DOI: 10.1002/pul2.12271

REVIEW ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Evolution and optimization of clinical trial endpoints and design in pulmonary arterial hypertension

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Funding information
Bayer HealthCare Pharmaceuticals Inc.

Abstract

Selection of endpoints for clinical trials in pulmonary arterial hypertension (PAH) is challenging because of the small numbers of patients and the changing expectations of patients, clinicians, and regulators in this evolving therapy area. The most commonly used primary endpoint in PAH trials has been 6-min walk distance (6MWD), leading to the approval of several targeted therapies. However, single surrogate endpoints such as 6MWD or hemodynamic parameters may not correlate with clinical outcomes. Composite endpoints of clinical worsening have been developed to reflect patients' overall condition more accurately, although there is no standard definition of worsening. Recently there has been a shift to composite endpoints assessing clinical improvement, and risk scores developed from registry data are increasingly being used. Biomarkers are another area of interest, although brain natriuretic peptide and its *N*-terminal prohormone are the only markers used for risk assessment or as endpoints in PAH. A range of other genetic, metabolic, and immunologic markers is currently under investigation, along with conventional and novel imaging modalities. Patient-reported outcomes are an increasingly important part of evaluating new therapies, and several PAH-specific tools are now available. In the future, alternative statistical techniques and trial designs, such as patient enrichment strategies, will play a role in evaluating PAH-targeted therapies. In addition, modern sequencing techniques, imaging analyses, and high-dimensional statistical modeling/

Abbreviations: 6MWD, 6-min walk distance; BN, Bayesian network; BNP, brain natriuretic peptide; cMRI, cardiac magnetic resonance imaging; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; CT, computed tomography; EMA, European Medicines Agency; FC, functional class; FDA, US Food and Drug Administration; FDG, fluoro-D-glucose; IGFBP, insulin-like growth factor binding protein; m, meters; MRI, magnetic resonance imaging; NT-proBNP, *N*-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type-5 inhibitor; PET, positron emission tomography; PH, pulmonary hypertension; PHORA, Pulmonary Hypertension Outcome Risk Assessment; PRO, patient-reported outcome; PVR, pulmonary vascular resistance; QoL, quality of life; RDT, randomized discontinuation trial; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; RHC, right heart catheterization; RV, right ventricular; SUV, standardized uptake value; TAPSE, tricuspid annular plane systolic excursion.

machine learning may reveal novel markers that can play a role in the diagnosis and monitoring of PAH.

KEYWORDS
biomarker, endpoint, pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a rare and underdiagnosed condition, making it a challenge to recruit enough patients for clinical trials to give reliable results.[1] This leads to variability in trial populations, as broad inclusion criteria are necessary to maximize recruitment.[1,2] The introduction of PAH-targeted treatments has shifted the expectations of patients and clinicians from prevention of deterioration to clinical improvement,[3,4] even though such endpoints are not yet accepted by agencies such as the US Food and Drug Administration (FDA) or European Medicines Agency (EMA). Mortality-driven trials may not be appropriate for PAH, because there are few mortality events, particularly in the presence of targeted therapies.[4] This article discusses the selection, strengths, and weaknesses of endpoints for PAH clinical trials, and proposes a path forward to the development of more relevant and validated endpoints for future studies.

SINGLE ENDPOINTS

Up to now, the most common primary endpoint in PAH trials, particularly during phase 3, has been 6-min walk distance (6MWD), and statistically significant improvements in this parameter have led to regulatory approval of targeted therapies.[3–5] However, meta-analyses have indicated that exercise capacity at baseline or changes after treatment do not reliably predict overall or event-free survival,[6] or the effects of treatment on mortality.[7] Threshold values of 6MWD, rather than changes, have been used previously as prognostic predictors, with higher mortalities in patients with 6MWD $< \approx 250$ meters (m), and lower mortalities in patients with 6MWD > 440 m.[8,9] Accordingly, treatment guidelines in PAH include 6MWD in assessments of mortality risk, with values > 440 m representing low risk, 165–440 m representing intermediate risk, and <165 m representing high risk.[5] However, these 6MWD thresholds can be arbitrary and there is often within-interval heterogeneity in patients. To improve the analysis of this important patient-centered outcome, a nonlinear term could be included in the analysis (i.e., no assumption of a linear relationship between 6MWD and mortality risk) rather than creating threshold values.

Hemodynamic measures, such as pulmonary vascular resistance, are commonly used as primary endpoints in PAH trials, particularly during phase 2, and as secondary endpoints in phase 3 trials.[4] While fewer patients are needed to show an improvement compared with other outcomes, and they have the potential to predict survival at baseline and after therapy,[10] drug-induced changes in hemodynamics may not predict clinical events and explain little of the variance in outcomes.[11,12]

COMPOSITE ENDPOINTS

Composite endpoints of clinical worsening have been used in several PAH trials,[3–5] but there is no standard definition of clinical worsening, its relationship with survival is not well defined, and individual components are not weighted based on frequency or clinical importance.[3,4] Although there are some clinical trial data showing that patients who experience clinical worsening are more likely to experience further clinical worsening and mortality, further assessment of whether time to clinical worsening is a valid surrogate for mortality would be useful.[3,13] Additionally, such event-driven trials may require longer follow-ups with larger patient populations, potentially increasing the time and costs associated with the assessment of new drugs.[4] Composite endpoints of clinical improvement have been less widely used than clinical worsening and it remains to be seen how they might be employed in trials of add-on therapy.[4,14–17]

PAH risk scores, such as those derived from the French, Swedish, Comparative, and Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registries, and the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), combine various measures to predict prognosis, reflecting how a patient functions (World Health Organization/New York Heart Association functional class, 6MWD, right atrial pressure, and cardiac index), feels (quality of life [QoL] measures), and improves (mortality and morbidity).[4,18,19] Studies that applied risk scores to clinical trials as post hoc analyses or exploratory endpoints have previously suggested that risk scores distinguish between treatment arms in

clinical trials[15,18,20–22]; however, an individual patient data meta-analysis of the SERAPHIN, GRIPHON, and AMBITON clinical trials did not find that risk scores were predictive of long-term outcomes.[23] REVEAL 2.0 and REVEAL Lite 2.0 have been shown to predict prognosis in individual patients on treatment and have excellent concordance indices (> 0.7),[24–27] demonstrating that they may have the potential to be used in clinical practice. Risk scores can be seen as more clinically meaningful than single endpoints, with a dynamic relationship between changes in score and changes in outcome, a key requirement for surrogate endpoints[28]; however, further refinement of risk scores may be necessary to infer surrogacy. It should also be noted that no current scores examine right ventricular (RV) function, which is essential to prognosis.

BIOMARKERS

Brain natriuretic peptide (BNP) and *N*-terminal prohormone of BNP (NT-proBNP) are the only circulating biomarkers currently used for risk assessment or as PAH trial endpoints.[2,5] Neither marker has been formally validated, nor do they meet regulatory criteria, and there is no standard testing protocol.[2] In the GRIPHON study, NT-proBNP levels at baseline and after selexipag treatment were prognostic for morbidity or mortality,[29] and similarly in PATENT-2, NT-proBNP levels before and after riociguat treatment were associated with survival and clinical worsening-free survival.[30] However, in the SERAPHIN study, absolute levels of BNP and NT-proBNP, but not their changes, correlated with morbidity and mortality.[31]

Several markers appear to be associated with prognosis in patients with PAH. For example, plasma levels of galectin-3, a circulating biomarker of fibrosis, appear to be correlated with risk profile and mortality in PAH.[32,33] Insulin-like growth factor binding protein (IGFBP)-4 has been linked to disease severity and patient survival in PAH.[34] IGFBP-1 levels, along with eight other PAH-related proteins, were also correlated with a high risk of mortality, and upon addition to the REVEAL equation, improved the concordance indices.[35] Proteomic analyses have also revealed a panel of proteins that provides prognostic information in PAH.[35] Metabolic pathways affected in PAH include glucose oxidation, fatty acid oxidation, and glutamine metabolism.[36] One study reported that correction of metabolic abnormalities was associated with improved outcomes in patients with PAH.[37] Gene variants have also demonstrated a similar association, with bone morphogenetic protein receptor type II mutations increasing disease severity, risk of death, transplantation, and all-cause mortality.[38]

There is a growing interest in identifying gene variants that may predict responses to PAH drugs; however, they have not been widely studied.[2] Endothelin-1 plays a critical role in the pathophysiology of PAH; polymorphisms affecting endothelin metabolism may influence the efficacy of endothelin receptor antagonists.[39] Based on gene-expression profiles, tadalafil has been reported to alter the expression of genes associated with interleukin-12 and maintenance of the intracellular matrix in patients with PAH associated with systemic sclerosis.[40] Thus, differential gene-expression profiles may act as prognostic markers for responders versus non-responders.

IMAGING-BASED ENDPOINTS

Echocardiographic markers of adverse outcomes in PAH based on European Society of Cardiology/European Respiratory Society guidelines include pericardial effusion and right atrial enlargement.[41] Follow-up data from a 12-week trial of prostacyclin in patients with PAH showed that pericardial effusion, right atrial area, and degree of septal shift in diastole were significant predictors of the composite endpoint of death or transplantation, while pericardial effusion and right atrial area were independent predictors for mortality.[41] In a prospective study of 63 patients with pulmonary hypertension, every 1-mm decrease in tricuspid annular plane systolic excursion (TAPSE) was associated with a 17% increase in mortality.[42]

Several cardiac magnetic resonance imaging (cMRI) parameters can assess hemodynamics and predict outcomes such as clinical worsening and mortality.[2,43] In a meta-analysis of eight studies assessing 21 different cMRI parameters, RV ejection fraction was the strongest predictor of mortality in PAH, while RV end-diastolic and end-systolic volume index, and left ventricular end-diastolic volume index were also significant predictors of mortality.[44] cMRI parameters could therefore serve as clinical trial endpoints,[2,43,45] as seen in the REPAIR study,[46] although the use of cMRI is limited by availability and patient acceptability. Utilizing high-resolution computed tomography pulmonary angiography to evaluate changes in cardiac, vascular, and lung parenchymal findings in patients with PAH may also have the potential to predict and evaluate outcomes.[2,47] Multivariate analyses based on data from the ASPIRE registry, for example, have shown that inferior vena caval area, and the presence of pleural effusion and septal lines, were significant predictors of mortality in untreated patients with PAH.[47]

PATIENT-REPORTED OUTCOMES

Early trials of PAH-targeted therapies used generic QoL scores or those developed for patients with heart failure.[48] The first pulmonary hypertension-specific patient-reported outcome (PRO) questionnaire was the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), which has good internal consistency and the potential for applications in clinical trials and cost–utility analyses.[49] However, it contains 65 items, and repeated assessments over time do not add predictive value over that obtained at diagnosis.[50] The 10-question emPHasis-10 survey appears sensitive to clinical parameters and has been reported to predict prognosis.[51] The 41-item PAH Symptoms and Impact questionnaire differentiates well between degrees of PAH severity.[52] The 21-item Living with Pulmonary Hypertension questionnaire has been shown to be valid and reliable.[53]

PAH-targeted therapies improve QoL in patients with PAH.[51] PROs may therefore be a quick, practical way to identify treatments with little or no long-term benefit. It is advised by the FDA that PRO instruments are used when measuring concepts best known by the patient or best measured from the patient's perspective. It is important to ensure that instruments yield consistent and reproducible results; thus, PRO instruments are thoroughly reviewed alongside clinical trial data to substantiate any label claims.[54] The amount and kind of evidence required for a label claim are the same as for a claim based on other data. In some populations, such as PAH associated with connective tissue disease, improvement of QoL is difficult[55]; therefore, this approach should be applied with caution.

FUTURE DIRECTIONS

Adapting endpoints to the stage of drug development

For phase 2 studies, invasive hemodynamics are likely to remain an important endpoint until a reliable biomarker of drug efficacy is discovered. For phase 3 studies, composite endpoints, especially clinical improvement, are expected to become the norm.

Surrogate endpoints

Biomarkers should be identified that can detect deterioration of the patient before symptoms or functional class change, predict clinical worsening and/or hospitalization for heart failure, or detect potential "super responders."[56]

Various genomic, transcriptomic, proteomic, and metabolomic approaches have been used to identify pathways in PAH that could serve as surrogate endpoints.[2] Proteins related to myocardial stress, inflammation, pulmonary vascular cellular dysfunction, circulating cells, microRNAs, exosomes, and cell-free DNA are being investigated.[2,57] Probing blood and tissue repositories, such as the National Institutes of Health/National Heart, Lung, and Blood Institute Pulmonary Vascular Disease Phenomics Program database,[58] may reveal further potential novel biomarkers and trial endpoints. The Redefining Pulmonary Hypertension through Pulmonary Vascular Disease Phenomics initiative aims to enroll patients to undergo deep clinical phenotyping to aid in the development of a new pulmonary hypertension classification scheme based upon shared biologic features, in addition to identifying molecular risk factors, pulmonary vascular disease markers, and potential disease mediators.[58]

Advances in imaging, with xenon MRI, three-dimensional echocardiography, positron emission tomography (PET), or advanced computed tomography, possibly combined with other modalities such as genetic testing, may disclose potential surrogate endpoints.[2,43] RV–pulmonary arterial coupling detected by cMRI has been shown to predict clinical worsening even in patients with preserved RV ejection fraction.[59] PET allows abnormal glucose metabolism in PAH-associated pulmonary vasculature remodeling to be visualized and measured by assessing the accumulation of the glucose analog 2-deoxy-2-[(18)F]-fluoro-D-glucose (18FDG).[60] Results from studies of 18FDG PET have shown that lung standardized uptake values (SUVs) are significantly higher in patients with pulmonary hypertension than in healthy controls.[61] Lung SUVs do not, however, appear to correlate with other markers such as NT-proBNP levels, 6MWD, or echocardiography parameters.[60,61] In addition, lung SUV does not appear to predict mortality in patients with idiopathic PAH.[60] The value of 18FDG PET for monitoring treatment response therefore remains unclear.

Advances in monitoring

Continuous monitoring devices will provide new indices of physical activity that could be used to assess functional capacity; small studies of these devices in PAH and related conditions have been reported.[62–65] Home-measured 6MWD by digital devices and mobile phone applications takes away the practical limitations of conducting the traditional 6MWD test, which requires dedicated hospital corridors, physicians, and travel time for the patients.[65] In addition, data can be collected more

frequently and compared with hospital tests, potentially providing a more accurate reflection of health status. Although home-measured 6MWD could prove useful for routine outpatient monitoring and patient-centered studies, particularly in countries that lack resources, it is unlikely to function as a reproducible clinical trial endpoint due to the nature of unsupervised home testing. Additionally, any digital device measuring 6MWD would have to be validated to ensure accuracy versus the traditional 6MWD test. Nevertheless, as 6MWD remains an important outcome to patients, its prognostic value still stands and improving its practicality in clinical trials may still be of interest even if additional steps have to be taken to ensure reproducibility.

As right heart catheterization (RHC) and imaging techniques such as cMRI usually require the patient to be prone, most hemodynamic studies report resting values. In PAH, however, many symptoms are related to exertion, and it may be valuable for future research to focus on exercise hemodynamics, RV pressure–volume loops,[66] RV–pulmonary arterial coupling,[67] and similar endpoints. Noninvasive or minimally invasive hemodynamic monitoring devices[68–70] could enable endpoints to be measured more frequently than with RHC and under safer and more natural conditions. This might be especially relevant to phase 2 trials. The CardioMEMS Heart Failure system is an FDA-approved ambulatory implantable hemodynamic system that allows clinicians to remotely monitor measures such as the capacity of the right ventricle to respond to physiologic stress, pulmonary arterial pressure, and stroke volume on a daily or even hourly basis.[70] This remote system has the potential to be utilized in clinical trials to bring research opportunities to more patients and may play a key role in therapy optimization.

Patient-focused endpoints

PROs must be further researched and validated, potentially as secondary endpoints. The generic Short Form-36 QoL score has been shown to predict prognosis in patients with PAH.[71–73]

Patient utility assessments, such as the standard gamble, which directly measures patients' assessment of their health state, and time trade-off assessments, which identify what costs (e.g., payment, pill burden, or longer-term outcomes) they are willing to pay for a given improvement in their condition,[74] should be performed. These may be conducted alongside or within a study, either as a standard endpoint or part of a composite endpoint or PRO. Improvements in QoL with targeted therapies do not always correlate with objective assessments such as clinical failure[14]; this issue requires investigation.

Refinement of risk scores

Prospective validation of multiple risk scores is needed, including how they change over time, minimal clinically important differences, and correlations between changes in risk scores and patient outcomes. Patient health state utility studies[75] could be used to assign a weighting to each component of a risk score according to its impact on the patient; this would require consensus on the weightings and validation of the modified score. Combination of imaging with risk scores may refine risk stratification. Recent studies have reported that prediction of 1-year mortality can be improved by the addition of right heart reverse remodeling detected by echocardiography to the REVEAL 2.0 risk score,[76] and by use of percentage-predicted RV systolic volume index on cMRI in conjunction with the REVEAL 2.0 or French risk scores.[45] A study reporting on the addition of various echocardiographic parameters to REVEAL Lite 2.0 demonstrated that a combination with left ventricular end-diastolic eccentricity index provided more statistically accurate risk predictions compared with the risk stratification tool alone.[77] Another study also reported that the addition of surrogate markers of RV–pulmonary artery coupling (RV basal diameter, right atrial area/pressure, tricuspid regurgitation velocity, and TAPSE) to COMPERA and French risk stratification tools improved risk stratification.[78] The REVEAL echocardiographic risk score was derived using retrospective echocardiographic data from the REVEAL registry database (RV chamber enlargement, reduced RV systolic function, tricuspid regurgitation severity, and pericardial effusion), and was shown to discriminate risk and signal probability of 12-month survival.[79] However, these findings should be validated in larger, multicenter cohorts.

Current risk scores assume that the variables used are independent of each other. A Bayesian network (BN)-based machine learning approach (titled Pulmonary Hypertension Outcome Risk Assessment [PHORA]), allowing for variables to affect outcomes both independently and through their effects on other variables, was recently shown to be superior to REVEAL 2.0 in predicting 1-year survival of patients with PAH.[80] BN models that analyze continuous data, as well as the categorical variables used in current risk scores, are under development.[80]

New longitudinal composite ordinal outcomes could increase statistical power, especially in comparison with time-to-event analysis, and increase interpretability by including death as part of the outcome scale without the necessity of numerically scaling death against nonfatal outcomes. While experience with these scales in PAH is limited, a COVID-19 trial recently used ordinal outcome measures (hospitalization, death, and symptom count) to

assess the effectiveness of a treatment in reducing symptoms.[81] The use of longitudinal ordinal outcomes gives superior power when compared with the use of pooling in composite outcomes, which is not able to distinguish component outcome severities.

Analyses should be performed to determine whether surrogate endpoints meet the coefficient of determination statistic, as proposed for validation of surrogate outcomes in oncology.[82]

Fully sequential trials, enrichment strategies, and patient phenotyping

The rarity of PAH means that many clinical trials recruit modest numbers of patients and are statistically underpowered. For example, the recent TRITON study recruited only 247 patients to assess triple versus double therapy in newly diagnosed patients.[83] Fully sequential trials may overcome this limitation as they incorporate a flexible sample size calculation that avoids unnecessarily large patient populations while ensuring that the trial is appropriately powered. The design also incorporates analyses at intervals during the trial to assess efficacy, harm, or futility with the potential to inform the decision to terminate the trial. Attempts could also be made to recruit larger trial populations. Alternatively, enrichment of trials with intermediate- or high-risk patients could improve their statistical power by increasing the frequency of clinical endpoints. A preliminary study has demonstrated the feasibility of using the REVEAL 2.0 risk algorithm for this purpose.[84]

Further research is needed to inform enrichment strategies and better identify patient phenotypes and their variations in response to treatment. "Deep phenotyping" with metabolomics, proteomics, transcriptomics, and other technologies (e.g., advanced DNA and RNA sequencing) might identify the molecular basis for the variability in treatment response and aid the selection of more appropriate trial populations.[57] BN-based machine learning has been used to identify PAH immune phenotypes associated with different clinical risks.[85]

Machine learning and big data analysis

High-dimensional statistical models or machine learning may permit deeper analysis of data to identify and/or refine PAH endpoints and optimize study design. cMRI coupled with machine learning has shown that RV motion has greater prognostic benefits compared with conventional imaging and biomarkers.[86] Machine learning or big data analysis should also be utilized to combine data from PAH registries to enable data mining to link genomic, demographic, and clinical data and outcomes to identify surrogate endpoints and facilitate the design of more representative clinical trials. For example, the PHORA was designed to utilize BN-based machine learning as a risk prediction model and has been demonstrated to successfully predict 1-year mortality and depict risk in the REVEAL registry from which it was derived, but also in external registry cohorts (COMPERA and Pulmonary Hypertension Society of Australia and New Zealand registry).[80] Artificial intelligence may also play a part in future trial design, but its role in the immediate future is unclear. Retrospective analysis of clinical trial databases to examine data continuously will likely demonstrate that power can be increased while better revealing the time course of treatment effects. Amalgamation of the numerous PAH trial registries currently running throughout the world could also reveal potential new endpoints.

Regulator perspectives

The FDA and the EMA encourage the use of time to clinical worsening in PAH trials.[4] The FDA has emphasized the importance of PROs for such trials,[87] has no objection to a PRO as the basis for drug approval,[88] and has described enrichment strategies for clinical trials to identify a population in whom it is more likely that a beneficial effect of treatment will be detected.[89] The FDA considers randomized discontinuation trials (RDTs) an important enrichment strategy, in which all patients are treated with the study drug, and then responders only are randomized to a short-term trial of placebo or study drug in the next stage of the trial, and non-responders are excluded.[89] RDTs may be particularly appropriate when placebo-controlled trials are no longer ethical, and statistical models suggest that they reduce the sample size needed for phase 2 trials.[90] The EMA has published recommendations for the design of clinical trials in pediatric PAH.[91]

Equity, diversity, and inclusion

Diversity is an important aspect that should be scrutinized in future PAH clinical trials to ensure trial populations are representative of the general patient population. Overall, registries report that 70%–80% of patients with PAH are female,[92,93] which is consistent with studies such as GRIPHON, SERAPHIN, PATENT-1, SUPER, PHIRST, and ARIES where between 78% and 80% of total patients were female.[94–99] Although much is still unknown about racial predispositions in PAH, the REVEAL registry and data from the National Inpatient

Sample showed that around 28% and 30% of patients with PAH were from Black, Hispanic, Asian, or other non-White ethnic groups.[100,101] In studies that quote data on race/ethnicity, populations were predominately White, with poor representation of ethnic minorities. For example, the populations AMBITION, SUPER, and PHIRST included only 12%, 15%, and 20% of non-White patients, respectively.[14,97,98] Furthermore, pivotal studies in PAH have primarily been conducted in high-income countries (Europe, North America, Australia, and Japan), with some representation from countries in South America, Asia, and the Middle East.[14,94,96,98] Thus, many patients are still facing health disparities due to the accessibility of specialist centers and availability of specific PAH therapies.[102]

Importantly, there appear to be treatment differences among racial and ethnic groups, potentially caused by socioeconomic disparities.[103] To ensure equity and inclusivity for minority and underrepresented populations with PAH, it is essential that clinical trials are truly representative of the wider population. Some of the aforementioned future directions of clinical trial endpoints may support a move toward equity, diversity, and inclusion, with home testing and monitoring systems allowing patients who were previously unable to be enrolled in clinical trials due to socioeconomic barriers to be recruited, increasing access to PAH treatment. Furthermore, enrollment in clinical trials can be a means for patients with low incomes or from countries with limited resources to access novel medications.

CONCLUSIONS

In clinical trials of PAH-targeted therapies, emphasis has moved away from single surrogate endpoints such as 6MWD to hard clinical outcomes such as clinical worsening (Figure 1). In the future, this evolution will continue, placing more emphasis on clinical improvement rather than simply prevention of deterioration. The role of risk scores in patient monitoring through the disease process will also be further refined. The higher cost of trials able to assess hard clinical endpoints, and particularly event-driven trials that can demonstrate improvement, may prove too high for many smaller, start-up companies and affect the development of new drugs. Hopefully, enrichment strategies and other novel trial designs will help to make trials of clinical

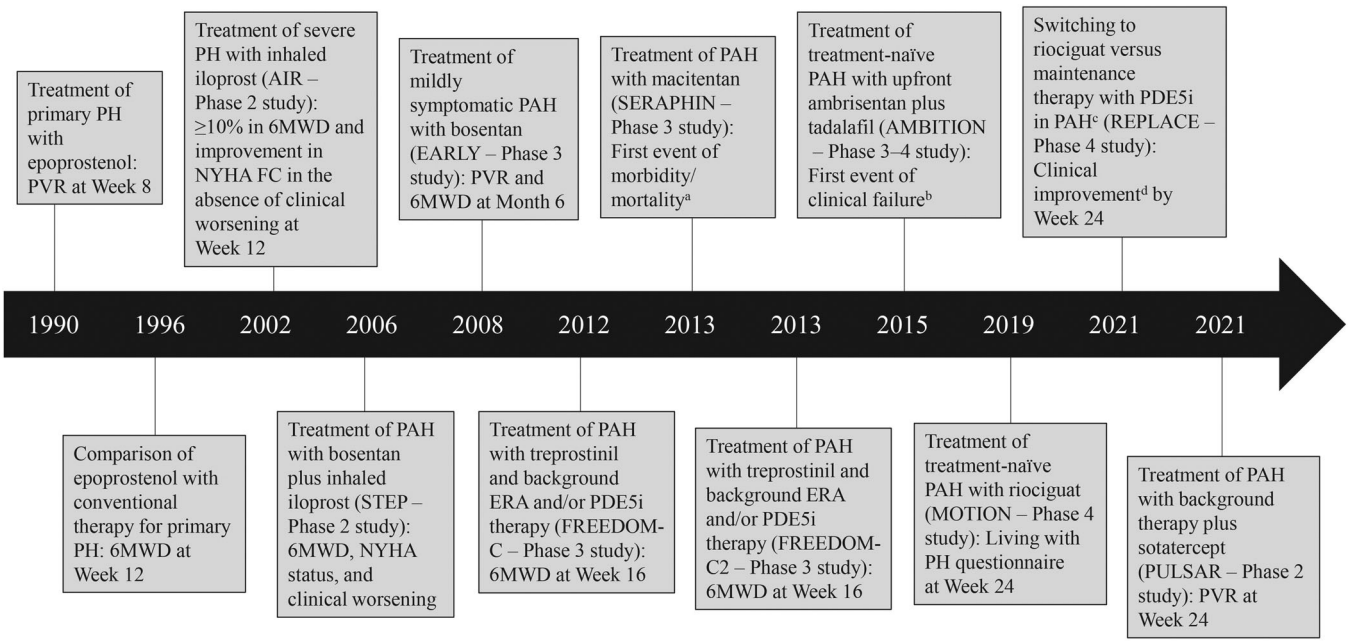

FIGURE 1 Timeline of clinical endpoints in trials of pulmonary arterial hypertension (PAH)-targeted therapies.[9,14,15,17,95,104–109] [a]Time to death, atrial septostomy, lung transplantation, initiation of treatment with intravenous/subcutaneous prostanoids, or worsening of PH. [b]First event of clinical failure, which was defined as the first occurrence of a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response. [c]Patients at risk of 1-year mortality with PDE5i treatment. [d]Absence of clinical worsening and prespecified improvements in at least two of three variables (6MWD, WHO functional class, and *N*-terminal prohormone of brain natriuretic peptide). 6MWD, 6-min walk distance; ERA, endothelin receptor antagonist; FC, functional class; NYHA, New York Heart Association; PDE5i, phosphodiesterase type-5 inhibitor; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WHO, World Health Organization.

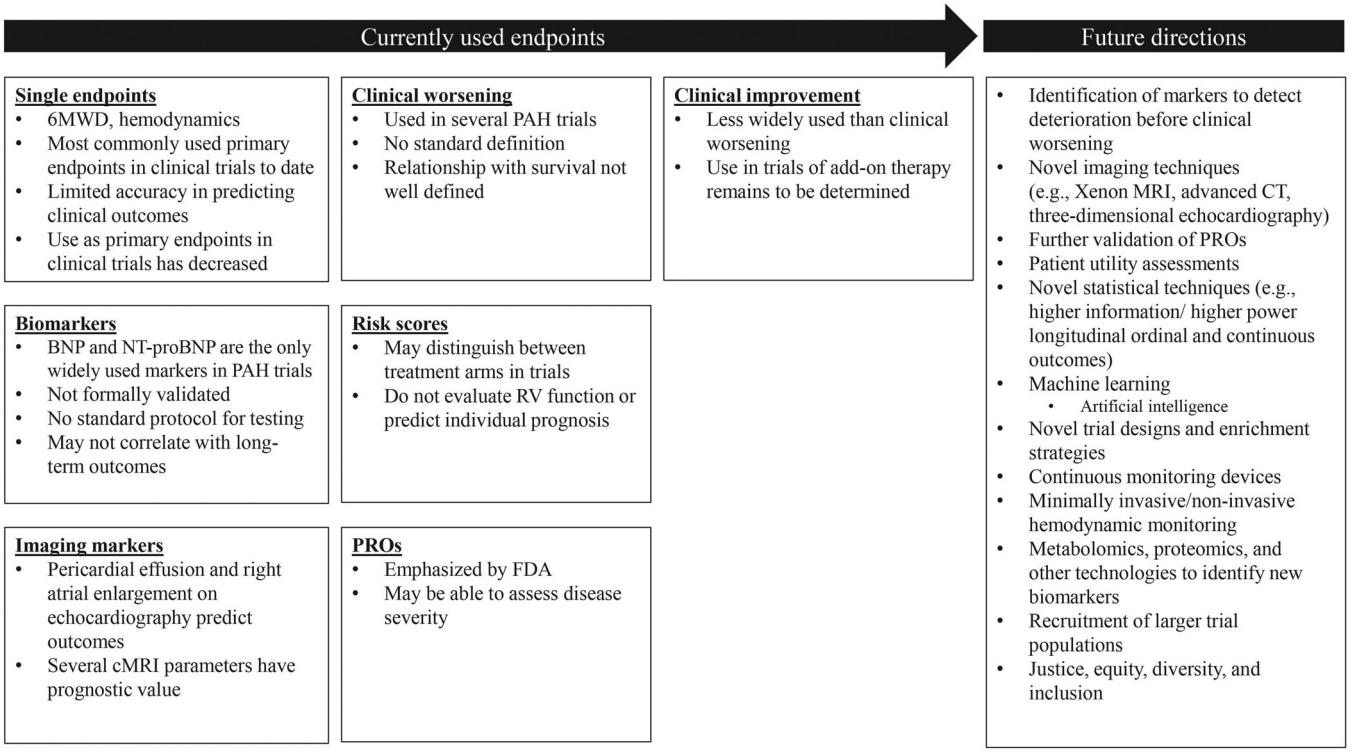

FIGURE 2 Evolution of clinical endpoints in trials of PAH-targeted therapies. 6MWD, 6-min walk distance; BNP, brain natriuretic peptide; cMRI, cardiac MRI; CT, computed tomography; FDA, US Food and Drug Administration; MRI, magnetic resonance imaging; NT-proBNP, *N*-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PRO, patient-reported outcome; RV, right ventricular.

improvement more practical. Figure 2 summarizes the current situation and potential future developments.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of the manuscript, revised the manuscript critically, approved the final manuscript, and agreed to be accountable for its overall content.

ACKNOWLEDGMENTS

The medical writing support was provided by Richard Murphy, PhD, of Adelphi Communications Limited, Macclesfield, UK, supported by Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA in line with Good Publication Practice (GPP) guidelines.

CONFLICTS OF INTEREST STATEMENT

Marco Caccamo has received consulting and speaker fees from Bayer. Frank E. Harrell has received consulting fees from the American Statistical Association, Annexon Biosciences, the Arnold Foundation, AstraZeneca, and Johnson & Johnson/Janssen, receives textbook royalties from Springer, and received an honorarium for a Janssen Pulmonary Hypertension Key Opinion Advisory Committee in late 2021. None of the funding relates to the current work. Anna R. Hemnes has received consulting fees from Bayer, Gossamer Bio, Janssen, and United Therapeutics, has grants from the National Institutes of Health and the Cardiovascular Medical Research and Education Fund, and owns stock in Tenax Therapeutics.

ETHICS STATEMENT

Ethical approval was not required for this review.

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How to cite this article: Caccamo M, Harrell FE, Hemnes AR. Evolution and optimization of clinical trial endpoints and design in pulmonary arterial hypertension. Pulm Circ. 2023;13:e12271. https://doi.org/10.1002/pul2.12271