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End-points and clinical trial design in pulmonary arterial hypertension: have we made progress?

A.J. Peacock*, R. Naeije#, N. Galiè¶ and L. Rubin+

ABSTRACT: There is enormous interest in the treatment of pulmonary arterial hypertension (PAH), so it is appropriate to consider the design of trials of new therapies and the end-points to be measured when trying to decide whether or not a therapy is effective.

In May 2003, the first meeting devoted solely to the discussion of end-points and trial design in PAH was held in Gleneagles, UK. At that time, most of the randomised controlled trials in PAH had used 6-min walking distance and/or resting haemodynamics as their primary end-points.

The present article considers the progress that has been made since 2003. It deals with aspects of clinical trial design (such as noninferiority, superiority and withdrawal trials), considers end-points used in previous and current studies (such as 6-min walking distance, time to clinical worsening, haemodynamics, imaging and plasma brain natriuretic peptide), and considers what end-points might be used in the future.

The second end-points meeting was held in Turnberry, UK, in June 2007. It had a similar format to the first meeting. Much of what is presented here is a summary of the workshops from that meeting. An attempt has been made to both summarise the current state of end-points and trial design and suggest new ways in which they could be improved. The present article forms one of a series being published in the *European Respiratory Journal* on pulmonary hypertension.

KEYWORDS: Clinical trials, end-points, pulmonary arterial hypertension, trial design

Between 2000 and 2007, >2,000 patients with pulmonary arterial hypertension (PAH) were randomised into placebo-controlled trials, or, in the case of epoprostenol, a comparison with conventional, *i.e.* non-disease-targeted therapy. At the time of writing, the results of most of these trials have been published and seven therapies are now licensed for PAH. This is remarkable success by any medical standard and has led, in turn, to many more trials of new therapies, combinations of therapies and therapies given at time-points earlier in the course of the disease. However, there is rightly concern that these trials are well-designed and use end-points that adequately reflect the success or failure of the new approaches. Given the interest in the treatment of PAH, it is appropriate to consider the design of trials of new therapies or combinations of therapy for pulmonary hypertension, and also to consider the end-points to be measured when trying to decide whether or not a drug or combination of drugs is effective.

AFFILIATIONS
*Scottish Pulmonary Vascular Unit, Regional Heart and Lung Centre, Golden Jubilee National Hospital, Glasgow, UK,
#Dept of Pathophysiology, Faculty of Medicine, Free University of Brussels, Brussels, Belgium,
¶Institute of Cardiology, University of Bologna, Bologna, Italy, and
+Division of Pulmonary and Critical Care Medicine, University of California, San Diego School of Medicine, La Jolla, CA, USA.

CORRESPONDENCE
A.J. Peacock
Scottish Pulmonary Vascular Unit,
Regional Heart and Lung Centre
Golden Jubilee National Hospital
Glasgow G81 4HX, UK
E-mail: apeacock@udcf.gla.ac.uk

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In May 2003, the first meeting devoted solely to the discussion of end-points and trial design in PAH was held in Gleneagles, UK. The format of the meeting was a series of workshops for each of the end-point areas. Their deliberations were subsequently published in the *European Respiratory Journal* [1]. At that time, many of the randomised controlled trials in PAH had used the 6-min walking distance (6MWD) and/or resting haemodynamics as their primary end-points. The validity of these end-points was considered, as was what other end-points might be of equal or greater value in the future. At the Gleneagles meeting, an end-point was defined as ''a measurement used by investigators conducting a drug trial to determine whether patients with pulmonary hypertension would benefit by drug administration'' [1]. It was considered that end-points should have certain ideal characteristics and that some fell short of these ideals.

An ideal end-point might have the following characteristics: 1) it should be heart- or lung-specific; 2) it should be abnormal in PAH; 3) information collection should be simple; 4) the markers should be easy to measure; 5) values should be reproducible and the variation in normal subjects known for comparison with PAH patients; 6) values should follow the course of the disease (by deteriorating if the patients deteriorate and improving if the patients improve); and 7) abnormal values should be indicative of poor survival.

The present article considers the progress that has been made since 2003. It deals with some aspects of clinical trial design, considers end-points used in previous and current studies and how these end-points fulfil ideal characteristics, and considers which end-points might be used in the future. The second end-points meeting was held in Turnberry, UK, in June 2007. It had a similar format to the first meeting. Much of what is presented here is a summary of the workshops from that meeting, with recommendations for the future conduct of trials in PAH.

Treatments for PAH are always expensive, sometimes invasive and carry significant side-effects. In order to convince patients, treating physicians, funding agencies and regulatory bodies of the value of treatment, it is, therefore, extremely important to conduct trials of appropriate design using end-points of appropriate quality.

The present article forms one of a series being published in the *European Respiratory Journal* on pulmonary hypertension [2–7].

END-POINTS IN TRIALS OF THERAPY FOR PULMONARY ARTERIAL HYPERTENSION

The most usual primary end-point in previous trials has been the 6MWD. However, in current trials, additional end-points, such as time to clinical worsening (TTCW), biomarkers and quality of life, are also being used. This change reflects the fact many people feel that the traditional end-points (*e.g.* 6MWD) are not sufficiently robust to describe the effect of therapy. When considering these issues, some definitions must be developed as follows.

A primary end-point is one that is clinically meaningful. In the context of PAH, the most clinically meaningful end-point is survival, but, in the current treatment era, it is considered unethical to withhold treatment from a sick patient, and so it is unlikely that survival trials will be performed in the future. Another clinically meaningful end-point is exercise tolerance. Most trials have measured exercise tolerance using the 6MWD. There are advantages and disadvantages to the 6-min walking test (6MWT) (see below).

A secondary end-point is also called a surrogate end-point [8]. These may be haemodynamic variables, blood biomarkers, imaging results, quality of life or others. Both the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) permit the use of surrogate end-points for the licensing of drugs for PAH, but they must be convinced that the end-point predicts clinical benefit based on epidemiological, therapeutic or pathophysiological evidence. The strengths of secondary (surrogate) end-points are as follows: 1) they are usually continuous variables, meaning that smaller numbers are required for adequately powered studies than for categorical end-points (*e.g.* survival); 2) they can be repeated over time and rate of change incorporated; and 3) they may shed light on the mechanism of disease and be more biologically relevant than a clinical end-point. The disadvantages of secondary (surrogate) end-points are as follows: 1) the treatment may improve the secondary end-point but not improve the patient; and 2) secondary (surrogate) end-points may miss an important change, *e.g.* because they are performed at the wrong time.

Many clinicians, including the authors of the present article, feel that the current end-points used in clinical trials in PAH are not as relevant as they might be. This frustration has recently been articulated [9]. Although some may come to the view that the only thing that really matters is quality of life, and that all other end-points are simply surrogates, this does not appeal to clinicians with physiological training, who feel that, in PAH, the problem lies primarily in the small peripheral arteries of the pulmonary circulation and secondarily in the right heart. For most treating physicians, a therapy that influences neither of these two variables, even if it improves quality of life, is not the way forward.

What is clear, however, is that, since the trials of currently licensed therapies mostly used a combination of the 6MWD, functional class and haemodynamics, all new studies will probably require significant improvements in one or more of these variables before they are approved. Any new end-point would probably need to be tested alongside traditional end-points and shown to be demonstrably better if it is to be considered a primary or first-level secondary end-point in the future. It is worth now considering the various end-points that have been or could be used in the assessment of patients with PAH.

Exercise testing

The most common symptoms of patients with PAH are shortness of breath and fatigue. These symptoms initially appear only on exercise and it is only later that they are present at rest, as the patient makes the transition from World Health Organization (WHO) class II through III to class IV. The progressive nature of the symptoms as a consequence of the haemodynamic derangement is shown in figure 1. From this diagram, it is clear that, in the initial stages, as the peripheral pulmonary arterial disease develops, pulmonary arterial pressure rises but cardiac output is maintained. At this point, there are no symptoms. Later, as pulmonary vascular

resistance increases, symptoms develop on exercise because the cardiac output cannot rise with exercise. Finally, in the later stages, although the pulmonary arterial pressure may not rise further, there is a decline in cardiac output because of the high outflow impedance, and symptoms occur even at rest. At this point, the pulmonary arterial pressure may indeed fall. This fall in pulmonary arterial pressure with advanced disease has confused the non-expert, who may feel that treatment has been effective because of the fall in pressure, when, in reality, the fall in pressure is a consequence of the diminishing cardiac output and cardiac reserve. Given that the cardiac output is so critical to the maintenance of well-being and cardiac failure is the normal mode of death, end-points need to reflect cardiac output and, in the absence of noninvasive measures of cardiac output, the best measure has been some form of exercise testing.

A measure of exercise capacity (6MWD) has been used in nearly all clinical trials in pulmonary hypertension. The 6MWD is really just a measure of steady-state exercise capacity. Measurement of the variables that are likely to be affected by pulmonary hypertension, namely physiological dead space, oxygen delivery to the tissues, arterial hypoxaemia and the early anaerobic threshold, necessitates full cardiopulmonary exercise testing (CPET).

6-min walking test

The 6MWD is a measure of functional limitation, and correlates loosely with peak aerobic capacity [10]. The test was originally developed as a measure of functional capacity in patients with heart disease. The 6MWD is of prognostic significance in PAH [11–13], and it is a relatively simple and inexpensive test. In addition, the 6MWD has been accepted by regulatory agencies as a primary end-point for drug trials when secondary end-points, such as WHO functional class, cardiopulmonary haemodynamics and/or TTCW, are supportive of clinical improvement.

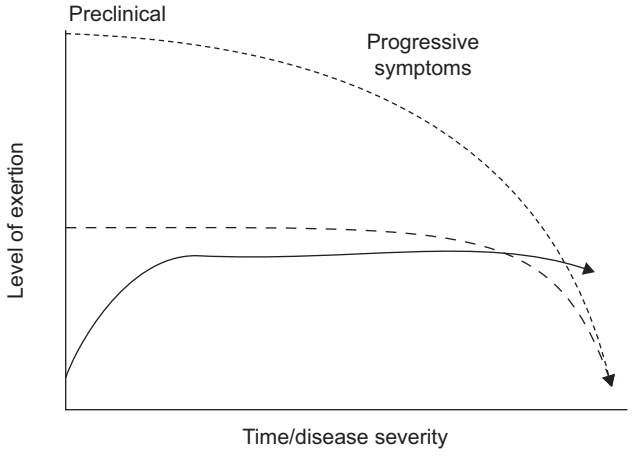

FIGURE 1. Disease progression in pulmonary arterial hypertension. In the early phase of disease, patients show an asymptomatic rise in pulmonary arterial pressure (———), with preservation of cardiac output at rest (– – – –) and on exertion (------). As the disease progresses, resting cardiac ouput remains stable but the ability to increase stroke volume and cardiac output on exercise is progressively impaired, resulting in progressive exertional symptoms. In the later stages of disease, advanced right ventricular failure results in a fall in resting cardiac output, with fatigue and breathlessness at rest and right heart failure.

Most of the PAH drug studies in which a significant change in 6MWD has been demonstrated have enrolled patients with advanced pulmonary vascular disease, in whom the 6MWD is at least moderately reduced and pulmonary vascular resistance is already severely elevated. In future studies of PAH treatments, patients may already be being treated and may have already realised gains in exercise capacity, which could limit the utility of the 6MWT in detecting a meaningful clinical benefit from additional treatment. Further, in patients with less advanced disease irrespective of treatment, it is unclear whether the 6MWT can be used to measure meaningful clinical improvements. This may be, in part, related to a ceiling effect [14], but may also be related to the inability of the 6MWD to describe the nature of the physiological abnormalities of pulmonary vascular disease. An example of the ceiling effect was seen in the Endothelin Antagonist tRial in miLdlY symptomatic PAH patients (EARLY) study of bosentan in patients with less-symptomatic disease (functional class II), in whom the drug did not improve the 6MWD [15] but did prevent clinical worsening.

Although most clinical trial protocols for PAH treatments and consensus guidelines have outlined the methodology for the performance of the 6MWT, it is not universally standardised among medical centres. It is likely that most PAH specialty referral centres perform an unencouraged test; however, some may not be unencouraged, and this may affect the results. A lack of standardisation of normal values for the 6MWD may also affect the interpretation of 6MWT results. In most patients, factors such as stride length, body weight and walking skills may be more important determinants of 6MWD than aerobic capacity [10]. In addition, the 6MWT may fall short in young and old patients, and/or in patients with conditions in which lung gas exchange may be affected, such as interstitial lung disease. Normalisation of the test and standardisation of a formula for calculating percentage predicted 6MWD based on age, height, weight, *etc.* may improve its usefulness [16].

Cardiopulmonary exercise testing

CPET is a comprehensive exercise test that measures cardiopulmonary performance at rest and during exercise [17]. CPET is of prognostic significance in PAH patients [18], and can help determine the physiological nature of a patient's limitation when the diagnosis is in question [19, 20]. In patients with PAH, the hallmark abnormalities found on CPET are: 1) an abnormally high ratio of ventilation to carbon dioxide production; and 2) a low end-tidal carbon dioxide tension [17], termed ventilatory inefficiency. The reduction in peak oxygen consumption and increased ventilatory inefficiency correlate with PAH disease severity, in a pattern that reflects the blunting of the expected increase in cardiac output and perfusion of the pulmonary vascular bed during exercise, the pathophysiological trait of the disease. These measures track the physiological changes in response to therapy [21, 22]. Ventilatory inefficiency, measured by CPET in particular, may be useful in future clinical trials in patients with earlier and perhaps less-severe PAH. CPET has been used in one randomised controlled trial in PAH (the Sitaxsentan To Relieve ImpaireD Exercise (STRIDE)-1 trial of the endothelin

receptor antagonist sitaxsentan) but was not useful, probably because of technical failings of the measuring laboratories.

Additional measures of exercise capacity

Measurement of exercise duration at a constant work-rate may amplify the changes in exercise capacity with drug therapy [23]. Measurement of treadmill exercise time has been employed in smaller studies of PAH treatments as a primary [24–26] or secondary end-point [27] with favourable results. In PAH, exercise time may be a more sensitive method of detecting clinically relevant changes in patients with impaired exercise capacity; however, the magnitude of the change probably overestimates the improvement relative to what would be seen using the 6MWD as the measure of exercise capacity [28]. Nevertheless, in patients with less-severe disease or in those already treated with PAH drugs, measurement of exercise time may permit more sensitive tracking of exercise capacity [29].

Biological markers

The ideal biological marker would be one that directly reflected the ongoing activity of the disease process at the level of the pulmonary vasculature. Ideally, there would be a blood test that reflected increased or decreased vasoconstrictive and remodelling activity and this marker would be exquisitely sensitive to improvements rendered by new therapies. The currently available markers of vascular function are largely markers of endothelial cell and/or platelet dysfunction. Proteomic studies are underway, with the aim of identifying new PAH biomarkers [30]. None of these, on current evidence, can be used as end-points.

To date, the most useful markers have been those that monitor right ventricular dysfunction, in particular the natriuretic peptides but also, in the future, the stress-responsive transforming growth factor-β-related cytokine growth differentiation factor-15 [31]. It is known that stretching of the atria or the ventricles releases natriuretic peptides, particularly brain natriuretic peptides (BNPs). N-terminal-pro-BNP (NT-proBNP) can be measured in the peripheral blood, and its levels are less affected by acute activity than those of BNP and thus no special conditions of posture or rest are required. Serial measurement of plasma NT-proBNP is very attractive as an end-point. Its presence in the blood is related to the problem (*i.e.* right ventricular dysfunction), and it is simple and relatively cheap to measure. Some remarkable relationships between plasma BNP/NT-proBNP and various elements of right ventricular dysfunction have been shown. For example, BNP/NT-proBNP level is related proportionally to WHO class [32], pulmonary haemodynamics, including pressures and cardiac output [33], and also maximal oxygen uptake and 6MWD [34]. Improvements in haemodynamic function lead to improvements in BNP level [33, 35]. Deterioration in right ventricular function is associated with a rise in levels [36]. It would appear that BNP/NT-proBNP measurement is a dynamic measurement reflecting the current state of the right ventricle. Furthermore, there appears to be a threshold for severe cardiac dysfunction. For NT-proBNP, this has been shown to be ~1,400 $pg \cdot mL^{-1}$ whether measured by echocardiography [37] or by magnetic resonance imaging (MRI) [38]. BLYTH *et al.* [38] found that there was a linear relationship between levels of BNP and right ventricular function as assessed by cardiac MRI. This relationship was manifest only above the threshold and thus it would appear that BNP is a sensitive measure of the onset of right heart dysfunction before there are appropriate symptoms or signs. Thus it could be used as a screening test in patients with pulmonary hypertension in whom clinicians might be considering more aggressive therapy [38].

BNP/NT-proBNP levels are related proportionally to survival whether measured at baseline or at treatment follow-up [32]. Interestingly, serum troponin, usually a measurement of myocardial damage following myocardial infarction, is also related proportionally to survival [39]. From the above, it would appear that there are easily performed blood tests that can indicate the onset of right ventricular dysfunction and which may have the potential to track right ventricular dysfunction in both deteriorating and improving patients. Furthermore, this measurement is related proportionally to all of the relevant variables including survival, the ultimate end-point. Not surprisingly, this good press has meant that BNP or NT-proBNP levels are now used routinely in nearly all expert centres around the world and have been used in at least two clinical trials: the EARLY study of bosentan in functional class II patients [15]; and the ARIES (Ambrisentan in PAH – a phase III, randomized, double-blind, placebo-controlled, multicenter, efficacy study of ambrisentan in subjects with pulmonary arterial hypertension) study of ambrisentan. Further large scale studies are awaited in order to see whether or not these promises are fulfilled.

Haemodynamics

Invasive catheterisation of the right heart has been available for over one hundred years [40], and is still considered essential for the proper diagnosis and staging of patients with PAH [41–43]. Routinely, measurements of pulmonary arterial pressure and blood flow are made, permitting calculation of pulmonary vascular resistance. There are relationships between these measurements and clinical state, functional class, exercise capacity and prognosis [44–46], but these relationships are not tight For example, MIYAMOTO *et al.* [11] found that there was little relationship between pulmonary arterial pressure and 6MWD, and KAWUT *et al.* [47] found that haemodynamics were similar when comparing patients with primary pulmonary hypertension and those with connective tissue disease associated with pulmonary hypertension, even though survival was considerably worse in those with connective tissue disease. The main problems with routine right heart catheterisation as it is currently practiced are that the measurements are made: 1) with the patient supine and at rest; and 2) in unfamiliar and possibly frightening circumstances (the cardiac catheterisation laboratory).

A number of attempts have been made to try and improve the information available from invasive haemodynamics as follows.

1) Pressure–flow relationships. Use of single-point measures of pressure and flow to calculate vascular resistance can result in either underestimation or overestimation because of assumptions that are made about the zero crossing of the pressure–flow relationship. Multipoint measurements [48], performed at rest

and then on exercise, are better. It has been shown that patients who exhibit no change in pulmonary vascular resistance as measured by single-point estimation may indeed show a change in the slope of the line describing pressure *versus* flow, indicating that there has been improvement [49, 50].

2) Measurement of vascular properties. In pulmonary hypertension, there is change in the function of the vessel wall. REEVES *et al.* [51] measured a distensibility quotient called α and showed that, although there was no change in distensibility in acute hypoxic pulmonary hypertension, in chronic hypoxia or in an ageing subject, it decreased. BLYTH *et al.* [52] found a relationship between α, pulse pressure and survival in PAH. It also appears that the function of the major vessels can dictate prognosis. MAHAPATRA *et al.* [53] showed, in patients with idiopathic pulmonary hypertension, that pulmonary arterial capacitance as measured by stroke volume divided by pulmonary arterial pulse pressure was predictive of survival.

3) Ambulatory pulmonary arterial pressure. Given the concerns regarding single measurements of pulmonary arterial pressure, it is tempting to attempt to measure pulmonary arterial pressure over a prolonged period, preferably during normal physical activity. RAESIDE and co-workers [54–56] showed that pulmonary arterial pressure can more than double on exercise in patients with PAH or during sleep in patients with chronic hypoxic lung disease. These measurements are, however, specialised, requiring a micromanometer-tipped pulmonary artery catheter that is attached to an online processing system, and do not provide concurrent measurements of flow. Clearly, these measurements will be of use in validating other techniques rather than being widely used in the pulmonary hypertension community.

Ultimately, noninvasive techniques will be needed, particularly for the measurement of cardiac output since this is so fundamental in the assessment of status in patients with PAH.

Imaging

Echocardiography

Echocardiography was, and is likely to remain for some time, the most important screening tool for patients with suspected PAH [57, 58]. In most developed countries, a patient referred with unexplained breathlessness undergoes echocardiography. Abnormal echocardiographic findings are often the first indication of PAH, and these should prompt referral to a pulmonary hypertension centre. Using echocardiography, it is routinely possible to measure pulmonary arterial systolic pressure from the pressure difference across the tricuspid valve; the flow of blood in the pulmonary outflow tract; and the size of the cardiac chambers; and document the presence of a pericardial effusion.

Echocardiography has the appeal that it is widely available and relatively easy to perform and repeat, although considerable technical expertise is required for good and reproducible results. Some studies have also shown that echocardiographic variables are proportional to outcome. For example, RAYMOND *et al.* [59] showed that survival in patients with pulmonary hypertension was reduced when there was right atrial enlargement, septal shift or pericardial effusion. Since the usual measure of pulmonary arterial pressure quoted in the literature is mean pulmonary arterial pressure, attempts have been made to calculate this using echocardiography [60]. Indeed, there is a tight mathematical relationship between mean pulmonary arterial pressure and systolic pulmonary arterial pressure under all conditions, and it should thus be possible to calculate mean pulmonary arterial pressure from systolic pressure measurements made in the echocardiographic laboratory [61, 62]. Attempts have also been made to measure pulmonary vascular resistance by echocardiography. For example, ABBAS *et al.* [63] ''sought to test whether the ratio of peak tricuspid regurgitant velocity (TRV, ms) to the right ventricular outflow tract time–velocity integral (TVI(RVOT), cm)'' compared well with pulmonary vascular resistance measured by cardiac catheterisation and found that it did. However, none of this obviates the need for a right heart catheter in an established pulmonary hypertension centre to make a sound diagnosis. The right heart catheter measures all of the right-sided pressures and also the indirect left atrial pressure and cardiac output, variables which are difficult or impossible to obtain by echocardiography.

The main problem with echocardiography has been the semi-subjective nature of the findings, making objective analysis difficult. Additionally, several mathematical assumptions must be made in order to describe chamber size and shape and flow from two-dimensional measurements. Positive effects on echocardiographic variables including right ventricular size, left ventricular size, right ventricular systolic function and left ventricular early diastolic filling, were, however, confirmed in a study of the effects of bosentan [64].

Newer techniques, such as the systolic excursion of the tricuspid annulus, which is a measure of the longitudinal contraction (the dominant direction of contraction) of the right ventricle, amplification of echocardiographic signals by hypoxia, dobutamine or exercise, or the new technologies of three-dimensional echocardiography and tissue Doppler echocardiography [65–68] may alter perceptions, but, currently, the place of echocardiography is largely in screening.

Magnetic resonance imaging

MRI with a cardiac package permitting measurements throughout the cardiac cycle both at rest and on exercise is now held to be the gold standard in right heart imaging in patients with pulmonary hypertension. MRI is technically demanding, expensive and not always available. Some patients suffer claustrophobia, and the presence of a high-powered magnet means that patients cannot be studied with any sort of metal in place. It does, however, offer great possibilities as follows.

1) It can be used to measure right ventricular mass, which is likely to be a function of both right ventricular outflow impedance and other variables that promote muscular hypertrophy. Right ventricular mass relates well to mean pulmonary arterial pressure measured by catheterisation, particularly when mass is expressed as the ventricular mass index, *i.e.* right ventricular mass/left ventricular mass [69]. Currently, it appears that right ventricular mass changes little with therapy for pulmonary hypertension [70], but not enough is yet known to know whether this is a good or a bad thing. The studies conducted thus far that have assessed the effects of disease-targeted treatment on right ventricular mass have

variously found improvement [71, 72] or stability [72] of right ventricular mass with (apparently beneficial) therapy.

2) It can be used to measure chamber size of all four chambers during a cardiac cycle, at rest and on exercise. These measurements have shown that, when patients with pulmonary hypertension exercise, the normal increase in right ventricular stroke volume does not occur [73]. Using dynamic images from MRI videos, the relationship between right ventricular size, intraventricular septal shift and left ventricular size can be studied during the cardiac cycle. It is known that septal shift into the left ventricle is proportional to systolic pulmonary arterial pressure [74]. Improvements in these indices with disease-targeted treatments have been confirmed in small studies [70, 72]. Specifically, dramatic changes in left ventricular filling and stroke volume are sometimes seen, and these are probably the cause of exertional syncope in patients with pulmonary hypertension.

3) MRI can show evidence of right ventricular myocardial damage. For example, BLYTH *et al.* [75] showed a pattern of delayed gadolinium contrast enhancement in patients with severe pulmonary hypertension. This contrast enhancement was concentrated at the right ventricular insertion points and in the interventricular septum, and its extent correlated with right ventricular function and pulmonary haemodynamics, suggesting that it may be a useful prognostic marker. Interestingly, this pattern of delayed contrast enhancement matched the pattern of atrial natriuretic peptide staining in the ventricles of chronically hypoxic rats [76].

Longitudinal studies of right ventricular mass and chamber size following prolonged therapy are needed, and a large-scale European project is currently underway (the Euro MRI project) to examine these changes. It will also be necessary to validate MRI-derived measures of cardiac output and pulmonary arterial flow. At present, the expense and lack of availability of MRI means that it cannot be used in large-scale clinical trials. In the future, the availability of MRI is likely to increase. In the meantime, there is evidence that MRI variables in human pulmonary hypertension relate to NT-proBNP measurements [38], and so BNP may be a surrogate for the abnormalities in right ventricular function detected on MRI.

Computed tomographic scanning

Computed tomography (CT) scanning is a rapidly evolving technique in cardiovascular imaging. Recent technical advances, such as the development of multi-slice and multidetector-row CT, make it possible to measure dynamic heart images in an acceptable period of time [77]. Although its main role in phenotyping pulmonary hypertension is well established [78], the role of CT in the longitudinal assessment of PAH is largely unexplored. However, it is reasonable to expect similar results to those of MRI as regards right ventricular structure and function with the now widely available 64-slice ECG-gated scanners. However, it is debatable whether the radiation burden received during repeated CT scanning is acceptable in patients with PAH. An advantage of both MRI and multi-dose CT is that imaging of the heart can be combined with imaging of the pulmonary vasculature and quantification of pulmonary perfusion [79, 80]. Although serial perfusion measurements in PAH might contain information on the effects of therapy on restoration of perfusion, studies in this field are currently lacking.

It is concluded that, although it is too early to use an imaging end-point as a primary study end-point, there is a need for use of these variables as secondary or additive end-points. In addition, imaging of right ventricular structure and function during treatment might lead to a better understanding of the effects of therapy. Right ventricular end-diastolic volume and stroke volume or cardiac output seem to be the most sensitive variables for monitoring during treatment. Although it is recognised that imaging of the heart during exercise might provide more valuable information, these measurements are highly technically demanding, limiting their use as end-points.

Clinical variables including time to clinical worsening and quality of life

Quality of life

It has been suggested, not least by the regulatory agencies, that quality of life is the most important end-point in measurements of efficacy of drug therapy. Unfortunately, it has always been very difficult to objectify quality-of-life measurements, and, until recently, there had been no specific health-related quality-of-life measures in pulmonary hypertension. Previously, quality of life in PAH had been evaluated by generic health status measures, such as the 36-item short-form health survey [81], Nottingham Health Profile [82], European quality of life scale [83] and Minnesota Living with Heart Failure Questionnaire [84]. SHAFAZAND *et al.* [85] used a number of these questionnaires in 53 patients with PAH and found that, compared with population norms, the participants reported moderate-to-severe impairment in multiple domains of heath-related quality of life, including physical mobility, emotional reaction, pain, energy, sleep and social isolation. Clearly, these findings are important, but it is unproven whether generic questionnaires are useful in the description of specific symptoms in pulmonary hypertension. In an attempt to overcome this deficiency, the Cambridge group developed a specific quality-of-life (symptoms and function) scale for pulmonary hypertension [86]. They did this by interviewing 35 patients and analysing their responses. They found good internal consistency and reproducibility, but, as yet, this questionnaire has not been compared with the previous generic questionnaires nor used in clinical trials. There is some preliminary evidence that the findings relate to 6MWD, but definitive proof is awaited. Quality of life is undoubtedly important, and, if ways can be found of making it an objective measure, it is likely it will be more useful as an end-point in clinical trials in the future, but, before that can happen, it is necessary to develop and test versions for other languages and other countries. At the time of writing, there are US, Canadian English and Canadian French versions but, as yet, no trials of these adaptations.

Time to clinical worsening

The most important end-point in the evaluation of the efficacy of treatments in clinical medicine is mortality. Measurement of several individual variables constituting morbidity in rare and severe diseases such as PAH poses difficult challenges, including a large sample size for study populations and prolonged follow-up periods in multicentric cooperative trials.

Therefore, a composite end-point, defined as TTCW, has been developed and included among the secondary-efficacy end-points in recent trials. TTCW is defined as the time from randomisation to the first event, which usually includes: 1) all-cause mortality; 2) hospitalisation due to PAH; 3) the need for interventional procedures (listing for transplantation or performance of balloon atrial septostomy); and 4) clinical progression of PAH.

The problems with TTCW are as follows.

1) Lengthening of the TTCW does not co-track with improvement in 6MWD or QoL. This is not surprising in view of the fact that the 6MWD, in particular, is a measure of improvement, whereas TTCW is a measure of absence of deterioration. It seems likely that measures such as TTCW are more suitable for patients in functional class II, whereas the 6MWD is more suitable for patients in functional classes III and IV. One solution might be to use both end-points as co-primary end-points or reserve each for appropriate groups of patients.

2) Criteria for hospitalisation in PAH differ between different units and different countries, often depending upon variables such as the distance of the patient from the centre, availability of beds, *etc.*

3) The availability of transplantation and atrial septostomy vary between countries, depending upon the wealth of the country, availability of donors, *etc.*

4) The definition of clinical progression of PAH is extremely heterogeneous, and includes a variable combination of the following criteria: deterioration in 6MWD from baseline (usually 10–20%), increases of one or more New York Heart Association/WHO functional classes, signs and symptoms of right heart failure, escalation of medical treatments (usually the addition of targeted therapies, such as prostanoids, endothelin receptor antagonists and phosphodiesterase-5 inhibitors). Table 1 provides a schematic representation of different definitions of the events included in the TTCW in different trials [87–95].

The most reliable definition of TTCW should require the physician/investigator to provide some measurable variables for the determination of PAH progression. Variables may include a reduction in 6MWD from baseline (usually 10–20%), weight increase due to fluid retention (to confirm right heart failure), echocardiographic or haemodynamic measures, *etc.* Owing to the subjective nature of many of the criteria, it is advisable to appoint a blinded adjudication committee of PAH experts who have access to the patient's information and may confirm or not that the event constitutes PAH progression. The analysis by the adjudication committee can be performed prospectively (in real time) or retrospectively after the end of the study.

If TTCW is chosen as primary end-point in a randomised clinical trial, its components influence the sample size calculation according to the rate of events in the control group and the expected improvement in the treatment arm. Obviously, the higher the number of events (and the larger the number of target events included in the option) the smaller the sample size and observation period that is needed.

CLINICAL TRIAL DESIGN

Epoprostenol was approved, at least in the USA, for the treatment of PAH in the 1990s, but the first oral therapy for the treatment of this condition was bosentan, an oral endothelin A and B receptor antagonist. Following its approval, a number of questions needed to be asked about trial design as follows. 1) Can placebo-controlled studies continue to be performed? 2) Is it possible to carry out noninferiority studies in PAH? 3) Can withdrawal studies be performed in PAH?

Placebo-controlled studies (superiority)

All of the currently approved therapies for PAH, with the exception of epoprostenol, which was compared with conventional therapy, have been subjected to placebo-controlled studies in order to demonstrate superiority against placebo. These were remarkable undertakings given the rarity of the disease, and required a degree of multinational cooperation rarely seen in modern medicine. At the time of writing, the following are licensed for treatment of PAH, albeit with variability across countries in the categories of patient that can be treated: 1) intravenous epoprostenol, 2) subcutaneous treprostinil, 3) inhaled iloprost, 4) bosentan, 5) sildenafil, 6) sitaxsentan, and 7) ambrisentan.

All of these studies investigated morbidity in the form of exercise tolerance, with various other secondary end-points. Only epoprostenol has been shown to improve survival (compared with conventional, *i.e.* not disease-targeted, therapy) [96]. Most experts believe that placebo-controlled mortality studies are no longer ethical, and, if survival studies are to be carried out in the future, they will need to be performed using intravenous epoprostenol as comparator. Clearly, survival is an extremely important end-point for these studies, and, in order to try to circumvent the ethical problem, some authors [45, 97] have recently compared the survival of patients on therapy with survival based on data from the National Institutes of Health registry, which was, of course, formulated in the pre-treatment era [45, 97, 98]. These are not true comparative survival studies because they were not designed as such; however, given the ethical considerations, they are likely to be the best that can be achieved.

Since placebo-controlled survival studies are now considered not possible, consideration should also be given, in the future, to whether placebo-controlled morbidity studies are ethical. All of the early trials were placebo-controlled, and, indeed, one or two of the studies currently being performed are also placebo-controlled, but most studies that have lasted 3–4 months have shown a significant deterioration in the placebo-controlled group, and the current view is that, if placebo-controlled studies are to be performed in the future, they will need to be combination studies in which the patients always receive an active agent even if the additional agent is a placebo. A possible exception to this rule is patients with WHO class II function, where it might be reasonable to plan a placebo-controlled study. This would need to be carried out with very tight control such that, if there is any deterioration, the patients can be put on treatment. It is known that, for example, in the EARLY study [15] of bosentan in functional class II patients, there was deterioration in the placebo group. Another possibility is to perform a placebo-controlled study of both morbidity and mortality in patients who are already

TABLE 1 Different components of time to clinical worsening in different trials in pulmonary arterial hypertension (PAH)

	BREATHE-1/351	EARLY	STRIDE-1	STRIDE-2	ARIES-1	ARIES-2	SUPER-1	STEP	PACES
[Ref.]	[87, 88]	[89]	[90]	[91]	[92]	[92]	[93]	[94]	[95]
Death	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hospitalisation	✓	✓		✓	✓	✓	✓	✓	✓
Lung Tx	✓		✓	✓	✓	✓	✓	✓	✓
Atrial septostomy	✓		✓	✓	✓	✓			
Symptomatic progression#	✓	✓		✓	✓	✓			
Lack of improvement or worsening PAH¶	✓	✓		✓	✓	✓		✓	
Need for additional PAH therapy	✓		✓	✓	✓	✓	✓	✓	✓
p-value	<0.05	<0.05	NS	NS	NS	<0.05	NS	<0.05	<0.005

BREATHE: Bosentan Randomized trial of Endothelin Antagonist THErapy; EARLY: Endothelin Antagonist tRial in miLdlY symptomatic PAH patients; STRIDE: Sitaxsentan To Relieve ImpaireD Exercise; ARIES: Ambrisentan in PAH – a phase III, randomized, double-blind, placebo-controlled, multicenter, efficacy study of ambrisentan in subjects with pulmonary arterial hypertension; SUPER: Sildenafil Use in Pulmonary Arterial Hypertension; STEP: Safety and pilot efficacy Trial in combination with bosentan for Evaluation in Pulmonary arterial hypertension; PACES: Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil; Tx: transplantation; NS: nonsignificant. #: New York Heart Assocation/World Health Organization functional class; ¶: including 6-min walking distance.

receiving maximal combination therapy. Whether or not patients would wish to be recruited to such a study is not known.

Noncomparative (noninferiority) studies

Clearly, it will not be possible to perform comparative superiority studies between drugs because of the very large numbers of patients needed. An alternative approach is the comparative noninferiority study, in which drug A is compared with drug B and the sponsors need to show that it is not worse than the original therapy. Although the numbers needed are not as great as for superiority studies, they are still considerable, and it is very unlikely that any company would wish to sponsor such a study, which would involve considerable expense with an indeterminate outcome. Furthermore, noninferiority studies can only be performed using identical experimental conditions (inclusion criteria, exclusion criteria, patient population, study protocol, end-points, *etc.*) as for the original comparator [99, 100]. Given all of these constraints and the relatively large numbers of patients involved, it is unlikely that noninferiority studies of one drug against another will be seen in the field of PAH.

Withdrawal studies

The world's experts in PAH were rather surprised when the regulatory agencies (FDA and EMEA) asked whether or not they would consider performing withdrawal studies in patients on established therapy. The reasons for asking for withdrawal studies are sensible, specifically when a study has shown only marginal benefit or benefit of low clinical importance. Although this may be an interesting academic question, most experts feel that withdrawal studies are unethical for the following reasons: 1) it is already known that patients treated with placebo deteriorate over time and hence patients would be subjected to the possibility of deterioration; and 2) experts are concerned that, if a patient should deteriorate when a drug is withdrawn, reintroduction of the drug may not restore the patient to their baseline state.

Possible alternatives to withdrawal studies are transition or switch studies, in which one drug is withdrawn and another drug is substituted. This approach, although valid, has not found favour with most experts, and there are currently no published trials of such an approach. In most cases, if a patient deteriorates, drugs are simply added so that the patient is on a combination of two of more therapies. There are good reasons, however, for considering switch studies in the future: 1) if a patient improves on drug A but subsequently deteriorates again, it is uncertain whether drug A is really having an effect; and 2) drugs for PAH are extraordinarily expensive and the funding agencies need to be convinced that the combination approach is more effective than the switch approach; at the time of writing, no switch studies have been carried out, and, to the present authors' knowledge, none are planned.

CONCLUSIONS AND RECOMMENDATIONS

End-points

Exercise testing

1) The 6MWD will remain an important end-point, particularly in sicker patients, and efforts should be made to establish normal values, depending on age, sex, body habitus, *etc.* Consideration should be given to adding the cardiac frequency response, which would increase the discriminatory response of the test.

2) CPET has shown great promise and is safe even in the sicker patients, but the technical demands are such that it should only be carried out under stringent conditions.

Biomarkers

1) Biomarkers have been developed in order to assess the function of both the pulmonary vessels (largely endothelial markers) and the right heart.

2) Only the markers of right heart function/dysfunction have proven to be successful, particularly BNP and NT-proBNP.

3) It is not yet certain whether changes in the levels of these markers adequately track the changes in cardiac function,

either improvement with therapy or deterioration.with progression of disease.

Haemodynamics

1) Resting haemodynamics are essential for the diagnosis of PAH, but the measurement of changes in resting haemodynamics in the assessment of response to therapy have proven disappointing.

2) More interesting are the changes in exercise haemodynamics. These measurements are currently performed by invasive catheterisation, but, in future, there may be non-invasive techniques offering information of a similar value.

Imaging

1) Echocardiography is likely to remain the screening tool of choice in the diagnosis of PAH and the exclusion of certain causes of PAH, such as intracardiac shunt. Owing to the difficulty in performing three-dimensional measurement with echocardiography, it has not, in the past, been considered a technique for the assessment of right ventricular function. However, with the advent of three-dimensional echocardiography and also tissue Doppler, which can measure important variables such as tricuspid valvular excursion, echocardiography will play an increasing role.

2) Cardiac CT, at present, is valuable for diagnosis alone, but newer cardiac function algorithms will permit measurement of right ventricular function. The problem remains, however, of the radiation dose.

3) Cardiac MRI does not have the problem of radioactivity, and a number of studies have shown it to be useful in the measurement of right ventricular mass, morphology and function. Whether or not measurement of these variables will be useful as an end-point must await the outcome of the large trials currently underway.

Clinical variables:

1) Quality of life is an important component of patient assessment, and a new disease-specific questionnaire (Cambridge Pulmonary Hypertension Outcome Review) has been developed, but it needs to be translated and culturally adapted before it can be used in large-scale multinational clinical trials.

2) TTCW is valuable, particularly in fitter patients, but, since it is a composite end-point, a common definition of the adverse clinical events which comprise TTCW is needed. This should include all-cause mortality, hospitalisation for PAH, a measure of deterioration in exercise tolerance and need for additional disease-targeted therapy. We recommend the appointment of adjudication committees in order to ensure consistency in the reporting of clinical events.

Clinical trial design

Most of the clinical trials have been blinded comparisons of the effects of the new drug compared with placebo on the morbidity of the disease. These have been performed in either a monotherapy setting or a combination setting. It is unlikely that any of the following will be seen for the reasons stated above: 1) survival trials, 2) withdrawal trials; and 3) comparisons of one drug against another.

Consideration should, however, be given to: 1) targeted trials in which patients of a particular disease category, *e.g.* connective tissue disease-associated PAH, are examined separately from the other types of PAH; 2) crossover designs; and 3) induction trials, in which aggressive early therapy with combinations of drugs is used to try to bring the disease under control before continuing with maintenance therapy.

Further clinical trials in PAH are going to be of combination therapies and will include patients at an earlier stage of disease (WHO class II). Clinical trial design will, therefore, be more difficult and crucial if it is desired to be able to come to firm conclusions regarding the advisability or otherwise of combination therapy or early therapy with extremely expensive drugs. In order to convince patients, their doctors, the payers and the regulators of the benefits of these therapies, end-points will need to be increasingly sophisticated and relevant to the condition being treated, pulmonary arterial hypertension.

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STATEMENT OF INTEREST

Statements of interest for A.J. Peacock, R. Naeije and L. Rubin can be found at www.erj.ersjournals.com/misc/statements.dtl

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