Outcome Measures Used in Studies of Rehabilitation in Pulmonary Hypertension: A Systematic Review.

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Introduction

Pulmonary hypertension (PH) is a condition with many causes which results in breathlessness, reduced functional ability and diminished quality of life. Once viewed as an untreatable condition, advances in medical and surgical treatment have resulted in more people living with the disease and for longer(1).

While exercise rehabilitation was first shown to improve exercise capacity and quality of life in patients with PH in 2006(2), greater understanding of the benefits of rehabilitation in patients with pulmonary hypertension is still required(3, 4). Effective rehabilitation is a complex, multi-faceted intervention with the potential to impact not just the underlying health condition, but also the daily life of patients, their independence and community connections(5). It is important that this wider potential impact is given due consideration in studies of rehabilitation.

The World Health Organisation International Classification for Functioning, Disability and Health(6) (ICF) is a dynamic multi-dimensional classification of health and health-related domains. It is designed to support clinicians and health policy makers to examine and understand the health of individuals and populations, not simply in terms of diagnoses, but also reflecting the impact of disease on individuals and the lives that they are able to live. The ICF considers: i) Body Functions/Structures i.e. aspects of physiology and anatomy, ii) Activity i.e. actions and tasks undertaken by individuals, iii) Participation i.e. involvement in life situations, and iv) the environmental and personal factors which affect these experiences.

To understand the impact of rehabilitation on patients with PH, outcomes used in studies of rehabilitation need to capture the influence of those interventions across all domains of health. This study uses the WHO ICF model as a framework to examine the literature of rehabilitation interventions in patients with PH.

Methods

This systematic review comprised comprehensive searching of the literature and combined tabular and narrative synthesis(7). It was prospectively registered on the PROSPERO database (CRD42019127590).

Research Aim

Characterisation and clinical meaning of outcome measures in studies of rehabilitation in patients with pulmonary hypertension.

Search Strategy

A comprehensive search was conducted of the following electronic databases: MEDLINE (EBSCO); CINAHL Complete (EBSCO); Cochrane Central Register of Controlled Trials (Wiley); Scopus (Elsevier); ASSIA (Proquest). Searches were conducted in February 2019 and databases were monitored for updates until September 2019. The strategy included searches for words and phrases relating to pulmonary hypertension and exercise or rehabilitation. The Boolean operators AND and OR were used, alongside phrase, proximity and truncation operators. The search syntax was adapted accordingly for each information source and controlled vocabulary terms used where available.

Where indicated, author and citation searches were undertaken of papers included in the review. Searches were conducted for conference proceedings to identify full articles if they had been published. Search strategies for each database are detailed in Appendix 1.

Study selection

Selection of studies was undertaken by one author (CK) and a sample was checked at each stage of selection by a second author (MHG). Disagreement was resolved by discussion and consensus involving a third author (KS) as necessary.

Articles from all databases were combined and duplicates removed before title and abstract were screened; if studies were considered to be eligible, then full-text was reviewed. Studies were included if they met the following criteria; quantitative studies of any design, which included primary data; peer reviewed protocols of planned studies; originating from any time period. Studies were excluded if they were: abstract-only papers; single case studies (case series were included); review papers (although references were checked for primary data sources); non-English language papers.

Study populations had to include adults (age≥18 years) with a diagnosis of pulmonary hypertension(8). Studies were excluded if subjects were: animals; patients with exercise-induced pulmonary hypertension; patients undergoing post-operative rehabilitation.

Data Extraction

Data were extracted from all articles which met the inclusion criteria after full-text review. Data extraction focused on identifying study design details for each article including the rehabilitation interventions, plus detailed examination of the outcomes measures used.

As the purpose of the study was to evaluate the outcome measures used in studies of rehabilitation, a risk of bias assessment of the studies was not carried out.

Data Synthesis

Data were examined to identify the characteristics of the studies, number and type of outcomes used and their frequency of use.

Outcomes were categorised according to type, and the number of times each outcome was used across studies was collated. A single outcome capturing several parameters was counted only once e.g. cardiopulmonary exercise testing or echocardiographic assessment.

To develop a clear understanding of what is being measured in studies of rehabilitation in PH, the outcomes used in the studies identified in this review were analysed against the ICF classification, to identify whether the outcomes were measures of the ICF domains of Body Function/Structure, Activity or Participation. Details of each outcome were examined and items were compared to the ICF Checklist(9) to determine which domain or sub-domain they represented. Initial classification was carried out by CK before being checked and verified by DGK and KS. Disagreement was resolved by discussion and consensus.

As pulmonary hypertension is a haemodynamic state arising from a number of causes, there is no single measure of the disease itself; all clinical or physiological outcome measures were classified as measures of body function or structure. Delineation between Activity and Participation was based on ICF guidelines(10) adopting distinct non-overlapping sets of Activities (domains 1-4: learning and applying knowledge; general tasks and demands; communication; mobility) and Participation (domains 5-9: self-care; domestic life; interpersonal interactions and relationships; major life areas; community, social and civic life). Measures of survival and time to clinical worsening were determined to be measures of Body Functions/Structures, as were outcomes related to use of healthcare resources. Outcomes which encompassed more than one of the domains e.g. Activity and Participation were counted in both categories.

The ICF model considers health in the context of environmental and personal factors which may be barriers or facilitators to patients' performance. Environmental factors might include access to supportive equipment or the building or health system in which the individual lives; personal factors may include age, gender, education or profession. While these are important aspects in understanding the health of an individual, they are not factors which will be influenced by rehabilitation interventions and therefore were not included in this analysis.

Results

Searches across five databases yielded 2564 articles after removal of duplicates. These were screened on title and abstract, leaving 62 articles which underwent full review and 34 articles which were included in the final data synthesis, as show in the Flow Diagram (Figure 1). Details of the studies included in this review are in Table 1.

Studies were published between 2006 and 2019, with the majority of publications (94%) in the last 10 years (Table 2) reflecting a growing number of randomised controlled trials over that time period. Studies were most commonly of patient populations with pulmonary arterial hypertension (56%) or with pulmonary hypertension of a non-specified cause (29%). Rehabilitation interventions varied in content and length but were most frequently a form of whole-body exercise training involving a mix of cardiovascular, resistance and respiratory training alongside education around disease and symptom management.

Across the 34 studies in the review, there were 50 distinct outcome measures used (Table 3). Studies used an average of 5 outcome measures (min=1, max=9) giving a total of 176 instances of outcome measure usage across the studies. Exercise testing (n=56), quality of life measures (n=31) and biomarkers (n=23) were the most frequently used, with several different outcomes being used within each category.

6MWD was used in 32 of the 34 studies; in the 2 studies not using 6MWD, 1 used CPET(11) and 1 attainable treadmill speed(12). Several studies used more than one exercise test.

There was no quality of life measure used in 9 (26%) studies. Of these, two studies used symptom-specific patient reported outcomes.

When mapped against the ICF domains of Body Functions/Structures, Activity and Participation the outcomes were identified as measures of a single domain (68%), two domains (14%) or all three domains (14%). It was not possible to source sufficiently detailed information to allow classification for 2 (4%) of the outcomes (Living with Pulmonary Hypertension Questionnaire and Nagasaki University Respiratory ADL questionnaire).

The most common outcomes were measures of Body Functions/Structures (n=36) followed by measures of Activity (n=20) and Participation (n=13). Figure 2 maps study outcomes to the ICF domains. When weighted according to the frequency with which the outcomes were used, 48% of instances of outcome usage were measures of Body Functions/Structure, 33% were measures of Activity and 18% were measures of Participation. Seven (21%) of the studies in this review did not include any measure of Participation in their outcomes, the remainder (34%) captured measures across all three domains.

Table 4 shows further details of the sub-domains of Activity and Participation included in each of the outcomes. Several outcomes include only 1 or 2 of the 9 possible sub-domains, including the most common 6MWD. Outcomes encompassing higher numbers of sub-domains are less frequently used - Nottingham Health Profile (n=7), CAMPHOR (n=7), St George's Respiratory

Questionnaire (n=6). SF-36, the most commonly patient reported outcome measure, encompasses 5 sub-domains domains.

Discussion

This review has examined outcome measures used in studies of rehabilitation in pulmonary hypertension since the first study published in 2006. The use of outcome measures is heterogonous across the studies, employing 50 different outcomes across 34 studies, with an average of 5 outcomes per study. When mapped onto the World Health Organisation International Classification for Functioning, Disability and Health(6), it is clear that outcomes measuring changes in Body Functions/Structure predominate, with fewer measures capturing Activity and even fewer considering changes in Participation that might arise from the rehabilitation intervention. Of the studies included in this review, 21% did not use any measure of Participation.

The first randomised controlled trial of a pharmaceutical intervention in pulmonary hypertension in 1990 used 6MWD as its primary endpoint, and subsequent trials of drug therapies have tended to follow suit(13). Reflective of the limitations of 6MWD to capture wider aspects of health, trials of drug therapies in pulmonary hypertension have incorporated patient reported outcomes to capture changes in health related quality of life, although these have been found to be less responsive to therapeutic impact(14). Pulmonary hypertension lacks strong surrogate disease end-points; the use of invasive measures such as haemodynamics has decreased over time in pharmaceutical studies with a shift instead to composite end-points reflecting time to clinical worsening and, more recently, a focus on time to clinical improvement(14). Studies of rehabilitation in pulmonary hypertension demonstrate a similar pattern to studies of pharmacological interventions, with initial studies focussing on 6MWD and quality of life measures also being captured, although with less frequency.

It is understandable that early studies of rehabilitation in PH chose end-points used in trials of pharmacological interventions where there was evidence for a clinically meaningful difference. The extensive use of physiological markers in earlier studies may be justified to establish the safety and mechanisms of rehabilitation as a relatively new intervention, however, the potential for rehabilitation interventions to have wider consequences must also be considered and reflected in the outcome measures used.

Implications

It is essential that research into rehabilitation interventions in pulmonary hypertension demonstrates its impact on the issues that are most important to patients, which will include not only aspects of Body Functions/Structure but also Activity and Participation.

Pulmonary hypertension impacts the physical, practical and social aspects of the daily lives of patients and their carers. Studies show the impact of the disease on levels of anxiety and depression as well as cognitive function. Emotional and relationship issues are common, with high levels of depression and anxiety(15, 16). In living with the disease on a day-to-day basis, parameters of survival, biomarkers, exercise capacity and haemodynamics can have less relevance to patients than their concerns about employment, reliance on others for help, or loneliness(17). Diminished quality of life(18) and reducing the burden of living with PH are priorities for organisations supporting patients(19).

Rehabilitation is a broad term which captures an active and enabling approach to optimising function for individuals. Rehabilitation in other respiratory diseases has been shown not only to deliver on increased physical functioning, as demonstrated by changes in exercise capacity, but also to impact aspects of living with long-term conditions such as fatigue, emotional function, understanding and mastery of the disease and its management(20).

By limiting the outcomes used to measure the impact of rehabilitation in pulmonary hypertension, focusing predominantly on clinical and physiological outcomes as seen in this review, researchers, clinicians and service providers risk overlooking the wider benefits that might arise from rehabilitation of patients in this area. The interventions in most studies in the review are multi-faceted, including psychological and educational components, yet this is not effectively reflected in the outcomes captured.

Rehabilitation it is not yet embedded in clinical practice in pulmonary hypertension, despite a growing evidence base(21). Health care resources are scarce and the case for development of new services must be compelling. The cost of caring for people with respiratory disease is significant arising both from medical care of the condition - drug therapies, hospital admissions - but also from the social costs of respiratory disease - inability to work, requirement for care and support at home, dependence on benefits. Rehabilitation interventions that can be shown to address these problems, as well as associated functional limitations on comorbidities such as mental health and obesity, are important in making the case for developing services.

Future considerations

Measures which capture aspects of Activity and Participation should be used in studies of rehabilitation in pulmonary hypertension, to assess change across a broad spectrum of patients' lives. Of the outcomes which assess Participation in this review, SF-36 is the most used, and also widely used in trials of pharmacological therapies in PH. Although a generic instrument, its measures have been shown to converge well with other physiological markers in PH and a minimally clinically important difference (MCID) has been estimated(22). Whilst several items on the questionnaire address pain and energy levels, which fall within the domains of Body Functions/Structure, it encompasses only 5 of the 9 sub-domains of Activity and Participation (Table 4).

The Cambridge Pulmonary Hypertension Outcome Review questionnaire (CAMPHOR) is a disease specific questionnaire used in five studies in this review. It addresses issues of breathlessness, mobility, energy and the emotional consequences of living with pulmonary hypertension, encompassing 7 of the 9 sub-domains in Activity and Participation (Table 4). While it may not track other PH clinical measures over time(14) its validity, reliability and MCID have been established(23). emPHasis10(24) is an alternative pulmonary hypertension specific patient reported outcome measure. Initially designed as a tool for use in clinical practice, it is widely used in this capacity to monitor disease progression in patients with pulmonary hypertension. Covering 5 of the 9 domains of Activity and Participation (Table 4), it is yet to be tested in studies of rehabilitation.

The use of disease specific measures may have less relevance in rehabilitation than in the assessment of pharmacological therapies or clinical progress. Many patients with pulmonary hypertension will have significant comorbidities and complex health problems for which rehabilitation may also be beneficial. In such situations, attempting to capture outcomes which reflect the impact of rehabilitation on a single disease might overlook the wider benefits to health. The World Health Organisation Disability Assessment Schedule(25) (WHODAS 2.0) is a

self-administered questionnaire which covers 8 of the 9 domains of Activity and Participation (Table 4). It is not disease specific, however its psychometric properties have been repeatedly validated in diverse populations, locations and languages. Its inclusion of items relating to relationships, intimacy, dignity, practical and financial burden, which reflect concerns frequently raised by people with pulmonary hypertension(26), suggest it may warrant further exploration and adoption in studies exploring rehabilitation. Although its use is growing there is only a single instance of its use to date in pulmonary hypertension, in a study that uses the measure to characterise patients with the disease(27). While used in only one study of rehabilitation, the Nottingham Health Profile covers 7 of the 9 domains (Table 4) and therefore may also warrant further investigation.

It is likely that the recent global COVID-19 pandemic will result in an increased number of non-face-to-face patient assessments taking place. Outcomes which can be used in this setting will need to be examined; there may be an increased use of questionnaires, self-administered tests or remote monitoring of patients

There are limitations on the ability of even the most rigorous questionnaires to fully capture the outcomes of complex rehabilitation interventions. In-depth exploration through qualitative research of patients' experience of rehabilitation in pulmonary hypertension and the impact on their lives and the lives of their carers would also have a valuable role in deepening our understanding of this important topic.

Adopting the best measures to capture the outcomes of rehabilitation will allow the design, commissioning and delivery of services which best meet the needs of patients.

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Conclusion

Studies of rehabilitation in pulmonary hypertension have focussed primarily on measures of Body Functions/Structure; the impact in other domains is less well characterised. Greater inclusion of outcome measures reflecting activity and participation in society is needed to allow assessment of the wider impact of rehabilitation in patients with pulmonary hypertension.

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Tables

Table 1- Full Text Studies

Study	Cohort	Study Design	Sample size (intervention /control)	Exercise Intervention	Control	Outcomes used
Awdish(28) (2015)	Pulmonary hypertension	Case series	3	Hatha yoga program designed for patients with pulmonary hypertension	NA	Health Promoting Lifestyle Questionnaire; 6MWD; oxygen saturation at rest
Babu(29) (2019)	Pulmonary hypertension	RCT, non-blinded	84 (42/42)	12 week home based exercise program plus patient education manual	education manual	6MWD; SF-36; WHO FC; RV function (via echo)
Becker-Grünig(30) (2013)	Congenital heart disease associated pulmonary arterial hypertension	Prospective non-randomised trial	20	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	NA	6MWD; CPET; SF-36; NT-proBNP; WHO FC; TTCW; survival
Brown(31) (2018)	Pulmonary arterial hypertension	Prospective non-randomised pilot study	12	Incremental walking programme plus arginine supplement	NA	6MWD; CPET; SF-36; cardiac function (via echo); NT-proBNP; step count; heart rate recovery
Bussotti(32) (2017)	Pulmonary arterial hypertension	Prospective non-randomised trial	16	4 weeks daily training combined aerobic, resistance, IMT, psychological support	NA	CPET; 6MWD; NT-proBNP; pulmonary function tests; EQ-5D; HADS
Chan(33) (2013)	Pulmonary hypertension	RCT, single blinded	26 (13/13)	10 weeks treadmill exercise plus education	Education only	CPET; 6MWD; SF-36; CAMPHOR; IPAQ
Chia(34) (2017)	Pulmonary arterial hypertension	RCT, single blinded (Protocol)	NA	12 weeks of weekly group exercise (combined endurance, respiratory muscle training, strength, psychological support)	Written advice on walking program	cardiac function (via MRI); haemodynamics (via RHC); Grip strength; 6MWD; CAMPHOR; Depression and Anxiety Severity Scale; Lawton Instrumental Activities of Daily Living Scale; NT-proBNP; pulmonary function tests
de Man(35) (2009)	Idiopathic pulmonary arterial hypertension	Prospective non-randomised trial	19	12 weeks cycling and strengthening, 3 times per week	NA	CPET; quadriceps strength; pulmonary function tests; NT-proBNP; 6MWD; muscle biopsy
Ehlken(a)(30) (2014)	PH and right heart insufficiency	Prospective group and age-	104 (58/46)	3 week in-patient rehabilitation (cycle ergometer, walking, light weights,	No rehabilitation input	6MWD; TTCW; WHO FC; Health and Social Care Resource Usage; EQ-5D; survival

		gender matched control group		respiratory exercises) followed by 12 week home-based exercise program		
Ehlken(b)(36) (2016)	PAH and inoperable or persistent CTEPH	RCT, single blinded	87 (46/41)	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	No rehabilitation input	CPET; haemodynamic (via RHC); 6MWD; SF-36; WHO FC; NT-proBNP
Fox(37) (2011)	Pulmonary arterial hypertension	RCT	22 (11/11)	12 weeks combined cardiovascular and resistance exercise plus home exercise programme	No rehabilitation input	6MWD; CPET; cardiac function (via echo); NT-proBNP
Ganderton(38) (2011)	IPAH, familial PAH, PAH associated with connective tissue disease	RCT, single blinded (Protocol)	NA	12 weeks combined cardiovascular and resistance exercise plus home exercise programme	No rehabilitation input	6MWD; CAMPHOR; SF-36; IPAQ; CPET
Gerhardt(39) (2017)	Pulmonary arterial hypertension	RCT, non-blinded	22 (11/11)	4 weeks of exercises on a oscillatory whole body vibration plate	No rehabilitation input	6MWD; RV function (via echo); CPET; single two-leg jump; SF-36; Living with Pulmonary Hypertension Questionnaire; chair raising test
González-Saiz(40) (2017)	PAH or inoperable CTEPH	RCT, single blinded	40 (20/20)	8 weeks of exercise (combined aerobic, resistance and IMT)	No rehabilitation input	upper/lower body muscle power; NP-proBNP; CPET; 6MWD; 5STS; Respiratory Muscle Strength; SF-36; Physical activity levels (via accelerometer); muscle mass
Grünig(a)(41) (2011)	pulmonary hypertension and right heart failure	prospective cohort study	58	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	NA	6MWD; SF-36; TTCW; WHO FC; CPET; survival
Grünig(b)(42) (2012)	pulmonary hypertension	prospective cohort study	183	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	NA	6MWD; SF-36; WHO FC; CPET
Grünig(c)(43) (2012)	PAH associated with connective tissue disease	prospective cohort study	21	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	NA	6MWD; CPET; WHO FC; SF-36
Ihle(44) (2014)	pulmonary hypertension	prospective cohort study	17	10 months strengthening, breathing exercises and education plus home exercise programme	NA	6MWD; SF-36; CAMPHOR

Inagaki(45) (2014)	inoperable CTEPH or persistent PH after surgery	prospective cohort study	8	12 weeks pulmonary rehabilitation classes plus home exercise programme	NA	MRC dyspnoea scale; baseline and transition dyspnoea index; peripheral muscle force; pulmonary function tests; 6MWD; Nagasaki University Respiratory ADL questionnaire; St George's Respiratory Questionnaire
Kabitz(46) (2014)	pulmonary arterial hypertension	prospective cohort study	7	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	NA	Pulmonary function tests; NT-proBNP; 6MWD; Respiratory Muscle Strength
Karapolat(47) (2019)	2019	RCT, single blind	30 (15/15)	8 weeks of group cardio-pulmonary exercise classes	8 weeks home exercise programme	CPET; 6MWD; SF-36; Beck Depression Index; Cardiac Function (via echo)
Ley(48) (2013)	PAH or CTEPH	RCT, single blind	20 (10/10)	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	No rehabilitation input	6MWD; cardiac function (via MRI); pulmonary perfusion (via MRI)
Mainguy(49) (2010)	idiopathic pulmonary hypertension	prospective cohort study	5	12 weeks combined treadmill, cycling, upper and lower limb resistance	NA	6MWD; CPET; thigh muscle area; muscle biopsy; quadriceps strength
Martínez-Quintada(50) (2010)	pulmonary hypertension associated with congenital heart disease	non-randomised controlled trial	8 (4/4)	3 months progressive cycle resistance training	Education	6MWD; step count; grip strength; quadriceps strength; SF-36
Mehani(11) (2017)	pulmonary hypertension	prospective cohort study	50	5 months interval bike or treadmill training	NA	CPET; right ventricular function (via echo)
Mereles(2) (2006)	pulmonary hypertension	RCT, single blind	30 (15/15)	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	No rehabilitation input	6MWD; SF-36; WHO FC; CPET
Morris(51) (2018)	pulmonary hypertension	RCT, single blind (Protocol)	50	8 weeks outpatient supervised progressive cycling and treadmill training, followed by home walking programme	No rehabilitation input	6MWD; CPET; CAMPHOR; SF-36; cardiac function (via MRI); cardiac function (via echo); survival; TTCW
Nagel(52) (2012)	Inoperable CTEPH	prospective cohort study	35	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	NA	6MWD; CPET; WHO FC; NT-proBNP; SF-36; TTCW; survival

Raskin(53) (2014)	pulmonary hypertension	Retrospective	23	30-60 minutes treadmill, cycling and cross trainer 2-3 times per week	NA	6MWD; St George's Respiratory Questionnaire
Saglam(54) (2015)	pulmonary arterial hypertension	RCT	29 (15/14)	6 weeks progressive daily IMT	6 weeks sham IMT	Pulmonary function tests; respiratory muscle strength; 6MWD; MRC dyspnoea scale; Fatigue Severity Scale; Nottingham Health Profile
Souza Leão(55) (2018)	pulmonary hypertension	RCT, double blind (Protocol)	24 (12/12)	12 weeks progressive daily IMT	12 weeks sham IMT	Respiratory muscle strength; respiratory muscle endurance SF-36; 6MWD
Talwar(12) (2017)	pulmonary arterial hypertension	Retrospective	18	12 weeks group pulmonary rehabilitation	NA	Attainable treadmill speed
Tulloh(56) (2018)	pulmonary arterial hypertension	Pilot RCT	34 (18/16)	8 weeks of group mindfulness sessions including stretching and breathing exercises	No rehabilitation input	Beck Anxiety Index; Beck depression index; cardiac function (via echo); cardiac function (via ECG); WHO FC; 6MWD; Health and Social Care Resource usage; SF-36
Weinstein(57) (2013)	pulmonary arterial hypertension	RCT	28 (14/14)	Progressive treadmill walking for 10 weeks plus education	Education	Fatigue Severity Scale; Human Activity Profile; 6MWD; Incremental Treadmill Test

Abbreviations:

6MWD: 6 minute walk distance; TTCW: time to clinical worsening; CPET: cardio-pulmonary exercise testing; IMT: inspiratory muscle training; RCT: randomised controlled trial; WHO: World Health Organisation functional class; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; 5STS: five times sit-to-stand test; IPAQ: International Physical Activity Questionnaire; SF-36: 36 item quality of life survey; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; HADS: Hospital Anxiety and Depression Scale; EQ-5D:quality of life score; CAMPHOR: Cambridge Pulmonary Hypertension Outcome review; MRC: Medical Research Council

Table 2 – Study Characteristics

	Studies n (%)			
	2006 - 2009 (n = 2)	**2010-2014 (n = 16)**	**2015-2019 (n = 16)**	**Total (n = 34)**
Study design				
Prospective single cohort	1 (50)	8 (50)	4 (25)	13 (38)
RCT	1 (50)	3 (19)	8 (50)	12 (3)
Protocol	0 (0)	1 (6)	2 (13)	3 (9)
Non-randomised two-armed	0 (0)	3 (19)	0 (0)	3 (9)
Retrospective	0 (0)	1 (6)	1 (6)	2 (6)
Case series	0 (0)	0 (0)	1 (6)	1 (3)
Patient population				
PAH	1 (50)	8 (50)	10 (63)	19 (56)
PH	1 (50)	5 (31)	4 (25)	10 (29)
PAH or CTEPH	0 (0)	1 (6)	2 (13)	3 (9)
CTEPH	0 (0)	2 (13)	0 (0)	2 (6)
Intervention				
Whole Body Exercise training	2 (100)	14 (88)	10 (63)	26 (76)
Walking Programme	0 (0)	2 (12.5)	1(6)	3 (9)
Inspiratory muscle training	0 (0)	0 (0)	2 (13)	2 (6)
Oscillation plate	0 (0)	0 (0)	1 (6)	1 (3)
Yoga	0 (0)	0 (0)	1 (6)	1 (3)
Mindfulness	0 (0)	0 (0)	1 (6)	1 (3)
Intervention period				
up to 1 month	0 (0)	0 (0)	2 (13)	2 (6)
2-4 months	2 (100)	15 (94)	13 (81)	30 (89)
5 - 12	0	1 (6)	1 (6)	2 (6)

Abbreviations
RCT - randomised controlled trial; PAH - pulmonary arterial hypertension; PH - pulmonary hypertension; CTEPH - chronic thromboembolic pulmonary hypertension

Table 3 - Outcome Measures

	Category	Measure	Frequency of Use
Clinical Measure (n=128)	Exercise Test (n=56)	6MWD	32
		CPET	19
		5STS	1
		Incremental Treadmill test	1
		Single two leg jump	1
		Attainable treadmill speed	1
		Chair raising test	1
	Biomarker (n=23)	NT-proBNP	10
		Pulmonary function tests	6
		Muscle biopsy	2
		Peripheral muscle force (quads and handgrip)	1
		Muscle mass	1
		Thigh muscle area	1
		Heart rate recovery	1
		Oxygen Saturation at rest	1
	Cardiac Function (n=15)	Cardiac Function including LV and RV function (via echo)	5
		RV function (via echo)	3
		Cardiac Function (via MRI)	3
		Haemodynamics (via RHC)	2
		Cardiac Function (via ECG)	1
		Pulmonary Perfusion (via MRI)	1
	Strength (n=11)	Respiratory Muscle Strength	4
		Quadriceps strength	3
		Grip strength	2
		Upper/lower body muscle power	1
		Respiratory Muscle Endurance	1
	Long Term Outcomes (n=10)	Time to clinical worsening	5
		Survival	5
	Function (n=10)	WHO Functional Class	10
	Physical Activity (n=3)	Step count	2
		Physical activity levels (via accelerometer)	1
Patient Reported Outcome Measure (n=48)	Quality of Life (n=31)	SF-36	19
		CAMPHOR	5
		EQ-5D	2
		Health Promoting Lifestyle Profile II (HPLPII)	1
		Nottingham Health Profile	1
		The Lawton instrumental activities of daily living scale	1
		Nagasaki University Respiratory ADL questionnaire	1
		Living with Pulmonary Hypertension Questionnaire	1
	Symptom Specific measures (n=12)	St George's Respiratory Questionnaire	2
		Fatigue Severity Scale	2
		Beck Depression index	2
		Hospital Anxiety and Depression Scale	1
		Beck Anxiety Index	1
		Depression and Anxiety Severity Scale (DASS21)	1
		Baseline and transition dyspnoea index	1
		MRC dyspnoea scale	2
	Physical Activity (n=3)	International Physical Activity Questionnaire	2
		Human Activity Profile	1
	Health Resources (n=2)	Health and Social Care Resource Usage	2

Abbreviations:
6MWD: 6 minute walk distance; TTCW: time to clinical worsening; CPET: cardio-pulmonary exercise testing; IMT: inspiratory muscle training; RCT: randomised controlled trial; WHO: World Health Organisation functional class; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; 5STS: five times sit-to-stand test; IPAQ: International Physical Activity Questionnaire; SF-36: 36 item quality of life survey; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; HADS: Hospital Anxiety and Depression Scale; EQ-5D:quality of life score; CAMPHOR: Cambridge Pulmonary Hypertension Outcome review; MRC: Medical Research Council

Table 4 - Outcome measures mapped to the sub-domains of ICF Activity and Participation

			Activity				Participation				
	Frequency of use	No. of domains	Learning and Applying Knowledge	General tasks and demands	Communic-ation	Mobility	Self-care	Domestic life	Interpersonal interactions and relationships	Major Life Areas	Community Social and Civic Life
Outcomes identified in the study											
5STS	1	1									
6MWD	32	1									
Attainable treadmill speed	1	1									
Baseline and transition dyspnoea index	1	2									
CAMPHOR	5	7									
Chair raising test	1	1									
EQ-5D	2	3									
Fatigue Severity Scale	2	4									
Health Promoting Lifestyle Profile II (HPLPII)	1	5									
Hospital Anxiety and Depression Scale	1	1									
Human Activity Profile	1	5									
Incremental Treadmill test	1	1									
International Physical Activity Questionnaire	2	4									
MRC dyspnoea scale	2	2									
Nottingham Health Profile	1	7									
Physical activity levels (via accelerometer)	1	1									
SF-36	19	5									
St George's Respiratory Questionnaire	2	6									
Step count	2	1									
The Lawton instrumental activities of daily living scale	1	3									
WHO Functional Class	10	2									
Outcomes not identified in the study											
emPHasis 10	0	5									
WHODAS 2.0	0	8									
Key:											

Shaded cells denotes that the outcome measures captures information relevant to this domain

Abbreviations:

6MWD: 6 minute walk distance; WHO: World Health Organisation functional class; 5STS: five times sit-to-stand test; SF-36: 36 item quality of life survey; EQ-5D:quality of life score; CAMPHOR: Cambridge Pulmonary Hypertension Outcome review; MRC: Medical Research Council