Check for updates

SYSTEMATIC REVIEWS

Outcome Measures Used in Studies of Rehabilitation in Pulmonary Hypertension

Carol Keen[1,2], Deborah Harrop[2], Molly N. Hashmi-Greenwood[2], David G. Kiely[1,3], Janelle Yorke[4], and Karen Sage[5]

[1]Sheffield Pulmonary Vascular Diseases Unit, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom; [2]Department of Allied Health Professions, College of Health, Wellbeing and Life Sciences, Sheffield Hallam University, Sheffield, United Kingdom; [3]Department of Infection, Immunity and Cardiovascular Disease, The University of Sheffield, Sheffield, United Kingdom; [4]Nursing, Midwifery and Social Work, The University of Manchester, Manchester, United Kingdom; and [5]Department of Nursing, Faculty of Health, Psychology and Social Care, Manchester Metropolitan University, Manchester, United Kingdom

ORCID ID: 0000-0001-7803-1235 (C.K.).

Abstract

Rationale: The evidence base for rehabilitation in pulmonary hypertension is expanding, but adoption in clinical practice is limited.

Objectives: The World Health Organization International Classification for Functioning, Disability and Health identifies three health domains: Body Functions/Structures, Activity and Participation in society. To ensure that the wider impact of rehabilitation in pulmonary hypertension is accurately assessed, it is important that study endpoints reflect all three domains.

Methods: A systematic review of the literature was conducted to identify studies of rehabilitation in patients with pulmonary hypertension from 2006 to 2019.

Results: Searches across five databases yielded 2,564 articles, of which 34 met eligibility criteria; 50 different outcome measures (mean = 5, minimum = 1, maximum = 9) were identified. When mapped onto the World Health Organization International Classification for Functioning, Disability and Health, 48% of instances of outcome usage were measures of Body Functions/Structure, 33% were measures of Activity, and 18% were measures of Participation. Measures of Participation were not included in seven studies (21%).

Conclusions: Studies of rehabilitation in pulmonary hypertension have focused primarily on measures of Body Functions/Structure; the impact in other health domains is not well characterized. 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.

Keywords: pulmonary hypertension; rehabilitation; outcome measures

(Received in original form May 24, 2020; accepted in final form September 18, 2020)

Author Contributions: C.K.: substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data for the work; and drafting the work. D.H.: substantial contributions to the conception and design of the work and the acquisition, analysis, and interpretation of data for the work. M.N.H.-G.: substantial contribution to the acquisition, analysis, and interpretation of data for the work. D.G.K.: revising the work critically for important intellectual content. J.Y.: substantial contributions to the conception and design of the work. K.S.: substantial contributions to the conception and design of the work and revising the work critically for important intellectual content.

Correspondence and requests for reprints should be addressed to Carol Keen, B.Eng.B.Comm., B.Sc., M.Sc., M.C.S.P., Pulmonary Vascular Diseases Unit, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK. E-mail: carol.keen@nhs.net.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Ann Am Thorac Soc Vol 18, No 2, pp 321–335, Feb 2021

DOI: 10.1513/AnnalsATS.202005-541OC
Internet address: www.atsjournals.org

Pulmonary hypertension (PH) is a condition with many causes that 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).

Although 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 PH is still required (3, 4). Effective rehabilitation is a complex, multifaceted intervention with the potential to impact not only the underlying health condition but also the daily lives of patients, their independence, and their community connections (5). It is important that this wider potential impact is given due consideration in studies of rehabilitation.

The World Health Organization International Classification for Functioning, Disability and Health (6) (ICF) is a dynamic multidimensional 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 *1*) Body Functions/Structures (i.e., aspects of physiology and anatomy), *2*) Activity (i.e., actions and tasks undertaken by individuals), *3*) Participation (i.e., involvement in life situations), and *4*) the environmental and personal factors that 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 World Health Organization 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

Characterization and clinical meaning of outcome measures in studies of rehabilitation in patients with PH.

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); and 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 PH 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 E1 in the online supplement.

Study Selection

Selection of studies was undertaken by one author (C.K.) and a sample was checked at each stage of selection by a second author (M.N.H.-G.). Disagreement was resolved by discussion and consensus involving a third author (K.S.) 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 the 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; and 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); or non–English language papers.

Study populations had to include adults (age $\geq$ 18 years) with a diagnosis of PH (8). Studies were excluded if subjects were animals; patients with exercise-induced PH; or patients undergoing postoperative rehabilitation.

Data Extraction

Data were extracted from all articles that 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 outcome 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 performed.

Data Synthesis

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

Outcomes were categorized 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 analyzed 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 with the ICF Checklist (9) to determine which domain or subdomain they represented. Initial classification was performed by C.K. before being checked and verified by D.G.K. and K.S. Disagreement was resolved by discussion and consensus.

Because PH is a hemodynamic 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 nonoverlapping sets of Activities (domains 1–4: learning and applying knowledge; general tasks and demands; communication; and mobility) and Participation (domains 5–9: self-care; domestic life; interpersonal interactions and relationships; major life areas; and 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 that 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 that 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, sex, education, or profession. Although these are important aspects in understanding the health of an individual, they are not factors that will be influenced by rehabilitation interventions and therefore were not included in this analysis.

Results

Searches across five databases yielded 2,564 articles after removal of duplicates. These were screened on title and abstract, leaving 62 articles that underwent full review and 34 articles that were included in the final data synthesis, as shown 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 randomized controlled trials over that time period. Studies were most commonly of patient populations with pulmonary arterial hypertension (56%) or with PH of a nonspecified 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 (minimum = 1, maximum = 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.

Six-minute walk distance (6MWD) was used in 32 of the 34 studies; in the 2 studies not using 6MWD, 1 used cardiopulmonary exercise testing (11) and 1 attainable treadmill speed (12). Several studies used more than one exercise test.

There was no quality of life measure used in nine (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 two (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 (79%) captured measures across all three domains.

Table 4 shows further details of the subdomains of Activity and Participation included in each of the outcomes. Several outcomes include only one or two of the nine possible subdomains, including the most common, 6MWD. Outcomes encompassing higher numbers of subdomains are less frequently used—Nottingham Health Profile ($n = 7$), Cambridge Pulmonary Hypertension Outcome Review questionnaire ($n = 7$), and St. George's Respiratory Questionnaire ($n = 6$). The 36-Item Short Form Health

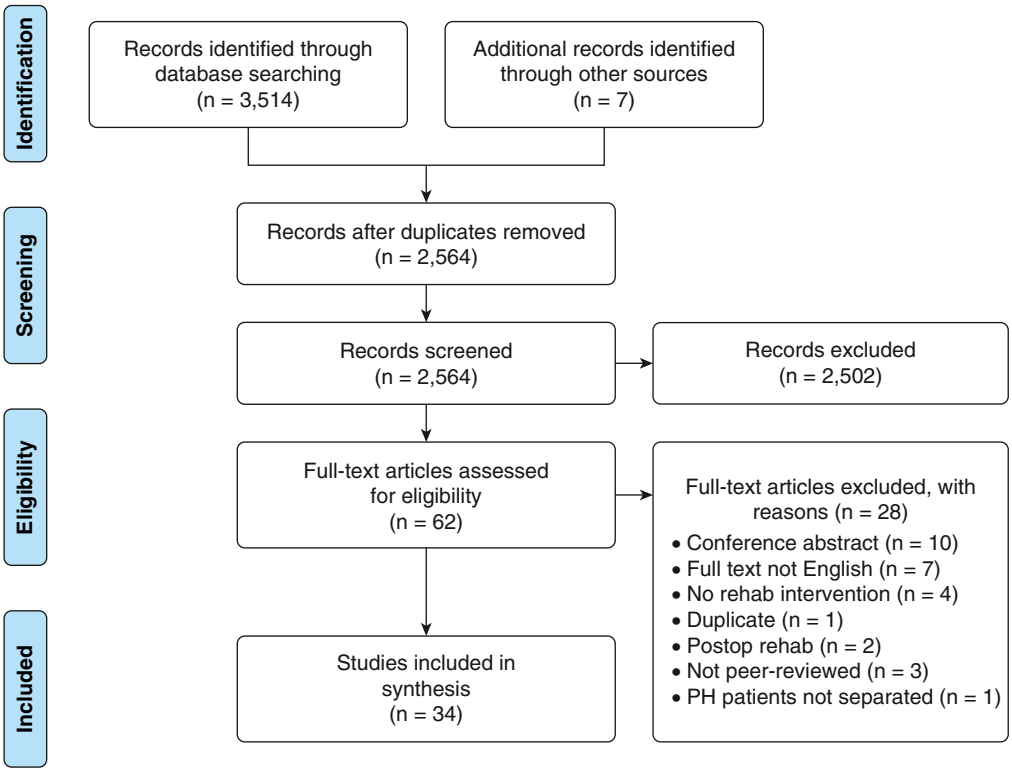

Figure 1. Search flow diagram. PH = pulmonary hypertension.

Table 1. Full text studies

Study	Cohort	Study Design	Sample Size (Intervention/ Control)	Exercise Intervention	Control	Outcomes Used
Awdish *et al.* (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 *et al.* (29) (2019)	Pulmonary hypertension	RCT, nonblinded	84 (42/42)	12-wk home-based exercise program plus patient education manual	Education manual	6MWD; SF-36; WHO FC; RV function (via echo)
Becker-Grünig *et al.* (30) (2013)	Congenital heart disease–associated pulmonary arterial hypertension	Prospective nonrandomized trial	20	3 wk of inpatient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12-wk home-based exercise program	NA	6MWD; CPET; SF-36; NT-proBNP; WHO FC; TTCW; survival
Brown *et al.* (31) (2018)	Pulmonary arterial hypertension	Prospective nonrandomized pilot study	12	Incremental walking program plus arginine supplement	NA	6MWD; CPET; SF-36; cardiac function (via echo); NT-proBNP; step count; heart rate recovery
Bussotti *et al.* (32) (2017)	Pulmonary arterial hypertension	Prospective nonrandomized trial	16	4 wk of daily training combined aerobic, resistance, IMT, psychological support	NA	CPET; 6MWD; NT-proBNP; pulmonary function tests; EQ-5D; HADS
Chan *et al.* (33) (2013)	Pulmonary hypertension	RCT, single blinded	26 (13/13)	10 wk of treadmill exercise plus education	Education only	CPET; 6MWD; SF-36; CAMPHOR; IPAQ
Chia *et al.* (34) (2017)	Pulmonary arterial hypertension	RCT, single blinded (Protocol)	NA	12 wk of weekly group exercise (combined endurance, respiratory muscle training, strength, psychological support)	Written advice on walking program	Cardiac function (via MRI); hemodynamics (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 *et al.* (35) (2009)	Idiopathic pulmonary arterial hypertension	Prospective nonrandomized trial	19	12 wk of cycling and strengthening, three times per wk	NA	CPET; quadriceps strength; pulmonary function tests; NT-proBNP; 6MWD; muscle biopsy

(Continued)

Table 1. (*Continued*)

Study	Cohort	Study Design	Sample Size (Intervention/ Control)	Exercise Intervention	Control	Outcomes Used
Ehlken (58) (2014)	PH and right heart insufficiency	Prospective group and age-and sex-matched control group	104 (58/46)	3 wk of inpatient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12-wk home-based exercise program	No rehabilitation input	6MWD; TTCW; WHO FC; Health and Social Care Resource Usage; EQ-5D; survival
Ehlken *et al.* (36) (2016)	PAH and inoperable or persistent CTEPH	RCT, single blinded	87 (46/41)	3 wk of inpatient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by- 12-wk home-based exercise program	No rehabilitation input	CPET; hemodynamic (via RHC); 6MWD; SF-36; WHO FC; NT-proBNP
Fox *et al.* (37) (2011)	Pulmonary arterial hypertension	RCT	22 (11/11)	12 wk of combined cardiovascular and resistance exercise plus home exercise program	No rehabilitation input	6MWD; CPET; cardiac function (via echo); NT-proBNP
Ganderton *et al.* (38) (2011)	IPAH, familial PAH, PAH associated with connective tissue disease	RCT, single blinded (Protocol)	NA	12 wk of combined cardiovascular and resistance exercise plus home exercise program	No rehabilitation input	6MWD; CAMPHOR; SF-36; IPAQ; CPET
Gerhardt *et al.* (39) (2017)	Pulmonary arterial hypertension	RCT, nonblinded	22 (11/11)	4 wk of exercises on an 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 *et al.* (40) (2017)	PAH or inoperable CTEPH	RCT, single blinded	40 (20/20)	8 wk 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 *et al.* (41) (2011)	Pulmonary hypertension and right heart failure	Prospective cohort study	58	3 wk of inpatient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12-wk home-based exercise program	NA	6MWD; SF-36; TTCW; WHO FC; CPET; survival

(Continued)

Table 1. (*Continued*)

Study	Cohort	Study Design	Sample Size (Intervention/ Control)	Exercise Intervention	Control	Outcomes Used
Grünig *et al.* (42) (2012)	Pulmonary hypertension	Prospective cohort study	183	3 wk of inpatient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12-wk home-based exercise program	NA	6MWD; SF-36; WHO FC; CPET
Grünig *et al.* (43) (2012)	PAH associated with connective tissue disease	Prospective cohort study	21	3 wk of inpatient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12-wk home-based exercise program	NA	6MWD; CPET; WHO FC; SF-36
Ihle *et al.* (44) (2014)	Pulmonary hypertension	Prospective cohort study	17	10 mo of strengthening, breathing exercises, and education plus home exercise program	NA	6MWD; SF-36; CAMPHOR
Inagaki *et al.* (45) (2014)	Inoperable CTEPH or persistent PH after surgery	Prospective cohort study	8	12 wk of pulmonary rehabilitation classes plus home exercise program	NA	MRC dyspnea scale; baseline and transition dyspnea index; peripheral muscle force; pulmonary function tests; 6MWD; Nagasaki University Respiratory ADL questionnaire; St. George's Respiratory Questionnaire
Kabitz *et al.* (46) (2014)	Pulmonary arterial hypertension	Prospective cohort study	7	3 wk of inpatient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12-wk home-based exercise program	NA	Pulmonary function tests; NT-proBNP; 6MWD; Respiratory Muscle Strength
Karapolat *et al.* (47) (2019)	2019	RCT, single blind	30 (15/15)	8 wk of group cardiopulmonary exercise classes	8 wk home exercise program	CPET; 6MWD; SF-36; Beck Depression Index; Cardiac Function (via echo)

(Continued)

Table 1. (*Continued*)

Study	Cohort	Study Design	Sample Size (Intervention/ Control)	Exercise Intervention	Control	Outcomes Used
Ley *et al.* (48) (2013)	PAH or CTEPH	RCT, single blind	20 (10/10)	3 wk of inpatient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12-wk home-based exercise program	No rehabilitation input	6MWD; cardiac function (via MRI); pulmonary perfusion (via MRI)
Mainguy *et al.* (49) (2010)	Idiopathic pulmonary hypertension	Prospective cohort study	5	12 wk of combined treadmill, cycling, upper and lower limb resistance	NA	6MWD; CPET; thigh muscle area; muscle biopsy; quadriceps strength
Martínez-Quintada *et al.* (50) (2010)	Pulmonary hypertension associated with congenital heart disease	Nonrandomized controlled trial	8 (4/4)	3 mo of progressive cycle resistance training	Education	6MWD; step count; grip strength; quadriceps strength; SF-36
Mehani and Abdeen (11) (2017)	Pulmonary hypertension	Prospective cohort study	50	5 mo of interval bike or treadmill training	NA	CPET; right ventricular function (via echo)
Mereles *et al.* (2) (2006)	Pulmonary hypertension	RCT, single blind	30 (15/15)	3 wk of inpatient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12-wk home-based exercise program	No rehabilitation input	6MWD; SF-36; WHO FC; CPET
Morris *et al.* (51) (2018)	Pulmonary hypertension	RCT, single blind (Protocol)	50	8 wk of outpatient supervised progressive cycling and treadmill training, followed by home walking program	No rehabilitation input	6MWD; CPET; CAMPHOR; SF-36; cardiac function (via MRI); cardiac function (via echo); survival; TTCW
Nagel *et al.* (52) (2012)	Inoperable CTEPH	Prospective cohort study	35	3 wk of inpatient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12-wk home-based exercise program	NA	6MWD; CPET; WHO FC; NT-proBNP; SF-36; TTCW; survival
Raskin *et al.* (53) (2014)	Pulmonary hypertension	Retrospective	23	30–60 min treadmill, cycling, and cross-trainer two to three times per wk	NA	6MWD; St. George's Respiratory Questionnaire

(Continued)

Table 1. (*Continued*)

Study	Cohort	Study Design	Sample Size (Intervention/ Control)	Exercise Intervention	Control	Outcomes Used
Saglam *et al.* (54) (2015)	Pulmonary arterial hypertension	RCT	29 (15/14)	6 wk of progressive daily IMT	6 wk sham IMT	Pulmonary function tests; respiratory muscle strength; 6MWD; MRC dyspnea scale; Fatigue Severity Scale; Nottingham Health Profile
Leão *et al.* (55) (2018)	Pulmonary hypertension	RCT, double blind (Protocol)	24 (12/12)	12 wk of progressive daily IMT	12 wk sham IMT	Respiratory muscle strength; respiratory muscle endurance SF-36; 6MWD
Talwar *et al.* (12) (2017)	Pulmonary arterial hypertension	Retrospective	18	12 wk of group pulmonary rehabilitation	NA	Attainable treadmill speed
Tulloh *et al.* (56) (2018)	Pulmonary arterial hypertension	Pilot RCT	34 (18/16)	8 wk 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 *et al.* (57) (2013)	Pulmonary arterial hypertension	RCT	28 (14/14)	Progressive treadmill walking for 10 wk plus education	Education	Fatigue Severity Scale; Human Activity Profile; 6MWD; Incremental Treadmill Test

Definition of abbreviations: 5STS = five times sit-to-stand test; 6MWD = 6-minute walk distance; ADL = activities of daily living; CAMPHOR = Cambridge Pulmonary Hypertension Outcome review; CPET = cardiopulmonary exercise testing; CTEPH = chronic thromboembolic pulmonary hypertension; ECG = electrocardiogram; EQ-5D = quality of life score; HADS = Hospital Anxiety and Depression Scale; IMT = inspiratory muscle training; IPAH = idiopathic pulmonary arterial hypertension; IPAQ = International Physical Activity Questionnaire; MRC = Medical Research Council; MRI = magnetic resonance imaging; NA = not applicable; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RCT = randomized controlled trial; RHC = right heart catheter; RV = right ventricular; SF-36 = 36-item quality of life survey; TTCW = time to clinical worsening; WHO FC = World Health Organization Functional Class.

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)
Nonrandomized 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 program	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 mo	0 (0)	0 (0)	2 (13)	2 (6)
2–4 mo	2 (100)	15 (94)	13 (81)	30 (89)
5–12 mo	0	1 (6)	1 (6)	2 (6)

Definition of abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RCT = randomized controlled trial.

Survey (SF-36), the most commonly used patient-reported outcome measure, encompasses five subdomains.

Discussion

This review has examined outcome measures used in studies of rehabilitation in PH since the first study published in 2006. The use of outcome measures is heterogeneous across the studies, using 50 different outcomes across 34 studies, with an average of 5 outcomes per study. When mapped onto the World Health Organization 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 randomized controlled trial of a pharmaceutical intervention in PH 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 PH 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). PH lacks strong surrogate disease endpoints; the use of invasive measures such as hemodynamics has decreased over time in pharmaceutical studies with a shift instead to composite endpoints reflecting time to clinical worsening and, more recently, a focus on time to clinical improvement (14). Studies of rehabilitation in PH demonstrate a similar pattern to studies of pharmacological interventions, with initial studies focusing 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 endpoints 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 PH 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.

PH 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 hemodynamics 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 organizations supporting patients (19).

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
		Right ventricular function (via echo)	3
		Cardiac function (via MRI)	3
		Hemodynamics (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	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 dyspnea index	1
		MRC dyspnea 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

Definition of abbreviations: 5STS = five times sit-to-stand test; 6MWD = 6-minute walk distance; ADL = activities of daily living; CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; CPET = cardio-pulmonary exercise testing; DASS21 = Depression and Anxiety Severity Scale; ECG = electrocardiogram; EQ-5D = quality of life score; LV = left ventricular; MRC = Medical Research Council; MRI = magnetic resonance imaging; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; RHC = right heart catheter; RV = right ventricular; SF-36 = 36-item quality of life survey; WHO = World Health Organization.

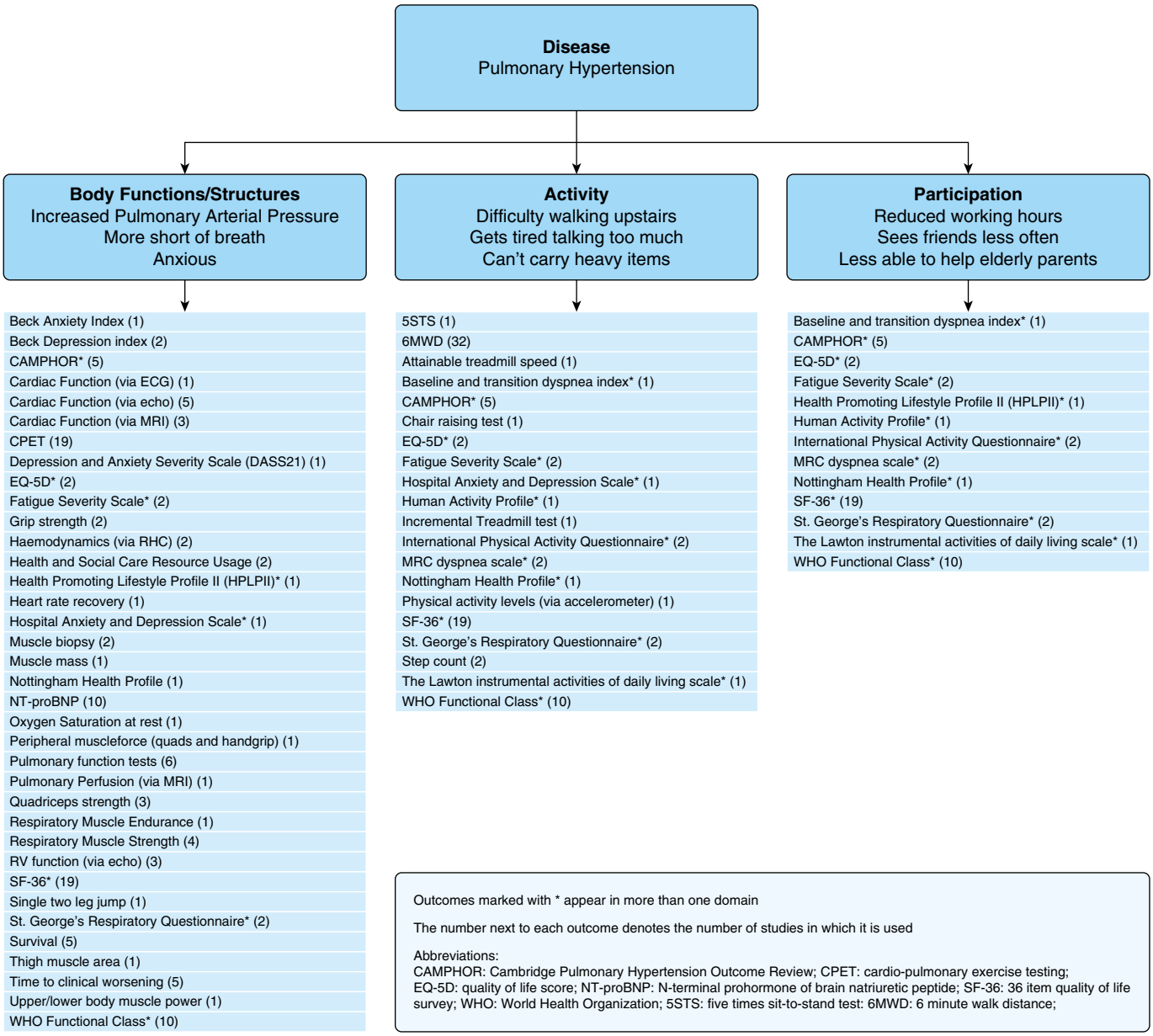

Figure 2. International Classification for Functioning, Disability and Health classification. 5STS = five times sit-to-stand test: 6MWD = 6-minute walk distance; CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; CPET = cardiopulmonary exercise testing; ECG = electrocardiogram; EQ-5D = quality of life score; MRC = Medical Research Council; MRI = magnetic resonance imaging; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; RHC = right heart catheter; RV = right ventricle; SF-36 = 36-item quality of life survey; WHO = World Health Organization.

Rehabilitation is a broad term that captures an active and enabling approach to optimizing 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, and understanding and mastery of the disease and its management (20).

By limiting the outcomes used to measure the impact of rehabilitation in PH, 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 multifaceted, 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 PH, despite a growing evidence base (21). Healthcare resources are scarce and the case for development of new services must be compelling. The cost of caring for people with respiratory disease is

Table 4. Outcome measures mapped to the subdomains of International Classification for Functioning, Disability and Health Activity and Participation

			Activity				Participation				
	Frequency of Use	Number of Domains	Learning and Applying Knowledge	General Tasks and Demands	Communication	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 dyspnea 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	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 dyspnea 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	■		■	■	■	■	■	■	■

Definition of abbreviations: 5STS = five times sit-to-stand test; 6MWD = 6-minute walk distance; CAMPHOR = Cambridge Pulmonary Hypertension Outcome review; EQ-5D = quality of life score; MRC = Medical Research Council; SF-36 = 36-item quality of life survey; WHO = World Health Organization; WHODAS 2.0 = World Health Organization Disability Assessment Schedule 2.0. Shaded cells denote that the outcome measure captures information relevant to this domain.

significant, arising both from medical care of the condition (e.g., drug therapies and hospital admissions) and from the social costs of respiratory disease (e.g., inability to work, requirement for care and support at home, and 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 that capture aspects of Activity and Participation should be used in studies of rehabilitation in PH, to assess change across a broad spectrum of patients' lives. Of the outcomes that assess Participation in this review, SF-36 is the most used, and it is also widely used in trials of pharmacological therapies in PH. Although it is a generic instrument, its measures have been shown to converge well with other physiological markers in PH and a minimal clinically important difference has been estimated (22). Although several items on the questionnaire address pain and energy levels, which fall within the domains of Body Functions/Structure, it encompasses only five of the nine subdomains of Activity and Participation (Table 4).

The Cambridge Pulmonary Hypertension Outcome Review questionnaire 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 PH, encompassing seven of the nine subdomains in Activity and Participation (Table 4). Although it may not track other PH clinical measures over time (14) its validity, reliability, and minimal clinically important difference have been established (23). emPHasis10 (24) is an alternative PH-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 PH. Covering five of the nine 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 PH will have significant comorbidities and complex health problems for which rehabilitation may also be beneficial. In such situations, attempting to capture outcomes that reflect the impact of rehabilitation on a single disease might overlook the wider benefits to health. The World Health Organization Disability Assessment Schedule 2.0 (25) is a self-administered questionnaire that covers eight of the nine 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, functional activities, and financial burden, which reflect concerns frequently raised by people with PH (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 PH, in a study that uses the measure to characterize patients with the disease (27). Although used in only one study of rehabilitation, the Nottingham Health Profile covers seven of the nine domains (Table 4) and therefore may also warrant further investigation.

It is likely that the recent global coronavirus disease (COVID-19) pandemic will result in an increased number of non–face-to-face patient assessments taking place. Outcomes that 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 PH 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 that best meet the needs of patients.

Conclusions

Studies of rehabilitation in PH have focused primarily on measures of Body Functions/Structure; the impact in other domains is less well characterized. 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 PH. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the staff in Library services at Sheffield Hallam University who facilitated access to the materials used in this study.

References

1 Kiely DG, Elliot CA, Sabroe I, Condliffe R. Pulmonary hypertension: diagnosis and management. *BMJ* 2013;346:f2028.
2 Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, *et al*. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation* 2006;114:1482–1489.
3 Keen C, Hashmi-Greenwood M, York J, Armstrong IJ, Sage K, Kiely D. Exploring a physiotherapy well-being review to deliver community-based rehabilitation in patients with pulmonary hypertension. *Pulm Circ* 2019;9:2045894019885356.
4 Grünig E, Eichstaedt C, Barberà J-A, Benjamin N, Blanco I, Bossone E, *et al*. ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. *Eur Respir J* 2019;53: 1800332.
5 NHS England. Commissioning guidance for rehabilitation. 2016 [accessed 2020 Jan 12]. Available from: https://www.england.nhs.uk/wp-content/uploads/2016/04/rehabilitation-comms-guid-16-17.pdf.
6 World Health Organization. Towards a common language for functioning, disability and health. Geneva: WHO; 2002 [accessed 2020 Feb 14]. Available from: https://www.who.int/classifications/icf/icfbeginnersguide.pdf?ua=1.
7 Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Info Libr J* 2009;26:91–108.
8 Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, *et al*.; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by: association for European Paediatric and Congenital Cardiology (AEPC), International Society

for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;37: 67–119.
9 World Health Organization. ICF checklist. Geneva: WHO; 2003 [accessed 2020 Jan 25]. Available from: https://www.who.int/14 classifications/icf/icfchecklist.pdf?ua=1.
10 World Health Organization. How to use the ICF: a practical manual for using the International Classification of Functioning, Disability and Health (ICF). Geneva: WHO; 2013 [accessed 2020 Jan 23]. Available from: https://www.who.int/classifications/ drafticfpracticalmanual2.pdf?ua=1.
11 Mehani SHM, Abdeen HAA. Cardiopulmonary rehabilitation program impact on prognostic markers in selected patients with resting and exercise-induced ventilatory inefficiency: a clinical trial. *J Phys Ther Sci* 2017;29:1803–1810.
12 Talwar A, Sahni S, Verma S, Khan SZ, Dhar S, Kohn N. Exercise tolerance improves after pulmonary rehabilitation in pulmonary hypertension patients. *J Exerc Rehabil* 2017;13:214–217.
13 Rich S. The 6-minute walk test as a primary endpoint in clinical trials for pulmonary hypertension. *J Am Coll Cardiol* 2012;60:1202–1203.
14 Sitbon O, Gomberg-Maitland M, Granton J, Lewis MI, Mathai SC, Rainisio M, *et al*. Clinical trial design and new therapies for pulmonary arterial hypertension. *Eur Respir J* 2019;53:1801908.
15 Löwe B, Gräfe K, Ufer C, Kroenke K, Grünig E, Herzog W, *et al*. Anxiety and depression in patients with pulmonary hypertension. *Psychosom Med* 2004;66:831–836.
16 White J, Hopkins RO, Glissmeyer EW, Kitterman N, Elliott CG. Cognitive, emotional, and quality of life outcomes in patients with pulmonary arterial hypertension. *Respir Res* 2006;7:55.
17 McGoon MD, Ferrari P, Armstrong I, Denis M, Howard LS, Lowe G, *et al*. The importance of patient perspectives in pulmonary hypertension. *Eur Respir J* 2019;53:1801919.
18 Delcroix M, Howard L. Pulmonary arterial hypertension: the burden of disease and impact on quality of life. *Eur Respir Rev* 2015;24: 621–629.
19 Pulmonary Hypertension Association. PHocus 2021. PHA UK; 2016 [accessed 2020 Feb 27]. Available from: https://www. phocus2021.org/.
20 McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015;(2):CD003793.
21 Morris NR, Kermeen FD, Holland AE. Exercise-based rehabilitation programmes for pulmonary hypertension. *Cochrane Database Syst Rev* 2017;1:CD011285.
22 Gilbert C, Brown MCJ, Cappelleri JC, Carlsson M, McKenna SP. Estimating a minimally important difference in pulmonary arterial hypertension following treatment with sildenafil. *Chest* 2009;135: 137–142.
23 Bunclark K, Abraham N, Ali S, Cannon JE, Sheares K, Speed N, *et al*. P118 Defining a minimal clinically important difference in CAMPHOR. *Thorax* 2019;74:A155.
24 Yorke J, Corris P, Gaine S, Gibbs JSR, Kiely DG, Harries C, *et al*. emPHasis-10: development of a health-related quality of life measure in pulmonary hypertension. *Eur Respir J* 2014;43:1106–1113.
25 World Health Organization. WHO Disability Assessment Schedule 2.0 18 (WHODAS 2.0). 2018 [accessed 2020 Mar 20]. Available from: https://www.who.int/classifications/icf/more_whodas/en/.
26 Armstrong I, Billings C, Kiely DG, Yorke J, Harries C, Clayton S, *et al*. The patient experience of pulmonary hypertension: a large cross-sectional study of UK patients. *BMC Pulm Med* 2019;19:67.
27 Reis A, Santos M, Furtado I, Cruz C, Sa-Couto P, Queirós A, *et al*. Disability and its clinical correlates in pulmonary hypertension measured through the World Health Organization Disability Assessment Schedule 2.0: a prospective, observational study. *J Bras Pneumol* 2019;45:e20170355.
28 Awdish R, Small B, Cajigas H. Development of a modified yoga program for pulmonary hypertension: a case series. *Altern Ther Health Med* 2015;21:48–52.
29 Babu AS, Padmakumar R, Nayak K, Shetty R, Mohapatra AK, Maiya AG. Effects of home-based exercise training on functional outcomes and quality of life in patients with pulmonary hypertension: a randomized clinical trial. *Indian Heart J* 2019;71:161–165.
30 Becker-Grünig T, Klose H, Ehlken N, Lichtblau M, Nagel C, Fischer C, *et al*. Efficacy of exercise training in pulmonary arterial hypertension associated with congenital heart disease. *Int J Cardiol* 2013;168: 375–381.
31 Brown MB, Kempf A, Collins CM, Long GM, Owens M, Gupta S, *et al*. A prescribed walking regimen plus arginine supplementation improves function and quality of life for patients with pulmonary arterial hypertension: a pilot study. *Pulm Circ* 2018;8:2045893217743966.
32 Bussotti M, Gremigni P, Pedretti RFE, Kransinska P, Di Marco S, Corbo P, *et al*. Effects of an outpatient service rehabilitation programme in patients affected by pulmonary arterial hypertension: an observational study. *Cardiovasc Hematol Disord Drug Targets* 2017;17:3–10.
33 Chan L, Chin LMK, Kennedy M, Woolstenhulme JG, Nathan SD, Weinstein AA, *et al*. Benefits of intensive treadmill exercise training on cardiorespiratory function and quality of life in patients with pulmonary hypertension. *Chest* 2013;143:333–343.
34 Chia KS, Faux SG, Wong PK, Holloway C, Assareh H, McLachlan CS, *et al*. Randomised controlled trial examining the effect of an outpatient exercise training programme on haemodynamics and cardiac MR parameters of right ventricular function in patients with pulmonary arterial hypertension: the ExPAH study protocol. *BMJ Open* 2017;7: e014037.
35 de Man FS, Handoko ML, Groepenhoff H, van 't Hul AJ, Abbink J, Koppers RJH, *et al*. Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2009;34: 669–675.
36 Ehlken N, Lichtblau M, Klose H, Weidenhammer J, Fischer C, Nechwatal R, *et al*. Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thrombo-embolic pulmonary hypertension: a prospective, randomized, controlled trial. *Eur Heart J* 2016;37:35–44.
37 Fox BD, Kassirer M, Weiss I, Raviv Y, Peled N, Shitrit D, *et al*. Ambulatory rehabilitation improves exercise capacity in patients with pulmonary hypertension. *J Card Fail* 2011;17:196–200.
38 Ganderton L, Jenkins S, Gain K, Fowler R, Winship P, Lunt D, *et al*. Short term effects of exercise training on exercise capacity and quality of life in patients with pulmonary arterial hypertension: protocol for a randomised controlled trial. *BMC Pulm Med* 2011;11:25.
39 Gerhardt F, Dumitrescu D, Gärtner C, Beccard R, Viethen T, Kramer T, *et al*. Oscillatory whole-body vibration improves exercise capacity and physical performance in pulmonary arterial hypertension: a randomised clinical study. *Heart* 2017;103:592–598.
40 González-Saiz L, Fiuza-Luces C, Sanchis-Gomar F, Santos-Lozano A, Quezada-Loaiza CA, Flox-Camacho A, *et al*. Benefits of skeletal-muscle exercise training in pulmonary arterial hypertension: the WHOLEi+12 trial. *Int J Cardiol* 2017;231:277–283.
41 Grünig E, Ehlken N, Ghofrani A, Staehler G, Meyer FJ, Juenger J, *et al*. Effect of exercise and respiratory training on clinical progression and survival in patients with severe chronic pulmonary hypertension. *Respiration* 2011;81:394–401.
42 Grünig E, Lichtblau M, Ehlken N, Ghofrani HA, Reichenberger F, Staehler G, *et al*. Safety and efficacy of exercise training in various forms of pulmonary hypertension. *Eur Respir J* 2012;40:84–92.
43 Grünig E, Maier F, Ehlken N, Fischer C, Lichtblau M, Blank N, *et al*. Exercise training in pulmonary arterial hypertension associated with connective tissue diseases. *Arthritis Res Ther* 2012;14:R148.
44 Ihle F, Weise S, Waelde A, Meis T, Knedinger N, Schild C, *et al*. An integrated outpatient training program for patients with pulmonary hypertension - the Munich pilot project. *Int J Phys Med Rehabil* 2014; 2:1000204.
45 Inagaki T, Terada J, Tanabe N, Kawata N, Kasai H, Sugiura T, *et al*. Home-based pulmonary rehabilitation in patients with inoperable or residual chronic thromboembolic pulmonary hypertension: a preliminary study. *Respir Investig* 2014;52:357–364.
46 Kabitz HJ, Bremer HC, Schwoerer A, Sonntag F, Walterspacher S, Walker DJ, *et al*. The combination of exercise and respiratory training improves respiratory muscle function in pulmonary hypertension. *Lung* 2014;192:321–328.
47 Karapolat H, Çınar ME, Tanıgör G, Nalbantgil S, Kayıkçıoğlu M, Moğulkoç N, *et al*. Effects of cardiopulmonary rehabilitation on

pulmonary arterial hypertension: a prospective, randomized study. *Turk J Phys Med Rehabil* 2019;65:278–286.
48 Ley S, Fink C, Risse F, Ehlken N, Fischer C, Ley-Zaporozhan J, *et al*. Magnetic resonance imaging to assess the effect of exercise training on pulmonary perfusion and blood flow in patients with pulmonary hypertension. *Eur Radiol* 2013;23:324–331.
49 Mainguy V, Maltais F, Saey D, Gagnon P, Martel S, Simon M, *et al*. Effects of a rehabilitation program on skeletal muscle function in idiopathic pulmonary arterial hypertension. *J Cardiopulm Rehabil Prev* 2010;30:319–323.
50 Martínez-Quintana E, Miranda-Calderín G, Ugarte-Lopetegui A, Rodríguez-González F. Rehabilitation program in adult congenital heart disease patients with pulmonary hypertension. *Congenit Heart Dis* 2010;5:44–50.
51 Morris NR, Louis M, Strugnell W, Harris J, Lin A, Feenstra J, *et al*. Study protocol for a randomised controlled trial of exercise training in pulmonary hypertension (ExTra_PH). *BMC Pulm Med* 2018;18:40.
52 Nagel C, Prange F, Guth S, Herb J, Ehlken N, Fischer C, *et al*. Exercise training improves exercise capacity and quality of life in patients with inoperable or residual chronic thromboembolic pulmonary hypertension. *PLoS One* 2012;7:e41603.
53 Raskin J, Qua D, Marks T, Sulica R. A retrospective study on the effects of pulmonary rehabilitation in patients with pulmonary hypertension. *Chron Respir Dis* 2014;11:153–162.
54 Saglam M, Arikan H, Vardar-Yagli N, Calik-Kutukcu E, Inal-Ince D, Savci S, *et al*. Inspiratory muscle training in pulmonary arterial hypertension. *J Cardiopulm Rehabil Prev* 2015;35:198–206.
55 Leão MS, Bergamascki LM, Xavier VB, Jaenisch RB, Stirbulov R, Alves V. Inspiratory muscle training in pulmonary hypertension: TREMMI protocol. *Man Ther Posturology Rehabil J* 2020;2018:1–5.
56 Tulloh RMR, Garratt V, Tagney J, Turner-Cobb J, Marques E, Greenwood R, *et al*. A pilot randomised controlled trial investigating a mindfulness-based stress reduction (MBSR) intervention in individuals with pulmonary arterial hypertension (PAH): the PATHWAYS study. *Pilot Feasibility Stud* 2018;4:78.
57 Weinstein AA, Chin LMK, Keyser RE, Kennedy M, Nathan SD, Woolstenhulme JG, *et al*. Effect of aerobic exercise training on fatigue and physical activity in patients with pulmonary arterial hypertension. *Respir Med* 2013;107:778–784.
58 Ehlken N, Verduyn C, Tiede H, Staehler G, Karger G, Nechwatal R, *et al*. Economic evaluation of exercise training in patients with pulmonary hypertension. *Lung* 2014;192:359–366.