Clinical trial design in phase 2 and 3 trials for pulmonary hypertension

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Abstract

This article on clinical trial design incorporates the broad experience of members of the Pulmonary Vascular Research Institute's (PVRI) Innovative Drug Development Initiative (IDDI) as an open debate platform for academia, the pharmaceutical industry and regulatory experts surrounding the future design of clinical trials in pulmonary hypertension. It is increasingly clear that the design of phase 2 and 3 trials in pulmonary hypertension will have to diversify from the traditional randomised double-blind design, given the anticipated need to trial novel therapeutic approaches in the immediate future. This article reviews a wide range of differing approaches and places these into context within the field of pulmonary hypertension.

Introduction

An important hurdle to overcome in drug development of pulmonary hypertension (PH) is the ability to recruit a large enough number of patients to detect whether the drug is effective, safe and well tolerated. Novel treatment options should become available to patients with this life-threatening and progressing condition as fast as possible. As the mode of action of novel compounds may vary, and patients may respond differently, an appropriate patient-focused clinical trial design should be adopted. The focus of this article on clinical trial design is based on the considerable experience gained in pulmonary arterial hypertension (PAH), a disease that appears well suited for smaller trial designs that selectively target patients based on pathobiology beside clinical phenotyping based on existing regulatory guidance. Utilising this experience is important in patients with PH associated with pre-existing cardiovascular or chronic respiratory disease, as the long-term outcomes remain similarly poor as in PAH.[1]

The most recent World Health Organization (WHO) clinical classification of PH consists of five main groups and includes patients with PAH (Group 1), with PH in association with left heart disease (Group 2), with respiratory disease (Group 3), with chronic thrombo-embolic PH (Group 4), as well as those with PH with unclear or multifactorial mechanisms (Group5).[2] Currently, the reported incidence of idiopathic and hereditary PAH in the developed world is 1.1–7.6 per million adults per year, and the prevalence of PAH is 6.6–26.0 per million adults.[3] In contrast, a population-based study of 3381 participants in Rotterdam, Netherlands, reported echocardiographic signs suggestive of PH in 2.6% of the overall population[4] with increased prevalence noted in older individuals. The increased

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prevalence in an older population has been seen in other studies.[5]

In both economically high-and-low income countries, left-sided heart disease and lung disease are by far the most common causes of PH. About 80% of patients with PH live in the developing world, where heart disease and lung disease also have become the most frequent causes of PH, but other disorders such as schistosomiasis, rheumatic heart disease, HIV, or sickle cell disease also play an important role. Therefore, pulmonary hypertension is increasingly recognised as a growing global health issue.[3,6]

Clinical phenotyping has hitherto played the major role in identifying those patients suitable for treatment based on evidence from clinical trials in Group 1 PAH disease. The future, however, promises a molecular phenotyping approach to identify relevant abnormal cell signalling pathways fundamental to disease progression in any individual and treating the same.

To date, four signalling pathways implicated in the pathogenesis of PAH have been targeted using a conventional randomised clinical trial design (RCT). These introduced four novel drug classes to clinical practice.[7–13] Nevertheless, a continued rate of morbidity and mortality indicates optimal treatment and the ability to predict therapeutic responsiveness in an individual with PAH remains insufficient, requiring the identification of additional molecular treatment targets.[14]

Research and drug discovery is shifting collectively in the PAH field towards a personalised medicine approach to disease categorisation, diagnosis, and ultimately, treatment implementation. The National Institutes of Health recently announced a major funding initiative to stimulate investigations that promote the value of proteomics and genomics for the characterisation of pulmonary vascular disease phenotypes and to identify potential new therapeutic targets and the UK research collaborative is studying this via its cohort study in PAH. Finally, the Pulmonary Vascular Research Institute (PVRI) is undertaking a large deep phenotyping study in PH via its "Go-Deep" study.

These developments are generic in medicine, where increasing use of molecular signatures reveals that the traditional tools used for diagnosis are lumping diverse phenotypes together based on common molecular drivers of disease. Precision medicine, using genomic, epigenetic, exposures and other data to define individual patterns of disease and distinct phenotypes with more granularity, potentially leads to better individual treatment. Precision medicine couples established clinical-pathologic indexes with state-of-the-art molecular profiling to create diagnostic, prognostic and therapeutic strategies tailored for specific groups of patients.

This article focuses on assessing clinical trial design in the past with suggestions for the future to facilitate the development and registration of novel drugs.

The randomised clinical trial

The randomised clinical trial (RCT) is the principle clinical trial design used in the past to assess the efficacy of PAH-directed treatments and has been instrumental for identifying approved therapies for this disease. RCTs have been successful at providing positive outcome data despite PAH being a rare disorder.

One weakness of the RCT design to date, in part driven by the rareness of the disease, is the wide inclusion/exclusion criteria based on clinical phenotypes, increasing the probability that a study cohort includes a heterogeneous range of PAH patients with differing responses to the drug(s) under study.

The optimal duration of therapy in PAH clinical trials is unresolved. RCTs completed over the last two decades have demonstrated that a 12-week endpoint correlates positively with outcomes assessed in longer extension studies.[15] In contrast, other RCTs have demonstrated a benefit at 12 weeks only to observe diminished benefit at nine months.[16]

The potential for a rapid clinical decline in many patients is an important consideration in trial design, especially in the setting of delayed clinical presentation and diagnosis that often characterises PAH in clinical practice.[17] Consequently, most previous RCTs have required clinical stability before recruitment and randomisation of subjects thus not mirroring clinical practice.

In the past, there was much discussion of the ethics of undertaking placebo-controlled studies, with patients remaining off active treatment for the duration of RCTs.[18] However, in the future, certainly for patients with PAH, any novel therapy will be trialled in subjects already receiving background therapy. This will pose significant limitations to the standard RCT, as a design, because of the likely increased number of patients and duration needed for the trial to have adequate statistical power leads to an increased cost.

Finally, there is an awakening interest in developing a personalised medicine approach to therapy in PH and, as discussed previously, the current format of RCT used to date has depended on using clinical phenotyping alone as the basis for inclusion of subjects.

Decentralised trials

The academic research and industry have been looking to decentralise trials for years. Now, as health authorities worldwide struggle to contain the Covid-19 (Coronavirus Disease 2019) pandemic outbreak with major impact on running clinical trials in the conventional way, there is a renewed push to rapidly implement remote healthcare delivery capabilities. Decentralised trials (DT), as those executed through telemedicine and mobile/local healthcare providers, use procedures that vary from the traditional clinical trial model.

The experience in technologies to improve direct patient access has been advanced. The smart application of those

technologies can overcome barriers to trial execution and improve data sharing and process efficiency across organisations. Those technologies can be used immediately to ensure progress for clinical trials in an environment where patients are expected to stay at home.

However, there are challenges with such modern technologies to be considered. Integrating such new types of data from digital health technologies into the standard datasets needs to be customised to be handled by industry or academic research. Although regulatory agencies are increasingly interested in working collaboratively to implement and pilot these new digital technologies, an important concern, however, is endpoint validation using a specific digital health technology, which requires implementing a time to validate the technology into a clinical development plan.

It deserves – in fact, it *requires* – further collective attention and effort.

Trial population enrichment studies

Enrichment strategies aim at improving the ability of a study to detect a drug's effectiveness. Prospectively obtained patient characteristics are used to select a study population in which detection of a potential drug effect is more likely than it would be in an unselected population.[19] Three broad categories of enrichment strategies have recently been described by the US Food and Drug Administration (FDA): strategies to decrease variability; prognostic enrichment strategies and predictive enrichment strategies,[20] which are further discussed within the frame of PH trials.

Strategies to decrease variability

At baseline, patients are selected based on measurements of a phenotype or a biomarker characterising the disease in a narrow range to decrease interpatient variability and to thereby increase study power. An example would be targeting patients with mutations in bone morphogenetic protein receptor type 2 (BMPR2) as the cause of PAH. A more simple approach to decrease variability includes encouraging patients to adhere to treatment and study requirements. Practices that have become standard include making patients aware of the conditions and demands of the trial within the patient's informed consent, carefully titrating drugs that could cause intolerable early adverse reactions, as done with epoprostenol, riociguat or selexipag, and using counting devices on bottles of medication.

Another aspect is to decrease placebo response and spontaneous improvement. This can be achieved in PH trials having often the six-minute walk distance (6MWD) as a primary endpoint by using a standardised procedure and familiarisation test prior to the baseline test itself.[21,22] Another option is to limit the range of 6MWD, e.g. 150–450 m, to avoid including too severely ill patients who are not able to perform the test sufficiently, and patients with a near normal test.

Prognostic enrichment strategies

Patients are chosen with a greater likelihood of having a disease-related endpoint event (for event-driven studies) or a substantial worsening in condition (for continuous measurement endpoints). In PAH trials, risk stratification and risk scores provide an estimate for individual patients' risk.[23–27]

Patients having an intermediate or high-risk profile could be included for enrichment purposes. The ability of the different risk assessment tools to discriminate not only between the different risk profiles but also between treatment arms was successfully tested post-hoc in the PATENT-1 and -2, as well as in the GRIPHON and AMBITION studies.[26,28–31]

The responder rate at the end of the study will largely depend on the composition of included patients at baseline, such as the proportion of having intermediate or high-risk criteria at baseline.[32] Such an enrichment strategy may be employed to select patients who are likely to have changes in the risk category. Missing data, in case no risk assessment can be made available at the end of the study, could be counted as non-responders.

Predictive enrichment strategies

These include selecting patients who are more likely to respond to the drug treatment based on a specific aspect of a patient's physiology, a biomarker, or a disease characteristic that is related in some manner to the study drug's mechanism.

Biomarkers can play many different roles in drug development, including a predictor of response or resistance to specific therapies, being a novel endpoint or, as in this context, used as a means for patient-enrichment designs.

Furthermore, factors used to limit the study population to patients believed more likely to benefit from the experimental therapy are termed enrichment factors.[33,34] They may be predictive biomarkers, specific clinico-pathological features or indeed any characteristic associated with the biological target of a therapeutic agent. Quite clearly, the rarer the disease, the fewer potential patients in a trial and the more advantageous it is to consider studying an enriched population. This would apply then to patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH) rather than patients with PH due to Group 2 or Group 3 disease.

The main purpose of using an enrichment biomarker to refine patient selection for a clinical trial in drug development is to improve the chances that the drug will show benefit and require fewer randomised patients for adequate power to establish that the drug is worth pursuing further. The enrichment approach will also lead to a faster result in terms of determining a new drug's efficacy. If information is available to suggest subgroups of patients who are more likely to benefit from a therapy, it may be reasonable to conduct a confirmatory trial only in those patients. An example within PAH would be patients with inheritable

PAH associated with mutations in BMPR2. There exists further evidence supporting the use of genetic susceptibility data in clinical trial inclusion criteria. Accumulating evidence indicates that metabolism and mitochondria are critical in the pathogenesis of PAH. Mitochondrial glucose oxidation is suppressed in the pulmonary arteries of patients with PAH and glycolysis is upregulated to compensate, all of which leads to inhibition of apoptosis and promotion of proliferation. A new study shows that dichloroacetate (DCA), an inhibitor of the mitochondrial enzyme, pyruvate dehydrogenase kinase (PDK), improves haemodynamics and functional capacity in genetically susceptible patients with PAH. Previous work had determined that PDK, an inhibitor of pyruvate dehydrogenase, could be a therapeutic target in PAH. Using ex vivo assays in explanted lungs from patients with PAH, Michelakis et al. show that treatment with the PDK inhibitor DCA activated PDH and increased mitochondrial respiration. Furthermore, in a four-month phase 1 trial in patients with idiopathic PAH who were already taking approved PAH therapy, DCA treatment led to a reduction in mean pulmonary arterial pressure and pulmonary vascular resistance, as well as an improvement in functional capacity. However, the response to DCA varied in both the ex vivo assays and the clinical trial. The investigators showed that the presence of functional inactivating variants in SIRT3 and UCP2 were associated with a poor clinical response to DCA. This trial showed that gene variants could be used as novel biomarkers of the metabolic remodelling in PAH and specifically predict the resistance to DCA and other metabolic modulators targeting mitochondria.[35] The results suggest that future clinical trials of novel agents should have a precision medicine design that considers patient genotype to maximise a beneficial response.

In summary, the aspect of "one size fits all" surrounding the conventional design of clinical trials is thus challenged, particularly when the diseases are heterogeneous due to observable clinical characteristics and/or unobservable underlying genomic and epigenetic characteristics and/or the experimental therapy is tailored to specific mechanism of action.[36] This is then of great relevance to proposed new trials within the PH field. An extension from the traditional single population design objective to one in which several possible patient subpopulations are studied will allow more informative evaluation in the patients having different degrees of responsiveness to the therapy.[33] Building into traditional clinical trials, a prospectively planned selection of subpopulations with higher response to the therapy is appealing from the patient's perspective, as it addresses personalised medicine in adequate and well-controlled clinical trials. These new adaptive designs, called adaptive patient-enrichment or population-enrichment designs, allow modification to study hypotheses, the reallocation of patients and the re-estimation of the sample size midstream to achieve the pre-planned objective. The benefit arises from the inclusion of the final stage data on the selected subpopulations,

suitably adjusted for multiplicity, in the final analysis at the end of the trial.[34]

Randomised discontinuation trials (withdrawal study design)

Randomised withdrawal trial (RDT) design has been used in clinical research as well as in applications for marketing authorisation for various indications over decades.[37–39] The design was first described by Amery and Dony in 1975 to avoid exposing patients unnecessarily to placebo treatment.[38] The aim was, from the beginning, to provide adequate and well-controlled data acceptable to both research academia as well as governmental regulatory bodies. In the RDT, in contrast to the classic randomised clinical trial (RCT), only those patients who appear to improve when treated with the medication under study (the "responders") are selected for the second, randomised phase.[37]

Especially when the use of placebo is deemed unethical, an RDT is optimal for studying long-term, non-curative therapies.[37] The FDA considers RDTs as an important enrichment strategy as detailed in section D of the respective guidance.[20] The RDT consists of two phases. In the first phase, all patients are treated with the study drug, and in the second phase, drug therapy responders are randomly assigned to switch to placebo or continue the same treatment.[37] Predictive enrichment techniques may be used to select subjects for study who have the greatest chance of benefit, as medication non-adherent patients, or those reporting adverse events, are generally not considered for study enrolment.[19]

Withdrawal studies, which are similar to RDTs in principle, aim to determine if patients may be transitioned safely to an alternative form of therapy, including placebo. According to ICH Topic E 10 "Choice of Control Group in Clinical Trials,"[39] the randomised withdrawal design is defined as: "In a randomised withdrawal trial, subjects receiving a test treatment for a specified time are randomly assigned to continued treatment with the test treatment or to placebo (i.e., withdrawal of active therapy)". However, "as with the early escape design, careful attention should be paid to procedures for monitoring patients and assessing study endpoints to ensure that patients failing on an assigned treatment are identified rapidly."

Such a randomised, placebo-controlled withdrawal trial was performed by Rubenfire et al.,[40] in which clinically stable PAH patients on epoprostenol (PGI2) therapy were randomised to transition to subcutaneous treprostinil (PGI2) or placebo in a 2:1 manner over a period of up to 14 days. In this study, of the eight patients withdrawn to placebo, seven (88%) had clinical deterioration, while only 1 of 14 patients (7%) withdrawn to treprostinil deteriorated.[40]

A withdrawal design was employed by Channick in a retrospective transition study of 37 consecutive patients.[41] The transition period began on the first day of inhaled

iloprost with intent of discontinuing parenteral prostacyclin and completed on the first day of treatment with inhaled iloprost free of parenteral prostacyclin. Almost 92% of patients had an overlapping transition with a mean transition period of 10.5 ± 13.9 days. At one year follow-up, 78% of the patients remained on inhaled iloprost alone, and 81% were free of clinical worsening. It should be noted, however, that successful transition in this study appeared related to concomitant oral medication use, which must be considered during RDT planning.

Experts in PAH have raised ethical and safety issues concerning randomised withdrawal designs from two perspectives. First, to withdraw an effective therapy from a patient and to switch the therapy to placebo could lead to deterioration and violate the necessary provision of the standard of care for the trial to be ethical. Second, even if a patient who deteriorates is withdrawn from the trial and given active therapy again, there is no guarantee that the patient would return to the pre-randomisation state.[34] An important safety consideration is, in addition, the possibility for adverse events to occur upon therapy withdrawal. Therefore, the RDT planning phase requires consideration of the individual patient's clinical profile, particularly disease severity, when determining appropriateness for RDT trial enrolment.

In response to the issues raised and to avoid undue placebo treatment, another randomised withdrawal design has been developed. An increasing medical need occurred transitioning patients from insufficient PAH drug therapy to a potentially more effective one. Recent PAH guidance has recommended initial combination therapy with phosphodiesterase 5 inhibitors (PDE-5i) plus ERA for patients with WHO FC II or III disease based on the outcome of the AMBITION trial.[42] However, a sizeable proportion of PAH patients fail to reach or maintain treatment goals with PDE-5i monotherapy and/or combination therapy.[43,44] Further, recent trial results suggest that triple therapy provides no additional benefit in comparison to double therapy, however, with an increased frequency of adverse events.[45]

There is a scientific rationale to switch PAH patients with an insufficient response to PDE-5i (NO dependent), defined as WHO FC III despite therapy, to the direct sGC stimulator riociguat (NO independent). However, the RESPITE study was an open-label, multicentre, uncontrolled, single-arm phase 3b study,[46] and the benificial effects were seen as exploratory with regard to improvement in functional class (FC), 6MWD, biomarkers and a composite endpoint.[47] Therefore, another study the REPLACE study was started to prove the hypothesis that switching may be.[48] Whereas RESPITE was single-arm uncontrolled study, REPLACE is a randomised, double-arm controlled, multicentre 24-week study with a completed recruitment of 225 subjects. The aim was to avoid putting patients unnessarily on placebo, while PDE-5i and riociguat have already been marketed and available to patients. Therefore, patients were randomly assigned to continue PDE5-i therapy or switch to riociguat (up to 2.5 mg tid). Further, a composite endpoint was used composed of improvement in FC, 6MWD, NT-proBNP without deterioration or death. The results were presented at the recently held ERS conference: 41% of patients transitioning to riociguat therapy achieved the composite primary endpoint of clinical improvement in the absence of clinical worsening, compared with 20% in the PDE5i group (odds ratio (OR) = 2.8, 95 percent confidence interval (CI) (1.5–5.1); $p = 0.0007$).[49]

Factorial design

In the tension between innovation and stagnation, the FDA identified, in their analysis, a pharmaceutical pipeline problem with a slowdown in the approval of innovative medical therapies.[50] This occurred despite of the increased understanding of many diseases unfolding in recent years and the increased spending in research and development. Therefore, the FDA called for methods that may achieve reliable results more quickly. One of these methods is called factorial design.

One of the fundamental assumptions used in factorial designs to find the critical value and required sample size is the additivity of the treatment effects.[51] Factorial studies allow investigators to test multiple hypotheses at once. The simplest example is a 2×2 design, where two treatments are studied. For example, if studying drug A and drug B, a factorial design would comprise four groups: (1) active drug A plus placebo drug B, (2) placebo drug A plus placebo drug B, (3) placebo drug A plus active drug B, (4) active drug A plus active drug B. When deciding on the various therapies to be tested using a factorial design, it is important to consider the potential for drug–drug interaction(s) between each therapy as a confounder.[14]

Kawut et al. conducted a randomised, double-blind, placebo-controlled 2×2 factorial clinical trial of simvastatin and aspirin in PAH patients receiving background PAH therapy.[52] The study was both informative and instructive from a clinical trial perspective in a field of PH. Despite demonstrating no significant benefit from either aspirin or statin therapy on 6MWD at six months, findings highlighted the feasibility and role of performing a factorial study in PAH, particularly when different mechanistic pathways are under investigation.

Crossover study

Whereas the use of crossover design in early drug development phases is well established, the use in phase 2/3 studies in orphan diseases, such as PAH, remains challenging.

The crossover study design is divided into specific phases. In phase 1, the endpoint is assessed at baseline and following randomisation to treatment with study drug, placebo or other drug for a pre-determined duration of time. In phase II, patients are administered therapy opposite to phase I and the endpoint is re-assessed at the completion of the study.

Within-subject analyses are performed to compare the differences in outcomes between the study drug and placebo. Advantages of this trial design include blinding and the use of a smaller sample size compared to parallel trial designs.[19] However, such designs assume that a short time to wash out the therapeutic is adequate, and that there are no "carry-over" treatment effects.[53] Crossover trials including PAH patients may be of further concern, as a washout may cause rebound clinical worsening.

These challenges may have been the reason why only one study in PAH used a crossover design. Singh et al. used this approach in a group of PAH Group 1 patients with Eisenmenger syndrome.[54] This was a randomised, double-blind, placebo-controlled crossover study. Twenty patients, 10 of each of idiopathic PAH and Eisenmenger syndrome, were randomised to receive placebo or sildenafil in a double-blind manner for six weeks and, after a washout period of two weeks, were crossed over. The primary endpoint of efficacy was the improvement in distance covered in 6MWD test. Secondary endpoints were the reduction in pulmonary artery pressure as measured by Doppler echocardiography after six weeks of treatment, improvement in clinical condition, New York Heart Association (NYHA) class, and exercise duration and metabolic equivalents (Mets) achieved on modified Bruce exercise protocol. The study was positive confirming the value of sildenafil over placebo in these two groups of patients.

It is worth pointing out that crossover studies, in which a proportion of patients are randomised to upfront placebo, generally involve patients with moderate symptom burden and do not control for timing of drug initiation. Additionally, owing to the observation that PAH-specific therapies appear more efficacious in patients with more severe disease, delayed drug therapy may be a confounding factor in the interpretation of crossover study design results in demonstrating drug efficacy in PAH.

N of 1 studies

Generally, following informed consent, a patient enrolled in an n-of-1 trial undergoes baseline measurement of a specific outcome measure. The patient is randomised to receive a therapeutic intervention for a pre-specified time period, after which performance on the outcome measure(s) is reassessed. Following a drug washout period, the same experimental design is repeated to measure the effect of a second therapy on the same outcome measure(s). Ultimately, a comparison of the effect of each treatment on outcome is performed to characterise drug efficacy. Similar to RCTs, clinicians and patients are generally blinded to the therapeutic agent (or placebo) during the study to avoid the introduction of bias on outcomes.[55,56] Various permutations in study design involving the number of therapy cycles, duration of therapy, role of blinding, sequence of randomisation and potential for co-therapy are considered according to the disease process and pharmacokinetics of the drug(s)

under investigation. A limitation of the n-of-1 trial in PAH is the potential rapid nature of disease progression as well as the perils of drug withdrawal. Indeed, n-of-1 trials may be better suited for chronic, progressive diseases characterised by a predictable mortality and event rate, as demonstrated in a recent n-of-1 analysis of statin therapy.[56] Nevertheless, certain PAH patients may warrant consideration for n-of-1 trial protocols when the underlying mechanisms driving the disease are known in order to characterise individualised response to therapy.

Adaptive designs

Whereas interim monitoring and group sequential designs have been well established to stop a trial or treatment as soon as the utility, efficacy and/or safety question addressed by the trial or related to that treatment is answered.[57] There is a need for looking further into adaptive trial design scenarios from clinical as well as regulatory perspective. Especially as escalating costs of cardiovascular trials are limiting medical innovations, prompting the development of more efficient and flexible study designs such as Bayesian adaptive trials.[58]

The term "adaptive design" refers to a clinical trial in which data collected during the course of the trial are used to change aspects of the trial design in such a way as to maintain the validity and integrity of the trial. There are a number of objections to the use of adaptive designs in general, not confined specifically to PAH.[34] These objections are statistical, methodological and ethical. In the context of pharmaceutical drug development, any adaptive design will need to meet the standards laid down in the guidelines issued by the regulators.[59,60] The requirements of these guidelines address some of the issues which have been raised, especially concern for confirmatory phase 3 trials.[59,61] The use of an adaptive design should be done with caution and, if so, only with a limited number of adaptations. There is a potential risk of loss of thinking time between the adaptions. The type-1 error must be controlled to provide unbiased estimates of the treatment effect, as well as confidence intervals with correct coverage of probability. Of course, confidentiality of interim results must also be ensured. Only few compounds were approved based on an adaptive design, and none for the indication PAH to date.

There is more flexibility, however, in hypothesis generating trials of earlier drug discovery phases.[59] It is of advantage to use more efficient approaches in dose-finding trials rather than using pairwise tests of individual doses against placebo. The target population can carefully be investigated as to whether it is suitable for the confirmatory trial. The use of omics and biomarkers is encouraged for phase 2 adaptive studies.[62] Therefore, type-1 error would not be as critical as in confirmatory trials since hypothesis and dose finding are in focus for phase 2 trials.[62] Nevertheless, trial sponsors will still want to be reasonably assured that they are not being

overly optimistic or tricked by a bias to continue with an ineffective drug.

There is a continued interest from trial sponsors to combine phase 2 and 3 studies in order to save development time and be more resource effective. In this case, and as recommended by regulatory bodies, the study protocol should then discuss why enough evidence is expected from the phase 2/3 combination trial compared to the strategy with another phase 2 trial that is followed by a separate phase 3 trial. Using Bayesian adaptive designs, it may be critical to use simulations to evaluate the chance of an erroneous conclusion. Sponsors should consider carefully the value of independent replication of results and the value of waiting to confirm the detailed design of the confirmatory study until all important exploratory data are available.[59,60]

To structure adaptive clinical trial design master protocols have been proposed:[33,57]

Type of trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm.

Learning from the oncology field the use of biomarkers in adaptive design can strengthen trial efficiency.[33,63]

Umbrella or basket trials describe master protocols designed to integrate proven molecular, genetic or serological biomarkers that are associated with treatment response. Risk assessment tools may be used as biomarkers at enrolment or during the study to stratify subjects.[64]

The recently held Clinical Trial Design Taskforce of the World Symposium on Pulmonary Hypertension[64] critically assessed the downside of the platform approach, as the later added arms can only be compared with the control patients randomised from the identical time-point of enrolment. This may not be an easy task to organise as multiple industry partners need to collaborate in the trial design, control and privacy of data, funding and regulatory requirements.[65]

In summary, it is important to note that while some adaptive approaches allow almost total flexibility in changing many aspects of a trial during its course, such approaches are inherently difficult to accept when the trial is part of drug discovery. Such a trial may, however, be adaptive by design, that is to say, those aspects of the trial that are open to adaptation should be prespecified in the study protocol, and the consequences of these changes should be investigated through a comprehensive set of simulations prior to the commencement of a study in close exchange with regulatory agencies.

Conclusions

There are important characteristics of PH and its different groups that may influence use or success of novel trial designs. PH comprises a series of progressive diseases with a variable clinical trajectory, which may confound drug efficacy within each individual patient. Along these lines, since currently available therapies for PH have never been shown to reverse disease pathobiology, the assessment of drug efficacy within a patient across different clinical stages of PH may be influenced by that stage. The recognition now that prognostic risk factors present at the onset of a study within the randomised population of patients may influence the endpoint responses, such as morbidity and mortality, indicates the need to carefully match the groups.

Many current RCT studies used as the evidence base for treatment are flawed because group mean data hides potentially large numbers of non-responders whose negative data is matched by super responders. Generalising RCT findings to patients in clinical practice is then made difficult and supports the value of real-world data collection after a positive clinical trial.

Enrichment strategies, such as including patients with intermediate or high-risk profile into clinical trials, may help improving the ability of a study to detect a drug's effectiveness.

In earlier or exploratory trials, crossover and n-of-1 study designs may be well positioned to study outcomes in selected PH patient cohorts defined by converging genetic or molecular PAH pathophenotypes and provide hypothesis-generating data for future studies in larger RCTs which include enrichment features as inclusion criteria.

The success of developing patient focused treatment strategies in PH hinges on the application of appropriate clinical trial designs. Furthermore, these strategies are necessary for developing cost-effective methods that identify PH patients likely to benefit from disease-targeted pharmacotherapies.

Take home messages

Many current RCT studies used as the evidence base for treatment in PH are flawed because group mean data hides potentially large numbers of non-responders whose negative data is matched by super responders. Generalising RCT findings to patients in clinical practice is then made difficult and supports the value of real-world data collection after a positive clinical trial.

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