for evaluating disabling fatigue and previously used in PH [36]. Each item is rated on a seven-point scale, from strongly disagree to strongly agree. A total score is derived from all nine questions; a higher score indicates a greater impact of fatigue on everyday activities.

7. World Health Organisation (WHO) functional class: a modified New York Heart Association functional classification system adopted by WHO and used ubiquitously in PH. Participants are graded on their ability to perform physical tasks, and classified as (I) no limitation, (II) mild

limitation, (III) marked limitation, (IV) unable to perform any activity [37]. This will be assessed by a research practitioner at each trial assessment.

8. Medication use: class, drug, dose and frequency of all regular medication will be recorded. Participants will be asked to bring their repeat prescription to outcome assessment appointments.

9. Time to clinical worsening: defined as one of; PH related death; listing for/completed lung transplant; hospitalisation for PH; clinical worsening leading to initiation of new PH treatment; decreased WHO functional class and ≥15% decrease in 6MWT distance [38]

10. Health and social care resource use: participant self-report and NHS records. The primary health-economic analysis will concentrate on direct intervention and healthcare/personal social services costs, while wider impact (societal) costs will be included within the sensitivity analyses. Participants will complete resource use questionnaires at four and 12 month follow-up points, to collect resource use data associated with the interventions under examination. At the end of the follow-up period a copy of the participant's medical record will be requested from their GP. This will provide information on GP consultations and include copies of any hospital discharge letters allowing us to accurately cost in-patient care costs. Where appropriate, data will be triangulated from GP records, participant self-report, and data held in participating hospitals to achieve a robust estimate of health service activity.

11. All cause hospital admissions from GP records (see point 10. above).

12. Adverse events (see section 4.0 below).

13. All-cause mortality. Participants will be flagged with NHS digital to ensure notification of any deaths and cause of death both during the current study and for longer term follow-up.

Follow-up: The primary outcome is an objective measure of exercise capacity. This means participants will need to attend the treatment centre for assessment. Patient reported outcomes will be collected at follow-up assessments. If any participants are unable to attend, a postal questionnaire will be used to collect patient reported outcomes. In the case of non-response, two key secondary outcomes (CAMPHOR and EQ-5D-5L) will be collected by phone. Fluency in written English is not an inclusion criterion for this study. For those fluent in spoken, but not written English, CAMPHOR and EQ-5D-5L will be collected verbally at each follow-up. The EQ-5D-5L is well validated for verbal administration.

Long-term follow-up: Consent will be sought from participants to keep their personal data, and have access to their NHS data following the end of the current trial. This will allow longer term postal follow up to assess quality of life and to monitor deaths using NHS Digital data.

2.4.2 Safety

SPHERe will be delivered in cardiopulmonary rehabilitation units with access to emergency equipment and qualified staff. Condition specific monitoring of exercise responses, as per cardio-pulmonary rehabilitation guidelines, will reduce and manage risk [13, 30, 39]. Guided home exercise will be lower intensity and fully manualised with instructions and photographic images. Intervention practitioners will be specialist exercise physiologists or physiotherapists, experienced in assessment, prescription and delivery of exercise in high risk clinical populations. Training in the standardised

delivery of SPHERe will be provided. WCTU and UHCW have extensive experience of training people to deliver complex interventions for chronic disorders. This, and experience of quality control of practitioner training, will ensure work is delivered to a high standard.

See section 4.0 for AE and SAE information.

2.4.2.1 SPHERe intervention participant manual

This will be a professionally produced, comprehensive resource detailing, in a patient-friendly fashion, all information relating to the trial. It will be developed in the pre-pilot feasibility phase and submitted for ethical approval prior to commencing the internal pilot. In the form of a workbook, this resource will be introduced to the participant at the individual assessment and exercise familiarisation sessions. The manual will include: 1) general information about the trial; 2) background information about PH; 3) schedule for the participant's exercise programme, education and psychosocial and motivational sessions; 4) guided home exercise plan; 5) exercise diary; 6) general advice on safe and effective lifestyle physical activity; 7) useful links and contacts. Content will be developed with lay partners. It will also be available as an on-line resource with additional material orientated towards family and friends.

2.5 Eligibility criteria

People are eligible to be included in the trial if they meet the following criteria:

2.5.1 Inclusion criteria

1. Adults (18+) with confirmed PH (groups 1 to 5) as detailed in ESC/ERS guidelines [17].

2. Clinically stable: Groups 1, 4, & 5 - stable on optimal PH specific drug therapy (for those in whom it is appropriate) for at least 1 month, or evidence that these drugs cannot be tolerated. Groups 2 & 3 - stable on drug therapy for underlying cardiac or pulmonary disease for at least one month. Clinical stability will be confirmed by the lead practitioner at each site, in consultation with the responsible clinician, and determined as: presenting with, reproducible, manageable symptoms, not requiring any treatment other than routine follow-up care, and no PH related hospital admission in the last four weeks.

3. World Health Organisation (WHO) functional class II, III or IV. The modified New York Heart Association functional classification system adopted by WHO is used ubiquitously in PH. People are graded on ability to perform physical tasks, and classified as (I) no limitation, (II) mild limitation, (III) marked limitation, (IV) unable to perform any activity [37]. This will be determined by the lead practitioner further to contact with the patient.

People in functional class IV will not be excluded as symptoms and functional ability can vary considerably over time. Instead, those most severely affected will be excluded, on the basis that they are too unwell to attend a SPHERe centre, or to undertake exercise training.

4. Fluent in spoken English to allow engagement with intervention and physical outcome measures.

5. Live within reasonable travelling distance (as defined by the participant) of a SPHERe exercise rehabilitation centre.

6. Ability to provide informed consent.

   For adults lacking capacity to consent, e.g. people with PH secondary to Down's syndrome, but who are able to participate in the SPHERe intervention, we will seek advice from a personal consultee on whether they would wish to be included in our research study.

2.5.2 Exclusion criteria

1. Absolute contra-indications to exercise as per international clinical guidelines [30, 40].

2. PH related complications, or comorbidities severe enough to prevent attendance at a SPHERe centre, or participation in exercise rehabilitation.

3. Any mental health issue that will prevent engagement with study procedures.

4. Unable to make suitable travel arrangements.

5. Previous randomisation in the present trial

6. Pregnancy

2.6 Participant identification / Screening

Clinical pathway: the patient pathway from referral to diagnosis of PH is well defined in ESC/ERS guidelines [17], and is adopted by all SPHERe trial hospitals. The largest pool of potential participants is those not referred to specialist centres, but treated locally for underlying cardiac and pulmonary disease; i.e. predominantly groups 2 & 3 PH.

Participant identification: Participants will be identified and screened by the clinical care team only, via multiple, co-ordinated screening strategies will be used (see figure 2):

1. *Local secondary care disease registers:* Groups 1 and 4 PH are typically well recorded on disease registers (regardless of referral history to a specialist centre).

2. *Hospital discharge data:* Diagnosis specific coded discharge data (Performance and Programme Management Office, PPMO) identifies PH admissions.

   Discharge data from all hospitals will be regularly screened, using PPMO data, to identify admissions of all diagnostic groups of PH. All Trusts use the generic NHS coding system. Recruitment teams at each hospital will screen these data and identify potential participants. This strategy is currently employed clinically at all trial hospitals to identify people suitable for cardiopulmonary rehabilitation, meaning robust, effective systems are already in place.

3. *Specialist nurse/medical clinics:* People with less prevalent PH aetiology, not captured through other routes, are likely to attend the following clinics: Rheumatology, haematology, chronic heart failure, general cardiology, respiratory, adult congenital heart disease, nephrology, haemodialysis. At individual Trusts, research nurses will be allocated to support recruitment from these out-patient clinics.

4. *Liaise with all specialist PH centres*: To identify patients that live local to SPHERe centres who can be approached.

5. *Referrals to cardiopulmonary rehabilitation*: Staff running clinical services will be involved in SPHERe. They will identify and approach people referred for rehab, who have diagnosed PH.

6. *Echocardiogram records:* If necessary, clinical echocardiogram records will be searched for patients with a peak tricuspid regurgitation >3.4 m/s on transthoracic echocardiogram who have not already been approached. Treating clinicians will be contacted to ascertain if a subsequent diagnosis of PH was made and, if appropriate, ask them to contact the person about the trial. Because of the large number of such investigations performed, the low prevalence of PH, and the likelihood that such patients will already have been seen in a relevant clinic, this will be very labour intensive for a low yield. Nevertheless, if recruitment is slow, it is an additional strategy.

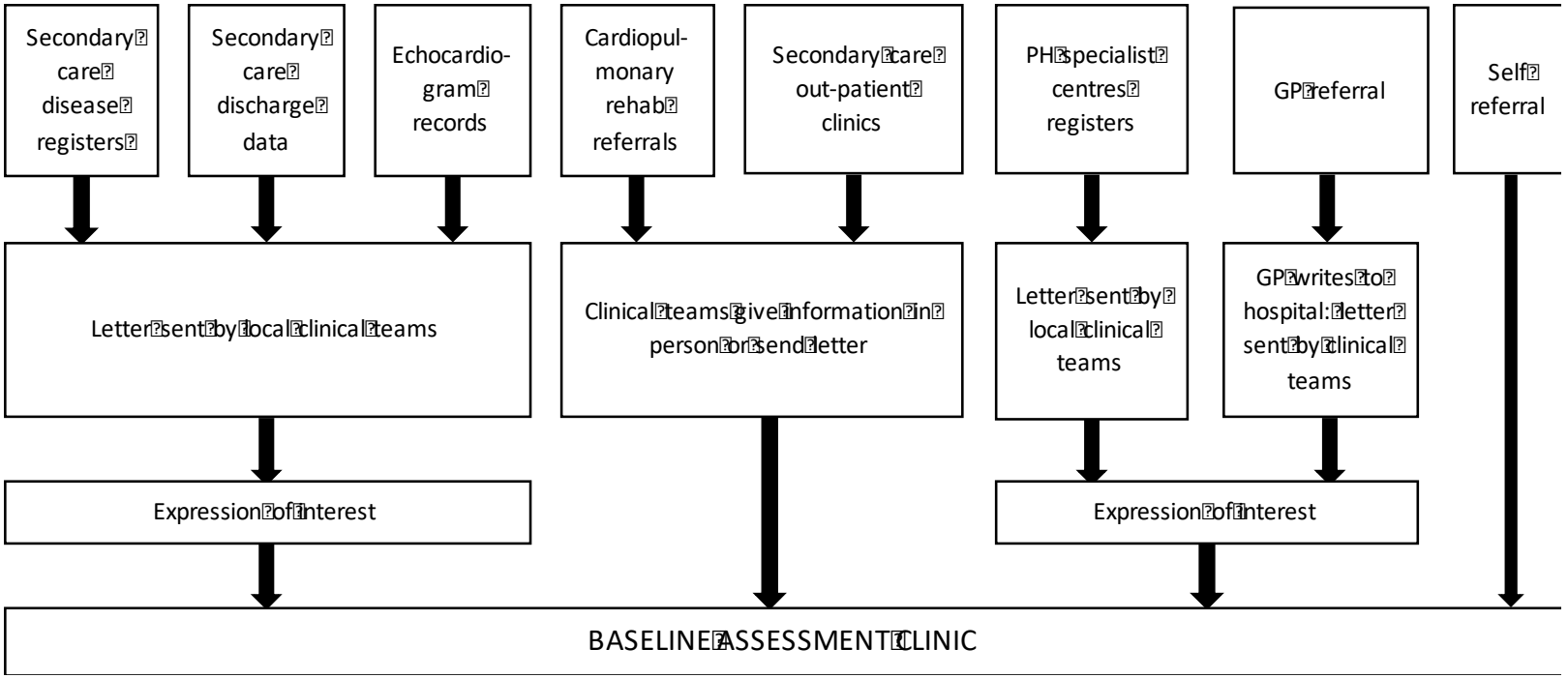
7. *GP or self-referral:* Most potential participants will be under the care of secondary/tertiary services; however, recruitment opportunities will be maximised by:

    a) Inviting GPs local to SPHERe centres to refer people with PH to the trial. Preliminary searches of GP record data indicate that the number of recorded diagnoses of PH are too few to make formal screening of GP records worthwhile. Nevertheless, the trial will be promoted to GPs.
    b) The trial will be promoted though local media/social media, relevant charities and on the trial website (text for this will be submitted to the REC for approval as a substantial amendment). People living with PH will be able to self-refer.

As individual people may be identified from multiple sources within each hospital, screening logs will record who has been approached to reduce risk of multiple approaches.

Screening logs will be populated at each hospital, to provide accurate information on patient eligibility, and reasons for non-participation, to inform future NHS service design.

Figure 2: Participant identification and approach flow-chart



2.7 Site Staff Training

Intervention practitioners: Practitioners delivering the SPHERe intervention at each centre will be Clinical Exercise Physiologists or Physiotherapists with appropriate professional registration, relevant continued professional development (CPD), and good clinical practice (GCP) training. An exercise lead (exercise physiologist/physiotherapist) at each Trust will be responsible for ensuring trial procedures are followed and standardised for intervention delivery.

SPHERe training: All intervention practitioners will undergo three days of SPHERe training. Day one will ensure an appropriate level of clinical knowledge and skills for exercise rehabilitation in PH. A further two days training will be delivered by a health psychologist, to upskill practitioners on the psychosocial components of the intervention. All three days, and subsequently the trial, will be supported by a comprehensive practitioner intervention manual. Access to expertise and support will be maintained and monitored throughout the duration of the trial. The exercise lead at each site will be responsible for ensuring additional practitioners are appropriately trained and familiarised with the manual. Full training will be provided by the SPHERe research fellow and health psychologist for new staff, as needed.

SPHERe practitioner manual: This detailed manual will guide practitioners through each component of the intervention, graphically and with written instruction. It will also include general information about the trial, key components of GCP, and contact details of the study team. The content will reflect information delivered during the three-day training for SPHERe intervention practitioners.

Exercise intervention: To enhance practitioners' knowledge of exercise assessment and prescription in PH, ensuring intervention efficacy and safety, the manual will provide an overview of key evidence and exercise guidance. To provide a level of standardisation, parameters within which the exercise intervention should be delivered and progressed, will be detailed.

Psychosocial and motivational intervention: The manual will give a detailed description of each psychosocial topic, with hints and tips of questions to ask, and the aims of each session. The content will map onto the intervention participant manual (see section 2.4.2.1), allowing the practitioner to tailor the discussion.

2.8 Consent

Confirmation of eligibility, and participant approach:

1. Clinical care team identify potential participants (as per recruitment strategy above section 2.6).
2. Screen recent electronic record to identify any obvious contra-indications to exercise.
3. If the potential participant may be eligible, confirmation of PH diagnosis will be sought from the relevant clinician.
4. The eligibility checklist will be completed and signed, confirming that eligibility has been approved by a suitably qualified clinician at each hospital.

5. Potential participant contacted in person (at clinic), by letter, or phone by a member of their clinical team. All approaches to potential participants will come from clinical teams involved in their care.
6. If the potential participant is interested, verbal information will be provided in person, and written information by email, or in the post.

Informed consent: potential participants will be invited to a baseline assessment appointment where consent will be taken in person by an appropriately trained member of the clinical or research team.

Adults lacking capacity: MRC guidelines will be followed; the trial will be discussed with the potential participant's personal consultee from whom advice will be continually sought during the trial. Any relevant issues will be discussed with the consultee prior to the study and clear accessible (to authorised personnel) records kept. The consultee will be kept fully informed during the study and will be invited to attend all appointments to support to the participant. All study information will be provided to the consultee who will be able to share and discuss it with the potential participant at an appropriate level. Clinical and research staff can be involved in these discussions at the discretion of the consultee.

GP notification: The participant's GPs will be informed by letter that they are taking part in the trial

Timing of consent: At the baseline assessment appointment, written informed consent will be obtained by a suitably trained member of the research team at each site, as per the delegation log, after allowing sufficient time for the potential participant to consider their decision and ask questions about the trial. Sufficient time for some potential participants may result in a decision to take part in the trial immediately after receiving all the relevant information in clinic. Alternatively, if potential participants would like to leave the clinic with the information and decide later, they will be free to do so, and will be contacted by phone at least 24 hours later.

Responsibility: Local PIs will retain overall responsibility for informed consent at their site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, qualified and competent.

When confirming consent for those unable to read English, a second person will be present to confirm correct explanation, i.e., family member or translator according to WCTU SOP 7.

New information: Any new information that arises during the trial that may affect participants' willingness to take part will be reviewed by the TSC; if necessary this will be communicated to all participants. A revised consent form will be completed if necessary.

Incidental findings relating to participants' medical conditions or general health, will be discussed with the managing consultant, and communicated to the participant as required.

Decline/withdrawal: Participants (or personal consultee) will have the option to withdraw before treatment starts (i.e. between baseline assessment and the beginning of the intervention/ control), if for any reason they change their mind. This will be recorded on a withdrawal form. The right of a potential participant to refuse participation without giving reasons will be respected and recorded on the screening log. A reason will be documented if participant is willing to offer one. The participant will remain free to withdraw at any time without giving reasons and without prejudice to any further

treatment, and will be provided with a contact point where he/she may obtain further information about the trial.

2.9 Randomisation

2.9.1 Randomisation allocation concealment and blinding

Pre-randomisation eligibility checks will be carried out to ensure that potential participants meet the eligibility criteria and are not randomised in error. Written consent for entry into the trial and baseline assessment must be obtained prior to randomisation. Subjects will be randomised once they have been registered as eligible for randomisation on the web-based system and attended their baseline assessment.

Randomisation will be undertaken using a computer-generated randomisation sequence, performed by minimisation, based on centre, PH group, and World Health Organisation (WHO) functional class. Allocation concealment will be maintained by using WCTU centralised randomisation service; with minimisation by centre, PH group (1-5), and WHO functional class [two categories: 1) Class II; 2) Class III or IV]. Where PH has multiple underlying aetiologies, the predominant diagnosis will be confirmed by the managing clinician. To maintain allocation concealment, all baseline data will be collected prior to randomisation. The treating practitioner will only receive the randomisation allocation once all baseline measures are complete. It is not possible to blind participants or practitioners to group allocation.

To maintain blinding, all follow-up data will be collected by staff not directly involved in intervention delivery who are blind to treatment allocation. Participants will be asked not to tell the assessing practitioner their group allocation. The quality of blinding will be tested by asking the assessor which treatment they thought each participant had received.

2.9.2 Post-randomisation withdrawals, exclusions and moves out of region

Participants may decline to continue involvement in the trial at any time, without prejudice. This will not affect the standard of care they receive. They will be advised to discuss their ongoing treatment with their clinician. For participants withdrawing from the trial, data obtained prior to the point of withdrawal, will be retained for the final analysis unless explicitly withdrawn at the participant's request. For participants who withdraw, a withdrawal CRF will be completed.

Participants may be withdrawn from the trial, at any time, at the discretion of the investigator and/or TSC.

Follow up: Core outcomes will be completed over the telephone, if postal copies are not returned. Text messages may also be sent to those participants, who have given their prior consent by initialling the corresponding box on the consent form and providing their mobile telephone number. Details pertaining to the timing and nature of planned follow up procedure for telephone/post/text message are further detailed in the data management plan. Contact details will be recorded, such as addresses, telephone numbers, mobile telephone numbers, email addresses and contact details of next of kin, to prevent loss to follow up. Informed consent to hold contact details and to contact the next of kin, will be taken from the next of kin. This identifiable information will be held securely on a password protected database accessible only to authorised personnel. Paper CRFs containing identifiable data will be stored separately from CRFS that correspond to the participant by participant ID number only.

2.10 Trial treatments / intervention

2.10.1 Trial treatment(s) / intervention

Format: To ensure generalisability to the NHS, the underpinning framework of SPHERe is based on UK cardio-pulmonary rehabilitation guidelines and service delivery models [13, 39, 41], and enhanced with PH specific recommendations [13, 16, 17].

Cardio-pulmonary rehabilitation: Participants randomised to the SPHERe intervention will access existing cardio-pulmonary rehabilitation programmes; i.e. they will exercise with people with a range of cardio-pulmonary disorders, as well as other trial participants randomised to the SPHERe intervention. Service design in the UK is heterogeneous, as is the case for SPHERe centres. Some centres provide separate cardiac and pulmonary rehabilitation programmes, whereas other centres combine these programmes. To maintain consistency of the intervention package, participants, regardless of PH aetiology, will be included, in a pulmonary rehabilitation programme wherever possible. Henceforth, this will be referred to as 'cardio-pulmonary rehabilitation'.

Programme design: To maximise accessibility and resource, whilst ensuring that the benefits of group interaction are retained, SPHERe will be delivered as a 'rolling' programme. Participants randomised to the SPHERe intervention will immediately join cardio-pulmonary rehabilitation exercise programmes running at each centre, rather than waiting for the recruitment of sufficient numbers to form a discrete group of trial participants.

The SPHERe intervention has **four components**:

Component 1. Individual assessment and exercise familiarisation
Individual assessment: A one-to-one appointment with a SPHERe 'practitioner' (specialist cardio-pulmonary clinical exercise physiologist or physiotherapist), independent of the research team. Participants will undergo a one hour 'assessment', as per standard practice in UK cardio-pulmonary rehabilitation programmes. This will include assessment of medical history, medication, clinical parameters (i.e. height, weight, resting blood pressure, O_2 saturation), exercise/physical activity history, and discussion of participant goals. Current exercise tolerance/capacity will be assessed to inform exercise prescription starting level, according to usual practice in participating centres (i.e functional capacity test such as ISWT).

Exercise prescription: The SPHERe practitioner will prescribe a tailored, individualised exercise programme [13, 30, 39] within pre-specified parameters, as detailed in the intervention manual. Clinical information, data from the exercise assessment, and patient centred goal setting will be used to devise a safe and effective exercise prescription.

Familiarisation sessions: Exercise guidance, specific to the underlying PH aetiology, will be delivered on an individual basis during two one-on-one familiarisation exercise sessions in the first week of the programme, and reinforced throughout, by clinical staff. Familiarisation sessions, conducted within the cardio-pulmonary rehabilitation programmes, will enable participants to build confidence, whilst SPHERe practitioners refine and optimise the exercise prescription. Practitioners will begin to introduce the principles of psychosocial and motivational support (see below – component 3) during these sessions.

Component 2. Supervised out-patient exercise programme:
Undertaken within existing cardio-pulmonary rehabilitation programmes delivered by NHS clinical staff. Up to twice weekly, one hour, supervised exercise sessions for the remaining seven, to ten weeks [13, 39] (maximum 14 sessions [16, including familiarisation sessions]), with a quantifiable and progressive dose of individualised, multi-modal, aerobic, muscular strength and endurance, and 'functional fitness' exercise. Adequate warm-up and cool-down will be incorporated. Intensity will be monitored and adjusted using heart rate, rating of perceived exertion, dyspnoea scale and pulse oximetry (O_2 saturation) [42].

The SPHERe exercise component is optimised to be appropriate for a broad spectrum of patients including frailer, deconditioned, low-mobility, exercise-naive participants. It will target physical goals identified as important by patients:

"less breathless, less fatigue, do more, walk further, climb stairs, fitter, more independence".

Equally, it will address their psychosocial priorities including:

"confidence to exercise, anxiety, motivation, frustration, social interaction, fun, engaging, something different".

These goals are unlikely to be satisfied by conventional gym exercise alone, so will be combined with 'functional fitness' training (described below). The programme will be highly adaptable to allow personalisation to lower or higher ability participants, whilst ensuring safety and efficacy. This is common practice within cardio-pulmonary rehabilitation programmes in the UK.

Gym exercise can be effective in improving cardiorespiratory fitness, muscular strength and endurance. However, it can lack physiological and biomechanical specificity to activities of daily living. Standard gym exercise is performed almost exclusively in the longitudinal plane (forwards/ backwards). In addition, adherence to this form of exercise is commonly poor [43, 44]. Much of this is thought to relate to the repetitive nature of this mode of exercise, the lack of perceived application to activities of daily living, and the limited opportunity for constructive social contact. Engagement with, and adherence to, exercise is enhanced by social, fun activities [45].

To address both these issues, SPHERe combines conventional gym-based aerobic exercise with 'functional fitness training'. This uses multi-plane motion (rather than just longitudinal), to target not only cardiorespiratory fitness, but also essential pre-requisites of active, independent living; e.g. agility, co-ordination, proprioception, balance and functional strength [43]. In addition to treadmills, cycle and rowing ergometers, SPHERe will make use of low-cost, readily available, functional fitness equipment; e.g. steps, floor agility ladder, low rise balance beam, power bags, plyometric boxes, ball (throw/bounce) etc.

Central to SPHERe is the expertise and experience of the specialist cardio-pulmonary exercise physiologists and physiotherapist at all trial centres who will ensure holistic, safe, individualised and effective exercise training. This conforms to existing recommendations of specialist exercise supervision for this population [13, 16, 17].

Component 3. Psychosocial and motivational support; and education:
Once per week, before or after exercise, participants will receive a one-to-one 30 minute psychosocial and motivational support session and a 30-minute group education session (six sessions). The former will be delivered by a SPHERe practitioner, and the latter by clinical staff. They will not necessarily be delivered back-to-back.

Psychosocial and motivational support: The aim is to improve short and long-term adherence to exercise, thus maximise benefit. As such, SPHERe will draw on social cognitive approaches to behaviour change [46], including scrutiny of multiple interactions between environment, personal factors and behaviours. Based on the COM-B framework, three basic aspects of peoples' lives will be addressed: capability (increasing confidence through supervised practice), opportunity (identifying internal and external opportunities), and motivation (education, self-reflection, goal setting) [47]. There will be a focus on increasing participants' awareness of their priorities, through an investigation of the pros and cons of changing a specific behaviour (self-management e.g. fear avoidance of exercise), and assisting them to develop a specific plan of changing behaviour (planning, goal setting). The SPHERe practitioners will be trained to use open questions and motivational interviewing to assess patients' current beliefs and encourage behaviour change.

Education: The underlying causes of PH are very heterogeneous; the World PH symposium classification records five main groups [7]. It will, therefore, be essential for participants to access disease specific education. Equally, living with PH involves management of symptoms, experiences and challenges that are common to all aetiologies of PH.

SPHERe participants will access both generic and disease specific group education sessions (with non-trial cardio-pulmonary rehabilitation patients), provided by clinical staff at all SPHERe centres, as part of existing cardio-pulmonary rehabilitation services. Generic and disease specific sessions for each participant will be identified and scheduled by a SPHERe practitioner at the individual assessment at the start of the intervention. Each participant will receive a timetable indicating which education sessions they are recommended to attend.

All participants (regardless of PH group) will attend generic sessions, provided as standard clinical practice by existing clinical staff, on: 1) managing breathlessness; 2) breathing control and relaxation; 3) anxiety and depression; and 4) activity pacing and energy conservation.

Disease specific topics, which may include medication, sputum clearance, managing cardiac symptoms, risk factors, smoking cessation, oxygen therapy etc, provided routinely by clinical staff, will be accessed as relevant. For people with PH groups 2 & 3, this specialist advice/education will be available as standard through the cardio-pulmonary rehabilitation programmes. Prior to enrolling in SPHERe, groups 1, 4, & 5 will have had discrete and extensive education with practitioners at local and national specialist clinics, as per their routine clinical treatment. Further advice, if required will be provided by SPHERe practitioners under the guidance of the managing consultant.

Component 4. Guided home exercise plan:
To complement supervised exercise, all participants will be provided with a manualised home exercise plan and access to online content. This will include material targeting family and friends to help ensure maximum support with the exercise programme. This will form part of the SPHERe intervention participant manual (see below) and will be developed during the pre-pilot phase. Detailed but simple

information relating to replication of the supervised exercise they have undertaken, in the home-based setting, will be provided graphically and with written instruction. The manual will include a diary to record time spent exercising.

Control intervention: The control arm, will be an intervention that could be described as 'best usual care', in the form of an individual practitioner (not intervention practitioner) appointment, with general advice on safe and effective physical activity in PH. A 30-minute appointment will allow the practitioner to discuss individualised ways in which the participant can undertake physical activity at home. They will not be provided with a structured exercise plan, rather comprehensive freely available leaflets, detailing ways in which low level physical activity can be safely and effectively incorporated into their everyday lives. No specific psychological techniques will be used to support the provision of this information. Doing this allows the usual care group to be offered best current practice, whilst retaining the aim of the study comparing a group who receive comprehensive PH exercise rehabilitation and psychosocial and motivational support, with a group who do not.

2.10.2 Compliance/contamination

Compliance: Attendance at assessments and intervention (familiarisation sessions, supervised exercise, home exercise and psychosocial/motivational) and control sessions will be recorded as one measure of compliance. The impact of compliance on outcomes will be assessed using a CACE (compliers average causal effect) analysis. For the intervention group, partial compliance will be defined as completion of the initial assessment and at least half of the familiarisation, supervised exercise, home exercise and psychosocial/motivational sessions. Full compliance will be considered as attending at least 75% of exercise, home exercise and psychosocial/motivational sessions. The psychosocial/motivational sessions, in themselves, are designed not only to help improve QoL, but equally to improve compliance and adherence.

Fidelity: The initial practitioner assessment, the two exercise familiarisation sessions and the psychosocial/motivational sessions will all be delivered 1:1, and will be audio-recorded and scored against criteria. These sessions will be audio-recorded to reduce the risk of those delivering the intervention behaving differently when being recorded. From these sessions, a purposively selected subset (10%) of recordings will be analysed, covering all centres and across relevant intervention sessions. This will enable assessment of fidelity, and an understanding of which areas generated discussion, and what issues were discussed.

Fidelity of supervised exercise dose will be monitored with total exercise duration and intensity compared to the exercise prescription. Guided home exercise will be monitored via diaries. The effectiveness of complex interventions can be influenced by the skill of those delivering the intervention, so in addition to fidelity, criteria for competence will be developed from the training manuals and assessed with a checklist. The control group individual practitioner appointments will also be audio recorded and scored against criteria.

Contamination: To reduce risk of contamination at each centre, the one-to-one components of the SPHERe and control interventions will be delivered by different practitioners. This is possible, as cardio-pulmonary rehabilitation programmes at all trial centres are run by teams of practitioners. To avoid any bias consequent upon the selection process for intervention practitioners, practitioners will be randomly allocated to delivery of either the SPHERe, or the control one-to-one components at each centre. Practical issues in delivery of regular clinical exercise rehabilitation sessions, in which our SPHERe participants are a small minority, mean that these may be led by practitioners who have not

been trained in the one-to-one components of the SPHERe intervention. They will, however, be competent in exercise rehabilitation supervision in PH.

2.11 Blinding and allocation concealment

Allocation concealment will be maintained by using WCTU centralised randomisation service; with minimisation by centre, PH group (1-5), and WHO functional class [two categories: 1) Class II; 2) Class III or IV]. Where PH has multiple underlying aetiologies, the predominant diagnosis will be confirmed by the managing clinician. To maintain allocation concealment, all baseline data will be collected prior to randomisation. The treating practitioner will only receive the randomisation code once all baseline measures are complete. It is not possible to blind participants or practitioners to group allocation.

To maintain blinding, all follow-up data will be collected by staff not directly involved in intervention delivery who are blind to treatment allocation. Participants will be asked not to tell the assessing practitioner their group allocation. The quality of blinding will be tested by asking the assessor which treatment they thought each participant had received.

2.12 Concomitant illness and medication

2.12.1 Concomitant illness

A medical history will be recorded for each participant at trial entry and recorded on the CRF. Only medical issues, most prominent and relevant, will be recorded using a tick box system.

2.12.2 Concomitant medication

A full medication list will be recorded for each participant at trial entry and recorded on the CRF

2.13 End of trial

The trial will end when all participants have completed their 12-month follow-up.As part of the process evaluation n=20 controls and n=20 intervention will be interviewed **after** their 12-month follow-up.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Recommended by the DMC
- Funding for the trial ceases

The Research Ethics Committee will be notified in writing within 90 days when the trial has been concluded or within 15 days if terminated early.

3 METHODS AND ASSESSMENTS

3.1 Schedule of data collection

Table 1. Trial visits/assessments

Visit	Phone/Clinic	1	2	3
Time-point	Pre-consent	Baseline	4 months	12 months
Eligibility checks (on phone/in person)	**X**			
Written/verbal information	**X**			
Written informed consent		**X**		
Case report from		**X**	**X**	**X**
Incremental shuttle walk test		**X**	**X**	**X**
Six-minute walk test		**X**	**X**	**X**
CAMPHOR		**X**	**X**	**X**
EQ-5D		**X**	**X**	**X**
HADS		**X**	**X**	**X**
Generalised self-efficacy scale		**X**	**X**	**X**
Fatigue severity scale		**X**	**X**	**X**
WHO functional class		**X**	**X**	**X**
Time to clinical worsening			**X**	**X**
Medication use		**X**	**X**	**X**
Health/social care resource use			**X**	**X**
All-cause mortality			**X**	**X**
Adverse events		**X**	**X**	**X**
Semi-structured interviews				**X**

3.2 Long term follow-up assessments

Consent will be sought from participants to keep their personal data, and have access to their NHS data following the end of the current trial. This will allow longer term postal follow up to assess quality of life and to monitor deaths using NHS registry data.

3.3 Process evaluation

Semi-structured interviews with participants: Information about interviews will be provided to all participants during trial recruitment. Participants will be asked to consent (or not) to being contacted at the end of the trial to share their views and experiences of the intervention. Written informed consent will be taken before the interview.

Interviews will be conducted by a qualitative Research Fellow from WCTU, in person or on the phone/over skype as appropriate. Intervention and control participants will be interviewed to investigate their experiences, contextualise quantitative findings, and explore factors that helped or hindered participation, thus informing interpretation and wider implementation. Interviews will take place after the 12-month follow-up outcome data collection, so that the interview itself does not introduce bias to the analysis. A purposive sample of approximately n=20 intervention and n=20 control will be interviewed to ensure a diverse range of perspectives are included. The interviews will use a topic guide that will include participant response to the intervention (or control), what was difficult, what worked well, specific obstacles and enablers, what components were used/dropped/never used, and views on the guided home exercise content. They will last one hour, be digitally recorded, and piloted with up to five people from the internal pilot.

Practitioner interviews: At the end of the study, a purposive sample of n=20 intervention and control practitioners will be interviewed about their experiences of delivering the interventions, what worked well, what helped, and what was challenging. These interviews will last up to one hour, be digitally recorded, and piloted with up to five practitioners.

4. ADVERSE EVENT MANAGEMENT

4.1 Definitions

4.1.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence involving a participant, which does not necessarily have a causal relationship with the intervention or trial.

Expected AEs, related to the exercise outcome assessments or the exercise intervention (supervised or SPHERe home programme), include 'normal' levels (for the individual) of:

- Breathlessness
- light headedness/dizziness
- muscle stiffness/soreness
- tiredness/fatigue
- exertional chest pain
- O_2 desaturation

Recording procedures will be the same for both trial groups. For the **intervention group,** expected AEs will be recorded on the participants' exercise session notes (not on an AE form), for clinical purposes only. For the **usual care group** these will be recorded on the participants' exercise outcome assessment notes (not on an AE form) for clinical purposes only.

Unexpected AEs related to the exercise outcome assessments or the exercise intervention (supervised or SPHERe home programme) for both the intervention and usual care groups, will be recorded on the appropriate CRF and returned routinely to WCTU.

AEs in the **intervention group** will be determined through patient report at each intervention session visit. AEs in the **usual care group** will be determined via a phone call to the participant the day following their appointment. This call is not routine, and will be made by the SPHERe outcomes assessors.

4.1.2 Serious Adverse Events (SAEs)

A substantial number of serious adverse events (SAE) are expected in this population. Over the four-month follow-up period, many people will be admitted to hospital, possibly on multiple occasions, and some deaths are expected. Hospital admissions and deaths are important outcomes for this study. Admissions data will be collected from self-report and GP records, and deaths from NHS digital. These data will be presented to the TSC and DMC.

For SPHERe, an SAE will be an untoward medical occurrence that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is an important medical condition

SAEs that may be expected as part of the interventions will be pre-defined and recorded on the participant's CRF for routine return to WCTU (SPHERe office).

The following SAEs are expected with PH and **do not** require reporting for this trial, but must be recorded in the relevant section(s) of the CRF:

- Hospitalisation for respiratory infection or related complication
- Disease progression: worsening exercise tolerance, atrial arrhythmias or decreasing oxygen saturations; or up titration of pulmonary vasodilators.
- Disease related deaths
- Treatment, which was elective or pre-planned, for a pre-existing condition, not associated with any deterioration in condition
- General care, not associated with any deterioration in condition

Reportable SAEs - intervention group: SAEs directly related to exercise sessions (supervised or SPHERe home programme) or outcomes assessments are possible. In the intervention group, any event that occurs at any time (supervised, or at home) between baseline outcomes assessment and the four-month follow-up, or within 24 hours of the four and 12-month outcome assessment appointments, will be recorded and reviewed to determine if it is directly attributable to the intervention, and investigated in line with WCTU's SOP. This will be determined by participant report at each intervention session. If a participant has not attended two consecutive intervention appointments, their status will be checked on local electronic clinical records by the local SPHERe clinical rehabilitation team (with participant consent). If their status is unclear, the SPHERe clinical rehabilitation team will attempt to make contact on the phone at least three times. If, they remain uncontactable, the participant's next of kin will be contacted (with consent). SAEs related to the 4 and 12 month outcomes assessment appointments will be determined via a phone call to the participant, the day following their appointment.

Reportable SAEs - usual care group: any event occurring within 24 hrs of each of the assessment appointments (baseline, four months, 12 months) will be recorded and reviewed to determine if it is directly attributable to the trial; this will be determined via a phone call to the participant the day following their appointment. Any SAEs occurring between the baseline phone call and the four month follow-up appointment will be determined by participant self-report at the four month appointment.

All participants experiencing SAEs during the period up to the four-month follow-up assessment, or during the 24 hour periods after the four month and 12 month outcomes assessment appointments will be followed-up until resolution of the event.

4.2 Reporting related and unexpected SAEs

All SAEs will be entered onto the appropriate reporting form and returned to WCTU, using a dedicated SPHERe resource email, within 24 hours of the investigator being made aware. The trial manager will liaise with the local PI to compile all the necessary information. WCTU is responsible for reporting any related and unexpected SAEs to the sponsor and REC within required timelines. All SAEs will be recorded for inclusion in the annual reports to the REC. The CI, in consultation with the trial medical team, will review causality.

The causality of SAEs (i.e. relationship to trial intervention) will be assessed by the investigator(s) using the SAE form (table 2).

Table 2. SAE Causal relationship

Relationship to trial medication	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

To establish causality, the following information should be collected for each SAE:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to intervention), in the opinion of the PI
- whether the event would be considered expected or unexpected.

SAEs that are deemed to be unexpected and possibly, probably or definitely related to the trial interventions or outcomes assessments, will be notified to the Research Ethics Committee (REC) within 15 days. All such events will be reported to the TMG at their next meeting. All SAEs that occur

between the date of randomisation and the end of the four month follow-up, and within 24 hours following the 12 month assessment, will be reported.

Any change of condition or other follow-up information should be communicated to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed until resolution or a final outcome has been reached. A member of the PI's trial team will be instructed to closely monitor each participant who experiences a SAE, until the outcome of the SAE has been determined.

Annual reporting: All SAEs will be recorded for inclusion in annual reports to the Research Ethics Committee.

4.3 Responsibilities

Principal Investigator:

1. Checking for AEs when participants attend for treatment / follow-up.
2. Using clinical judgement in assigning seriousness, causality and expectedness.
3. Ensuring that all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event, and providing further follow-up information as soon as available.
4. Ensuring that AEs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using clinical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Using clinical judgement in assigning expectedness.
4. Immediate review of all related and unexpected SAEs
5. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
6. Production and submission of annual reports to the relevant REC.

Sponsor:

1. Central data collection and verification of AEs, and SAEs, according to the trial protocol.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (DMC and TSC) according to the Trial Monitoring Plan.
4. Expedited reporting of related and unexpected SAEs to the REC within required timelines.
5. Notifying Investigators of related and unexpected SAEs that occur within the trial.

Trial Steering Committee:

In accordance with the Trial Terms of Reference and/or charter for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee:
In accordance with the Trial Terms of Reference and/or charter for the DMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

4.4 Notification of deaths

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the intervention, or an unrelated event.

4.5 Reporting urgent safety measures

If any urgent safety measures are taken, the CI/Sponsor shall immediately and, in any event, no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

5. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the General Data Protection Regulation.

Personal identifying information will be sent to and stored at WCTU for follow up purposes. Handling of personal data will be clearly documented in the participant information sheet and consent obtained.

Disclosure of confidential information will only be considered if there is an issue which may jeopardise the safety of the participant or another person, according to WCTU SOPs (WCTU SOP 15 part 1) and the UK regulatory framework. There is no reason to expect this situation to occur in this trial more than any other.

5.1 Data collection and management

The CRFs will be developed by the trial manager in consultation with the CI, statistician, health economist and other relevant members of the trial team to collect all required trial data. A suitably trained member of the research team at each site will complete the CRFs and enter the data onto a secure online trial database hosted by WCTU as outlined in the data management plan and in accordance with the WCTU SOPs. Paper CRFs will be returned to WCTU for data checking and quality assurance. Various methods will be used to chase missing data/unreturned questionnaires including post, phone, text and email (section 2.9.2), the procedures for managing this will be outlined in the data management plan and appropriate consent will be sought to contact participants. Data will still be collected for participants who discontinue or deviate from the intervention protocol, unless they withdraw their consent (section 2.9.2).

5.2 Database

The database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff including the trial statistician.

5.3 Data storage

All essential documentation and trial records will be stored at WCTU in conformance with the applicable regulatory requirements and access to stored information (paper and electronic) will be restricted to authorised personnel. All data will be stored in a designated storage facility within the WCTU. Electronic data will be stored on password protected university computers in a restricted access building.

5.4 Data access and quality assurance

All data will be pseudo-anonymised after the collection of the baseline demographic data for each participant. Confidentiality will be strictly maintained and names or addresses will not be disclosed to anyone other than the staff involved in running the trial. All electronic participant-identifiable information will be held on a secure, password-protected database accessible only to essential personnel. Paper forms with participant-identifiable information will be held in secure, locked filing cabinets within a restricted area of WCTU. Participants will be identified by a participant number only. Direct access to source data/documents will be available for trial-related monitoring or audit by UHCW or WCTU for internal audit or regulatory authorities. The PI must arrange for retention of trial records on site in accordance with GCP and local Trust's policies.

Direct access to source data/documents will be required for trial-related monitoring. For quality assurance, the data and results will be statistically checked. A full data management plan will be produced by the trial manager and statistician to outline the data monitoring checks required.

5.5 Data Shared with Third Parties

Requests for data sharing will be managed in accordance with University of Warwick/WCTU policy on data sharing. The datasets generated during and/or analysed during the current study are/will be available upon request after publication of the main study results. The publication of a trial protocol, trial results and trial data will be in line with the NIHR standard terms and will follow WCTU SOP 22: Publication & Dissemination.

5.6 Archiving

Trial documentation and data will be archived for at least ten years after completion of the trial. Trial documentation and data held by recruiting NHS sites will be stored in line with their local trust policy

6. STATISTICAL ANALYSIS

6.1 Power and sample size

The primary outcome will be distance walked measured using the ISWT at four months post-randomisation. As there are no directly applicable ISWT data with which to calculate a sample size,

or previously defined worthwhile effect sizes on IWST for people with PH, to inform a sample size calculation, so 6MWT data have been used to inform the sample size estimation. The 6MWT distance, unlike the alternative approach of using a standardised mean difference, has the advantage that it is meaningful to our participants and grounded in clinical reality.

The baseline pooled 6MWT distance in current studies of exercise rehabilitation for PH is 414 meters (SD 91) [18]. Whilst a useful starting point, these data indicate a comparatively fit group of people with PH (younger, group 1 PH). Typically, people with PH, seen in the cardio-pulmonary rehabilitation service at UHCW, walk around 300m in the 6MWT. Conventionally, the minimally clinically important difference for PH studies is 30m on 6MWT or a standardised mean difference (SMD) of 0.33 [19]. Our patient partners suggest that a larger difference is needed to make this treatment worthwhile; it requires a substantial commitment from people debilitated with potentially life-limiting PH to attend the treatment sessions. Therefore, sample size is predicated on showing a mean difference of 45m in 6MWT distance. This equates to a standardised mean difference of 0.5; conventionally a moderate effect size.

Further support for choosing this effect size comes from the related area of COPD research where patients indicate that the smallest difference in walk distance they might perceive as worthwhile is 54m (31-71) on 6MWT [48]. Using the convention that an effect size of around half of the minimally important within person change can be taken as a moderate between group effect, suggests that 27m might be a relevant between group difference in 6MWT distance for our trial. A difference of 45M in 6MWT should be a worthwhile benefit to patients with PH.

It is unusual to use a secondary outcome to inform a sample size. However, it is preferable to using a primary outcome with substantial concerns regarding its measurement properties in the population of interest (i.e. 6MWT) [31]. However, as the data are not available to make a robust estimate based on ISWT, this approach is preferred, grounded in clinical reality, and strongly supported by our patient group/partners, rather than simply using a statistical convention based on standardised mean difference.

To achieve 90% power at 5% significance level, to show a difference in 6MWT distance of 45m, with a standard deviation of 90, data from 170 people are needed. Experience across multiple studies has been that the effects of clustering by group or practitioner are trivial. Nevertheless, allowance has been made for clustering effects by site in the intervention arm, using Moerbeek's method [49] and an unbalanced randomisation. This allows calculation of the most efficient sample size for a study with clustering in just one trial arm, and generates an unbalanced randomisation.

The unequal allocation (1.15:1 for intervention vs control) was determined based on the following assumptions: a mean cluster size of 12 at follow-up, an ICC of 0.03 and same group variance. The ICC is an overall estimation of the site and practitioner effect, leading to an estimated design effect of 1.33, although a negligible practitioner effect in this trial is anticipated. Accordingly, the group sample sizes were calculated separately, given the power of 90% and a significance level of 5%. A minimum 80% retention rate is expected at four months based on clinical experience of working with this patient group, and exercise rehabilitation complex intervention trial experience in similar population. Therefore, 246 participants (132 in intervention) will be recruited to allow for 20% loss to follow-up (whilst striving to keep this below 10%)

The primary aim is to show an overall effect size for all groups without considering participant mix. Based on published data for prevalence of PAH and CTEPH, however, most participants will have PH groups 2 or 3; i.e. secondary to cardiac or pulmonary disease. These are also the groups where there is the most pressing need for data to inform clinical management. Existing data support the use of exercise rehabilitation to improve QoL in cardiac and pulmonary disease without PH, i.e. the underlying conditions of groups 2 & 3 PH. Sufficient data will be collected to assess outcome in a pooled group of people with group 2 or 3 PH as a secondary analysis. Approximately 70% of the total sample size will be people with group 2 or 3 PH. To ensure power of 90% power, for this sub-group, the latter sample size of 246 will inflated to around 352 patients. This will be the total sample for the trial which will ensure sufficient power for the main analysis as well as the sub-group analysis. There is some uncertainty about the final sample size because of the need to include 246 people with types 2/3 in our overall population and an ambition to include a minimum of 20 people each from sub-groups 1, 4, & 5

Representation of different sub-groups will be monitored during recruitment and, if necessary, steps taken to ensure each sub-group is represented appropriately.

6.2 Statistical analysis of efficacy and harms

6.2.1 Statistics and data analysis

Unless otherwise stated, further details in relation to the planned analyses will be detailed in a statistical analysis plan (SAP), which will be agreed with the DMC. All data will be analysed and reported in accordance with the CONSORT statement. All primary analyses are planned to be on an intention to treat basis with secondary per protocol analysis.

6.2.2 Planned recruitment rate

During a six month internal pilot, from four NHS Trusts, 60 (25-30 per arm) participants will be enrolled. Running seamlessly into the main trial, by the end of the pilot, the aim is to be recruiting 23 participants per month in total from all Trusts combined. This will continue for the remainder of recruitment.

6.2.3 Statistical analysis plan

Treatment effects will be presented, with appropriate 95% confidence intervals, for both the unadjusted and adjusted analyses. Tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05 (5% significance level). All analyses will be conducted as intention to treat unless otherwise specified.

6.2.3.1 Summary of baseline data and flow of patients

Baseline data will be summarised to check comparability between treatment arms, and screening data will be checked to highlight any characteristic differences between those individuals in the study, those ineligible, and those eligible but withholding consent. A CONSORT chart illustrating participant flow throughout the study will also be produced. Standard statistical summaries will be presented for the primary outcome measure (ISWT) and all secondary outcome measures.

6.2.3.2 Primary outcome analysis

The main analyses will be for overall treatment effect regardless of PH diagnostic group.

Data will be summarised and reported in accordance with CONSORT guidelines for RCTs, using intention-to-treat analyses [50]. Hierarchical linear regression models will be used to estimate the treatment effects (95% confidence intervals), adjusted for important patient-level covariates and centre effect. These will be defined in the final analysis plan. Estimation of, and adjustment for practitioner effects will be included. If there is negligible practitioner and centre effect, then the usual linear regression will be used for the analysis. Categorical data will be assessed in a similar way, using logistic regression models. The main analyses will all be intention to treat. Any control participants referred to cardio-pulmonary rehabilitation as part of their routine clinical care will be analysed according to their original randomisation. We will assess the impact of compliance on outcomes using a CACE (Compliers average causal effect) analysis. For the intervention group, partial compliance will be defined as completion of the initial assessment and at least half of the familiarisation, supervised exercise, home exercise and psychosocial/motivational sessions. Full compliance will be considered as attending at least 75% of the supervised exercise, home exercise and psychosocial/ motivational sessions. In addition we will aim to present probabilities for achieving the desired effect size in each of the groups using the magnitude based inference approach.[51]

In a planned secondary analysis the pooled effects for groups 2 & 3 will be presented (see below). Main outcomes will also be presented by diagnostic group (minimum 20 people contributing data) to inform decision makers and guidance developers interested in specific groups. To maximise data value, data from published trials (identified in an updated systematic review) assessing the same outcomes in RCTs of out-patient/community outreach interventions for specific PH group, will be included.

6.3 Subgroup analyses

Pre-specified sub-group analyses will examine the interaction of treatment assignment with the groupings of PH. Analysis will be conducted using formal tests of interaction. This trial is not powered to identify interactions. Thus, whilst pre-specified, these analyse should be considered as no more than exploratory. We will, however, present the effect size for pooled groups 2&3 as a separate analysis.

6.4 Subject population

The primary analysis and any secondary analyses will be applied to an all-randomised population on an intention-to-treat basis. That is, any subject randomised into the study, regardless of whether they received study intervention and regardless of protocol deviations, unless specified above.

6.5 Procedure(s) to account for missing or spurious data

Whilst every effort will be made to ensure compliance and data collection, it is inevitable that some data will be missing and likely that cross-overs will occur (i.e. exercise sessions not attended or participant requests for treatment). Careful monitoring of missingness and crossovers will be conducted. If judged appropriate, Multiple Imputation (MI) will be used to account for missing data, with all necessary assumptions reported. If large numbers of treatment cross-overs are observed, Complier-Average Causal Effect (CACE) models will be used. Similar to Per Protocol (PP) methods, CACE models evaluate the average effect of the intervention in participants who comply with their allocated treatment. This preserves randomisation groups and eliminates introducing any potential confounders introduced by PP analysis.

Some data may not be available due to voluntary withdrawal of participants, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for data 'missingness' will be ascertained and reported. The nature and pattern of the missingness will be carefully considered, including whether data can be treated as missing completely at random. If judged appropriate, missing data will be imputed using the multiple imputation facilities available in statistical analysis software.

If imputation is undertaken, the resulting imputed datasets will be analysed, together with appropriate sensitivity analyses. Any imputation methods used for scores and other derived variable will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated, and any patterns summarised. More formal analysis, for example using logistic regression with 'protocol violation' as a response, may also be appropriate and aid interpretation.

6.5 Qualitative data analysis

The semi-structured interviews with ~n=20 intervention group, ~n=20 control and ~n=20 practitioner's will be digitally recorded, subject to the permission of each participant/practitioner, pseudo-anonymised, and transcribed verbatim. Data will be analysed using the Framework method[52], broadly as follows:

- Data familiarisation: reading of complete interview transcripts, listening to original audio recordings and use of field notes;
- Identifying a thematic framework: key issues, concepts and themes are identified and an index of codes developed;
- Indexing: whereby the index generated through identification of the thematic framework is applied to all data;
- Charting: a summary of each passage of text is transferred into a chart to allow more overall and abstract consideration of index codes across the data set and by each individual;
- Mapping and interpretation: understanding the meaning of key themes, dimensions and broad overall picture of the data and identifying and understanding the typical associations between themes and dimensions;

The charting process provides an opportunity to code data from numerous perspectives. The computer package NVivo 11 will be used to organise the analysis.

The findings of the qualitative work will be reported as a separate chapter in the final report but will also be incorporated in the discussion to bring together a synthesis of all the results, thus helping to explore and explain the overall 'value' of the interventions. Quantitative and qualitative data will be integrated using a mixed methods matrix' where quantitative responses can be compared to interview data and recorded on a matrix [53]. This is particularly useful to reveal gaps between quantitative and qualitative insights.

From the intervention delivery recordings (initial practitioner assessment, the two exercise familiarisation sessions and the psychosocial/motivational sessions) and control (1:1 session) recordings, a purposively selected subset (10%) of recordings will be analysed, with a checklist to assess fidelity and using the qualitative approach detailed above to help understand which areas

generated discussion and what issues were discussed. Intervention fidelity will be assessed using the tenets highlighted by Mars et al. [53]

6.7 Health Economic Evaluation

A prospective economic evaluation, informed by the NICE Reference Case, will be described within a Health Economics Analysis plan (HEAP), to be set prior to any analysis.

The primary perspective will include NHS and Personal Social Services (PSS) costs. However, patient direct and indirect costs will also be included in a secondary broader societal perspective. Resource use collection will be tested in the internal pilot phase. Primary care and referral events will be captured both from health records and from participants, using a triangulation and adjudication approach to promote robust estimates of resource use. Participants will also report PSS and personal direct and indirect costs. Personal Social Services Research Unit (PSSRU) and national hospital reference costs will be used as principal unit cost sources. Patient level costs will be estimated by summing resources, costed using unit costs. Intervention costing will reflect the structure within which care is being given and will, by necessity, balance precision with practicality.

EQ-5D-5L responses will be used to generate quality-adjusted life years (QALYs) using the UK value set recommended by the EuroQol group [54]. These health state values will be used to estimate QALYs at the patient level, over one year, using the trapezoidal rule. Within its position statement, NICE supports continued use of the EQ-5D-5L descriptive system to collect QoL data within prospective clinical studies. Should NICE consider the SPHERe intervention as part of its future guidelines, trial-based EQ-5D-5L values will be mapped to 3L, if required. The EQ-5D-5L will be used as the overall HR-QoL outcome due to specific concerns about the sensitivity to change of other measures such as the SF-36, in this population. The EQ-5D-5L is likely to be more responsive to change than the 3L, and hence is preferred as a clinical outcome. Significant adverse events will be captured summatively in the QoL estimation.

Bivariate regression of costs and QALYs (with bootstrapping of models) will generate incremental cost per QALY estimates and credible intervals, cost-effectiveness acceptability curves, and value-of-information analysis. With regard to normality, invoking the central limit theorem avoids the problems that non-Gaussian link functions generate for the analysis. However, if distributions are very unusual, cost and QALYs will be conflated in a net benefit analysis evaluated at different thresholds of willingness to pay, reducing the analysis to a univariate regression problem.

Mechanisms of missingness of data will be explored following best practice, and (as appropriate) imputation sets will be used to avoid the potential bias of complete case analysis. The imputation model will use fully conditional (MCMC) methods (multiple imputation by chained equations). Predictive mean matching, drawing from the five nearest neighbours (knn=5), will be used to enhance the plausibility and robustness of imputed values. Each draw will be analysed independently using bivariate regression and the estimates obtained will be pooled to generate mean and variance estimates of costs and QALYs using Rubin's rule – managing within and between variances for imputed samples. To minimise the information loss of finite imputation sampling, 20 draws will be taken. The distribution of imputed and observed values will be compared visually and statistically to establish the consequences of estimation.

The time horizon for costs and outcomes will be 12 months for the within trial analysis. If incremental costs and benefits are not convergent within the trial duration, a long-term decision analytical model will be developed, partially informed by longer-term mortality follow-up.

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

UHCW NHS Trust will sponsor the trial. The day-to-day running of the trial will be managed by WCTU according to WCTU SOPs, with UHCW SOPs used for contracting.

7.2 Ethical approval

All ethical approvals will be sought using the Integrated Research Application System. The trial will be conducted in accordance with relevant regulations and guidelines. Before enrolling people into the trial, each trial site must ensure that the local conduct of the trial has the agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol people into the trial until written confirmation of R&D agreement is received by the co-ordinating team. Substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, analyses) will be communicated by the trial team to relevant parties i.e. investigators, RECs, participants, NHS Trusts and trial registries. Annual reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The REC and sponsor will be notified of the end of the trial (whether the study ends at the planned time or prematurely). The CI will submit a final report to the required authorities with the results, including any publications, within one year ending the trial.

7.3 Trial Registration

The trial is registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Register: ISRCTN 10608766

7.4 Notification of serious breaches to GCP and/or trial protocol

A “serious breach” is a breach which is likely to effect, to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial;
(b) the scientific value of the trial

If a serious breach occurs, the sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase

7.5 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol.

7.6 Trial timetable and milestones

Table 3. Trial timetable and milestones

Month	Activity	Milestone	Team
-3-0	Ethics submission	Approval	CI/TC
1-3	1. Start project 2. Finalise protocol & CRFs 3. Finalise trial manuals 4. Pre-pilot with 6-10 participants 5. Train practitioners at pilot centres	1. 1st TMG/TSC/DMC 2. Final versions approved 3. Final versions approved 4. Feasibility confirmed 5. Practitioners deemed competent	 CI/TC/TM/ TSC/DMC CI/RF
4-9	1. Recruitment at multiple pilot centres 2. Start 4-month follow-up 3. Recruit 60 4. Progress recruit rate to 23/month 5. Decision on trial progression	1. Initiate site opening 2. Initiate 4-month follow-up phase 3. 3 sites recruiting to target 4. Recruiting at target rate 5. Report to TSC and HTA	TC/CI/RF TMG CI/TC/RF CI/TC/RF TMG/TSC
10-23	Completion of site set-ups (recruit at 23/month)	4 sites set-up and recruiting	TC/CI/RF
	Start 12-month follow-up assessment and interviews	Initiate 12-month follow-up phase and interview phase	TMG/RF
	Data review of first 176 participants – decision on trial progression	DMC report	DMC via TSC to HTA
	50% total recruitment	176 participants enrolled	TMG/TSC
	End recruitment	352 participants enrolled	TMG/TSC
24-27	1. Complete 4-month follow-ups 2. Statistical/health economic analysis of primary outcome	4-month follow-up phase closed	TMG/TSC Lead Stat/HE
28-35	Complete 12-month follow-ups and interviews	12-month follow-up phase closed	TMG/TSC/Lead Stat /HE/RF
36-39	1. Statistical/health economic analysis secondary outcome data 2. Data review all patients	Final DMC and TSC meetings	DMC via TSC to HTA
27-83	5-year postal follow-ups	Final follow-ups complete	CI/TC/TM

7.7 Administration

The trial management team will be based at WCTU, University of Warwick.

7.8 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the TSC or Investigators, as appropriate.

7.9 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

The membership of the TSC will be approved and appointed by the NIHR.

The full remit and responsibilities of the TSC will be documented in the Committee Charter which will be signed by all members.

7.10 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant clinical research, and statistical experience. The DMC meeting frequency will be guided by the DMC chair, but will be suggested to be three months into the recruitment phase and regularly thereafter, as directed by the DMC chair. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated. The membership of the DMC will be approved and appointed by the NIHR.

DMC meetings may also be attended by the CI and Trial Manager (for non-confidential parts of the meeting) and the trial statistician.

The full remit and responsibilities of the DMC will be documented in the Committee Charter which will be signed by all members.

7.11 Essential Documentation

A Trial Master File will be set up according to WCTU SOP 11 and held securely at the coordinating centre. The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

7.12 Financial Support

The trial has been funded by a grant from the NIHR Health Technology Assessment (HTA) programme further to a commissioned call: HTA: 17/129/02

8 MONITORING, AUDIT AND INSPECTION

The study will be monitored by the Research and Development Department at UHCW as representatives of the lead Sponsor, and by the Quality Assurance team at WCTU as representatives of the trial coordinating centre and academic lead, to ensure that the study is being conducted as per protocol, adhering to Research Governance and GCP. The approach to, and extent of, monitoring will

be specified in a trial monitoring plan determined by the risk assessment undertaken prior to the start of the study. A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG) and TSC based on the trial risk assessment, including on site monitoring if applicable. Processes to be considered in the monitoring plan will include participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection. The plan will be available from the trial coordination centre and will also be lodged with the sponsor. Whilst the monitors work in the same institution as the CI and trial team (WCTU), they will act independently in this role.

Sites persistently late in reporting SAEs, receipt of multiple late/poorly completed CRFs, or evidence from CRFs that the trial protocols and procedures are not being adhered to (as assessed by the CI or the TMG) may be considered triggers for on-site monitoring visits. The sponsor will ensure investigator(s) and/or institutions will permit trial-related monitoring, audits and REC review, providing direct access to source data/documents as required. Monitoring will be performed by exploring the trial dataset or performing central monitoring procedures and/or site visits, as defined in the trial monitoring plan. Recruitment sites are obliged to assist the sponsor in monitoring the study. These may include hosting site visits, providing information for remote monitoring, or putting procedures in place to monitor the study internally.

9 PATIENT AND PUBLIC INVOLVEMENT (PPI)

Much of the SPHERe intervention was developed during the application process; the intervention was co-produced/developed/refined between January to June 2018, with patient and public involvement at every stage. Intervention components were modelled on existing clinical practice at NHS exercise rehabilitation centres, for people with severe COPD/CHF/ACHD/CHD (with co-existing PH). A three-stage process was followed as per MRC guidance: 1) systematic literature review; 2) expert opinion, stakeholder engagement and consensus meetings; 3) intervention piloting, acceptability and refinement

Lay co-applicants were fully integrated into the development of this trial, taking an active role in refining intervention components and reviewing the application. They will sit on the trial management group (TMG), initially meeting monthly and subsequently quarterly, and will have a pivotal role in steering the conduct of the trial. They reviewed the ethics application to ensure that trial documentation e.g. participant information leaflet, was user appropriate. They will be given the opportunity to engage in trial publicity and the dissemination of findings through appropriate channels i.e. social media, lay conferences, public engagement events, service provider events, newsletter articles. A role description and terms of reference for lay co-applicants has been produced in collaboration with our lay partners and the UHCW Patient and Public Research Advisory Group (PRAG). This will ensure that both parties understand the nature and extent of the collaboration, and their expectations of each other.

Lay co-apps and partners will be supported by the CI, trial coordination team, and through the peer support of lay partners on existing clinical trials. Comprehensive training and support will be provided by UHCW NHS Trust R&D department with regular lay seminars, group training and social events through the PRAG, with governance from PALS. All activity will be appropriately reimbursed at INVOLVE rates, for which there is adequate provision in the grant application. Lay partners will also benefit from training and support from UNTRAP (Universities/User Teaching and Research Action

Partnership), an active organisation through which local communities engage in research and teaching in health and social care, at the University of Warwick.

10 DISSEMINATION AND PUBLICATION

Results of the trial will be prepared by the research team and lay partners, and submitted to funders as a final report. Findings will be submitted to peer-reviewed journals and disseminated to the medical and exercise rehabilitation communities. Papers will be published in open-access journals describing the development of the SPHERe intervention, the trial protocol, and results and data, in accordance with recommended guidance for transparent reporting, the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org), the NIHR standard terms, and WCTU SOP 22: Publication & Dissemination. Abstracts will be submitted to national and international conferences e.g. British Thoracic Society, British Cardiology Society, European Respiratory Society, American College of Cardiology.

The SPHERe intervention will be fully manualised and available for public access once the trial has been completed. If appropriate, a practitioner training programme will be developed to support the implementation of SPHERe.

Lay co-apps and partners will assist with dissemination of trial results to patients and the wider public. A lay summary will be produced for participants and the hospitals/centres involved. Results will be publicised via the trial website and social media e.g. Twitter. WCTU, with the lead clinical centre (UHCW) and lay partners, will jointly lead on strategies for knowledge dissemination and engagement within the NHS and wider public. All organisations will work together to ensure that clinically important findings are disseminated as widely as possible and, by working collaboratively, facilitate the adoption of such outcomes within the NHS to enhance patient care. Towards the end of the trial, a joint investigator and participant event will be hosted to release and promote key trial findings. Commercial outputs are not expected from this publically funded trial, but intervention materials will be copyrighted as per institutional practice.

Work will be undertaken with national governing bodies (BACPR, BTS), charities (PHA-UK, BHF, BLF) and service audit providers (National Audit of Cardiac Rehabilitation [NACR], National Asthma and COPD Audit Programme [NACAP], NHS Digital PH audit), to promote the inclusion of people with PH in cardio-pulmonary rehabilitation programmes.

HRA guidance on information for participants at the end of a trial will be followed:
https://www.hra.nhs.uk/about-us/consultations/closed-consultations/guidance-participant-information-end-study-consultation/

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