

Development of a Complex Exercise Rehabilitation Intervention for People with Pulmonary Hypertension: The Supervised Pulmonary Hypertension Exercise Rehabilitation (SPHERE) Trial

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Abstract

Background: People with pulmonary hypertension (PH) are not routinely referred for exercise rehabilitation despite the potential for reducing breathlessness and improving quality of life. We describe the development of a supervised exercise-based rehabilitation programme for this group. The intervention will be tested in a randomised controlled trial (Supervised Pulmonary Hypertension Exercise Rehabilitation trial: SPHERE).

Methods: Work was completed in three phases; 1) systematic review, 2) stakeholder engagement with consensus from expert opinion, and 3) intervention piloting and acceptability testing. Our systematic reviews identified exercise interventions for pulmonary hypertension. The draft intervention was ratified through discussions with representatives from medicine, exercise physiology, psychology, and patients. We subsequently assessed the SPHERE intervention in a pre-pilot.

Results: Systematic reviews report that exercise might be safe and effective in this population. We found that other exercise interventions were within existing international cardiopulmonary rehabilitation guidelines. Stakeholder opinion and consensus shaped components of the SPHERE intervention, including addition of individual behavioural education sessions to promote adherence to exercise. Our pre-pilot investigation identified a number of condition-specific issues relating to safety and fear avoidance. We addressed these by adding two familiarisation sessions. The development of comprehensive intervention training manuals for participants and practitioners will ensure standardised delivery.

Discussion: The SPHERE intervention incorporates three main components: supervised gym exercise, behavioural strategies to encourage adherence, and a home exercise plan for people with pulmonary hypertension. We will evaluate the clinical and cost-effectiveness of the SPHERE intervention in a multicentre randomised controlled trial for people with pulmonary hypertension (ISCRTN no.:10608766)

Introduction

Pulmonary hypertension is a debilitating chronic condition causing poor exercise capacity and reduced health-related quality of life (1). It is characterised by increased pulmonary arterial pressure due to endothelial and vascular smooth muscle dysfunction. This leads to increased pulmonary vascular resistance, maladaptive remodelling, and altered ventricular-arterial coupling, combining to result in severe exercise intolerance (2). There are five pulmonary hypertension subgroups: Group 1 - pulmonary arterial hypertension (PAH); Group 2 - pulmonary hypertension due to left heart disease; Group 3 – pulmonary hypertension due to lung diseases and/or hypoxia; Group 4 - chronic thromboembolic pulmonary hypertension (CTEPH); and Group 5 – pulmonary hypertension with unclear multifactorial mechanisms. Considerable clinical heterogeneity is evident within each subgroup, thus highly specialised, individualised care is needed (3).

PAH (group 1) has a prevalence of 15–60 cases/million and an annual incidence of 7.6 cases/million in the UK. Groups 2 and 3 are the commonest forms of pulmonary hypertension however accounting for 65–80% of cases (4); mild pulmonary hypertension is often found in left heart disease and may be diagnosed in ~

50% of cases of chronic lung disease(5). Typical life expectancy is three to seven-years from diagnosis, dependant on group; comparable with several types of cancer (6).

People living with pulmonary hypertension have debilitating symptoms, most commonly excessive breathlessness, syncope and fatigue. Quality of life and the ability to undertake activities of daily living is greatly reduced. Furthermore, psychosocial morbidity is considerable (7, 8). The multiple underlying pathologies, varying clinical presentation, and considerable disease burden means that clinical management of people with pulmonary hypertension is challenging. Whilst the development of effective pharmacological treatment remains a priority, it is equally important to utilise existing long-term care pathways and test the effectiveness of therapies once medication is optimised.

Clinical rehabilitation interventions incorporating exercise training, behaviour change and psychosocial support can increase fitness, reduce breathlessness and improve quality of life in a range of cardiopulmonary diseases (9–11). A 2017 Cochrane systematic review (five trials, N = 206) provided moderate quality evidence of short-term improvements in exercise tolerance and health-related quality of life for people with pulmonary hypertension receiving supervised, exercise-based rehabilitation when compared to usual care, delivered over three to 15 weeks (12). There are no guidelines regarding the content or mode of delivery of exercise-based clinical rehabilitation in this population. A definitive trial of an exercise-based rehabilitation programme for people with pulmonary hypertension is needed. The UK Supervised Pulmonary Hypertension Rehabilitation (SPHERE) trial aims to investigate whether a supervised outpatient exercise rehabilitation programme, is clinically and cost-effective when compared to usual care, for people living with pulmonary hypertension. This paper describes the development of the SPHERE exercise intervention.

Overview Of Methods

We followed a three-stage process of intervention development and refinement, informed by the Medical Research Council framework for design of complex interventions,(Fig. 1) (13). We describe each phase of development in accordance with the template for intervention description and replication (TIDieR)(14) and the Consensus on Exercise Reporting Template (CERT, see additional file 1)(15) .

Stage 1a: Systematic review of exercise interventions for pulmonary hypertension

Stage 1a Methods

We performed a systematic review of the intervention content of previous studies of exercise-based interventions for pulmonary hypertension, reported in full elsewhere (11). We identified 19 studies (n = 673 participants), of which six were RCTs. Although exercise prescription was generally well reported, interventions were not described in sufficient detail to allow replication. The key findings from our review are summarised below (11).

Stage 1a Results

Table 1

Key findings from systematic review of the style and content of exercise interventions for people with pulmonary hypertension

Component of SPHERE Intervention	Finding	Implications
Setting for programme delivery	Half of included studies (10/19; 52%) delivered exercise during a residential inpatient stay. None of the outpatient studies were from the UK.	Inpatient exercise is not feasible in the UK healthcare system. Outpatient exercise programmes for pulmonary hypertension have not been assessed in the UK despite existing cardiopulmonary rehabilitation programmes having capacity to accommodate this population.
Supervised exercise dose	Dose of prescribed exercise was well reported in all studies: programme length: 4–15 weeks, exercise duration: 20–60 minutes, frequency: 2–3 times per week, intensity: low to moderate. All parameters were within UK guidelines for cardiac and pulmonary rehabilitation (16–18).	Dose of exercise prescribed was within existing UK rehabilitation (17) guidelines. Inclusion of supervised exercise for pulmonary hypertension patients within existing cardiopulmonary rehabilitation programmes is feasible.
Home/unsupervised exercise	Over half of studies (11/19; 58%) combined supervised sessions in a gym/centre with unsupervised home-based exercise training, or used home-based exercise as an addition to centre-based exercise, although this was not well reported.	The SPHERE intervention could include an unsupervised home exercise plan with exercises deemed safe to perform at home, with clear description and visual materials in a manualised format
Mode of exercise	Most studies (17/19; 89%) tested combinations of dynamic aerobic exercises with strength exercise and/or respiratory muscle training. Aerobic exercise consisted of cycle ergometry or walking. Strength exercises involved upper and lower body muscle groups with a number of sets of exercises with weights of low to moderate intensity.	There is evidence that it is safe and appropriate to prescribe both aerobic and strength exercise of moderate intensity for people with pulmonary hypertension.
Psychological support	Only one study (15) adequately described psychological and motivational strategies. Most studies (18/19; 94%) provided support group information sessions with limited information on content?.	Develop a bespoke behavioural change component for people with pulmonary hypertension based on evidence for behaviour change models and involve stakeholder engagement/expert opinion within consensus meetings.

Component of SPHERE Intervention	Finding	Implications
Safety	Sixteen studies (16/19; 84%) reported predefined criteria for adverse events. Inpatient and outpatient exercise for patients with pulmonary hypertension appears to be safe, with no reports of death occurring as a direct result of exercise.	Patients with pulmonary hypertension can safely attend supervised outpatient exercise programmes.

Table 1 Reproduced and adapted from McGregor et al 2018 (11) Re-use permitted under CC BY-NC

As included studies focused mainly on inpatient exercise programmes for people in groups 1 or 4, it was not possible to generalise the results of this systematic review across the spectrum of people with pulmonary hypertension. Our review of the published literature provided a broad framework within which our intervention could be developed. As many people with pulmonary hypertension have a primary diagnosis of heart failure or respiratory disease, we also reviewed existing guidelines for cardiopulmonary rehabilitation.

Stage 1b: Review of Rehabilitation Guidelines

Stage 1b Methods

We reviewed UK and other international guidance applicable to people living with chronic respiratory and cardiovascular conditions. The key guidelines include those published by the British Association of Cardiovascular Prevention and Rehabilitation (BACPR(16)), the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR,(17)) and the European Association of Cardiovascular Prevention & Rehabilitation (EAPC)(18).

Table 2
International guidelines for cardiopulmonary rehabilitation

Source	Country	Type	Intensity	Subjective Intensity RPE/Dyspnoea scale	Frequency (per week)	Duration
ACPICR/BACPR (16, 19) (2015)	UK	Aerobic Resistance	60–80% max. heart rate 40–70% HRR 30–40% 1RM upper body 50–60% 1RM lower Body	RPE: 11–14 (Dyspnoea:3– 4)	2–3 2–4	20–60 min
CACPR (20) (2005)	Canada	Aerobic Resistance	40–85% HRR 30–40% 1RM upper body 50–60% 1RM lower Body	Not specified	3–5	20–40 min 1–3 sets of 12–15 reps for 6–10 exercises

ACPICR; Association of Chartered Physiotherapists in Cardiac Rehabilitation, BACPR; British Association of Cardiovascular Prevention & Rehabilitation, CACPR; Canadian Association of Cardiac Rehabilitation, EAPC; European Association of Cardiovascular Prevention & Rehabilitation, ACRA; Australian Cardiovascular Health & Rehabilitation Association, JCS; Japanese Circulation Society, AACVPR; American Association of Cardiovascular & Pulmonary Rehabilitation, HRR; Heart Rate Reserve, 1RM; One Repetition Maximum. RPE; Rating of Perceived Exertion

Source	Country	Type	Intensity	Subjective Intensity RPE/Dyspnoea scale	Frequency (per week)	Duration
AACVPR (22) (2007)	USA	Aerobic Resistance	40–80% HRR 50% 1RM progressing to 60–70% 1RM	RPE:11–16 (Dyspnoea:3–4) RPE: 11–13	3–5 2–3	20–60 min 1–3 sets of 10–15 Repetitions for 8–10 exercises
ACPICR; Association of Chartered Physiotherapists in Cardiac Rehabilitation, BACPR; British Association of Cardiovascular Prevention & Rehabilitation, CACPR; Canadian Association of Cardiac Rehabilitation, EAPC; European Association of Cardiovascular Prevention & Rehabilitation, ACRA; Australian Cardiovascular Health & Rehabilitation Association, JCS; Japanese Circulation Society, AACVPR; American Association of Cardiovascular & Pulmonary Rehabilitation, HRR; Heart Rate Reserve, 1RM; One Repetition Maximum. RPE; Rating of Perceived Exertion						

Stage 1b Results

Findings from our review of cardiac rehabilitation guidelines are presented in Table 2.

International guidelines were broadly in agreement in relation to the safe and effective duration, intensity, frequency and type of exercise for cardiopulmonary rehabilitation. The guidelines are sufficiently flexible to allow different models of programme delivery, including home or centre based. We used these, combined with findings from our systematic review, to develop an outline of an exercise programme for people with pulmonary hypertension (Stage 2).

Stage 2: Expert opinion and stakeholder engagement

Stage 2 Methods

The SPHERE research team (n = 14) consisted of clinical academics with expertise in the development and implementation of complex exercise rehabilitation interventions (Fig. 2).

To holistically appraise the needs of people with pulmonary hypertension and their support network, we engaged widely with patients, multi-disciplinary professional agencies, and lay persons, identified through formal working relationships and informal networks. The research team identified key themes and priorities to form the outline for discussions, based on up-to-date evidence from our systematic reviews and review of clinical guidelines. We held a series of consensus meetings at the Warwick Clinical Trials Unit from April 2018 to September 2019. All stakeholders were invited to either attend in person or contribute remotely through telephone, e-mail, and video conference. Consensus responses were recorded and collated into the

following categories: exercise dose (Frequency, Intensity, Time and Type (FITT) principles), exercise progression, psychosocial support and the feasibility of incorporating the intervention into current NHS rehabilitation programmes.

Stage 2 Results

The findings from the consensus meetings are summarised in Table 3.

Table 3
Key findings from consensus meetings of intervention development

Component of SPHERE intervention	Outcome/consensus (s)
Exercise dose	<p>All agreed that two supervised and one unsupervised session per week of 20–60 min duration, dependent on fitness level, should be tested for acceptability during the pre-pilot phase. Some concerns were expressed by patients and respiratory physicians that this may not be tolerated by more debilitated patients.</p> <p>Patients requested inclusion of functional strength exercise to improve ease of activities of daily living (ADLs), and a home exercise programme to include functional and whole-body movements.</p> <p>All agreed that aerobic exercise at an intensity of 40–70% Heart Rate Reserve, RPE- 11–14 could be achieved after participants had received induction/familiarisation session.</p> <p>Strength training exercise intensity was discussed at length: there was some reticence for moderate intensity (CR 10 scale 3–4) due to perceived risk of dizziness/syncope from respiratory medicine/patients. Exercise physiologists/researchers felt that moderate intensity exercise would be safe following an appropriate warm-up and under careful supervision. All agreed to test acceptability during pre-pilot.</p>
Exercise progression	<p>Patients with pulmonary hypertension requested a one-to-one induction to overcome learned fear of activity. They agreed that two familiarisation sessions should be incorporated and piloted to ensure all participants felt safe exercising as many will be new to exercise.</p> <p>Duration of exercise should be progressed primarily until at least 20 minutes of aerobic exercise could be achieved for maximal therapeutic benefit. Researchers requested that exercise physiologists review participant programmes weekly and progress the prescription if intensity or duration targets were not met. This was agreed by all.</p>
Psychosocial support	<p>Fear avoidance and anxiety about activities that bring on breathlessness was emphasised heavily and identified as main barrier to adherence. It was agreed by all, further to a suggestion from the health psychologist, that six one-to-one psychosocial education sessions should be included. It was considered that participant numbers at any one time were unlikely to be great enough to deliver these sessions in group format. Motivation/goal setting, pacing of activities and managing negative emotions were chosen as topics.</p>
Delivery within NHS	<p>Exercise physiologist, GP, cardiology and respiratory medicine highlighted potential obstacles to delivery within the NHS rehabilitation setting: retention, busy classes, accurate intensity monitoring and psychosocial intervention training. Actions were agreed to mitigate these issues: (1) deliver up to three days training for practitioners led by health psychologist and research fellow and (2) provide a comprehensive manual for participants practitioners to follow.</p>

Following the consensus/stakeholder meetings, we generated a framework for the draft intervention programme for pre-pilot testing.

Stage 3: Pre- Pilot testing of draft intervention and refinement

Stage 3 Methods

The draft intervention programme was pre-pilot tested for acceptability with a small sample of people with pulmonary hypertension. Ethical approval was received via the Integrated Research Application System (261218) and the West Midlands Coventry & Warwickshire Research Ethics Committee (19/WM/0155) and Health Research Authority on 13th July 2019. We obtained informed signed consent from each participant. We delivered the pre-pilot phase in a community NHS exercise rehabilitation facility in one NHS Trust (Atrium Health Centre for Exercise and Health, Coventry). We gathered data on the acceptability and practicality of the intervention from participants and practitioners. Further, we collated feedback on written trial materials and practitioner/participant manuals to further refine and develop the intervention for the main trial.

Stage 3 Results/findings from piloting

Eight people with pulmonary hypertension took part in the pre-pilot study between November 2019 and February 2020. All received the intervention components and undertook baseline and follow-up outcome assessments. The main findings from the pre-pilot study are summarised in Table 4.

Table 4

Main findings from the SPHERE pre-pilot study testing intervention delivery

Component	Finding(s)	Implications for SPHERE Intervention
Intensity of exercise	Participants were unwilling at first to exert themselves to target intensity due to fear it would be harmful.	Two familiarisation sessions and a one-to-one fear avoidance session introduced in the first week of programme
Progression	Participants found the progression more acceptable once they had gained confidence in the gym environment and felt included in the decision-making process jointly with the practitioner.	Intervention protocol amended so that Practitioners review the programme with participant each week and jointly decide how to progress the programme.
Home exercise plan	Clearer explanations were needed on format and some exercises of home circuit. Concern over risk of overexertion during the unsupervised component. Adequate initial explanation, and demonstration of home programme took longer than anticipated.	Additional explanation added to the participant manual. Thirty minutes was allocated following the 2nd supervised session for the practitioner to comprehensively explain the home programme and select appropriate exercises with the participant.
Very debilitated participants	One participant could only walk 20 metres at assessment with a rollator, therefore conventional exercise e.g. bike/treadmill was too difficult and heart rate unreliable as intensity measure.	Provision of adapted functional exercises; e.g., sit to stand, step ups with handrail, added for those too debilitated to exercise. Breathlessness rating used alongside heart rate and perceived exertion as a measure of intensity.
Behavioural education	Participants preferred behavioural education to be called 'coaching' to reduce mental illness stigma. Participants required more support stopping negative thoughts around physical activity.	Additional material included in the participant workbook on negative thought patterns. Thought diary home worksheet introduced for those that request more support.
Practitioner training	Sites could not spare exercise staff for three days. Training condensed into one long day with provision of written materials in advance? Practitioners requested crib sheets to guide and standardise behaviour sessions.	Duration of practitioner training reduced from three days to one. This was tested at one site. Practitioners assessment introduced following the training day and more support given where necessary. Crib sheets for each behavioural session and laminated visual aids produced for all practitioners to deliver the behavioural component.

Rationale and Development of SPHERE Intervention

Type of Exercise

One of the findings from previous studies investigating exercise and pulmonary hypertension (11) was that most programmes included both aerobic and resistance exercise. This is appropriate for this population; regular aerobic and resistance exercise training in pulmonary hypertension groups 1 and 4, and in other clinical populations (heart failure and pulmonary disease), leads to adaptations that reverse many of the histochemical features of skeletal myopathy (23–25). Patients with pulmonary hypertension (through discussion and pre-pilot testing) requested types of exercise that both reduced breathlessness and improved their ability to perform activities of everyday living. Functional exercises such as sit to stand and/or step-ups, may help reduce atrophy and restore muscle function, improving mobility and balance (26). Therefore, four to six resistance or functional exercises were included, to target all the major muscle groups, and compound (more than one muscle) rather than isolation (single muscle) exercises were incorporated (27), so that fewer exercises would be needed for whole body training. Each centre will have different resources available and so these standardised principles can be adapted to whatever resistance equipment is available at each site.

Exercise Dose and Setting

During the stakeholder meetings, it was agreed that the SPHERE intervention should include three exercise sessions per week; two supervised in a rehabilitation centre and one unsupervised at home. This was based on our review of existing pulmonary hypertension studies and international rehabilitation guidelines. The supervised exercise sessions were subsequently planned to last up to an hour (including, warm-up, aerobic component, Muscle Strength and Endurance (MSE) component, and cool down) and the home exercise sessions to last up to 45 minutes. These could be altered, initially dependant on the degree of limitation in our population, and then up-titrated during the programme.

Intensity

Our review of the published literature and pre-pilot experiences revealed a general reluctance to prescribe exercise greater than low-moderate intensity for people with pulmonary hypertension, most likely due to concerns of adverse events during exercise; e.g., syncope, severe dyspnoea (28). However, moderate intensity exercise (40–70% heart rate reserve, Borg scale 12–14, breathlessness scale 3–4)(16), is recommended for other rehabilitation populations (16, 27) some of whom may have pulmonary hypertension (groups 2 and 3) as a secondary condition. During our pre-pilot study we found that participants were, at first, very unwilling to exert themselves to this level due to repeated warnings not to do so from health professionals, family, friends etc. This was particularly evident during resistance exercise. Some participants required substantial reassurance and encouragement from the practitioner to achieve moderate intensity levels. Alongside gym familiarisation sessions, we included a behavioural session in the first week of the programme to reduce fear avoidance of physical activity. The intention was to educate participants that exercise, contrary to being detrimental to health, may be safe and beneficial.

Monitoring Intensity

The intensity of exercise should be high enough to stimulate beneficial adaptations by gradually overloading the cardiovascular and musculoskeletal system. This must be standardised and monitored at each session to ensure all participants receive the same intervention dose. Heart rate is commonly used to prescribe intensity in exercise programmes at percentages of maximum or predicted maximum (27). However, heart rate monitoring is not always reliable e.g. due to arrhythmias, medication, caffeine, anxiety etc, therefore the Borg scales of perceived exertion and dyspnoea (breathlessness) (29) were included so that target heart rate could be crosschecked with the subjective perception of the participant.

Starting Levels of Exercise

It was decided that starting level of exercise intensity and duration should be calculated from the results of an individual assessment prior to the exercise programme. Resting heart rate (RHR) was recorded after the participant sat in a quiet room and completed a medical history consultation with the practitioner. The peak heart rate response from participants during an Incremental Shuttle Walk Test(30) was used as the maximum heart rate (max. HR) required to calculate 40–70% heart rate reserve using the Karvonen formula (31). It was found to be preferable to initially prescribe exercise at the lower end of this range so as not to create undue anxiety around excessive fatigue and breathlessness. We opted to include Muscle Strength and Endurance (MSE) exercise in the programme as soon as possible, i.e. from week two onwards. Older adults (≥ 65 years) or those new to exercise, performed 10–15 repetitions at first to improve strength (27) at an intensity/weight resistance of 4–6 on the Borg Category Ratio (CR-10) scale after two repetitions(16). The CR-10 scale is a 10 point scale that differs from the 15 point RPE scale and is more accurate for resistance exercise(32).

Criteria for Progression

The duration and intensity of exercise prescribed must be progressed regularly for participants to receive a continual stimulus for adaptation and improvement for the whole programme. Therefore, we recommended that initially the duration of exercise was increased by 1–5 minutes per session until therapeutic levels of exercise were achieved i.e. at least 20 minutes duration at a moderate intensity range. During the pre-pilot, participants found the exercise sessions more acceptable once they had gained confidence in the gym environment, even as it became more challenging. Rate of progression was based on heart rate, perceived exertion and breathlessness recorded during exercise and through careful discussion with the participant. The exercise prescription booklet was used during the pre-pilot to record measures of intensity. This was reviewed each week by the practitioner and participant and progressed if intensity fell below the target ranges described earlier(16).

Progression of Resistance Training

We decided that the MSE sets, repetitions or resistance should be progressed if the CR-10 scale was lower than 3–4. One general rule for MSE progression is that if participants can perform 20 repetitions on their last set (27) then the resistance is almost certainly too low to produce an adaptation in strength. Therefore, it

should be increased, allowing for the fact that perhaps as few as 8–12 repetitions can be performed at the new resistance level.

Home Exercise Programme

Our draft home exercise plan was tested by four participants. We received helpful feedback on how to improve materials, for example; being clearer about the explanation of the format of exercises and how to progress each week. The risk of participants potentially overexerting themselves whilst unsupervised at home was highlighted when one participant took two hours to complete the full home exercise plan which was intended to last 30–45 minutes. There was no adverse event on this occasion but the need for greater explanation was apparent. Our training day materials, practitioner manuals and ongoing support to sites were changed to ensure that practitioners review all home exercise plan record sheets each week during the supervised session. During the pre-pilot study we found that thirty minutes was required to adequately explain and demonstrate the home exercise plan. This is now incorporated into the first week of supervised exercise sessions.

Duration of SPHERE Programme

Most other clinical trials report exercise programmes lasting four to 15 weeks (12). In the UK, NICE (33) recommend 12 weeks as the optimal length for cardiac rehabilitation programmes. In practice however, longer programmes require more capacity/resource and can result in longer wait times for patients. In addition, adherence to longer programmes becomes difficult due to ill health, return to work or loss of motivation. The most common length in UK cardiac rehabilitation programmes in the eight partner sites we had approached was eight weeks (16 sessions), slightly shorter than the national average of 10.3 weeks (34). As the intention of SPHERE was to embed participants in existing cardiac rehabilitation programmes, the study team took a pragmatic decision for an eight week programme to encourage engagement and uptake by clinical rehabilitation centres.

Promoting Adherence

Behavioural interventions have been shown to increase adherence to physical activity interventions in adults (35). This, in combination with our patient stakeholder feedback, led to the provision of behavioural sessions (referred to by practitioners as ‘coaching’ sessions following participant feedback) to run in parallel with the supervised exercise sessions. The six sessions were designed in collaboration with an experienced health psychologist with the objective of attenuating the most common psychosocial barriers to exercise for this group. We decided to focus on increasing participants’ awareness of how irrational thoughts and feelings can influence their behaviour. Sessions were designed to investigate the pros and cons of changing a specific behaviour, for example; fear avoidance of exercise, with assistance to develop a specific plan incorporating motivation and goal setting. This was encouraged from the first assessment so that the exercise prescriptions were targeted at physical goals identified as important by patients during the stakeholder meetings. These goals included becoming less fatigued and breathless on exertion, being able to walk further, being able to climb stairs, generally increasing fitness, and regaining independence. There is evidence that linking exercise to daily activities can encourage adherence (26). Furthermore, once goals are

agreed, a written 'contract' signed by practitioner and participant is recommended for improved adherence (36). This has been incorporated into the participant workbook and will be completed during week one of the programme.

Condition Specific Considerations for the Exercise Programme

Due to the higher risk of syncope in people with pulmonary hypertension, a thorough warm-up and cool-down are particularly important. A gradual increase in O₂ demand while muscles reach optimal metabolic efficiency and the cardiopulmonary blood vessels have had time to dilate fully, will avoid unnecessary breathlessness during activity. Likewise, the avoidance of sudden cessation of exercise via a gradual cool-down will reduce pooling of blood in the working muscles(37), light headedness, and vasovagal syncope (16).

We underestimated how ingrained activity avoidance was in this population, as result of years of health professional advice to avoid activity. We placed extra emphasis on this by introducing behavioural coaching and familiarisation sessions. Another consideration was that many people living with pulmonary hypertension were on long term oxygen therapy and extremely debilitated. During pre-pilot, one participant could only walk 30 metres with a rollator that carried her oxygen cylinder. Exercise programmes for the extremely debilitated cannot always use conventional exercise equipment as the minimum level of difficulty maybe too hard for patients to achieve for a meaningful duration. For some people, even getting onto some equipment, for example; an upright exercise bike or rower, may induce severe breathlessness. The introduction of adapted functional exercises, such as sit to stand from an elevated chair and step ups with a handrail, are more achievable and appropriate for the severely impaired. Furthermore, the necessity for ratings of breathlessness and exertion over heart rate was underlined by our experiences with the severely limited.

Overview of SPHERE Intervention

The final SPHERE programme has three core components (Figure. 3) See additional file 1 for TIDIER checklist.

1. **Supervised gym exercise sessions** (Weeks 1 to 8): up to 16 gym-based sessions held twice weekly over eight weeks, each session lasting for one hour, in an existing cardiopulmonary rehabilitation programme. The first two of these sessions will be 'familiarisation sessions' to introduce participants to the gym environment and programme.
2. **Behavioural 'coaching'** (Weeks 2 to 8); Six one-to-one sessions lasting 30 minutes each delivered before, or after, one of the weekly gym sessions.
3. **Home exercise plan** (Weeks 1 to 8); An individualised home exercise plan to be followed at least once each week, unsupervised at home.

Initial Assessment

To inform exercise prescription, an individual assessment will be performed with close clinical monitoring before starting supervised exercise,(28) as per standard practice in most cardiopulmonary rehabilitation centres. Exercise capacity will be assessed by the Incremental Shuttle Walk Test (30). Results will allow calculation of initial exercise prescription as per BACPR(16) guidelines.

Week 1: Gym Familiarisation Sessions

One-on-one familiarisation sessions will gradually introduce participants to the gym environment during the first week of the programme. The SPHERE practitioner will refine and optimise the exercise prescription, in agreement with the participant, to further reduce anxiety, whilst providing an induction into the gym/class setting.

Supervised Exercise Sessions

Participants will attend twice weekly, one-hour, supervised group exercise sessions within existing cardiopulmonary rehabilitation programmes. Exercise sessions will be individualised, moderate intensity exercise (40–70% heart rate reserve, Borg scale of perceived exertion;12–14, and breathlessness; 3–4)(16), that includes aerobic, muscular strength and endurance (MSE), and ‘functional’ exercise.

Behavioural Education Sessions

All participants will receive six, one-to-one, 30-minute, behavioural coaching support sessions with a trained SPHERE practitioner to promote adherence during the intervention period. These sessions will be held once per week, either before or after exercise.

Unsupervised Exercise: SPHERE Home Exercise Plan

Participants will be introduced to the home plan and then encouraged to follow the SPHERE home exercise plan every week. Participants and practitioners will select only 6–8 of the longer menu of 24 available exercises (Fig. 4, below)

The participant will then be instructed to perform these selected exercises in a ‘circuit’; i.e., one after another, and multiple circuits repeated as required. The practitioner will review the supervised and home exercise plan weekly with the participant and alternate and progress exercises as necessary.

Intervention Fidelity: Practitioner Training and Quality Control

To ensure standardisation of intervention delivery, all sites and practitioners involved in the SPHERE trial will have a full day of face to face practical and theoretical training with a clinical exercise physiologist (SE) and health psychologist (HS), who will provide input to deliver the behavioural education sessions, utilising motivational interviewing techniques and the COM B model (38). An assessment following training will be completed by practitioners to evaluate readiness to deliver the intervention and/or the need for further training. Practitioners will be given comprehensive manuals for intervention delivery (additional file 2) and phone call support as required.

The SPHERE intervention will be delivered by NHS clinical exercise physiologists (i.e. in possession of sport science degree) or chartered physiotherapists with a minimum of two years' experience working with clinical populations.

All sites will be subject to regular quality control visit every 4–6 weeks. This is to ensure that exercise and behavioural education sessions for the SPHERE programme are being delivered in a standardised manner and provide support to rehabilitation teams. A separate process evaluation will assess programme delivery across sites.

Discussion

Regular exercise can benefit people with pulmonary hypertension, increasing exercise capacity, muscle strength and reducing breathlessness. However, without mediating the psychosocial barriers to exercise and actively including intervention components to reduce anxiety and improve confidence, even the most well-designed exercise programme may prove ineffective. Hence, during development and pre-pilot testing it was consistently made clear that our intervention design would need to account for this, to avoid poor uptake and adherence. The introduction of familiarisation sessions, one to one behavioural coaching and a comprehensive participant workbook aimed to attenuate participants' perceptions of their condition. We aimed to diplomatically challenge traditional messages from some healthcare professionals and entrenched beliefs around activity avoidance. Our patient stakeholders expressed their desire to return to more activities of normal living without breathlessness, for example; walking to the shops, carrying shopping, or holding their grandchildren. This requires improved aerobic endurance and strength, thus both types of training were included.

In summary, the UK SPHERE trial will be the largest study to date to test whether exercise rehabilitation is clinically and cost-effective for people with pulmonary hypertension, when compared to best practice usual care. It will test exercise rehabilitation in a real-world NHS outpatient rehabilitation setting. To date, trials testing exercise training have been small, low quality and have been delivered as in hospital in-patient rehabilitation programmes to selective clinical subgroups (PH groups 1 and/or 4). The SPHERE intervention has been developed with patient and stakeholder engagement and is designed to be incorporated into existing NHS rehabilitation programmes.

Declarations

Ethics approval and consent to participate:

Ethical approval was received via the Integrated Research Application System (261218) and the West Midlands Coventry & Warwickshire Research Ethics Committee (19/WM/0155) and Health Research Authority on 13th July 2019. Each trial site will confirm local NHS Trust Research & Development (R&D) department capacity and capability prior to commencing recruitment. All participants will provide written informed consent prior to participating in the study. UHCW NHS Trust are the sponsor for the trial. The trial will be conducted in accordance with the declaration of Helsinki.

Consent for publication:

not applicable

Availability of data and materials:

The datasets used and/or analysed during the current study will be available from the corresponding author on reasonable request

Competing interests:

MU has received multiple research grants as chief investigator or co-investigator from the National Institute of Health Research (NIHR) and Arthritis Research UK. Until March 2020 he was an NIHR Journal Series Editor. He is a shareholder and director in Clinvivo Ltd. He is co-investigator on two NIHR funded trials receiving additional support from Stryker Ltd. He is part of an academic partnership involving Serco Ltd. GM and SE are directors of Atrium Health Ltd. GM holds grants from NIHR and British Heart Foundation

JB is supported by National Institute for Health Research (NIHR) Research Capability Funding via University Hospitals Coventry and Warwickshire. She has received multiple grants as chief investigator or co-investigator from NIHR and Diabetes Research UK.

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Contributorship:

GM is the chief investigator for the trial and obtained funding with support of MU, JB, ST, SS, DF, PB, SB, PC, ER, RL, CJ, JM, HS, TP, KS. All contributed to study design. MU, JB, ST (clinical trials); RL, CJ, KB (statistics); JM, AC (health economics); HS, TP (health psychology); KS (qualitative and process evaluation); GM, SE, SS (clinical exercise physiology/physiotherapy); ER (lay co-applicant) and ST, PB, DF, SB, PC (medical) provided expertise in their respective areas/disciplines. SE and GM searched the literature, led the development and piloting of the exercise intervention, and undertook acceptability testing. HS and TP developed and piloted the psychosocial components. All authors were involved in stakeholder engagement, consensus meetings, expert opinion, and intervention refinement. SE prepared the manuscript; MU, JB and GM edited the manuscript. All authors approved the final version of the manuscript.

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Figures

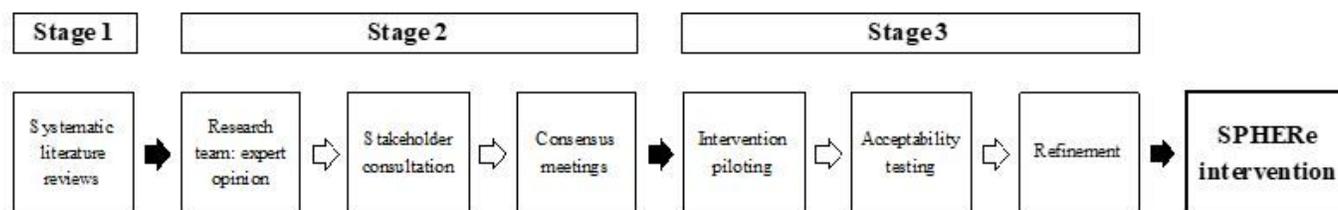


Figure 1

Overview of the intervention development process

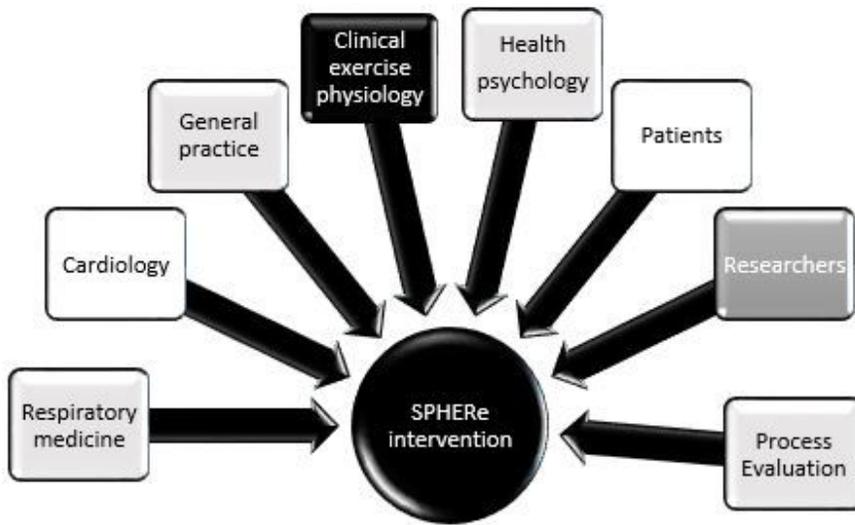


Figure 2

Clinical, research and patient expertise included in intervention design

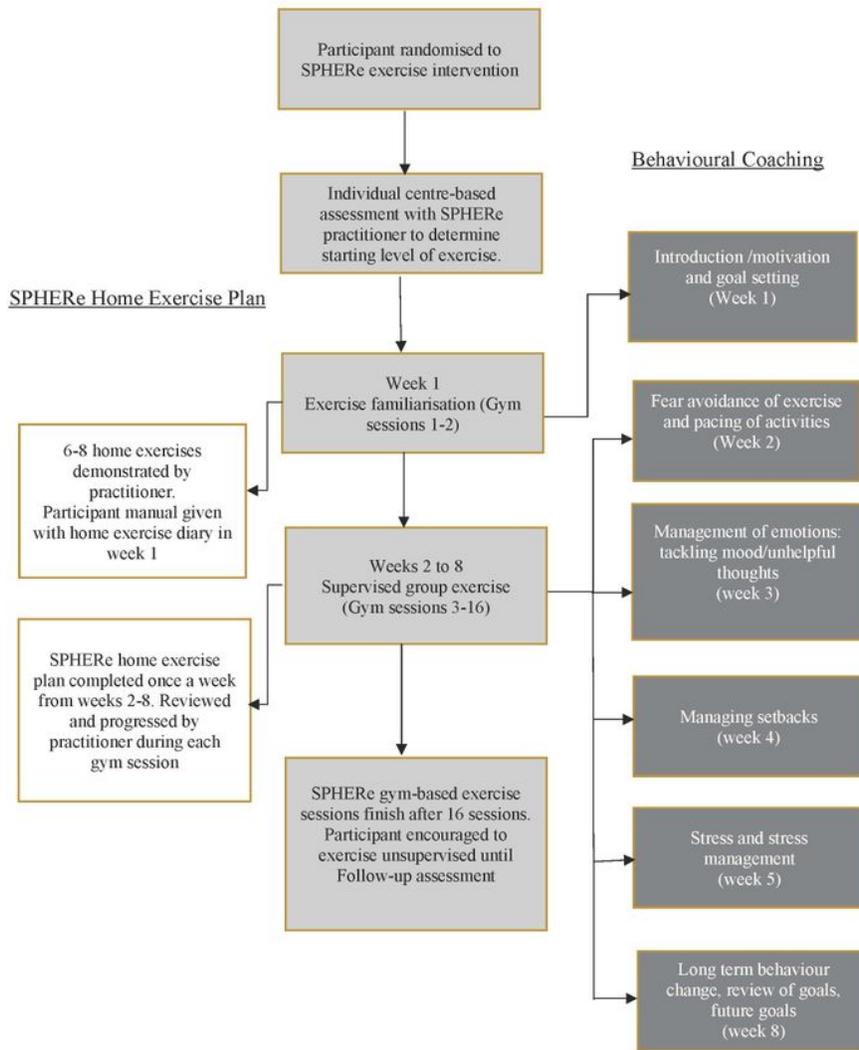


Figure 3

Summary of SPHERE Intervention

Circuit– Legs

1.Sit to stand

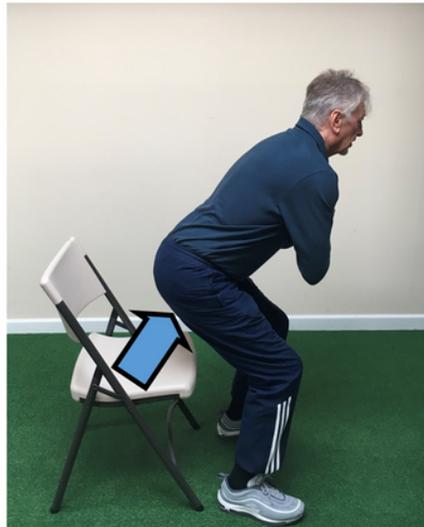


Instructions

1. Sit at front of chair with back straight feet apart and arms crossed
2. Lean forward and stand up fully

Considerations

- Push through heels to prevent knee pain



Progression/Alternative

- You may need to hold the back of another chair for support
- You can also add cushions to raise height assisting this exercise
- To progress exercise, weights can be held by sides or against chest

Figure 4

Example of exercises contained in SPHERE home exercise plan

Supplementary Files

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