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Relevance of patient-centered actigraphy measures in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: a qualitative interview study

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Abstract

Background Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are severe, progressive diseases characterized by key symptoms such as dyspnea and fatigue. These symptoms impair physical functioning, with patients struggling to perform their daily activities. One traditional measure of physical functioning and exercise capacity is the 6-minute walk test (6MWT). Actigraphy represents a promising tool to complement the 6MWT and provide a holistic picture of physical performance in patients with PAH or CTEPH. However, the current literature holds limited evidence on content validity of actigraphy in these populations, as reported by patients themselves. The primary objective of this study was to understand which physical functioning concepts are most meaningful to patients with PAH or CTEPH and identify relevant actigraphy variables and appropriate timeframes for their measurement.

Methods This was a cross-sectional, qualitative study in adults with a confirmed diagnosis of PAH or CTEPH. Participants from the UK and USA were interviewed one-on-one via a web-based platform, with interviewers using a semi-structured discussion guide that included concept elicitation and cognitive debriefing sections. Data within the anonymized interview transcripts were coded and thematically analyzed.

Results Concept elicitation identified the physical functioning concepts most meaningful to patients with PAH or CTEPH and generated a combined conceptual model of physical functioning, which strongly aligned with previous literature. During cognitive debriefing, of the four actigraphy variables debriefed in relation to these physical functioning concepts, study participants highly valued time spent in non-sedentary physical activity and time spent in moderate to vigorous activity, while step count and walking speed emerged as less relevant. Participants indicated four alternative variables as relevant: walking distance, walking up hills or inclines, duration of continuous walking

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bouts, and time spent walking. Regardless of the variable, participants suggested a timeframe of approximately 10 or 12 h/day over a minimum of 14 days for measuring physical functioning.

Conclusions By demonstrating the content validity of actigraphy measures of physical functioning, this qualitative study begins to address the evidence gaps identified by the regulatory requirements for using actigraphy endpoints in future PAH and CTEPH clinical trials.

Keywords Pulmonary arterial hypertension, Chronic thromboembolic pulmonary hypertension, Actigraphy, Accelerometry, Digital measures, Remote monitoring, Patient-reported outcomes, Activities of daily living, Physical activity, Health-related quality of life

Background

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are potentially life-threatening forms of pulmonary hypertension (PH). They are rare diseases with an annual incidence of approximately 6 patients per million (ppm) and 2–6 ppm, respectively [1, 2]. Both PAH and CTEPH are severe, chronic, and progressive diseases characterized by remodeling and increased resistance of the pulmonary vasculature, which, untreated, ultimately lead to right heart failure and death [1–6].

Although several treatment options are available to slow disease progression and alleviate symptoms (e.g., prostacyclin analogues, endothelin receptor antagonists, phosphodiesterase 5 inhibitors, the soluble guanylate cyclase stimulator riociguat, and the activin signaling inhibitor sotatercept), PAH and CTEPH remain incurable and adversely affect patients' health-related quality of life [2, 7–13]. The clinical presentations of PAH and CTEPH share similarities and are characterized by key symptoms such as dyspnea, fatigue, chest pain, palpitations, dizziness, and syncope [2, 4, 14]. These symptoms heavily impair physical functioning, with patients struggling to perform their daily activities. Limitations in daily activity include difficulty walking, standing for prolonged periods of time, carrying things, and completing housework [8, 11, 12, 14–16]. As a result of their physical functioning limitations, patients report considerable behavioral, social, and psychological impacts, such as exercise avoidance, increased social isolation, and loss of independence, as well as feelings of anxiety and depression [8, 11, 14, 17–21].

Physical functioning is assessed by researchers during clinical trials to understand the limitations experienced by trial participants. The 6-minute walk test (6MWT) is a traditional measure of physical functioning and exercise capacity widely used in clinical trials and daily clinical practice; it is a simple, self-paced, easily repeatable test to assess the distance a patient can walk in 6 min along a flat corridor [22, 23]. However, its use as a clinical trial endpoint has several limitations. For example, the 6MWT is associated with a ceiling effect in World Health Organization (WHO) functional class I/II patients or those already on treatment for PAH, and might not necessarily be representative of the patient's performance in everyday life [24–28]. Given the limitations of the 6MWT, actigraphy represents an objective measure of physical functioning that could be used in conjunction with the 6MWT to provide a holistic picture of physical performance in patients with PAH or CTEPH [26]. Actigraphy devices are non-invasive accelerometry sensors for continuous, remote monitoring of physical activity in real-world settings, with applications across various therapeutic areas [26, 29–34]. Currently, there is a growing academic and regulatory interest in actigraphy; the European Medicines Agency (EMA) approved the use of actigraphy for measuring stride velocity 95th centile in Duchenne muscular dystrophy [35], and actigraphy endpoints have recently been explored in PAH and CTEPH [36–38]. To be recognized as endpoints in future clinical trials, a sufficient level of content, analytical, and clinical validation is required by the Food and Drug Administration (FDA) and EMA [34, 39, 40]. However, to date, there is limited evidence of clinical validity and no qualitative evidence of content validity (i.e., the concept of interest is meaningful to the patients) of actigraphy in PAH or CTEPH [27, 41, 42].

Thus, the purpose of this study was to understand which physical functioning concepts are most meaningful to patients with PAH or CTEPH and identify relevant variables and appropriate timeframes for their measurement, from the user's perspective. Specifically, we aimed: (1) to understand how reduced physical functioning affects patients with PAH or CTEPH with respect to their physical limitations and activity participation restrictions, and (2) to explore how physical functioning concepts meaningful to patients could be measured by digital tools to support the content validity of digital measures of physical functioning in PAH and CTEPH.

Methods

Study design

This was a cross-sectional, qualitative interview study. One-on-one audio interviews of approximately 60 minutes were conducted via a web-based platform. Participant interviews were composed of two distinct parts:

a concept elicitation section and a cognitive debriefing section. The research protocol, discussion guide, and all patient communication templates were reviewed and approved by the WIRB-Copernicus Group Institutional Review Board prior to the study commencing (Confirmation ID 45282790). Ethical approval was also granted in the UK by the Yorkshire & The Humber – Leeds West Research Ethics Committee (Reference: 2/YH/0166). All participants provided written informed consent to participate in the study.

Participants

Adult participants with a confirmed diagnosis of PAH or CTEPH were recruited from the UK and USA between April 2022 and July 2022. Participants were recruited from clinical sites or via referral from practicing pulmonologists. Specifically, participants from the UK were recruited from Sheffield Teaching Hospital, whereas participants from the USA were recruited using a local specialized patient recruitment team upon referral from practicing pulmonologists. The sites screened patients directly in their medical practices based on specific eligibility criteria (Supplementary Table 1) and provided contact details (UK) or referred eligible patients to the study team (USA). Patients who qualified for inclusion in the study were scheduled for interviews by the study team upon completing the informed consent. Participants were compensated for their time and travel, with an amount that was considered fair market value.

Discussion guide development and content

A discussion guide was designed for this study, informed by a review of existing literature with evidence of: (1) the most relevant physical functioning concepts in PAH and CTEPH [8, 14, 15] and (2) clinical validity of digital measures in PAH and/or CTEPH [27, 41, 42].

The semi-structured discussion guide was composed of two separate sections (i.e., concept elicitation and cognitive debriefing) and included open-ended questions aimed at facilitating a fruitful discussion between the moderator and the participant. The two sections had independent goals and were presented separately to study participants. An outline of the discussion guide is presented in Supplementary Fig. 1, which also includes a glossary with key definitions.

The concept elicitation section explored the most meaningful physical functioning concepts in PAH and CTEPH identified in the existing literature, as mapped to the WHO International Classification of Functioning, Disability and Health (ICF) framework [43]. More specifically, questions in this section explored the participants' experience of symptoms, physical functioning limitations, activity participation restrictions, and impacts of PAH and CTEPH. Additionally, the concept elicitation portion of the interviews captured the most challenging aspects of PAH and CTEPH from the participants' point of view, as well as their general physical activity patterns over time.

For the cognitive debriefing section, the concepts explored aimed at investigating participants' view of the relevance of selected physical functioning variables that could be measured by actigraphy and identifying additional variables for consideration. These variables were identified and selected from endpoints used in previous PAH and CTEPH clinical trials [36–38] and mapped to the physical functioning concepts identified in the existing literature [8, 14, 15]. The four key variables were: (1) time spent in non-sedentary physical activity; (2) time spent in moderate to vigorous physical activity; (3) step count; and (4) walking speed.

Interview procedure

Individual semi-structured interviews were conducted by experienced and certified qualitative scientists. Study participants were debriefed on at least two variables, rotated between interviews to ensure even coverage of participant responses across all four variables. Participants could choose not to answer interview questions if they did not wish to.

Each interview was audio recorded, and a verbatim anonymized transcript was generated. All written transcripts were reviewed and quality-checked by the moderator against the audio recordings.

Data analysis

Data within the anonymized interview transcripts were coded and thematically analyzed by trained and experienced qualitative scientists, using MAXQDA 2022 software [44]. Specifically, the research involved one moderator responsible for keeping the moderation consistent, two coders, and a separate coding reviewer. Additionally, a senior qualitative researcher provided oversight and qualitative researchers in the USA and the UK helped interpret the results. The role of the researcher and the context, as well as their influence on the study findings, were considered by the study team during data analysis. However, the study team did not formally document these aspects, as no reflexive diaries were kept.

Both deductive and inductive coding approaches were used. Deductive coding allowed researchers to apply findings from previous research to the new coding framework, based on the topics included in the discussion guide. During inductive coding, codes were directly derived from the data as concepts and ideas naturally emerged. This combined approach ensured adequate coding structure for the analysis of this type of qualitative data. Furthermore, it provided an opportunity to

thematically analyze new concepts and ideas as they emerged spontaneously from the data. Dual coding took place for 20% of transcripts and inter-rater agreement was regularly assessed throughout the coding process.

Concept saturation

Concept saturation was assessed based on FDA recommendations for collecting comprehensive and representative input [45, 46]. Participants were interviewed through an iterative process in waves of five; concepts that emerged were compared across waves until saturation was achieved. The first waves of interviews focused on concept elicitation. As concept saturation was reached, later waves of interviews focused on the cognitive debriefing section. During coding, saturation tables organized by concept code were produced to continuously assess concept saturation. Saturation was calculated based on the overall population.

Results

Participant demographic and clinical characteristics

A total of 26 adult participants with PAH or CTEPH were interviewed. As presented in Table 1, participants ranged in age from 26 to 77 years, were predominantly female, were recruited from two countries (UK and USA), and had varied ethnicities, education levels, employment status, and living situations. Fifty percent of the participants were in WHO functional class II and 35% were in class III. With regard to demographic and clinical characteristics, our study population was proportionately representative of patients with PAH or CTEPH from large registry-based studies [47–52].

Supplementary Table 2 reports individual participant characteristics.

Concept elicitation

Combined conceptual model for physical functioning

From the analysis of the interview data, it was evident that similar experiences were reported by study participants with PAH and those with CTEPH. Analysis of the concept elicitation data resulted in the generation of a combined conceptual model for physical functioning in PAH and CTEPH (Fig. 1). The qualitative patient interviews confirmed most of the concepts identified in the existing literature, except for impacts on sleep and symptoms such as swelling of the feet/hands/stomach area, lack of muscle strength, and weakness [8, 14, 15]. The combined conceptual model included concepts related to both conditions divided into four key themes: (1) signs and symptoms; (2) physical functioning limitations; (3) activity participation restrictions; and (4) impacts. The fourth theme, "impacts," had two distinct sub-themes: behavioral impacts and cognitive/emotional impacts.

Concept saturation

Saturation of concepts was reached for PAH and CTEPH symptoms, physical functioning limitations, and activity participation restrictions, as well as for PAH and CTEPH impacts. Saturation data are reported in Supplementary Table 3.

Signs and symptoms

Shortness of breath was the most frequently described symptom, followed by fatigue and lack of energy. Participants often experienced multiple symptoms concurrently. The combined conceptual model for physical functioning (Fig. 1) reports all symptoms experienced by study participants, and a full list of symptoms with descriptions in participants' own words is included in Supplementary Table 4.

Physical functioning limitations

Nearly all participants mentioned walking limitations and limitations using stairs or walking up hills; walking limitations included difficulties walking while carrying things or difficulties running. For example, a participant described how her difficulties running limited her relationship with her son and the type of activities she would do with him: "*If I was a normal mom, I would do activities with him every day. I would take him out, take him to the park, let him run around. That's my dream, for me to be able to do those things with him. Even just letting him go so he can run around. I'm just too scared because if he was to run and I can't run after him, then that would be a potential danger.*" (ID:01). When describing their difficulties in using stairs or walking up hills, participants noted how they would limit their activity to avoid overexerting: "*I take a 40-minute walk. But if I start going over large inclines, or if I'm going up lots of sets of stairs, that's a completely different thing…I don't want to overexert and then just maybe create a myriad of problems for myself.*" (ID:18).

Most participants reported difficulties in engaging in prolonged activity: "*I feel like I'm going to faint if I'm doing something for a long period of time*" (ID:21); "*I do sometimes find cooking a bit of a trial. Because it's standing in one place for too long, that upsets my back and legs.*" (ID:12).

Approximately half the participants reported limitations performing core body movements (e.g., moving from standing to bending and vice versa, and bending over) and limb movements (e.g., carrying additional weight while being stationary/walking, lifting legs, lifting items above heart level, and pulling/pushing weight): "*Most of the time, I try to just sit down and then dress up because bending down and up can be bit difficult.*" (ID:03); "*You can't pick things up or reach too high up the shelves…When I'm reaching up real…to the top shelves at*

Table 1 Participant demographic and clinical characteristics

Characteristic, *n* (%)	Total (*N* = 26)	PAH (*N* = 15)	CTEPH (*N* = 11)
Age group			
26–35	4 (15)	3 (20)	1 (9)
36–45	3 (12)	3 (20)	0 (0)
46–55	6 (23)	1 (7)	5 (45)
56–65	8 (31)	3 (20)	5 (45)
66–77	5 (19)	5 (33)	0 (0)
Gender			
Female	15 (58)	10 (67)	5 (45)
Male	11 (42)	5 (33)	6 (55)
Race/ethnicity			
Asian, Asian British	2 (8)	1 (7)	1 (9)
Black, African/Caribbean/Black British/African American	2 (8)	0 (0)	2 (18)
Hispanic/Latino	1 (4)	0 (0)	1 (9)
White/Caucasian	15 (58)	11 (73)	4 (36)
Mixed/Multiple ethnic groups	2 (8)	0 (0)	2 (18)
Other ethnic group	3 (12)	3 (20)	0 (0)
Prefer not to answer	1 (4)	0 (0)	1 (9)
Recruitment country			
UK	16 (62)	15 (100)	1 (9)
USA	10 (38)	0 (0)	10 (91)
Employment status			
Employed by an organization	5 (19)	5 (33)	0 (0)
Self-employed	6 (23)	3 (20)	3 (27)
Unemployed	7 (27)	2 (13)	5 (45)
Highest level of education			
High school diploma or less	10 (38)	8 (53)	2 (18)
College[a] or vocational training	6 (23)	1 (7)	5 (45)
Undergraduate degree or higher	10 (38)	6 (40)	4 (36)
Living situation			
Lives in household with other people	14 (54)	13 (87)	1 (9)
Lives alone	12 (46)	2 (13)	10 (91)
WHO Group IV subgroup (CTEPH only)			
Persistent or recurrent PH	—	—	9 (82)
Inoperable	—	—	1 (9)
Not operated	—	—	1 (9)
PAH Group I subgroup (PAH only)			
Idiopathic	—	10 (67)	—
Associated	—	4 (27)	—
Familial	—	1 (7)	—
WHO functional class			
I	1 (4)	1 (7)	0 (0)
II	13 (50)	7 (47)	6 (55)
III	9 (35)	7 (47)	2 (18)
IV	3 (12)	0 (0)	3 (27)
PAH/CTEPH treatment regimen			
PDE5is/sGCs (sildenafil, tadalafil, or riociguat)	19 (73)	10 (67)	9 (82)
ERAs (bosentan, macitentan, or ambrisentan)	11 (42)	8 (53)	3 (27)
Iloprost (Ventavis)	5 (19)	5 (33)	0 (0)
Epoprostenol	3 (12)	3 (20)	0 (0)
Selexipag	2 (8)	2 (13)	0 (0)
Surgery and interventions (CTEPH only)			
PEA only	—	—	3 (27)

Table 1 (continued)

Characteristic, *n* (%)	Total (*N* = 26)	PAH (*N* = 15)	CTEPH (*N* = 11)
BPA only	—	—	3 (27)
PEA and BPA	—	—	3 (27)
Time on treatment			
0–1 year	15 (58)	10 (67)	5 (45)
1–2 years	5 (19)	3 (20)	2 (18)
≥ 3 years	6 (23)	2 (14)	4 (36)

BPA: balloon pulmonary angioplasty; CTEPH: chronic thromboembolic pulmonary hypertension; ERAs: endothelin receptor antagonists; PAH: pulmonary arterial hypertension; PDE5is: phosphodiesterase 5 inhibitors; PEA: pulmonary endarterectomy; sGCs: soluble guanylate cyclase stimulators; UK: United Kingdom; USA: United States of America; WHO: World Health Organization

[a]College refers to pre-university higher education, commonly known as community college in the USA

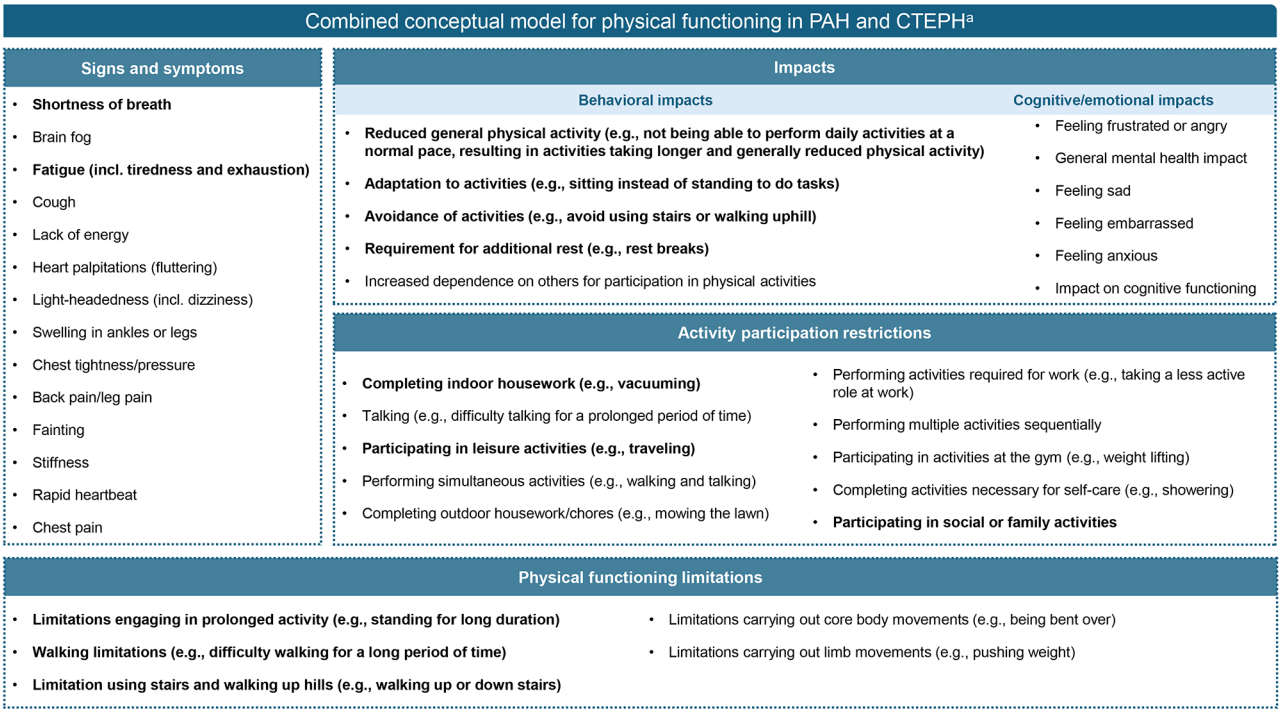

Fig. 1 Combined conceptual model for physical functioning in PAH and CTEPH
[a]The conceptual model demonstrates the concepts relevant to the patient population only; links between symptoms and impacts were not explored as part of this research. Concepts noted by more than half of the participants are in bold

the supermarket, I feel as if there's a lot of pressure on my chest." (ID:06).

A full list of limitations is reported in Supplementary Table 5.

Activity participation restrictions

Nearly all participants felt their physical activity participation was restricted due to PH. When asked which kind of restrictions they faced when participating in physical activities, most participants described difficulties completing indoor housework (e.g., changing the bed, vacuuming, washing the dishes) and restrictions participating in leisure activities, such as travelling, hiking, and dancing: *"this just got bad in the last year—like I might try to wash some dishes to help out or just to have something to do but, I mean, one time I picked up a stack of dishes and that was too heavy…"* (ID:23); *"I mean, I used to travel a lot. I was a big hiker. I used to love swimming, dancing, and I don't do that anymore. Dancing was my passion. I don't do that anymore."* (ID:17).

About half of the participants reduced their participation in social or family activities because they explained how *"people don't understand when you're not well…you get fed up trying to explain to people when they say, 'Oh, you don't look well' or 'You are very pale'."* (ID:06).

Additionally, just under half of the participants reported difficulties with completing outdoor housework and talking: *"I was doing some bit of gardening…*

but I think in some last…I would say last maybe 2 years or something, I find maybe I think things are getting a bit more challenging now where I have to put more effort, so I don't…" (ID:02); "*Yeah, when I'm on the phone talking, I get tired very easily…I get tired at times from talking. It wears me out.*" (ID:19).

A full list of restrictions is reported in Supplementary Table 5.

Impacts

Supplementary Table 5 reports a full list of PAH and CTEPH impacts. Nearly all participants described how their condition impacted their behavior; most of them reported a general reduction of physical activity and physical functioning limitations, which required behavioral adaptations like walking more slowly, allowing more time for completing routine tasks, completing activities while sitting rather than standing, or dividing tasks into smaller parts: "*I can't pack my calendar as I did in the past. Everything is taken slowly and taken at a minimum…Actually, I do everything in a slower pace.*" (ID:20); "*Well, cleaning the bathrooms and sometimes loading the washing machine. I have to sit down to load it and then I'm not as breathless…*" (ID:10); "*I'll either go to the supermarket to do a little bit, literally like a handful of shopping. This is quite regular because I can't do big bouts of shopping. I've kind of managed to do these little, little bits of shopping every day or every other day. It just helps me manage it all.*" (ID:20). Most participants reported needing rest breaks during activities or additional rest after completing the activity: "*…so I restrict… I might go 10 paces, stop, get me breath back do another 10 paces, get me breath back*" (ID:13). Other participants reported complete avoidance of activities: "*anything that's even slightly cardio based…or any activities relating to anything uphill I will avoid at any cost…*" (ID:01) and described increased dependence on others to perform physical activities: "*My wife has like…took pretty much everything over. I just, I sit by idly, watching her do everything.*" (ID:21).

When describing behavioral impacts, most participants detailed how these resulted from physical functioning limitations and vice versa; the interaction between behavioral impacts and physical functioning limitations is reported in Supplementary Fig. 2. The most frequently reported interaction was between limitations using stairs/walking up hills and adaptation to activities; half of the participants described how their difficulty with walking up hills or flights of stairs meant they had to adapt the way they engaged in physical functioning: "*I have to plan the day…because I find it hard to come up and down on the stairs. So I try to do most of the things, what I need to do upstairs, and then I come down. Then I try to do most of the things, obviously, then downstairs and go up.*" (ID:02). Additionally, participants described how walking limitations resulted in reduced levels of physical activity: "*Well, past history, I was a runner for many, many years, completing marathons, half marathons, 10ks, all the rest of it…From the diagnosis, I got to a point where I couldn't run probably a few hundred yards…I can run about ¾ of a mile, and then I have to stop because there's a kind of pressure build-up…*" (ID:05).

The majority of participants also reported emotional or cognitive impacts. The most commonly reported emotional impacts were frustration/anger and sadness: "*it's just really upsetting that I'm [inaudible] [41] years of age, and I can't even take my dogs for a walk without getting out of breath and without being in pain. It's just really frustrating that I can't give them what they need as well.*" (ID:03). A minority of participants felt their condition impacted their cognitive function, affecting "*how quickly your brain works*" (ID:09).

Most challenging aspects of PAH and CTEPH

During the interviews, the majority of participants disclosed the most challenging aspects of their condition. Using the stairs and walking up hills emerged as the main challenge, followed by completing indoor housework. Challenges with carrying out limb movements/core body movements, participating in leisure activities, and walking were each reported by nearly one fifth of respondents. For a minority of participants, challenges also derived from self-care activities, outdoor housework, gym activities, prolonged physical activity, talking, simultaneous activities, dependence on others, and social/family activities.

General physical activity patterns over time

When asked, most participants said their physical activity varied seasonally or daily. Nearly half of the participants reported a weekly variation in their physical activity. Physical activity was considered more challenging in more extreme hot or cold weather because of symptom exacerbation. In terms of daily variation, participants felt more active and energized in the morning or early afternoon. Participants reported "*[tending] to watch too much television*" (ID:11) and "*[being] kind of wiped out*" (ID:25) in the afternoon/evening. Additionally, physical activity differed between weekdays and weekends, with some participants being more active during the weekends and others during weekdays. The overall physical activity seems to also be affected by the participant employment status, with retired participants observing lower variability in their physical activity between weekends and weekdays compared with working individuals. For example, a participant who had retired years ago stated that "*it's all basically the same*" (ID:12). In contrast, a participant who was still working reported performing more physical

activity during the weekend "*We'd probably go off to a forest or a national trails property or something like that, and that would be the weekend…*" (ID:11).

Cognitive debriefing

Variable relevance and meaningful change

When asked about the four preselected variables (Table 2), most participants initially agreed on their relevance; indicative examples of participant responses are reported in Table 3. However, on closer examination of why participants valued these variables, step count and walking speed appeared to be proxies for other, more directly relevant variables.

When asked what change in each variable they would consider a meaningful improvement, as baseline levels of activity varied widely between participants, an increase in individual step count, walking speed, non-sedentary activity, and moderate to vigorous activity from baseline was considered meaningful improvement, overall. Similarly, a decrease from individual baseline levels was considered meaningful worsening.

When participants clarified why the described change was perceived as meaningful, an association between the meaningful change and improvements in specific physical functioning limitations emerged. Table 4 reports the main physical functioning limitations that study participants wanted to overcome to see meaningful improvements in each debriefed variable. From the analysis of participants' verbatim responses (Supplementary Table 6), a disconnect emerged between what the patients said was relevant to measure and indicative of meaningful improvement and their reasons for considering these improvements meaningful.

Most participants wanted to engage in physical activity for a longer time and/or distance and to walk more frequently. The majority of participants believed that higher step counts were indicative of their ability to engage in prolonged activity or overcome walking limitations: "*Well, I don't think it's just the steps, but I think that's part of it. Because you can do more cardiovascular activities that are in place or doing squats or doing things that can also exhaust you, that you can get your activity in versus just steps …*" (ID:16); "*I mean, 5,000 or 6,000 would be great…It could just be knowing that you could do more if you wanted to…it would be much nicer to be able to go off and do a walk of a few miles rather than just 100 yards up the road…*" (ID:24); "*Well, I guess counting steps is pretty much the same things as…that I could walk for longer. It pretty much would end up being the same measurement, wouldn't it? Yeah.*" (ID:22). Similarly, participants believed faster walking speed was meaningful as it would allow them to "*do things longer*

Table 2 Debriefed variable relevance and timeframe appropriateness

	Step count	Walking speed	Non-sedentary physical activity	Moderate to vigorous activity
Relevance, *n*(%)				
Relevant	16 (89)	11 (61)	17 (85)	14 (78)
Not relevant	0 (0)	5 (31)	3 (15)	2 (11)
Missing/not answered	2 (11)	2 (11)	0 (0)	2 (11)
Total	18 (100)	18 (100)	20 (100)	18 (100)
Measurement timeframe, *n*(%)				
7 h				
Appropriate	6 (33)	5 (28)	11 (55)	6 (33)
Not appropriate[a]	9 (50)	5 (28)	6 (30)	6 (33)
Missing/not answered	3 (17)	8 (44)	3 (15)	6 (33)
Total	18 (100)	18 (100)	20 (100)	18 (100)
7 days				
Appropriate	8 (44)	7 (39)	11 (55)	9 (50)
Not appropriate[a]	7 (39)	4 (22)	5 (25)	2 (11)
Missing/not answered	3 (17)	7 (39)	4 (20)	7 (39)
Total	18 (100)	18 (100)	20 (100)	18 (100)
14 days[b]				
Appropriate	13 (72)	7 (39)	13 (65)	9 (50)
Not appropriate[a]	3 (17)	3 (17)	3 (15)	3 (17)
Missing/not answered	2 (11)	8 (44)	4 (20)	6 (33)
Total	18 (100)	18 (100)	20 (100)	18 (100)

[a]Not appropriate was coded in all the instances where the participant was not wholeheartedly in favor of that specific timeframe (e.g., the participant's response suggested the particular timeframe was not appropriate to reflect their physical activity levels and a longer timeframe was needed). [b]The 14-day option was presented sequentially to the 7-day option by the moderator during the interview

Note: For the cognitive debriefing part, as not all participants were debriefed on each variable, percentages were calculated out of the total number of participants debriefed for the specific variable. Additionally, participants could choose not to answer questions as they wished

Table 3 Example responses on variable relevance, in participants' own words

Variable	Response
Step count	
Relevant	"I do because steps, well, the steps could be taken in moderation. But steps could also be taken with excessive exercise. If I go from 5,000 steps to now 10,000 steps, was I just walking at a nice pace? I think it'll show you a change of where I am normally, where I am not engaged or maybe I felt lousy, very lousy that day and I was exhausted, needed bed. Well…that's probably why." (ID:16)
	"Yeah, I say it would because you would just see how active a person is during the day. I mean, it would show…I suppose it captures even if you're just doing housework and walking around the house, say, it would show how active you are. I think that would be quite useful to see sort of in total how many steps you do every day, and whether you do the same sort of amount of steps or not, or whether there are marked differences." (ID:07)
Not relevant	—
Walking speed	
Relevant	"Walking speed? I think walking speed because…yes, because you could see where have I gone from. Have I gone from walking and now I'm really speed walking? Okay? Well, that's a big increase, right? I'm improving with the treatment. So I think that the speed will be helpful to see where my comfort level is at." (ID:25)
Not relevant	"I think the distance you walk is more relevant than the speed at which you're walking it." (ID:11)
Time spent in non-sedentary physical activity	
Relevant	"I think so, yes. Because it's all a part of my day." (ID:20)
	"Yes, because that's who I am. That's what I'm doing…That's part of me. You can see what I'm up to. Am I just non-movement all day? Versus getting up and staying active where it's slow but that's okay. I think it's, yeah, good to know, for sure." (ID:25)
Not relevant	*Moderator*: "Do you think that the amount of time you spend in non-sedentary activities has been affected by your CTEPH?" *Participant*: "No, I don't think so. No…But before I had it, I would have done the same things probably at the same times of day." (ID:11)
Time spent in moderate to vigorous activity	
Relevant	"Is that the vacuuming and things like that you said…Yeah. Yeah, I do all that, so yes, that would… You could measure that, yes." (ID:25)
Not relevant	"Well, I…I don't do any vigorous, but if you measure the moderate, that would be good." (ID:19)
	"I don't jog and I don't bicycle. I don't think so." (ID:26)

Table 4 Summary of why described changes in variables are meaningful to participants

Limitations participants want to overcome[a], *n* (%)	Step count (*N* = 18)	Walking speed (*N* = 18)	Non-sedentary physical activity (*N* = 20)	Moderate to vigorous activity (*N* = 18)
Limitations engaging in prolonged activity	17 (94)	10 (56)	14 (70)	13 (72)
Walking limitations	10 (56)	5 (28)	7 (35)	7 (39)
Limitations carrying out limb movements	3 (17)	1 (6)	4 (20)	7 (39)
Limitations carrying out core body movements	3 (17)	0 (0)	6 (30)	5 (28)
Limitations using stairs and walking up hills	2 (11)	1 (6)	1 (5)	1 (6)
Not asked/not mentioned	1 (6)	4 (22)	4 (20)	5 (28)

[a]Some participants provided multiple responses, which is why percentages total to a number greater than 100

and enjoy it whereas before I got tired" (ID:23), "*get a lot more done in a day*" (ID:21), or "*go a bit further because you're walking quicker*" (ID:10). Participants also felt that increased non-sedentary physical activity and moderate to vigorous activity would mostly allow them to engage in physical activity for longer time and interact with their family more: "*Kind of all of them, but at the top is walking. I would like to do more, not thinking of wanting to go up again, or even the cleaning. All those things, I would…*" (ID:02); "*…do a whole [yoga] routine without having to adapt to it, and maybe for longer*" (ID:05); "*Help my wife and play with the kids…Interact with them more. Being able to do social activities with them, go places. Just feeling better*" (ID:17); "*I've got grandchildren and they do things, and sometimes I'll do things with them, which would be nice if I wasn't tired*" (ID:24). Improvements in carrying out limb/core body movements and using stairs/walking up hills were less frequently indicated as reasons for considering a certain change meaningful; these improvements were associated with increased energy levels.

The underlying reasons why participants believed step count and walking speed to be meaningful pointed to

additional variables that would be more relevant to PAH and CTEPH physical functioning limitations. While most participants spontaneously reported these additional variables during the interviews, some others provided this information following probing from the moderator during related discussion points.

Walking distance was mentioned by most participants: "*I think the distance you walk is more relevant than the speed at which you're walking it because it would help your fitness, to be able to walk a little bit further…I think it would be quite important*" (ID:11). Walking up hills or inclines with more ease and less frequent rest breaks was also reported by the majority of participants: "*… I would be looking for going up and down hills, steep hills, and lots of steps more easily with taking less breaks*" (ID:07); "*if you can walk 8,000 steps uphill that is improvement*" (ID:07). Approximately half of the participants highlighted the relevance of continuous walking bouts and time spent walking; some participants discussed how they wanted to "*sustain walking a long period of time and constant*" (ID:25); others expressed their desire to walk and be outside for a longer time: "*if you go on longer walks, you get to see more and be out longer*" (ID:21). This participant went on to further explain how "*you get more benefits from being out longer, like health benefits.*"

Timeframes for measurement

Participants were also debriefed about the appropriateness of three timeframes (7 h daily, 7 days, or 14 days in a row) for measuring each of the four preselected variables with an actigraphy device during waking hours (Table 2).

In terms of daily timeframe, although 7 h could be sufficient, most participants felt a longer timeframe (e.g., 10 or 12 h) would be more likely to accurately capture their daily physical activity: "*I think it needs to be increased… Well, a total maybe 10 hours instead of 7*" (ID:21); "*I think 10 hours, 12 hours would be better*" (ID:19); "*Well, I would think at least 12 hours. Because really we're only asleep between 6 to 8 hours*" (ID:18).

When asked over how many days physical activity should be measured, most participants reported that 7 or 14 days could accurately reflect their physical activity levels. More specifically, most participants first responded that 7 days was appropriate. However, when asked about 14 days, participants preferred 14 days over 7 to better capture their typical physical activity variability: "*I think you need to do 2 weeks because it will give you a better idea. If I tell you both weeks are the same, it gives you a better indication.*" (ID:25). Some participants suggested an even longer timeframe: "*I would say something like 20 days. I know it's a lot of data and there's a lot of information to pick through. If you've got the right computer programs, it should be straightforward*" (ID:09). Some participants discussed the need for longer timeframes to capture the seasonal variation in their physical activity: "*…But we need to take more than one week to get a true average. Because what if in that Monday through Sunday was a summer week that had different things going on than my usual*" (ID:16).

Table 2 reports positive and negative responses for each variable–timeframe combination alongside the number of participants who did not provide any response. Regardless of the debriefed variable, the reason behind participant negative responses was the need for a longer timeframe to capture their usual physical activity.

Discussion

This cross-sectional, qualitative interview study aimed to understand which physical functioning concepts were most meaningful to patients with PAH or CTEPH and identify relevant variables and appropriate timeframes for their measurement. Of the four variables selected for debriefing with patients, two were considered relevant to capture the physical functioning concepts mentioned by study participants: time spent in non-sedentary physical activity and time spent in moderate to vigorous activity. Step count and walking speed were considered less relevant for the participants, who indicated four alternative variables were of higher relevance: walking distance, walking up hills or inclines, duration of continuous walking bouts, and time spent walking. Regardless of the variable, participants suggested that a timeframe of approximately 10 or 12 h/day over a minimum of 14 days would be most appropriate for measuring physical functioning.

The concept elicitation portion of the interviews identified the physical functioning concepts most relevant to patients with PAH or CTEPH and generated a combined conceptual model for physical functioning in this patient population. Participants in our study mainly reported limitations walking (in general and up hills), running, using stairs, and engaging in prolonged activity. Participants also described how their physical functioning limitations affected their everyday life, from their ability to complete indoor housework to their participation in leisure and social activities. However, unlike previous research, our study did not explore how the perception of physical activity changed with diagnosis or time since diagnosis, nor how the patients' attitude (i.e., disease-dominated versus solution-seeking) impacted their ability to cope with the disease [52, 53]. The symptoms and disease experience reported by study participants were in line with published literature, and the combined conceptual model strongly aligned with the concepts that were identified in the existing literature and used to develop the discussion guide [8, 14, 15]. However, a small number of physical functioning concepts (i.e., impacts on sleep and symptoms such as swelling of the feet/hands/

stomach area, lack of muscle strength, and weakness) published in the literature did not arise in our patient interviews [8, 14, 15]. The absence of clinicians' input in the design of our discussion guide may contribute to the observed inconsistency. Furthermore, in agreement with the WHO-ICF model and published knowledge, concept elicitation highlighted daily, weekly, and seasonal variability in physical activity as a result of environmental factors (e.g., extreme weather conditions), health conditions, and personal factors (e.g., patient age, behavior, and occupational status) [42, 54, 55].

The cognitive debriefing portion of the interviews explored participants' opinions on the four preselected actigraphy variables and the appropriateness of different timeframes for measuring changes that are meaningful for the participants. Participants in our study agreed that time spent in non-sedentary physical activity and time spent in moderate to vigorous physical activity were relevant actigraphy measures. Notably, these results aligned with the study by Okumus et al., which showed clinical validity for time spent in moderate to vigorous activity [27]. Furthermore, our findings corroborated the selection of time spent in non-sedentary physical activity, already identified as a relevant variable in the TRAndolapril Cardiac Evaluation (TRACE) study, which evaluated the effect of trandolapril on mortality and cardiovascular morbidity in patients with left ventricular dysfunction after myocardial infarction [36].

Although participants initially described step count and walking speed as relevant, when debriefed, they indicated that improvements in these variables would mean improvements in walking distance, walking up hills or inclines, duration of continuous walking bouts, and time spent walking, meaning that step count and walking speed in themselves were not particularly salient. In previous literature, the use of daily step count as a measure of physical functioning in a daily life setting was supported by the demonstrated correlation between 6-minute walk distance (6MWD) and daily life physical activity [7, 33, 36]. Similarly to step count, walking speed is highly correlated with 6MWD [56, 57]. Furthermore, two previously published interventional studies confirmed the clinical validity of step count; Cascino et al. provided construct validity evidence linking step count to physical functioning behaviors, while Okumus et al. demonstrated that the number of steps per day can discriminate between high- and low-functioning patients with PAH [27, 42]. However, step count was not debriefed with participants and no evidence of content validity was provided in these studies [27, 42]. Regarding walking speed, McCollister et al. identified this measure as being relevant to patients during the development of the Pulmonary Arterial Hypertension - Symptoms and Impact (PAH-SYMPACT) questionnaire conceptual framework [15]. However, the PAH-SYMPACT questionnaire did not provide any post-hoc validation relative to 6MWD, and future work is needed to better understand the correlation between walking speed and 6MWD. Although beyond the scope of our study, examining the correlation of a new digital measure against an existing validated measure could support the validation of the new digital measure.

When discussing timeframes, most participants felt that an interval longer than 7 h (e.g., 10 or 12 h) was needed to reflect their daily physical activity. Additionally, there was unanimous agreement that although 7 consecutive days could be sufficient, the longer the measurement period, the better. As such, a 14-day window was viewed as most appropriate across all debriefed variables. Such a timeframe has the potential to capture typical physical activity variability in patients with PAH or CTEPH, including variability between weekdays and weekends. For example, 90% of TRACE patients were less active on Sunday compared with other days of the week [36]. Despite having to wear the device for the whole waking period, participants suggested longer measurement durations, indicating that they are willing to wear the digital device when they perceive clear measurement objectives. Similarly, a recent patient survey conducted in the UK showed that, of the 112 respondents, 53% already used a wearable device to track their activity and 93% said they would use one if provided as part of a trial [58].

This study has several strengths. The concepts included in the qualitative interview were appropriately validated through a review of previous patient research and existing literature. Data were analyzed according to good qualitative research practice (i.e., achievement of concept saturation, iterative interviews with open-ended questions, combined coding approach), ensuring deep understanding of the patient experience, robustness of the data collected, and accuracy of the conclusions drawn [59–61]. An additional strength is the diversity of patients with PH in our sample; our participants varied in indication (PAH and CTEPH), geography (USA and UK), age, and disease severity. Overall, the qualitative data collected add to the existing literature by broadening our understanding of the physical functioning concepts relevant to patients with PAH or CTEPH and providing deeper insights into the experience of these rare patient populations, as directly reported by patients. Furthermore, this study could help shape relevance of activity measures in all PH-specific patient-reported outcome measures, which currently lack post-hoc content validation [62, 63].

Our study has a number of limitations. There was no patient and public involvement in the study design. Most participants were in WHO class II/III, and their perception of physical activity may not be representative of patients in WHO class IV. Regarding methodology, our study

specifically addressed regulatory requests; therefore, theoretical underpinning was not at the forefront of our study design. Furthermore, triangulation was not considered and reflexive diaries were not kept, limiting our ability to reflect on the researcher's impact and additional potential biases that could have influenced data collection and interpretation. The study population was assessed as one unified group, and we did not perform any subgroup analysis; therefore, we cannot draw any conclusions based on cross-cultural disease differences, age, or patients' diagnostic and therapeutic journeys. Nevertheless, given the broad similarities in disease experience between participants with PAH and CTEPH and between participants in the UK and the USA, this limitation is unlikely to significantly impact the overall findings. Additionally, we did not collect data about digital device usage; thus, we cannot draw any conclusions regarding participants' acceptance of actigraphy devices in their everyday life. Lastly, behavioral characteristics of the participants (i.e., solution seekers vs. disease-dominated patients) were not identified in coding.

Conclusions

This study provides content validation for actigraphy in PAH and CTEPH by demonstrating that, when the appropriate variables are selected, actigraphy can detect meaningful changes in the physical functioning concept most significant to patients.

Of the four debriefed variables, patients highly valued time spent in non-sedentary physical activity and time spent in moderate to vigorous physical activity. Walking distance, walking up hills or inclines, duration of continuous walking bouts, and time spent walking emerged as additional relevant variables for measurement. Based on the participants' perspective, it is recommended to measure the identified actigraphy variables for approximately 10 or 12 h/day over ≥14 days to capture a representative measure of physical activity.

These findings demonstrate that actigraphy measurement of physical functioning has the potential to complement traditional clinical endpoints in future PAH and CTEPH clinical trials.

Abbreviations

6MWD	6-minute walk distance
6MWT	6-minute walk test
CTEPH	Chronic thromboembolic pulmonary hypertension
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICF	International Classification of Functioning, Disability and Health
PAH	Pulmonary arterial hypertension
PAH-SYMPACT	Pulmonary Arterial Hypertension - Symptoms and Impact
PH	Pulmonary hypertension
ppm	Patients per million
TRACE	TRAndolapril Cardiac Evaluation
WHO	World Health Organization

Supplementary Information

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Additional file 1: Supplementary **Table 1**. List of inclusion and exclusion criteria. Supplementary **Fig. 1**. Glossary and discussion guide outline. Supplementary **Table 2**. Individual participant characteristics. Supplementary **Table 3**. Saturation analysis for symptoms, physical functioning limitations, activity participation restrictions and impacts. Supplementary **Table 4**. Symptoms of PAH and CTEPH, in participants' own words. Supplementary **Table 5**. Physical functioning limitations, physical activity restrictions, and impacts. Supplementary **Fig. 2**. Interaction between behavioral impacts and physical functionions, and impacts limitations. Supplementary **Table 6**. Example descriptions of meaningful change, in participants' own words

Additional file 2: Visual abstract

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Author contributions

Study conception: NP, SD, and AB. Study design: NP, AB, and KK. Data acquisition: RK, SA, and KK. Data analysis: RK, SA, and KK. All authors participated in data interpretation, manuscript drafting, and critical revision. All authors approved the final manuscript and consented to submit it for publication. All authors had full access to all of the data in this study and agree to be accountable for all aspects of the work, in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the provisions of the Declaration of Helsinki, International Conference on Harmonization Guideline for Good Clinical Practice, Good Pharmacoepidemiology Practice, and the applicable legislation on Non-Interventional Studies and/or Observational Studies. The participating study staff at Sheffield teaching hospital in the UK and physicians in the USA performed their duties in accordance with the regulations and guidelines governing medical practice and ethics in their country, and in accordance with currently acceptable techniques and know-how. The research protocol, discussion guide, and all patient communication templates were reviewed and approved by the WIRB-Copernicus Group Institutional Review Board prior to the study commencing (Confirmation ID 45282790). Ethical approval was also granted in the UK by the Yorkshire & The Humber – Leeds West Research Ethics Committee (Reference: 2/YH/0166). Participant interviews were conducted in line with the recommended guidelines provided by the International Society for Pharmacoeconomics and Outcome Research Good Research Practices Task Force [60, 61]. All patients were given the chance to ask questions throughout the study and had the right to withdraw at any point. Patient confidentiality and anonymity was ensured through the assignment of patient identification numbers and all transcripts were deidentified (i.e., any information that could possibly identify

a patient was removed) prior to analysis. All participants provided written informed consent prior to the interview. Clinical trial number not applicable.

Consent for publication
Not applicable.

Competing interests
AB and NP are employees of Actelion Pharmaceuticals Ltd, a Johnson & Johnson company. AB and NP own stock in Johnson & Johnson. SD is an employee of Janssen Global Services, LLC, a Johnson & Johnson company. DGK has received grants from Janssen Pharmaceuticals and Ferrer; consulting fees from Janssen Pharmaceuticals, MSD, Ferrer, Altavant and United Therapeutics; honoraria from Janssen Pharmaceuticals, MSD, Ferrer and United Therapeutics; funding from Janssen Pharmaceuticals, MSD and Ferrer to attend scientific meetings; has participated in a data safety monitoring board or Advisory Board for Janssen Pharmaceuticals and MSD; serves on the Specialist Respiratory Clinical Reference Group (unpaid) and as the UK National Audit Chair. RK, SA, and KK are employees of IQVIA Patient Centered Solutions, which received funding from Actelion Pharmaceuticals Ltd. for conducting this research. AR and FV declare no competing interests.

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