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End Points and Clinical Trial Design in Pulmonary Arterial Hypertension

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New and emerging therapies might provide benefit in patients with pulmonary arterial hypertension. Their efficacy and safety will be compared with existing combination therapies in randomized clinical trials. Appropriate end points for these trials need to be identified: these will include exercise testing, the composite end point of time to clinical worsening, and hemodynamic markers, including advanced imaging modalities and biomarkers. Quality-of-life questionnaires are useful and important secondary end points; pulmonary arterial hypertension-specific questionnaires are currently being developed. Advantages and disadvantages of various trial designs, including placebo-controlled monotherapy or add-on trials, noninferiority studies, and withdrawal trials are also discussed. (J Am Coll Cardiol 2009;54:S97–107) © 2009 by the American College of Cardiology Foundation

When the 2nd World Health Organization (WHO) conference on Pulmonary Hypertension met in Evian in 1998, the only approved medical treatment for pulmonary arterial hypertension (PAH) was intravenous epoprostenol. By the time of the 3rd World Symposium on PAH, which took place in Venice in 2003, new therapies had emerged that extended and improved the quality of our patients' lives. Since the Venice meeting, an increasing number of agents, including prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, are providing more options for treatment. With these new agents comes a new challenge: to design clinical trials that will guide us in making the best therapeutic choices on the basis of currently available therapies and those that are still in development. The views presented here are a summary from the Task Force on End Points and Clinical Trial Design that met at the 4th World Symposium on Pulmonary Hypertension, held in Dana Point, California, in 2008.

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Patient Populations in Randomized Clinical Trials of PAH

A key question concerns the types of PAH patients that can reasonably be considered together in a single randomized controlled trial (RCT). To date, most pivotal studies in PAH have grouped together several subcategories of patients. Because of the relative rarity of this disease (1–4), this strategy has allowed investigators to maximize recruitment. Nevertheless, it is clear that disparate PAH populations are not biologically identical and often not even similar. Subgroup analyses of these trials, moreover, have been limited because of the small numbers of subjects, and no studies to date have prespecified subgroup analyses. Such post-hoc subgroup analysis should be viewed as hypothesis-generating. Thus, we still have only rudimentary data in

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Abbreviations and Acronyms

BNP = brain natriuretic peptide
CMRI = cardiac magnetic resonance imaging
CPET = cardiopulmonary exercise test
CTEPH = chronic thromboembolic pulmonary hypertension
FDA = Food and Drug Administration
LV = left ventricular
NT-proBNP = N-terminal pro-brain natriuretic peptide
NYHA = New York Heart Association
PAH = pulmonary arterial hypertension
PH = pulmonary hypertension
RCT = randomized controlled trial
RV = right ventricular
6MW = 6-min walk
TtCW = time to clinical worsening
WHO = World Health Organization

subpopulations regarding the pathogenesis and natural history of the disease and clinical response to current PAH-targeted therapies.

Although more than 50% of the patients included in randomized trials of PAH have had idiopathic PAH, many trials have included a significant number of patients with other forms of PAH, such as that associated with connective tissue disease and congenital heart disease. Although regulatory agencies have been approving drugs for the global indication of PAH on the basis of data from such trials since 2001, a paucity of data in PAH subpopulations makes it difficult to extrapolate specific therapeutic approaches targeted to them. What we have learned from these trials is that most drugs for PAH, with the possible exception of sildenafil, seem to be more efficient in patients with idiopathic PAH than in those with nonidiopathic PAH and, furthermore, that patients with connective tissue disease consistently demonstrate a lesser response to treatment (5–9). With 2 notable exceptions, the intravenous (IV) epoprostenol in scleroderma study (10) and the BREATHE-5 (Bosentan Randomised trial of Endothelin Antagonist THErapy) trial in patients with congenital heart disease (11), most studies in subpopulations have been uncontrolled, and long-term data in these groups are scarce. The following options can be considered:

- Group all PAH patients together. This strategy has the advantage of facilitating patient recruitment, but the patients might not be biologically similar, and etiology might modify treatment effect.
- Do separate studies in each PAH subgroup. However, this approach is resource intensive, and the results of studies done in selected populations might not be generalizable to a broader population.
- Generalize in some cases, and do prototype studies in designated subgroups.

Recommendations. The pivotal studies in PAH treatment have included mainly subgroups within Group I. These patients share sufficient pathophysiologic and pathobiologic similarities that they might reasonably be grouped together in future studies (9,12,13). Recognizing that some compromise is necessary, the U.S. Food and Drug Administration (FDA) has not required significant effects within each Group I subgroup and is likely to continue to approve global indications on the basis of such trials.

Patients in Groups II through V (i.e., those with non-PAH pulmonary hypertension [PH]) should be studied in individual subgroups. The BREATHE-5 trial, in patients with Eisenmenger syndrome, a Group I subgroup, showed that such subgroup study is feasible and can be productive, despite logistical complications (11).

Patients with sickle cell disease, portopulmonary hypertension, or chronic thromboembolic pulmonary hypertension (CTEPH), who were underrepresented in the pivotal trials, represent unique challenges that compel separate investigative approaches (14,15). Substantial numbers of patients have sickle cell disease, although this is a heterogeneous group and might be difficult to study. As for patients with portopulmonary hypertension, they have been excluded from all studies, with the exception of the ALPHABET (Arterial Pulmonary Hypertension and Beraprost European Trial) (16), because of concerns for hepatic toxicity and the fact that the treatment algorithm incorporates consideration of liver transplantation early in the disease. Nonoperable CTEPH patients present a large collective. Although CTEPH patients have rarely been included in studies (6), the recent BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension) trial, which enrolled 157 patients with CTEPH, demonstrated the feasibility of such a study design (17). However, there remains an urgent need for evidence-based decision-making for the pharmacologic treatment of these patients.

It is possible that enrolling such subpopulations into clinical trials on the basis of a presumed pathogenesis might not be productive and that a lack of rigorous entry criteria could dilute treatment effect or even, in some cases, be unsafe. Therefore we need to continue to expand our knowledge of PH in these non-PAH groups and exercise restraint in enrolling these patients in RCTs until we know more about their disease.

End Points in RCTs of PAH

Primary and secondary end points. Primary end points in PAH trials, as in other RCTs, must meet 3 criteria; they should be: 1) clinically relevant; 2) sensitive to treatment effect; and 3) measurable and interpretable. Secondary end points complement the primary end points by providing a more global view of the benefit of the drug being tested and by clarifying its risk-to-benefit ratio. Secondary end points may be of 2 types: 1) those that, like primary end points, are clinically relevant and may be taken into consideration for drug indications; and 2) "feel-good" end points, which are not likely to lead to a new indication or a change in labeling but might provide reassurance about the primary end point along with new information about the disease. Some secondary end points might be exploratory analyses (i.e., although they might demonstrate biologically plausible

effects, they remain hypothesis-generating and will need to be confirmed by additional studies).

Exercise testing. Exercise capacity is one of the most important prognostic indicators in PAH. Several exercise protocols have been used in PAH assessment protocols (Table 1) (5,6,16,18–24). Of these, the 6-min walk (6MW) test has been accepted by regulatory agencies and is most commonly used as a primary end point in RCTs. The 6MW test correlates fairly well with peak aerobic capacity (25). It also has prognostic significance in PAH (26), and it can be performed simply and inexpensively. However, within-subject variability has been seen in the 6MW test, with repeat testing on the same day resulting in a 66-ft improvement in a study of patients with chronic obstructive pulmonary disease (27), an 18-m improvement on 2 successive days in post-myocardial infarction patients (28), and a 4.2% change in patients with interstitial lung disease after 1 week (29). In addition, the 6MW test might be less discerning in patients who are less ill (30). Drug effects on the 6MW test tend to be slow to manifest and modest (10% to 15%) and might not provide an accurate reflection of how patients really feel. Therefore, regulatory authorities are open to assessments of exercise capacity beyond the 6MW test, and these have been and continue to be explored (31).

Cardiopulmonary exercise testing (CPET) measures metabolic gas exchange at rest and during exercise. It quantitates aerobic capacity and ventilatory inefficiency in order to determine the severity of PAH (32) and might provide more sensitive exercise assessment than the 6MW test early in the course of the disease (33). It might also provide a more complete physiologic assessment of the pulmonary vasculature (32). The CPET is expensive and has proven to be technically challenging to perform and interpret in the setting of a multicenter RCT. Nevertheless, because exercise capacity measured by CPET (peak oxygen consumption) is prognostic in PAH patients (34), it has been used as a primary end point in 2 clinical trials (20,35). In the STRIDE-1 (Sitaxsentan To Relieve Impaired Exercise) multicenter trial, however, effects on peak oxygen consumption did not correlate with effects on the 6MW test, probably due to technical difficulties in the CPET protocol and equipment (36).

Exercise duration at a constant work rate has been proposed as an alternative to the 6MW test, because it might be more sensitive to changes in aerobic capacity (37). Treadmill and cycle ergometry have been successfully used as end points in PAH trials (38–40).

Recommendation. Although the 6MW test has been the most common primary end point in clinical trials and its use has led to the approval of many agents by regulatory authorities, several questions remain, including: 1) What is a clinically relevant improvement in 6MW test? 2) How should variables that are known to affect the 6MW test, such as age and height, be factored into this end point? 3) Is the 6MW test still a sensitive exercise test as we study patients earlier in the course of the disease?

Regardless of the type of assessment, some evaluation of change in exercise capacity will continue to be an important outcome measure in ongoing trials, if only as a secondary end point, and additional and more sensitive methodologies should be explored.

Time to clinical worsening. Recent studies in PAH have been similar in design, with exercise capacity as a primary end point, and with a blinded phase ranging from 3 to 6 months and, in 1 case (20), to 12 months. Because of the low event rate, mortality alone would not be an adequately powered end point in this setting. Therefore, a composite end point, time to clinical worsening (TtCW), has been developed and is generally included as a secondary end point.

Different definitions of TtCW have been used in different studies (5,20,22,24,35,41–44), making comparison difficult (Table 2). However, common components have been time-from-randomization to: 1) all-cause mortality; 2) hospital stay for PAH; 3) need for interventional procedures (transplantation or balloon atrial septostomy); and 4) clinical progression of PAH. Some definitions of TtCW have also included a combination of deterioration of 6MW test distance from a baseline of 10% to 20%, an increase in New York Heart Association/World Health Organization (NYHA/WHO) functional class, symptoms of right heart failure, and/or escalation of medical treatment. In considering a single definition of TtCW, the following definitions are possible:

- Only all-cause mortality and hospital stays for PAH. Despite the fact that thresholds for hospital stay might differ according to geographic areas and health sys-

Table 1 Functional Capacity Assessments

Test	Advantages	Disadvantages
6-min walk	• Inexpensive • Technically simple • Useful in large groups of patients	• Subject to patient effort • Unable to measure gas exchange, ventilatory efficiency
Formal exercise testing (treadmill, cycle ergometry)	• Most familiar	• Unable to measure gas exchange, ventilatory efficiency
CPET	• Provides objective measurements of peak metabolism and rate of exertion of ventilatory and circulatory reserves • Reproducible	• Technically more difficult
NYHA/WHO classification	• Simple, large body of scientific literature	• Subjective

CPET = cardiopulmonary exercise test; NYHA/WHO = New York Heart Association/World Health Organization.

tems, hospital admission for PAH progression is usually considered to be an objective measure of deterioration (45).

- Adding interventional procedures to death and hospital stay. However, the availability of such procedures might also vary from country to country, and in any case, they are very rarely performed in the setting of RCTs.
- Inclusion of an additional event, defined as progression of PAH that does not require hospital stay. This category might include progression of NYHA/WHO functional class, symptoms of right heart failure, and the need for additional therapies, as determined by the physician/investigator.

Because TtCW should be used only in blinded trials, disease progression might be a subjective and therefore a weak end point. To address this, the physician/investigator could be required to provide "measurable" parameters for supporting the definition of PAH progression or the decision to increase medical therapy.

As with all composite end points, the U.S. FDA has expressed concern about TtCW. Although they have accepted it as a primary end point, they have suggested that it could be more useful if it were possible to assign a numerical value to each component, on the basis of community input. They have also suggested that total events is a broader, more inclusive, and therefore stronger end point than time to first event.

Recommendations. We recommend that a uniform definition of TtCW be used in future pivotal (phase III) RCTs in PAH. In the definition of TtCW, hard events would include:

- All-cause mortality
- Nonelective hospital stay for PAH (with predefined criteria, usually for initiation of intravenous prostanoids, lung transplantation, or septostomy)
- Disease progression defined as a reduction from baseline in the 6MW test by 15%, confirmed by 2 studies done within 2 weeks plus worsening functional class (except for patients already in functional class IV)

We strongly suggest that, in all cases where TtCW is used as a primary end point in an RCT, some adjudication of events should be mandatory.

There might not be sufficient numbers of patients in phase IIb trials to use the TtCW end point. In these kinds of trials, some type of exercise assessment should be used, along with secondary confirmatory end points, to include hemodynamic data for new therapies. In phase III or pivotal trials, however, we recommend TtCW as a primary end point, with assessment of exercise ability as a secondary end point. Trials with TtCW as a primary end point will likely need to be of longer duration than typical 12- to 16-week trials that have used 6MW test as a primary end point. This strategy would be acceptable to regulatory authorities.

Quality-of-life assessments. A variety of instruments have been developed to measure outcomes in PAH. Dyspnea is the most frequent complaint for which persons with PAH seek medical attention, and numerous instruments exist to evaluate dyspnea during exercise and activities of daily living (46–52). The Borg score (53), developed in 1982, has been shown to be responsive to interventions aimed at reducing dyspnea as well as to therapeutic intervention in most PAH RCTs.

Global and health-related quality-of-life measurements are also used to evaluate patient perceptions of treatment effect. Those that have been used with PAH patients include the St. George's Respiratory Questionnaire (54), the Minnesota Living with Heart Failure questionnaire (55), the Chronic Heart Failure Questionnaire (52), and a general-health questionnaire, the Medical Outcomes Study Short Form-36 (56). In general, congestive heart failure-specific instruments have performed better than general health instruments in PAH patients. Two groups have now started to develop a quality-of-life instrument specific to PH (including collagen vascular disease) that will address concerns that have not been addressed in nondisease-specific instruments (57,58).

Regulatory agencies respond differently to these kinds of instruments. The European Medicines Agency might regard them more favorably than the FDA, although both organizations regard them with caution. The FDA has expressed concerns that this end point is too amorphous and needs validation, particularly if it is not consistent with the

Table 2 Definition of Time to CW in Different Trials

Component	BREATHE-1 & 351 (5,41)	EARLY (42)	STRIDE-1 (35)	STRIDE-2 (22)	ARIES-1 (43)	ARIES-2 (43)	SUPER-1 (21)	STEP (23)	PACES (44)
Death	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hospital stay	✓	✓		✓	✓	✓	✓	✓	✓
Lung transplantation	✓		✓	✓	✓	✓	✓	✓	
Atrial septostomy	✓		✓	✓	✓	✓			
Symptomatic progression (NYHA/WHO FC)	✓	✓		✓	✓	✓			
Lack of improvement or worsening PAH (±6-min walk)	✓	✓		✓	✓	✓		✓	
Need for additional PAH therapy	✓		✓	✓	✓	✓	✓	✓	✓
p value	<0.05	<0.05	NS	NS	NS	<0.05	NS	<0.05	<0.005

CW = clinical worsening; NYHA/WHO FC = New York Heart Association/World Health Organization functional class; PAH = pulmonary arterial hypertension.

primary end point. The FDA is also concerned that cultural differences, different types of assessments, and patient interpretation might affect the outcome. To date, only 5 RCTs in PAH have used health-related quality-of-life instruments.

Recommendations. Some evaluation of quality of life is important. There is a need to develop and validate in multicultural fashion a disease-specific questionnaire that will be acceptable to both the FDA and the European Medicines Agency as a secondary end point in future trials.

Imaging and hemodynamic assessment. Hemodynamic data are not currently accepted as an end point for regulatory authorities. Nonetheless, these data provide valuable information, because the functional capacity of the right ventricle is a major prognostic determinant in PH, and death from PH usually results from right ventricular (RV) failure (59–62). Therefore, techniques that image RV morphologic and functional change in the face of increasing outflow obstruction can greatly advance our understanding of the disease. Such techniques include echocardiography, computed tomography, radionuclide ventriculography, and cardiac magnetic resonance imaging (CMRI).

NONINVASIVE. Echocardiography is routinely used for assessing RV size and function and severity of PH. In 1 RCT (63), advanced PAH therapy improved many echocardiographic variables, including left ventricular (LV) area, systolic eccentricity index, RV/LV diastolic areas ratio, pericardial effusion score, RV ejection time, Doppler RV index, LV stroke volume and cardiac output, and parameters of LV filling. Improvements in exercise capacity were also related to echocardiographic changes. Thus, this technique is sufficiently sensitive to clinical changes to be used as a reinforcing end point. However, standardization of echocardiographic measurements, some of which can be highly technical, would be necessary to consider this as an end point in clinical trials. Two indexes that might be considered include the Tei Index and tricuspid annular plane systolic excursion (64,65). Although there is substantial interest in exercise stress echocardiography, particularly in early disease, this study is difficult to perform and interpret. Similarly, although 3-dimensional echocardiography might improve our understanding of the pathophysiology of RV failure in PAH, it has been minimally evaluated in PAH patients.

CMRI is a safe and reproducible technique that allows both morphologic and functional assessment of the right ventricle (66). CMRI findings in PAH include RV dilation, RV hypertrophy, interventricular septal flattening or paradoxical motion, and change in RV chamber morphology from a normal crescent shape to a more concentric form. Stroke volume, cardiac output, and distensibility of pulmonary arteries can also be assessed (67–69). CMRI imaging has not been validated to measure pulmonary vascular resistance, but good correlation between right heart catheterization and CMRI suggests that CMRI data could be used as a surrogate for right heart hemodynamic status. Preliminary data suggest that the prognostic importance of CMRI measurements in PAH includes low stroke volume, RV dilation, and impaired LV filling (70). Furthermore, because this technique is noninvasive, it can be used repeatedly to determine disease progress or response to therapy. Technical improvements in CMRI allow increasingly rapid and robust data acquisition.

In the SERAPH (Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension) study in patients with idiopathic PAH, changes in RV mass measured by CMRI were a primary end point (71). CMRI is now considered the gold standard for detailed study of the right ventricle and an established modality for the physiologic assessment of PAH patients in cross-sectional and longitudinal follow-up studies of therapy. It will likely be increasingly used as the primary modality for anatomic and functional assessments that will enable more complete and efficient evaluation of patients with PAH (72).

INVASIVE. Right heart catheterization, an invasive procedure, provides measurements of systemic blood pressure and saturation, pulmonary arterial pressure and saturation, pulmonary capillary wedge pressure, right atrial pressure, and cardiac output by thermodilution or Fick method if oxygen consumption is measured. The hemodynamic definition of PAH is based on catheter measurements, which are accurate and reproducible and, because the measurements are less noisy than noninvasive imaging, require fewer patients to power clinical trial end points. In addition, the data obtained have been shown to be prognostic (59). However, the fact that these measurements are made at rest rather than during exercise—when patients develop symptoms—limits its usefulness, as do procedural concerns, potentially including a need for dehydration after an overnight fast and sometimes the need for sedation. Some of the measurement techniques also have particular limitations. Despite these limitations, routine right heart catheterization provides a simple description of resting hemodynamic status that can be interpreted in the context of the underlying disease process.

Recommendations. Imaging of the right ventricle, either by echocardiography or CMRI, often provides clinically useful information to the experienced clinician caring for an individual patient. Similarly, invasive hemodynamic measures of RV function, particularly right atrial pressure and cardiac index, provide important clinical information and insight into disease progression. RV function has potent prognostic abilities, and it is reasonable to consider indexes of RV function as secondary end points in pivotal clinical trials.

Hemodynamic measures provide a rational basis for decisions on dose range and dosing intervals. At a minimum, these should be included in Phase II trials and should be considered as exploratory secondary end points that advance our understanding of PAH. They will very likely not be primary end points for registration in the foreseeable future.

Biomarkers. Echocardiography, CMRI, or right-heart catheterization provides accurate assessment of RV function, but right heart catheterization is invasive, and all these

modalities are costly. Therefore, various biomarkers have been increasingly explored to assess cardiac function in PAH patients. These include the cardiac hormone brain natriuretic peptide (BNP), a highly sensitive and specific marker of LV failure; however, levels of brain and atrial natriuretic peptides also seem to correlate with RV dysfunction (73–75). Many clinicians routinely order an assay for BNP or the inactive N-terminal-pro-fragment, NT-proBNP, in the setting of PAH or congestive heart failure. Measurement of NT-proBNP is preferred over BNP, because it is more stable both in vivo and in vitro than the active BNP molecule (76). Levels of NT-proBNP of approximately 1,400 to 1,700 ng/l^{-1} seem to suggest a poor prognosis (74,77). The NT-proBNP is now commonly used in congestive heart failure and PAH (78). The NT-proBNP levels also correlate with survival (74,77,79). Therefore, it might be reasonable to include NT-proBNP as a secondary end point in RCTs of PAH.

Acute RV strain might also be reflected in troponin elevation in patients with PH or CTEPH. Although the majority of stable patients with PAH do not have abnormal troponin values, measurement of troponin levels could improve prognostication in more advanced patients. In spite of similar hemodynamic status, patients with elevated troponin levels in 1 study had higher heart rates, shorter 6MW distances, lower mixed venous oxygen saturations, and higher NT-proBNP levels; all were statistically significant compared with normal troponin values (80).

Serum uric acid levels are increased in obstructive pulmonary disease (81), Eisenmenger syndrome (82), and other hypoxemic settings (83). Serum uric acid levels increase in proportion to the severity of idiopathic PAH, in which they also have a strong independent association with mortality (84). In functional class III patients with idiopathic PAH, serum uric acid levels and diastolic blood pressure at peak exercise independently predicted survival ($p < 0.005$) (34). Serum uric acid levels are readily available; however, they are somewhat nonspecific and might be affected by variables such as acute illness, drugs, tissue perfusion, decreased glomerular filtration, and hypoxia. Nevertheless, in PAH, in the absence of other causes of hypoxemia, uric acid levels might contribute to prognostication (84).

Other biomarkers that might potentially be useful in patients with PH are D-dimer levels (85), endothelin-1 (86), nitric oxide (87), prostaglandins (88), and cyclic guanosine monophosphate (89). Although these show promise, studies to date have been too small to be conclusive, and practical considerations currently preclude their routine use. Further studies are needed.

Although biomarker end points are important in clarifying our understanding of PAH, it is unlikely that they will be accepted by regulatory authorities as primary end points in registration trials in the foreseeable future.

Summary of end point recommendations. Although we believe TtCW to be an important, clinically relevant primary end point in the modern era, we realize that Phase II trials might not be large enough or of sufficient duration to detect a meaningful difference in TtCW. For Phase II trials, we recommend the 6MW test as a primary end point and encourage the inclusion of hemodynamic status as a secondary end point. For Phase III trials, we recommend TtCW as the primary end point. A number of the secondary end points discussed in the preceding text might also be studied in a Phase III trial. We suggest choosing a few but caution against including too many secondary end points.

Clinical Trial Design

The RCT environment is becoming increasingly complex. Six therapeutic agents have been approved for PAH in the U.S. and 7 in Europe, and many patients are already receiving some kind of approved therapy when they enroll in RCTs. Therefore, these trials increasingly involve add-on therapy. Several designs have been proposed and/or used for future RCTs in the PAH populations:

- Placebo-controlled monotherapy or add-on trials. Placebo-controlled trials are still considered to be among the strongest designs to evaluate new therapies. However, because many patients are already receiving or have access to some type of approved therapy, placebo-controlled monotherapy trials might be considered unethical (90,91). Nevertheless, because of the lack of evidence regarding the efficacy of advanced therapies in non-WHO Group I populations (e.g., patients with chronic obstructive pulmonary disease or interstitial lung disease, CTEPH, or PH due to diastolic dysfunction of the left ventricle), it is reasonable to consider enrolling these patients in placebo-controlled monotherapy RCTs. Placebo-controlled RCTs might be reasonable as well where the new treatment is added to standard therapy and is compared with placebo added to standard therapy.
- Noninferiority studies. Another approach might be to perform head-to-head comparisons by conducting noninferiority studies. A noninferiority study aims to demonstrate that the tested drug is not worse than the comparator by more than a prespecified, small amount, known as the noninferiority margin. The size of an acceptable margin depends on the smallest clinically significant difference, expected event rates, the established efficacy advantage of the control over placebo, and regulatory requirements. Noninferiority trials are statistically based on a 1-sided comparison with an active control in the positive direction. This trial design is useful in cases where: 1) bioequivalence cannot be established, as in modified-release products or topical presentations; 2) new products have a potential safety advantage, and therefore a risk-benefit assessment can be made; 3) a direct comparison against the active comparator is needed to assess risk-benefit; 4) no important loss of efficacy compared with the active comparator would be acceptable; and 5) a placebo arm is not possible, and an active control trial is required to demonstrate the efficacy

of the tested drug. In noninferiority studies, new end points can be used only along with primary end points already investigated—in PAH, the 6MW test. They must also replicate the setting of the pivotal study of the comparator (i.e., inclusion and exclusion criteria, patient population). One of the obstacles in conducting these trials is the sample size, which would often need to be >500 patients, which limits the feasibility of such a study, both in terms of cost and patient recruitment. Thus, noninferiority studies have a number of inherent weaknesses, and they have not yet been used in PAH registration studies.

- Withdrawal trials**.** The current standard of therapy for PAH usually involves initial use of oral endothelin antagonists or phosphodiesterase-5 inhibitors for patients in NYHA/WHO functional classes II and III and parenteral prostanoids for patients in class IV. Several RCTs have shown benefit when a second drug is added to the background of a single drug (23,92–95), but others have not (96). It is not known whether the benefits seen in some of these trials would have been seen had the first drug been withdrawn at the time the second drug was added. Because most agents do not have a progression claim, it might not be unethical to withdraw them, although there are some safety concerns. However, the FDA feels that there should not be a problem in a placebo-controlled setting where an investigator can withdraw a patient who is not doing well.

Induction therapy. Pulmonary vascular disease is very aggressive, and late therapy might be disadvantageous. Data show that patients randomized to placebo groups never really catch up: delaying therapy even 12 to 16 weeks might be injurious (97,98). Possible strategies might involve earlier treatment with parenteral prostanoids for patients in most NYHA/WHO classes, simultaneous initiation of 2 or more oral drugs or an oral drug in combination with an inhaled or a subcutaneous drug, simultaneous IV prostanoid therapy and 1 or more nonparenteral PAH drugs, or simultaneous use of 1 PAH drug from each category of pathologic targets. Objections to such strategies concern the potential for drug interactions or toxicity, the costs of PAH drugs, the need for end points other than the 6MW test (99), and the current lack of evidence-based information on drug combinations.

Recommendations. Various approaches to combination PAH therapy need to be explored in detail in well-designed RCTs. Head-to-head trials in which 2 drugs would be used both separately and in combination would be highly appropriate in the PAH population and would respond to many of the aforementioned objections. However, it will not be easy to garner industry support for such trials, because of the large numbers of patients required.

Adaptive design. Standard monitoring procedures for RCTs specify a primary end point and a test statistic to be used for the primary analysis before the initiation of the trial. The false positive error rate for the null hypothesis and the statistical power to detect the targeted size of treatment effect are also pre-specified. Adaptive monitoring procedures were developed in an attempt to streamline drug development without compromising safety. In contrast to standard procedures, adaptive procedures attempt to allow modification of pre-specified design features in the course of a trial, on the basis of early efficacy and safety findings. For example, at an interim analysis, if the effects of the drug being tested are modest and it seems that the effect size required for statistical significance will not be achieved, some adaptive procedures have been proposed to enable changing the sample size.

The primary goal of clinical research is to obtain a timely and reliable evaluation of the benefit-to-risk profile of an experimental intervention in order to provide benefit to public health (100). With that as a guiding precept, one might post the following objections to the use of these adaptive designs:

- One must be very cautious about using approaches that propose to allow development of hypotheses in the same data set used to confirm them.
- If additional patients are enrolled as the result of modest effects seen at interim analysis, the second stage of the trial would be "artificially" down-weighted, leading to a less efficient clinical trial and making interpretability more difficult.
- Early results are often quite unreliable. Hence, use of interim efficacy and safety data to redesign the trial might lead to making very inappropriate changes.
- Interim results regarding effects on efficacy or safety measures should be available only to the Data Monitoring Committee, to preserve the integrity and credibility of the trial. Adaptive measures that allow redesign of the trial on the basis of interim efficacy or safety data might put the integrity and the credibility of the trial at risk. This breach also reduces the flexibility to use results from external sources that emerge during the trial to alter key design features.
- If the sponsor considers early results to be sufficiently informative or reliable to warrant design changes, would there be an ethical obligation to provide patients access to this information as well?
- The use of the adaptive designs overemphasizes the importance of statistical significance relative to the importance of clinical significance. It is not adequate to rely on statistics to define a clinically significant effect.
- Finally, standard monitoring procedures already provide substantial flexibility to adapt to unexpected findings, while maintaining the integrity and credibility of the trial.

Conclusions

At the same time that the number of pharmacologic agents with potential for benefit in PAH continues to grow, new and improved modalities for measuring outcomes in RCTs

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continue to emerge. Randomized controlled trials must now be designed that will yield robust and reliable data on the safety and efficacy of these new treatment options. The identification of appropriate end points for these trials is an integral part of that process. Some measure of exercise testing, time to clinical worsening, hemodynamic markers, and quality-of-life assessment will be among those end points. However, although experts can and must make recommendations, ultimately, agreement on optimal end points for RCTs in PAH will involve collaboration between clinicians, investigators, regulatory authorities, and industry.

In the short term, new therapies will undoubtedly continue to extend our patients' lives and improve their quality of life. Our long-term goal—to reverse remodeling and achieve a cure for this devastating disease—has not changed. We continue to improve our understanding of the disease and to find better ways of treating it, and although our long-term goal is not yet within reach, we have reason to believe that the likelihood of its achievement is substantially increased.

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