Clinical trial design, end-points, and emerging therapies in pulmonary arterial hypertension

Jason Weatherald [1], Thomas R. Fleming [2], Martin R. Wilkins [3], Thomas M. Cascino [4], Mitchell A. Psotka [5,6], Roham Zamanian [7], Werner Seeger [8], Nazzareno Galiè [9] and Mardi Gomberg-Maitland [10]

[1]Department of Medicine, Division of Pulmonary Medicine, University of Alberta, Edmonton, AB, Canada. [2]Department of Biostatistics, University of Washington, Seattle, WA, USA. [3]National Heart and Lung Institute, Imperial College London, London, UK. [4]Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI, USA. [5]Inova Schar Heart and Vascular, Falls Church, VA, USA. [6]United States Food and Drug Administration, Silver Spring, MD, USA. [7]Vera Moulton Wall Center for Pulmonary Vascular Disease, Stanford University School of Medicine, Palo Alto, CA, USA. [8]Department of Internal Medicine, Universities of Giessen and Marburg Lung Center (UGMLC), Institute for Lung Health (ILH), Cardio-Pulmonary Institute (CPI), Member of the German Center for Lung Research (DZL), Giessen, Germany. [9]Cardiology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna and Dipartimento DIMEC, Università di Bologna, Bologna, Italy. [10]Division of Cardiovascular Medicine, Department of Medicine, George Washington University, School of Medicine, Washington, DC, USA.

Corresponding author: Jason Weatherald (weathera@ualberta.ca)

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PAH clinical trials face future efficiency challenges. Innovative end-points, validated surrogates, novel trial designs and emerging technologies may help overcome these challenges.
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Abstract

Clinical trials in pulmonary arterial hypertension (PAH) have led to the approval of several effective treatments that improve symptoms, exercise capacity and clinical outcomes. In phase 3 clinical trials, primary end-points must reflect how a patient "feels, functions or survives". In a rare disease like PAH, with an ever-growing number of treatment options and numerous candidate therapies being studied, future clinical trials are now faced with challenges related to sample size requirements, efficiency and demonstration of incremental benefit on traditional end-points in patients receiving background therapy with multiple drugs. Novel clinical trial end-points, innovative trial designs and statistical approaches and new technologies may be potential solutions to tackle the challenges facing future PAH trials, but these must be acceptable to patients and regulatory bodies while preserving methodological rigour. In this World Symposium on Pulmonary Hypertension task force article, we address emerging trial end-points and designs, biomarkers and surrogate end-point validation, the concept of disease modification, challenges and opportunities to address diversity and representativeness, and the use of new technologies such as artificial intelligence in PAH clinical trials.

Introduction

Randomised clinical trials have led to an increasing number of therapeutic options for patients with pulmonary arterial hypertension (PAH). Historically, licensed drugs focus on one of three pathobiological pathways, working predominantly by pulmonary arterial vasodilation to improve how patients "feel, function and survive". A clinical trial paradigm has grown around these drugs which is challenged by new therapies that target structural remodelling. Here we review the evolution of clinical trial end-points and discuss emerging and novel clinical trial designs that might enable further drug development for PAH.

Evolution of end-points in phase 3 trials

Efficacy end-points in phase 3 clinical trials must be consistently and readily measurable, sensitive to the effects of interventions, well-defined and reliable, and be direct measures of how patients feel, function or

TABLE 1 Ongoing or recently completed phase 2 and phase 3 clinical trials in pulmonary arterial hypertension (PAH)

	Mechanism of action	Trial name and registration	Phase	Sample size	Primary outcome	Status[#]
Ambrisentan	Endothelin receptor antagonist	TAPE (NCT04972656)	3	420	Incidence of PAH (mPAP ⩾25 mmHg) at 1 year[¶] Change in PVR at 1 year	Recruiting
Dapagliflozin	Sodium glucose co-transporter-2 inhibitor	DAPAH (NCT05179356)	2	52	Change in V'_{O_2}max at 3 months	Recruiting
DHEA	Activation of NO synthase, suppresses ET-1, cardiac remodelling	EDIPHY (NCT03648385)	2 crossover	24	RV longitudinal strain on CMR	Active, not recruiting
Empagliflozin	Sodium glucose co-transporter-2 inhibitor	Emphower PoC (NCT05493371)	2a	8	Tolerability, feasibility, safety at 12 weeks	Recruiting
eNOS-enhanced endothelial progenitor cells	Angiogenic stem cells	SAPPHIRE (NCT03001414)	2 crossover	12	Change in 6MWD at 6 months	Active, not recruiting
Famotidine	Antihistamine	REHAB-PH (NCT03554291)	2	80	Change in 6MWD at week 24	Completed
FK506	Activation of BMPRII signalling	TransformPAH (NCT01647945)	2a	23	Safety	Completed
KER-012	Activin signalling inhibitor	TROPOS (NCT05975905)	2	90	Change in PVR at week 24	Recruiting
Ifetroban	Selective thromboxane receptor antagonist	NCT02682511	2	34	Adverse events and serious adverse events up to week 56	Recruiting
Imatinib	Oral tyrosine kinase inhibitor	PIPAH (NCT04416750)	2	43	Highest tolerated dose; PVR at week 24	Active, not recruiting
Imatinib DPI (AV-101)	Inhaled tyrosine kinase inhibitor	IMPAHCT (NCT05036135)	2b/3	462	Phase 2b: PVR at week 24 Phase 3: change in 6MWD at week 24	Terminated 17 June 2024
LAM-001	Inhaled mTOR inhibitor	NCT05798923	2a	15	Change in V'_{O_2} at 24 weeks	Recruiting
LTP001	SMURF1 inhibitor	NCT05135000	2	47	PVR at week 25	Active, not recruiting
Macitentan (75 mg)	Endothelin receptor antagonist	UNISUS (NCT04273945)	3	900	Morbidity or mortality events (up to 4 years)	Recruiting
Metformin	Decreases gluconeogenesis, increases fatty acid oxidation, and reduces oxidative stress	NCT03617458	2	82	Change in 6MWD at week 2 Change in WHO-FC at week 12	Active, not recruiting
MK-5475	Inhaled soluble guanylate cyclase stimulator	INSIGNIA-PAH (NCT04732221)	2/3	450	Phase 2: PVR at week 12 Phase 3: change in 6MWD at week 12	Active, not recruiting
Olaparib	Poly(ADP-ribose) polymerase inhibitor	OPTION (NCT03782818)	2	20	Treatment-emergent adverse events at week 24	Recruiting
Ralinepag	Prostacyclin receptor agonist	ADVANCE (NCT03626688)	3	1000	TTCW	Recruiting
		ADVANCE CAPACITY (NCT04084678)	3	10	Change in peak V'_{O_2} at week 28	Terminated
Satralizumab	IL-6 receptor antagonist	SATISFY-JP (NCT05679570)	2	24	Change in PVR at week 24	Recruiting
Seralutinib (GB002)	Inhaled PDGF-R, CSF1R and c-KIT inhibitor	PROSERA (NCT05934526)	3	350	Change in 6MWD at week 24	Recruiting
Sodium valproate (CS1)	Histone deacetylase inhibition	NCT05224531	2	30	Patient-reported adverse events	Recruiting
Sotatercept	Activin-signalling inhibitor	HYPERION (NCT04811092)	3	444	TTCW	Recruiting
		ZENITH (NCT04896008)	3	166	Time to first morbidity or mortality event	Active, not recruiting
		MOONBEAM – paediatric PAH (NCT05587712)	2	42	Adverse events, pharmacokinetics/ pharmacodynamics	Recruiting
		MK-7962-020 (NCT05818137)	3	46	Change in PVR at week 24	Recruiting

Continued

TABLE 1 Continued

	Mechanism of action	Trial name and registration	Phase	Sample size	Primary outcome	Status[#]
Spironolactone	Mineralocorticoid receptor antagonist	NCT01712620	2	70	Change in 6MWD at 6 months	Recruiting
Tamoxifen	Selective oestrogen receptor modulator	T3PAH (NCT03528902)	2	18	TAPSE on echo at week 24	Completed
Treprostinil liposomal suspension (L606)	Inhaled prostacyclin analogue	NCT04691154	3	60	Adverse events after switching from inhaled treprostinil (Tyvaso)	Recruiting
Treprostinil palmitil DPI	Inhaled prostacyclin analogue	NCT05147805	2b	99	PVR at week 24	Recruiting
Vardenafil DPI (RT234)	Inhaled phosphodiesterase type-5 inhibitor	VIPAH-PRN (NCT04266197)	2b	60	Adverse events, change in vital signs, change in peak V'_{O_2}	Recruiting

Studies are ordered alphabetically, by intervention. DHEA: dehydroepiandrosterone; eNOS: endothelial nitric oxide synthase; DPI: dry powder inhaler; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; V'_{O_2}: oxygen consumption; NO: nitric oxide; ET: endothelin; RV: right ventricle; CMR: cardiac magnetic resonance imaging; PoC: proof of concept; 6MWD: 6-min walk distance; BMPR: bone morphogenetic protein receptor; mTOR: mammalian target of rapamycin; SMURF1: Smad-specific E3 ubiquitin-protein ligase 1; WHO: World Health Organization; FC: functional class; IL: interleukin; PDGFR: platelet-derived growth factor receptor; CSF1R: colony-stimulating factor 1 receptor; TTCW: time to clinical worsening; TAPSE: tricuspid annular plane systolic excursion. [#]: status as of 10 May 2024; [¶]: only patients with resting mean arterial pressure 21–24 mmHg are eligible.

survive, or a properly validated surrogate [1–3]. A trial may have any number of efficacy end-points, but control of the overall type 1 error is essential with clear alpha-preserving and pre-specified strategy to testing [4]. A list of ongoing phase 2 and phase 3 PAH trials is shown in table 1.

6-min walk distance

The most common primary end-point in phase 3 clinical trials until 2013 was change in 6-min walk distance (6MWD) measured during short-term double-blind placebo-controlled periods ranging from weeks to months [5]. A more nuanced discussion of the advantages and disadvantages of 6MWD as a primary end-point was addressed by the 2018 World Symposium on Pulmonary Hypertension (WSPH) clinical trials task force [5]. While imperfect for several reasons that include a ceiling effect [6], the need for an in-person clinic visit [7], a lack of a clear association between change in distance and mortality [8] and uncertainty regarding the magnitude of difference that is clinically meaningful, 6MWD remains a primary outcome in most recent phase 3 trials [9] and a core component of composite clinical worsening, disease progression [10–14] and clinical improvement [9, 15–17] end-points.

Composite outcome end-points

The low frequency of mortality events in PAH clinical trials makes survival a challenging primary outcome. Time to clinical worsening (TTCW) composite end-points that encompass death, morbidity events and clinical deterioration were recommended as primary outcomes for PAH trials at the 2008 WSPH [18] and are recognised by regulatory agencies if appropriately constructed [3]. Even so, the transition from 6MWD to TTCW necessitated larger trials with longer follow-up periods. However, a composite end-point is only as strong as its weakest link. “Death” and “lung transplantation” represent irreversible morbidity and mortality. A third component, “hospitalisation for worsening PAH”, represents major morbidity. A fourth component, “simultaneous confirmation of a worsening in World Health Organization functional class and a 15% decline in 6MWD”, dilutes the clinical meaningfulness compared to the other components, yet still retains the clinical relevance of the composite. In 31 PAH trials that used TTCW end-points, the proportion of events corresponding to each component was highly variable. More severe components were less frequent and less severe components were more frequent: death (6.7%, 95% CI 3.5–11.2%), lung transplantation or atrial septostomy (0.2%, 95% CI 0.0–0.5%), PAH-related hospitalisation (33.5%, 95% CI 22.6–45.4%) and symptomatic progression (frequently reported as PAH worsening based on decline in functional class and 6MWD) (32.3%, 95% CI 22.5–42.9%) [19]. Symptomatic progression and hospitalisation were the most common events, but there was heterogeneity in perceived importance between patients and their caregivers, suggesting that these are not valued equally [19, 20]. Moreover, in contrast to conclusions from two PAH trials [11, 12, 21], a reduction in clinical worsening events showed only a modest association with subsequent mortality [19]. Even so, clinical worsening, if properly formulated in the manner described, is a clinically meaningful end-point.

When formulating composite end-points in PAH, inclusion of an additional component, "initiation of rescue treatment", such as parenteral prostacyclins, is problematic, as it is an intercurrent event. Justification for such an inclusion in the composite would require confirmation either that initiation of this rescue treatment is of such clinical relevance, due to its toxicity/inconvenience/cost, that preventing such initiation would justify the toxicity/inconvenience/cost of the experimental intervention, or that initiation of this rescue treatment is a validated surrogate for clinically meaningful decline in health. In the latter instance, such validation would require trial-level evidence that the net effect of the experimental treatment on initiation of rescue treatment would reliably predict the net effect of that treatment a clinical end-point, such as death, transplantation or increased risk of PAH hospitalisation. Until such data are available, "initiation of rescue treatment" should be avoided in composite end-points.

Patient-reported outcomes

The United States Food and Drug Administration (FDA) defines a patient-reported outcome (PRO) as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" [22]. A similar definition has been used by the European Medicines Agency (EMA) [23]. Patients with PAH experience numerous symptoms that impact their ability to participate in activities of daily living [24]. Several validated PAH-specific PRO measures have been developed, including the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) [25], the Living with Pulmonary Hypertension Questionnaire [26], the emPHasis-10 [27] and the Pulmonary Arterial Hypertension – Symptoms and Impact (PAH-SYMPACT) questionnaire [28]. Of note, only the PAH-SYMPACT was developed in alignment with FDA guidance for PROs to support intervention labelling claims related to quality of life [22]. Non-qualified PROs can be used as end-points in clinical trials, but should measure a clearly described concept of interest within a specific context of use and have a clear rationale for interpretation, which often requires anchoring to another PRO to help determine the meaningful score difference.

Opportunities for novel clinical trial end-points and trial designs

Examine time to clinical improvement

TTCW end-points do not capture improvements. Multicomponent clinical improvement (MCI) end-points comprising 6MWD, N-terminal pro-brain natriuretic peptide (NT-proBNP) and functional class have been used as exploratory, secondary and primary end-points in clinical trials, with slightly varying definitions [9, 14–17]. Observational data support an association between MCI and survival that is greater than the association for the individual components [29]. The potential for MCI as a replacement or surrogate outcome for clinical end-points, such as survival, required by regulatory agencies is unlikely unless NT-proBNP is validated independently or removed altogether [1]. With ongoing trials, there is an opportunity to evaluate associations between patient-level and trial-level changes in MCI with changes in clinical outcomes, including survival, that would be a necessary step for establishing surrogacy. However, surrogacy remains a high bar. MCI might be more easily utilised if constructed with components that each reflect how a patient feels, functions or survives (*e.g.* a combination of 6MWD, functional class or PROs). To establish surrogacy for an MCI end-point that includes a biomarker component, the biomarker must already be a validated surrogate itself (which is currently lacking for PAH). Determining which components to include, optimal cutpoints and associations with PROs are additional critical next steps to operationalise MCI as an outcome.

Utilise change in risk

Multidimensional risk scores have been recommended to guide treatment decisions since 2015 [30] and are central to the current PAH treatment algorithm [31, 32]. They provide a global measure of the current clinical status and estimate future risk, making them interesting potential trial end-points [33, 34]. Several risk scores have been created, including those based on the 2015 European Society of Cardiology/European Respiratory Society guidelines [30] (*e.g.* COMPERA 2.0 (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) [35, 36], the French PAH registry [37, 38], the Swedish PAH Register [39]) and the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) from the United States of America (REVEAL 2.0 [40], REVEAL Lite 2 [41]) that contain between three and 13 measures, a mix of modifiable (*e.g.* 6MWD) and nonmodifiable (*e.g.* age) components, with differing evidence of validity and prognostic value [34]. Improvement in risk is associated with lower mortality in observational studies, and secondary analyses of clinical trials suggest risk scores are responsive to treatments and are associated with outcomes [42, 43]. However, a recent meta-analysis of patient-level data from three trials suggested that treatment effects on risk scores were not sufficiently associated with mortality for these scores to be utilised as surrogates currently [44]. Ongoing evaluation of changes in multidimensional risk or targeting low risk status in randomised controlled trials is required for validation as a surrogate outcome.

Actigraphy

Measuring real-world physical activity has potential advantages over 6MWD to evaluate functional capacity, but its utility remains to be established. Physical activity is associated with quality of life and other outcomes in PAH [45, 46]. The ability to monitor physical activity is enabled by a range of wearables; however, their reliability and responsiveness to interventions are uncertain [47–49]. Additional current challenges to implementation as an outcome include the choice of actigraphy measurement (*e.g.* total step counts *versus* peak steps [47]), uncertainty regarding handling of missing data, seasonal effects [50], unknown minimally important clinical differences and differences between devices and often proprietary algorithms [51]. Taken together, additional validation is needed before actigraphy is used as a primary outcome in therapeutic trials [52].

Implantable remote monitoring end-points

The CardioMEMS Heart Failure System is approved for the continuous monitoring of pulmonary arterial pressures to reduce hospitalisations in patients with heart failure, although it has not been shown to reduce mortality in randomised trials [53, 54]. As invasive haemodynamic measurements are associated with outcomes for patients with PAH and believed to characterise the pulmonary vascular changes pathognomonic for the disease [55–57], there is interest in using continuous haemodynamic monitoring to guide treatment and as an end-point for phase 2 trials. In a small, nonrandomised, uncontrolled feasibility study, CardioMEMS was safe, permitted serial measuring of haemodynamics, and was weakly associated with 6MWD [58]. An algorithm to determine cardiac output is being developed that could increase the utility and applicability of these devices in trials. Implantable haemodynamic monitoring device data could prove useful for early phase trials to measure the time course (*e.g.* onset, peak, offset) of haemodynamic effects from experimental therapies. For phase 3 trials, these measures do not reflect how patients feel, function or survive and therefore are not suitable primary end-points, but could be considered as secondary outcomes. Ongoing trials (CS1-003, clinicaltrials.gov identifier NCT05224531 and ARTISAN, NCT05203510) may better inform their long-term safety, tolerability and clinical impact in PAH.

Remote assessment of 6MWD

Remote measurement of 6MWD using wearable technology offers the potential advantage of self-administration and performance in a community setting, providing real-time data between scheduled clinic visits. Studies have explored both restricted and unrestricted walk approaches for remote 6MWD [59–61]. The restricted walk approach attempts to replicate the in-clinic gold standard, using a pre-defined and pre-measured course, yet it allows patients to undertake the 6MWD test in the community without limitations on location, course or walking style. The unrestricted walks have also exhibited correlations with the in-clinic gold standard and can be conducted with higher frequency. These advancements in remote 6MWD hold promise for more frequent assessments and, if validated in a nonclinical trial setting, can then be tested in a trial setting.

Novel approaches to analysing composite end-points

There is a need to refine composite end-points in PAH clinical trials. Composite end-points could provide greater sensitivity to treatment effects, yet have multiple drawbacks; some recognised and others frequently overlooked. In analyses of composite end-points, the relative influence of components driven by their frequency of occurrence rather than clinical relevance have not been weighted based on severity or importance to the patient, and only first events rather than all events are reported [51, 62, 63]. Patients with PAH have rated death as the most important outcome to prevent, but there is considerable variability in their ratings of importance to other composite end-point components [20]. As such, it should not be assumed that components of the composite in PAH trials have similar clinical relevance. There are several potential solutions to these shortcomings that could be employed in future PAH trials.

Win statistics analyse composite end-points according to the relative importance of components in a hierarchy [64, 65]. Hierarchies can include outcomes such as death, transplantation and hospitalisation and could permit the inclusion of PROs. The most widely used application is the win ratio which, in a common application, compares each possible pair of patients in the active treatment arm and control arm for each hierarchical outcome component (figure 1). The win odds are similar, but accounts for ties between patient pairs, which may yield more conservative estimates of a treatment effect [65, 66]. When there are no ties between pairs, the win odds and win ratio are the same. Net benefit is the difference between the number of wins and number of losses for the active treatment. There are several limitations of win statistics, most notably their sensitivity to follow-up time and censoring [67, 68]. From a regulatory standpoint, it is difficult to analyse and interpret win ratios that incorporate both morbidity and mortality dichotomous event data with continuous measurement data such as PROs. The win ratio has been used successfully in trials leading to the approval of medications for other rare diseases, such as tafamidis for transthyretin amyloidosis [69].

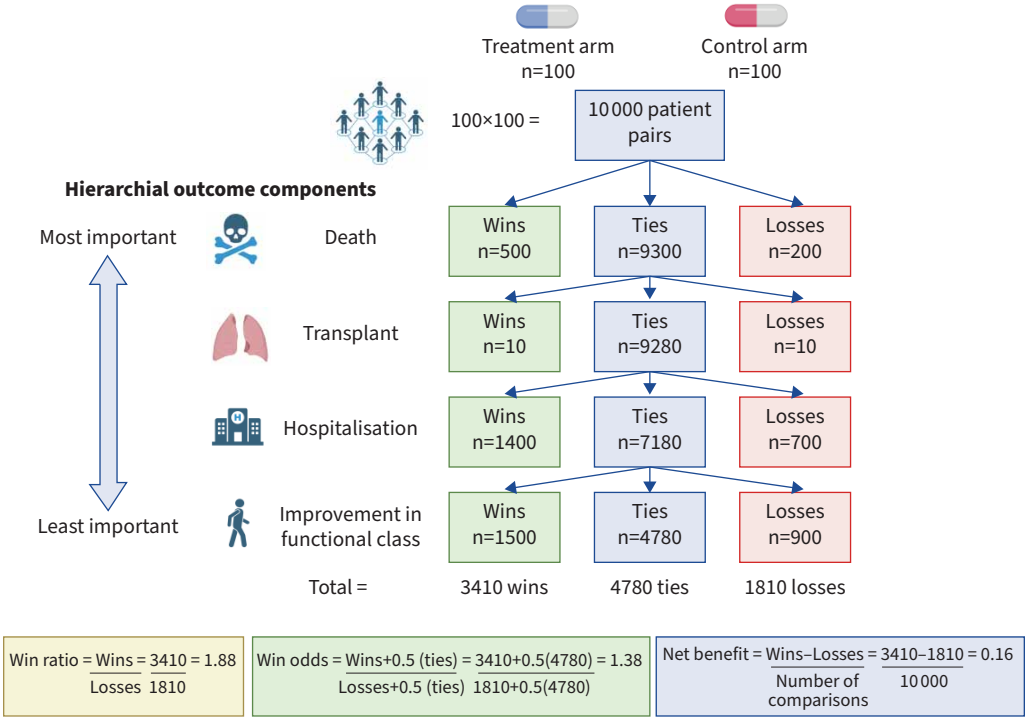

FIGURE 1 Win statistics for composite end-points. In a hypothetical trial of 200 patients with pulmonary arterial hypertension randomised to active treatment (n=100) or control (n=100), there are 10 000 pairs. Each pair is compared for each outcome in the hierarchy sequentially. Starting with death, pairs in which the patient on active treatment lives (wins) and the patient in the control arm dies (loss) are considered first. If neither patient in a pair dies, the next outcome (transplantation) is considered, then next component (hospitalisation), and so on. The total wins, ties and losses are tallied and win statistics such as the win ratio, win odds and net benefit are calculated. Created with BioRender.com.

This trial used a hierarchical end-point of mortality and morbidity events, with PROs and 6MWD considered as secondary end-points An analysis of patient-level data from 18 PAH trials showed that win statistics are feasible for estimating treatment effects on a ranked composite outcome [70], but more is needed to enable the use of win statistics in PAH trials, including properly addressing censoring in time-to-event analyses. The reality is that win statistics are still driven by the most frequent events, which may be of lesser clinical relevance. Furthermore, the magnitude of benefit may be difficult to interpret and communicate.

A weighted composite end-points approach accounts for all clinical events and for the relative importance by assigning weights to nonfatal events [71, 72]. However, there is currently no consensus on the relative weighting to be attributed to potential components in PAH trials. Rather than time-to-first event analyses, future PAH trials could consider measuring and reporting total disease burden by capturing recurrent nonfatal events, such as recurrent PAH hospitalisations, and total numbers of events. This approach could be particularly useful in more severe, high-risk cohorts and when longer term follow-up is feasible. Analytic methods for repeated events include the Lin–Wei–Yang–Ying model, Andersen–Gill method with robust variance estimate, or negative binomial models, although these approaches do not necessarily increase statistical power [73, 74]. From the regulatory perspective, recurrent hospitalisation is considered as a meaningful outcome since it represents a large burden on patients. Its use as an outcome could enhance clinical relevance and statistical power, although having a clear methodological strategy and adjudication of events are essential [75].

Novel trial designs: platform trials

Platform trials refer to a trial infrastructure to test multiple interventions within a disease or condition, guided by a master protocol. In general, interventions are not compared to each other but are compared to a common control group. New experimental therapies can be added to the platform as they are discovered, and can be discontinued when achieving the targeted information (*i.e.* recruitment) or at an interim analysis

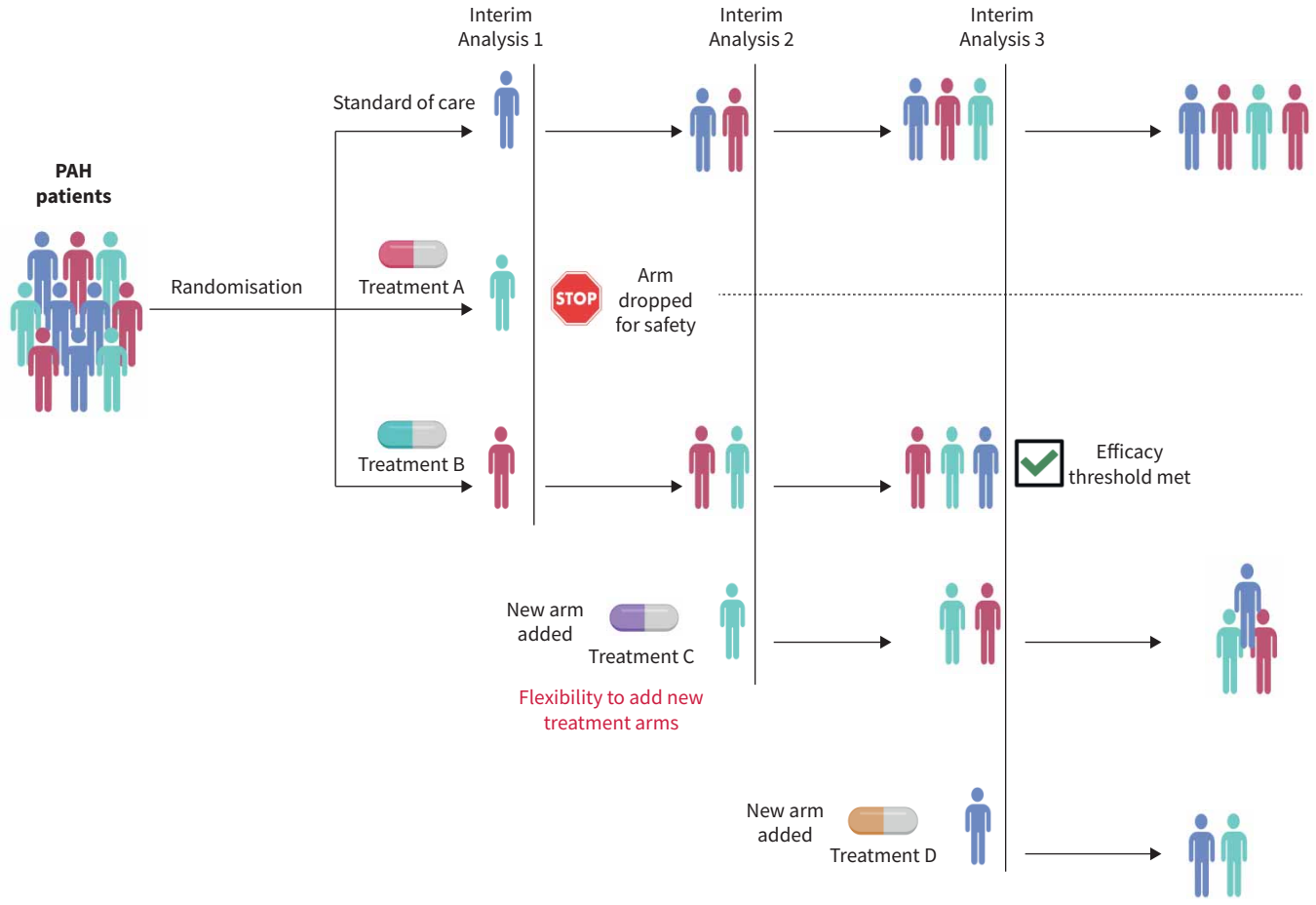

FIGURE 2 Example of a platform trial for pulmonary arterial hypertension (PAH). New therapies can be added to the platform at any time. At pre-specified interim analyses, statistical models are updated based on accumulated outcome data, statistical boundaries are assessed and randomisation probabilities may be updated. Based on interim analyses, recruitment may continue, stop for futility or safety, or stop due to efficacy for a given arm. Created with BioRender.com.

that reliably establishes benefit or lack thereof. Platform trials may improve operational efficiencies and have statistical efficiencies over separate traditional parallel-group randomised trials (figure 2) [76].

Platform trials were highly successful at rapidly and efficiently generating knowledge about therapies for coronavirus disease 2019 [77, 78]. Platform trials have not yet been implemented for PAH, although this could be a worthwhile pursuit to test multiple candidate therapies more efficiently than separate trials, if rigour and reliability are maintained. Patient and investigator-driven platform trials have been planned for other rare diseases, including systemic sclerosis (CONQUEST; https://srfcure.org/research/conquest/) and interstitial lung diseases (REMAP-ILD [79]). Undertaking a PAH platform trial would require considerable investment, engagement and agreement between multiple stakeholders, including regulatory agencies, sponsors/industry, patients and investigators. Potential challenges for a PAH platform trial include the administrative and logistical complexity required and establishing acceptable intermediate outcomes to permit interim analyses and adaptations within a reasonable time frame. A PAH platform trial would also need to address potential bias introduced if conducted over a long period of time where demographics or standards of care may change [80, 81]. With multiple active treatments, having a placebo control may not be feasible, which could also introduce challenges for pharmaceutical companies pursuing regulatory approval. Thus, a PAH platform trial may be better suited to testing repurposed therapies that are already approved for other indications. Lastly, funding a large-scale, long-term platform trial without a defined end poses a fiscal challenge, although one solution could be to partner with foundational organisations and governmental funding agencies to develop an academia-run platform, obtaining buy-in and funding from industry sponsors for individual treatment arms. Patient engagement in the design and prioritisation of investigational therapies in a platform trial would be essential.

Disease modification

Successes in clinical trials of sotatercept [9, 16] and seralutinib [82] have sparked interest in the potential for vascular reverse remodelling and the concept of "disease modification". A precise definition of disease modification in PAH remains uncertain and a framework for such a definition is urgently needed, as is the need for well-thought-out trial designs to formally test the concept. Any proposed definition of disease modification in PAH will likely need to address several key elements: improvement in clinical manifestations, impact on disease trajectory and sustainability of benefit beyond short-term pharmacological effects [83]. Most importantly, a formal definition will likely need to incorporate, but not be limited to, the construct of reverse pulmonary vascular remodelling, and address the role of right ventricular pathology as a hallmark of disease. Key considerations include the challenge of assessing effects on underlying pulmonary vascular pathology, the lack of validated surrogate markers, and the diverse responses to therapies based on individual patient factors. To support a claim of disease modification, demonstration of sustainability of treatment effects will likely be a key requirement, which can be tested using withdrawal or delayed start trial designs (figure 3). Later phase trials will need to address not only the design question of how disease modification is demonstrated, but also to distinguish it from anticipated beneficial effects on disease surrogates.

Biomarkers and surrogate end-points

Biomarkers, if used as replacement primary end-points, could potentially provide the ability to reduce the size or duration of clinical trials. As specified in the 2010 Institute of Medicine (IOM) report on the evaluation of biomarkers and surrogate endpoints, "Biomarkers are measurements of biological processes.

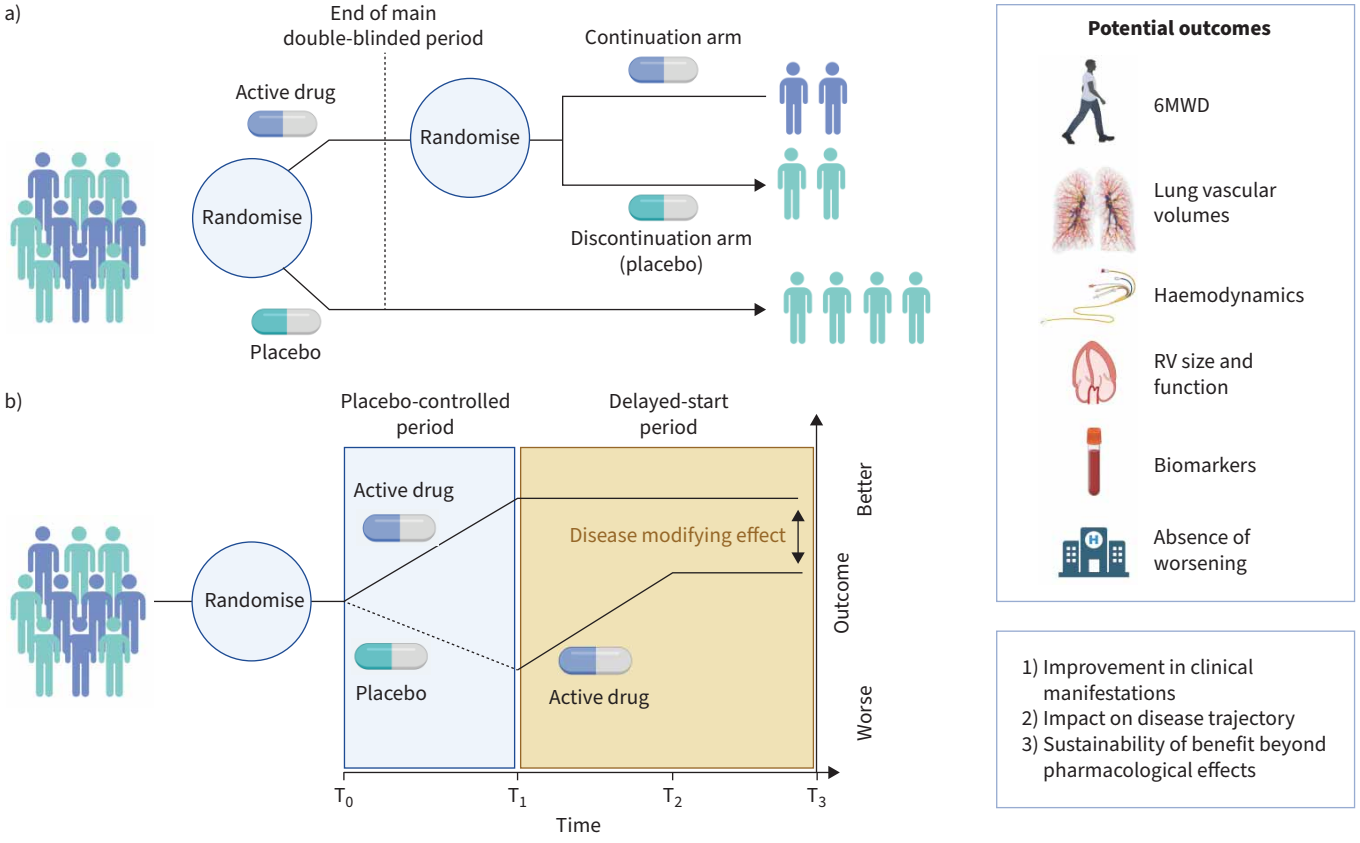

FIGURE 3 Trial designs to evaluate disease modification. a) Randomised withdrawal trial: following a placebo-controlled parallel-group trial, patients initially on placebo remain on placebo while patients on experimental treatment are randomised to continue or withdrawal to placebo. If the outcome measures in the withdrawal group deteriorate or regress to the initial placebo group, a disease-modifying effect is not present. Improvements in the outcome measures maintained beyond the washout of the direct vasodilatory effect of the intervention support a disease-modifying effect. b) Delayed-start trial: in the first period, patients randomly receive the experimental treatment or placebo in a double-blinded manner. In the second period, patients initially on placebo start the experimental treatment and outcomes are reassessed. Failure of the initial placebo group to "catch up" to the initial experimental group suggests a disease-modifying effect. 6MWD: 6-min walk distance; RV: right ventricle. Created with BioRender.com.

Biomarkers include physiological measurements, blood tests and other chemical analyses of tissue or bodily fluids, genetic or metabolic data, and measurements from images" [84]. Classic examples in PAH would be cardiac output, pulmonary arterial pressure, pulmonary vascular resistance, NT-proBNP or imaging (echo, cardiac magnetic resonance imaging).

A frequent approach to justifying use of a biomarker as a replacement end-point in registrational trials is to establish a strong patient-level correlation with one or more direct measures for "feels, functions, survives", then to establish the intervention's effect on that biomarker, and then to make the leap of faith that such evidence would establish that the intervention has clinical meaningful effects on how patients feel, function or survive, *i.e.* "*post hoc, ergo, propter hoc*". However, such patient-level correlations do not establish causality, and are necessary but not sufficient for establishing surrogacy, *i.e.* they do not establish that the effect of the treatment on the biomarker provides reliable evidence about its effect on how patients feel, function or survive: "A patient-level correlate does not a surrogate make" [85]. There are four principal reasons for this. First, the biomarker may not lie in a pathophysiological pathway through which the disease process influences the "feels, functions, survives" measure; second, the disease process might affect how a patient feels, functions, survives through multiple causal pathways, but only one of which is mediated through effects on the biomarker; third, the timing, magnitude and duration of the effect on the biomarker needed to meaningfully impact the clinical end-point may not be known; and fourth, an intervention may have unintended effects on measurements of how a patient feels, functions and survives that are not captured by the biomarker [1].

The reliability and interpretability of trial results are enhanced by selecting trial end-points that directly capture how patients feel, function or survive, or end-points that are properly validated replacement or "surrogate" end-points. Validation of biomarkers as replacement end-points in registrational clinical trials should be based on substantive clinical and statistical insights. Clinically, an understanding of the causal pathways of the disease process is needed, beyond insights about the causal pathway mediated through the biomarker, and the intervention's "unintended" effects not captured by the biomarker, as well as its intended mechanisms, need to be understood. Statistically, an overview of trials for interventions in the class of the experimental intervention is needed to determine whether there is a trial-level correlation between the net effect of the intervention on the biomarker with the net effect of the intervention on the measure of "feel, function, survive", as illustrated by the recent overview of trials by FDA in the idiopathic pulmonary fibrosis setting for validation of forced vital capacity as a replacement end-point for overall survival [86]. Such trial-level correlations are of integral importance to this validation because an intervention's effects that are "unintended", and thus frequently unrecognised, often are not captured by the effects on the biomarker. Furthermore, as recognised by the IOM in 2010, context of use matters, because a replacement end-point validated for one class of agents may not be valid for another class, even in the same disease setting [84, 86].

Biomarkers, even if only established to be patient-level correlates of outcomes, may be useful for assessments of disease diagnosis and prognosis. Additionally, as direct measures of biological activity, biomarkers are useful as primary end-points in proof-of-concept trials or as supportive end-points in registrational trials. However, where they would have greatest utility is as replacement end-points in registrational trials (and yet as indicated earlier, a correlate does not a surrogate make), and in enrichment using biomarkers that are mechanistically characterising patients most likely to benefit from a treatment (and yet a prognostic factor does not an effect modifier make). The EMA and FDA have outlined processes for biomarker qualification for drug development and registrational trials [87, 88]. An additional cautionary note is that reliance on biomarkers as replacement end-points in registrational trials results in having not only less reliable insights about the efficacy, but also less reliable evidence about safety of marketed products. If safety issues were then identified post-marketing, there would be increased concerns about whether evidence about efficacy is sufficiently strong to justify a conclusion of positive benefit-to-risk. For example, PAH, BNP and NT-proBNP are important biomarkers, but further validation is still needed to use these as replacement end-points because this is not provided by patient-level correlations between the biomarker and measures of how patients feel, function or survive.

Bridging biomarkers for paediatric extrapolation

In diseases affecting both adults and children, paediatric extrapolation uses the combination of the clinical evidence in adults and the relationship between a biomarker and the clinical outcome to obtain a reliable evaluation of the effect of an intervention in a paediatric population more efficiently. To do this an intervention must be reliably established to be safe and effective in adults and there should be substantive evidence that disease processes in paediatric and adult settings are biologically similar. In such settings, it has been argued that establishing safety as well as meaningful effects on a "bridging biomarker", that

satisfies three additional criteria that collectively establish it to be "reasonably likely to predict clinical benefit", would provide sufficient evidence to extrapolate efficacy to the paediatric population [89, 90]. FLEMING *et al*. [89] illustrated the use of NT-proBNP as a bridging biomarker for the extrapolation of efficacy of sacubitril/valsartan from adults to the paediatric population in the setting of nonischaemic dilated cardiomyopathy.

Challenges and opportunities for future PAH trials

The major challenge facing future PAH clinical trials is demonstrating additive or synergistic benefit on top of increasingly complex background therapy. Nonetheless, despite effective therapeutic options, there is still an unmet need to reduce clinical events, improve quality of life and increase functional capacity for many patients. Each new treatment will change the landscape and have impact on the efficiency of clinical trials (the balance between research value and research costs, measured in financial and clinical risk and burden to patients and industry). Issues will continue in trial design as more patients will be in functional class II and the sample size required to show an increase in functional capacity (*e.g.* using 6MWD) and a reduction in clinical events (*e.g.* death, hospitalisation) will increase. Moreover, in the current clinical trial format, looking for benefit from the simple addition of a novel therapy to existing treatments risks will hamper the ability to identify beneficial combination therapies because the sample size for subgroup analysis (*i.e.* by treatment combination) will be too small.

Improving diversity, access and participation in trials

PAH is not homogeneous in phenotype. Given the variability in patient and disease characteristics and aetiology, the participants in PAH clinical trials should be representative of the variation in gender identities, races, ages, ethnicities, socioeconomic groups and cultures in clinical practice. Typically, pivotal phase 2 and 3 trials have limited enrolment to a more homogeneous group (certainly in terms of aetiology and frequently age and comorbidities) to increase the chances of detecting a treatment predicted response. Clinical interpretation of results is based predominantly on data from trials including idiopathic, hereditary, anorexigen-, connective tissue disease- and corrected congenital heart disease-associated PAH. Only a few trials have included patients with HIV, and only a few placebo-controlled trials have focused on populations with associated PAH categories such as portopulmonary hypertension or Eisenmenger syndrome [91, 92]. Additionally, PAH clinical trials consist of mostly white women from the United States of America, Canada and Western Europe [93]. There is now more participation in pulmonary hypertension trials Eastern Europe, Asia and Latin America, but few in Africa. Enrolment of women and men should be proportional to the population epidemiology. Trialists, academic and community-based centres, along with industry need to improve communication and education, and alleviate social barriers to participation. The FDA recently put forth a draft guidance for clinical trial sponsors advising Diversity Action Plan submissions to increase members of historically underrepresented populations. These plans should specify the goals, rationale, and plan to meet these goals [94]. The National Academies of Science, Engineering, and Medicine have highlighted the need to improve representation, and also transparency and accountability [95]. Perhaps the pulmonary hypertension community should follow the example set by the cardiovascular trialists and design clinical trials that help determine how to improve trial diversity similar to the Diversity and Inclusion in cardioVascular trials through enrollment and education Resulting in Sustainable Equity Network (DIVERSE; https://med.stanford.edu/diversenetwork.html). Trials need to be designed in a manner to encourage participation of under-represented populations [96].

Unified definitions and master protocol trials can allow patient participation in multiple studies with ease by enabling participants to move efficiently from one experimental treatment to another, although problems arise based on concerns in industry around data sharing, exclusivity and competition. Technological advances can help expand participation by allowing video or telehealth visits, remote data capture and decentralisation of some clinical trial activities [97, 98]. Protocol design needs to adapt to include these features. In areas without internet and the means for this type of participation, transportation to comprehensive centres is needed.

Comorbidities and external validity

Patients with PAH are living longer with better quality of life compared with 30 years ago. As they age, patients develop comorbidities (*e.g.* hypertension, diabetes) perhaps unrelated to their pulmonary vascular disease. For clinical trials, including patients with only one comorbidity *versus* multiple comorbidities warrants discussion. In the AMBITION trial, patients with multiple cardiovascular risk factors had an attenuated treatment benefit and higher withdrawal rate due to adverse events with initial combination therapy compared to those without [99]. Conversely, in GRIPHON, which recruited predominantly patients with prevalent PAH, the effect was similar between patients with fewer than three comorbidities and those with three or more comorbidities [100]. Thus, it remains unclear whether exclusion of patients with PAH

and multiple or certain comorbidities (as done in trials of incident patients) is necessary to optimise trial success, especially in prevalent populations on background therapy, and it clearly limits generalisability of trial results to real-world populations. If such patients are excluded from future phase 3 trials, pragmatic post-authorisation phase 4 trials in patients with PAH and comorbidities may help fill the evidence gap on efficacy and safety in this group.

Artificial intelligence

There is already interest in using artificial intelligence (AI) in trial end-point analysis; for example, in the interpretation of cardiac magnetic resonance data. In the future, AI could be used to enable more efficient traditional clinical trials. It can be deployed to screen electronic patient records, using inclusion and exclusion criteria, to identify potential trial subjects and accelerate recruitment [101]. AI coupled to near real-time analysis of self-reported data and data from wearables and implanted devices could detect trends, both in improvement and in deterioration [102]. It may also improve subject retention by predicting the probability of subject dropout, allowing researchers to be proactive in subject outreach. In the future, AI can could be used to improve trial designs through *in silico* studies using a digital twin to represent the disease [103, 104]. Adaptive trials with AI knowledge can shorten the duration and decrease sample size. For example, in *post hoc* analyses of two cardiovascular trials, "phenomapping" signatures were generated using machine learning to predict treatment response based on pre-randomisation characteristics. Randomisation probabilities were adapted at interim analyses (*i.e.* predictive enrichment) if phenotypic signatures predicted heterogeneity of treatment effect to that point, which ultimately suggested 14–17% reductions in required trial sample sizes [105].

Responder studies

A common behaviour following clinical trial completion is to conduct a *post hoc* analysis to describe responders and nonresponders using clinical measurements and then to use these groups to mine distinguishing biomarkers. However, "response" may not be a permanent characteristic of a person receiving the treatment, and there are a number of traps [106]. Apart from lazy language, these include arbitrary dichotomies, multiplicity of testing, participant variability and subsequence rather than consequence. One solution is N-of-1 studies. When a patient is rechallenged with a medicine, that patient can be designated a responder or nonresponder according to the reproducibility of their response with greater confidence, or perhaps better, as someone representing a group more likely to improve or less likely to benefit. N-of-1 studies of new treatments for PAH would benefit from acceptable noninvasive end-points that can be serially measured.

Opportunities for improving future PAH trials

With emerging novel therapies, future PAH trials will need to improve design and efficiency and develop innovative but meaningful and rigorous end-points. To do so, the overarching recommendations of this task force include the following.

1) PAH clinical trials using composite clinical outcomes as primary or secondary end-points should ensure that each component is independently clinically meaningful or a validated surrogate and should account for the relative importance of each component. Patient engagement and input into end-point selection, and trial design in general, is essential.
2) Rigorous development and validation of biomarkers and other potential surrogate outcomes is required for their acceptance as replacement end-points in clinical trials, and this should be a priority for the PAH clinical trial community.
3) Emerging artificial intelligence technologies could be considered to improve PAH clinical trial efficiency, so long as statistical and methodological rigour is maintained.
4) Improving access to PAH trials globally, enhancing the diversity of patients in PAH trials, and ensuring evidence generation for therapeutics in patients with comorbidities should be measurable objectives for the PAH trialist community before the next WSPH, to improve equity and external validity of PAH trials.

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References

1 Fleming TR, Powers JH. Biomarkers and surrogate endpoints in clinical trials. *Stat Med* 2012; 31: 2973–2984.
2 US Food and Drug Administration. Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments. 2022. www.fda.gov/media/159500/download. Date last accessed: 6 December 2023.
3 European Medicines Agency. Guideline on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension. 2009. www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigations-medicinal-products-treatment-pulmonary-arterial-hypertension_en.pdf. Date last accessed: 8 August 2022.
4 US Food and Drug Administration. Multiple Endpoints in Clinical Trials – Guidance for Industry. 2017. www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf. Date last accessed: 5 May 2024.
5 Sitbon O, Gomberg-Maitland M, Granton J, *et al.* Clinical trial design and new therapies for pulmonary arterial hypertension. *Eur Respir J* 2019; 53: 1801908.
6 Frost AE, Langleben D, Oudiz R, *et al.* The 6-min walk test (6MW) as an efficacy endpoint in pulmonary arterial hypertension clinical trials: demonstration of a ceiling effect. *Vascul Pharmacol* 2005; 43: 36–39.
7 McLaughlin V, Bacchetta M, Badesch D, *et al.* Update on pulmonary arterial hypertension research: proceedings from a meeting of experts. *Curr Med Res Opin* 2018; 34: 263–273.
8 Savarese G, Paolillo S, Costanzo P, *et al.* Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. *J Am Coll Cardiol* 2012; 60: 1192–1201.
9 Hoeper MM, Badesch DB, Ghofrani HA, *et al.* Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. *N Engl J Med* 2023; 388: 1478–1490.
10 McLaughlin V, Channick RN, Ghofrani H-A, *et al.* Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. *Eur Respir J* 2015; 46: 405–413.
11 Pulido T, Adzerikho I, Channick RN, *et al.* Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013; 369: 809–818.
12 Sitbon O, Channick R, Chin KM, *et al.* Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2015; 373: 2522–2533.
13 White RJ, Jerjes-Sanchez C, Bohns Meyer GM, *et al.* Combination therapy with oral treprostinil for pulmonary arterial hypertension. A double-blind placebo-controlled clinical trial. *Am J Respir Crit Care Med* 2020; 201: 707–717.
14 Galiè N, Barberà JA, Frost AE, *et al.* Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015; 373: 834–844.

15 Hoeper MM, Al-Hiti H, Benza RL, *et al.* Switching to riociguat *versus* maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial. *Lancet Respir Med* 2021; 9: 573–584.

16 Humbert M, McLaughlin V, Gibbs JSR, *et al.* Sotatercept for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2021; 384: 1204–1215.

17 Hoeper MM, Simonneau G, Corris PA, *et al.* RESPITE: switching to riociguat in pulmonary arterial hypertension patients with inadequate response to phosphodiesterase-5 inhibitors. *Eur Respir J* 2017; 50: 1602425.

18 McLaughlin VV, Badesch DB, Delcroix M, *et al.* End points and clinical trial design in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54: S97–S107.

19 Tremblay É, Gosselin C, Mai V, *et al.* Assessment of clinical worsening end points as a surrogate for mortality in pulmonary arterial hypertension: a systematic review and meta-analysis of randomized controlled trials. *Circulation* 2022; 146: 597–612.

20 Mai V, Gosselin C, Tremblay É, *et al.* Patients' perceptions on clinical trials outcomes in pulmonary arterial hypertension therapy. *Thorax* 2023; 78: 721–725.

21 McLaughlin VV, Hoeper MM, Channick RN, *et al.* Pulmonary arterial hypertension-related morbidity is prognostic for mortality. *J Am Coll Cardiol* 2018; 71: 752–763.

22 US Food and Drug Administration. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims. 2009. www.fda.gov/media/77832/download. Date last accessed: 3 March 2022.

23 European Medicines Agency. Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products. 2005. www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-guidance-use-health-related-quality-life-hrql-measures-evaluation-medicinal-products_en.pdf. Date last accessed: 16 April 2024.

24 McGoon MD, Ferrari P, Armstrong I, *et al.* The importance of patient perspectives in pulmonary hypertension. *Eur Respir J* 2019; 53: 1801919.

25 McKenna SP, Doughty N, Meads DM, *et al.* The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. *Qual Life Res* 2006; 15: 103–115.

26 Bonner N, Abetz L, Meunier J, *et al.* Development and validation of the living with pulmonary hypertension questionnaire in pulmonary arterial hypertension patients. *Health Qual Life Outcomes* 2013; 11: 161.

27 Yorke J, Corris P, Gaine S, *et al.* emPHasis-10: development of a health-related quality of life measure in pulmonary hypertension. *Eur Respir J* 2014; 43: 1106–1113.

28 Chin KM, Gomberg-Maitland M, Channick RN, *et al.* Psychometric validation of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) questionnaire: results of the SYMPHONY trial. *Chest* 2018; 154: 848–861.

29 Hoeper MM, Pausch C, Olsson KM, *et al.* Prognostic value of improvement endpoints in pulmonary arterial hypertension trials: a COMPERA analysis. *J Heart Lung Transplant* 2022; 41: 971–981.

30 Galiè N, Humbert M, Vachiery J-L, *et al.* 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 Respir J* 2015; 46: 903–975.

31 Humbert M, Kovacs G, Hoeper MM, *et al.* 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2023; 61: 2200879.

32 Dardi F, Boucly A, Benza R, *et al.* Risk stratification and treatment goals in pulmonary arterial hypertension. *Eur Respir J* 2024; in press [https://doi.org/10.1183/13993003.01323-2024].

33 Weatherald J, Boucly A, Sahay S, *et al.* The low-risk profile in pulmonary arterial hypertension. Time for a paradigm shift to goal-oriented clinical trial endpoints? *Am J Respir Crit Care Med* 2018; 197: 860–868.

34 Sitbon O, Nikkho S, Benza R, *et al.* Novel composite clinical endpoints and risk scores used in clinical trials in pulmonary arterial hypertension. *Pulm Circ* 2020; 10: 2045894020962960.

35 Hoeper MM, Pausch C, Olsson KM, *et al.* COMPERA 2.0: a refined 4-stratum risk assessment model for pulmonary arterial hypertension. *Eur Respir J* 2021; 60: 2102311.

36 Boucly A, Weatherald J, Savale L, *et al.* External validation of a refined four-stratum risk assessment score from the French pulmonary hypertension registry. *Eur Respir J* 2022; 59: 2102419.

37 Boucly A, Weatherald J, Savale L, *et al.* Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J* 2017; 50: 1700889.

38 Weatherald J, Boucly A, Launay D, *et al.* Haemodynamics and serial risk assessment in systemic sclerosis associated pulmonary arterial hypertension. *Eur Respir J* 2018; 52: 1800678.

39 Kylhammar D, Kjellström B, Hjalmarsson C, *et al.* A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J* 2018; 39: 4175–4181.

40 Benza RL, Gomberg-Maitland M, Elliott CG, *et al.* Predicting survival in patients with pulmonary arterial hypertension: the REVEAL risk score calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. *Chest* 2019; 156: 323–337.

41 Benza RL, Kanwar MK, Raina A, *et al.* Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL Lite 2, for use in patients with pulmonary arterial hypertension. *Chest* 2021; 159: 337–346.

42 Sitbon O, Chin KM, Channick RN, *et al.* Risk assessment in pulmonary arterial hypertension: insights from the GRIPHON study. *J Heart Lung Transplant* 2020; 39: 300–309.

43 Benza RL, Boucly A, Farber HW, *et al.* Change in REVEAL Lite 2 risk score predicts outcomes in patients with pulmonary arterial hypertension in the PATENT study. *J Heart Lung Transplant* 2022; 41: 411–420.

44 Blette BS, Moutchia J, Al-Naamani N, *et al.* Is low-risk status a surrogate outcome in pulmonary arterial hypertension? An analysis of three randomised trials. *Lancet Respir Med* 2023; 11: 873–882.

45 Ulrich S, Fischler M, Speich R, *et al.* Wrist actigraphy predicts outcome in patients with pulmonary hypertension. *Respiration* 2013; 86: 45–51.

46 Cascino TM, McLaughlin VV, Richardson CR, *et al.* Physical activity and quality of life in patients with pulmonary hypertension. *Eur Respir J* 2019; 53: 1900028.

47 Lachant D, Light A, Lachant M, *et al.* Peak steps: capacity for activity improves after adding approved therapy in pulmonary arterial hypertension. *Pulm Circ* 2023; 13: e12285.

48 Howard LS, Rosenkranz S, Frantz RP, *et al.* Assessing daily life physical activity by actigraphy in pulmonary arterial hypertension: insights from The Randomized Controlled Study With Selexipag (TRACE). *Chest* 2023; 163: 407–418.

49 Hemnes AR, Silverman-Lloyd LG, Huang S, *et al.* A mobile health intervention to increase physical activity in pulmonary arterial hypertension. *Chest* 2021; 160: 1042–1052.

50 Garriga A, Sempere-Rubio N, Molina-Prados MJ, *et al.* Impact of seasonality on physical activity: a systematic review. *Int J Environ Res Public Health* 2021; 19: 2.

51 Weatherald J, Boucly A, Peters A, *et al.* The evolving landscape of pulmonary arterial hypertension clinical trials. *Lancet* 2022; 400: 1884–1898.

52 Psotka MA, Abraham WT, Fiuzat M, *et al.* Functional and symptomatic clinical trial endpoints: the HFC-ARC scientific expert panel. *JACC Heart Fail* 2022; 10: 889–901.

53 Abraham WT, Adamson PB, Bourge RC, *et al.* Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011; 377: 658–666.

54 Lindenfeld J, Zile MR, Desai AS, *et al.* Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. *Lancet* 2021; 398: 991–1001.

55 Weatherald J, Boucly A, Chemla D, *et al.* Prognostic value of follow-up hemodynamic variables after initial management in pulmonary arterial hypertension. *Circulation* 2018; 137: 693–704.

56 Nickel N, Golpon H, Greer M, *et al.* The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2012; 39: 589–596.

57 Ogawa A, Ejiri K, Matsubara H. Long-term patient survival with idiopathic/heritable pulmonary arterial hypertension treated at a single center in Japan. *Life Sci* 2014; 118: 414–419.

58 Benza RL, Doyle M, Lasorda D, *et al.* Monitoring pulmonary arterial hypertension using an implantable hemodynamic sensor. *Chest* 2019; 156: 1176–1186.

59 Lachant D, Kennedy E, Derenze B, *et al.* Cardiac effort to compare clinic and remote 6-minute walk testing in pulmonary arterial hypertension. *Chest* 2022; 162: 1340–1348.

60 Salvi D, Poffley E, Tarassenko L, *et al.* App-based *versus* standard six-minute walk test in pulmonary hypertension: mixed methods study. *JMIR Mhealth Uhealth* 2021; 9: e22748.

61 LaPatra T, Baird GL, Goodman R, *et al.* Remote 6-minute-walk testing in patients with pulmonary hypertension: a pilot study. *Am J Respir Crit Care Med* 2022; 205: 851–854.

62 Cordoba G, Schwartz L, Woloshin S, *et al.* Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. *BMJ* 2010; 341: c3920.

63 Armstrong PW, Westerhout CM. Composite end points in clinical research: a time for reappraisal. *Circulation* 2017; 135: 2299–2307.

64 Pocock SJ, Ariti CA, Collier TJ, *et al.* The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J* 2012; 33: 176–182.

65 Dong G, Huang B, Verbeeck J, *et al.* Win statistics (win ratio, win odds, and net benefit) can complement one another to show the strength of the treatment effect on time-to-event outcomes. *Pharm Stat* 2023; 22: 20–33.

66 Brunner E, Vandemeulebroecke M, Mütze T. Win odds: an adaptation of the win ratio to include ties. *Stat Med* 2021; 40: 3367–3384.

67 Ajufo E, Nayak A, Mehra MR. Fallacies of using the win ratio in cardiovascular trials: challenges and solutions. *JACC Basic Transl Sci* 2023; 8: 720–727.

68 Dong G, Huang B, Chang Y-W, *et al.* The win ratio: impact of censoring and follow-up time and use with nonproportional hazards. *Pharm Stat* 2020; 19: 168–177.
69 Maurer MS, Schwartz JH, Gundapaneni B, *et al.* Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018; 379: 1007–1016.
70 Weatherald J, Moutchia J, Al-Naamani N, *et al.* Win statistics in pulmonary arterial hypertension clinical trials. *Am J Respir Crit Care Med* 2023; 208: 1231–1234.
71 Bakal JA, Westerhout CM, Cantor WJ, *et al.* Evaluation of early percutaneous coronary intervention *vs*. standard therapy after fibrinolysis for ST-segment elevation myocardial infarction: contribution of weighting the composite endpoint. *Eur Heart J* 2013; 34: 903–908.
72 Bakal JA, Roe MT, Ohman EM, *et al.* Applying novel methods to assess clinical outcomes: insights from the TRILOGY ACS trial. *Eur Heart J* 2015; 36: 385–392.
73 Lin DY, Wei LJ, Yang I, *et al.* Semiparametric regression for the mean and rate functions of recurrent events. *JR Stat Soc B* 2000; 62: 711–730.
74 Gregson J, Stone GW, Bhatt DL, *et al.* Recurrent events in cardiovascular trials: JACC state-of-the-art review. *J Am Coll Cardiol* 2023; 82: 1445–1463.
75 European Medicines Agency. Guideline on Clinical Investigation of Medicinal Products for the Treatment of Chronic Heart Failure. 2017. www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-chronic-heart-failure-revision-2_en.pdf.
76 Saville BR, Berry SM. Efficiencies of platform clinical trials: a vision of the future. *Clin Trials* 2016; 13: 358–366.
77 WHO Solidarity Trial Consortium. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *Lancet* 2022; 399: 1941–1953.
78 RECOVERY Collaborative Group, Horby P, Lim WS, *et al.* Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021; 384: 693–704.
79 Kawano-Dourado L, Kulkarni T, Ryerson CJ, *et al.* Adaptive multi-interventional trial platform to improve patient care for fibrotic interstitial lung diseases. *Thorax* 2024; in press [https://thorax.bmj.com/content/early/2024/03/06/thorax-2023-221148].
80 Pallmann P, Bedding AW, Choodari-Oskooei B, *et al.* Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med* 2018; 16: 29.
81 Lawler PR, Hochman JS, Zarychanski R. What are adaptive platform clinical trials and what role may they have in cardiovascular medicine? *Circulation* 2022; 145: 629–632.
82 Frantz RP, McLaughlin VV, Sahay S, *et al.* Seralutinib in adults with pulmonary arterial hypertension (TORREY): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Respir Med* 2024; 12: 523–534.
83 Zamanian RT, Weatherald J, Sweatt AJ, *et al.* Constructing the framework for disease modification in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2024; 209: 1189–1195.
84 Institute of Medicine (US) Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease. Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease. Micheel CM, Ball JR, eds. Washington, National Academies Press, 2010. www.ncbi.nlm.nih.gov/books/NBK220297/. Date last accessed: 24 July 2017.
85 Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med* 1996; 125: 605–613.
86 Raghu G, Ghazipura M, Fleming TR, *et al.* Meaningful endpoints for idiopathic pulmonary fibrosis (IPF) clinical trials: emphasis on 'feels, functions, survives'. Report of a collaborative discussion in a symposium with direct engagement from representatives of patients, investigators, the National Institutes of Health, a patient advocacy organization, and a regulatory agency. *Am J Respir Crit Care Med* 2024; 209: 647–669.
87 European Medicines Agency. Qualification of Novel Methodologies for Medicine Development. www.ema.europa.eu/en/qualification-novel-methodologies-medicine-development. Date last accessed: 1 January 2024.
88 US Food and Drug Administration. Biomarker Qualification Program. www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/biomarker-qualification-program. Date last accessed: 1 January 2024.
89 Fleming TR, Garnett CE, Conklin LS, *et al.* Innovations in pediatric therapeutics development: principles for the use of bridging biomarkers in pediatric extrapolation. *Ther Innov Regul Sci* 2023; 57: 109–120.
90 Fleming TR. Surrogate endpoints and FDA's accelerated approval process. *Health Aff* 2005; 24: 67–78.
91 Sitbon O, Bosch J, Cottreel E, *et al.* Macitentan for the treatment of portopulmonary hypertension (PORTICO): a multicentre, randomised, double-blind, placebo-controlled, phase 4 trial. *Lancet Respir Med* 2019; 7: 594–604.
92 Galiè N, Beghetti M, Gatzoulis MA, *et al.* Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation* 2006; 114: 48–54.
93 Min J, Appleby DH, McClelland RL, *et al.* Secular and regional trends among pulmonary arterial hypertension clinical trial participants. *Ann Am Thorac Soc* 2022; 19: 952–961.

94 United States Food and Drug Administration. Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies. 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-action-plans-improve-enrollment-participants-underrepresented-populations-clinical-studies. Date last accessed: 15 July 2024.

95 National Academies of Sciences, Engineering, and Medicine. Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups. 2022. https://nap.nationalacademies.org/26479. Date last accessed: 6 December 2023.

96 Versavel S, Subasinghe A, Johnson K, *et al.* Diversity, equity, and inclusion in clinical trials: a practical guide from the perspective of a trial sponsor. *Contemp Clin Trials* 2023; 126: 107092.

97 Moore J, Goodson N, Wicks P, *et al.* What role can decentralized trial designs play to improve rare disease studies? *Orphanet J Rare Dis* 2022; 17: 240.

98 Van Norman GA. Decentralized clinical trials: the future of medical product development? *JACC Basic Transl Sci* 2021; 6: 384–387.

99 McLaughlin VV, Vachiery J-L, Oudiz RJ, *et al.* Patients with pulmonary arterial hypertension with and without cardiovascular risk factors: results from the AMBITION trial. *J Heart Lung Transplant* 2019; 38: 1286–1295.

100 Rosenkranz S, Channick R, Chin KM, *et al.* The impact of comorbidities on selexipag treatment effect in patients with pulmonary arterial hypertension: insights from the GRIPHON study. *Eur J Heart Fail* 2022; 24: 205–214.

101 Askin S, Burkhalter D, Calado G, *et al.* Artificial intelligence applied to clinical trials: opportunities and challenges. *Health Technol* 2023; 13: 203–213.

102 Williams GJ, Al-Baraikan A, Rademakers FE, *et al.* Wearable technology and the cardiovascular system: the future of patient assessment. *Lancet Digit Health* 2023; 5: e467–e476.

103 Corral-Acero J, Margara F, Marciniak M, *et al.* The 'digital twin' to enable the vision of precision cardiology. *Eur Heart J* 2020; 41: 4556–4564.

104 Coorey G, Figtree GA, Fletcher DF, *et al.* The health digital twin to tackle cardiovascular disease – a review of an emerging interdisciplinary field. *NPJ Digit Med* 2022; 5: 126.

105 Oikonomou EK, Thangaraj PM, Bhatt DL, *et al.* An explainable machine learning-based phenomapping strategy for adaptive predictive enrichment in randomized clinical trials. *NPJ Digit Med* 2023; 6: 217.

106 Senn S. Statistical pitfalls of personalized medicine. *Nature* 2018; 563: 619–621.