

# What have we learned from large drug treatment trials in COPD?

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Although the development of effective treatments for patients with chronic obstructive pulmonary disease (COPD) has not been seen as a high priority, the past decade has seen a substantial increase in the number of clinical studies examining different treatments for this disease. Large studies are needed to adequately assess the effectiveness of treatment because of the chronic nature of the disease and the intermittent occurrence of some key outcomes such as exacerbations. Data from randomised controlled trials show that treatment improves exercise performance by increasing lung volume rather than changing expiratory flow. Although assessment of lung function remains the cornerstone of drug assessment, improvements in health status, the number of exacerbations and admissions to hospital are now recognised as important treatment outcomes. Randomised controlled trial data provide the best evidence for treatment efficacy, but results of these studies can be affected by differences in inclusion criteria and patient dropout during the study. Bronchodilator reversibility testing does not reliably define subgroups that will respond to a particular treatment. Carefully done and adequately powered clinical trials continue to inform, not only our views about treatment, but also our understanding of COPD and how it is best assessed and managed. Ensuring that these expensive studies are done objectively to the highest standard is an important goal for the next decade.

## Introduction

Until the past decade, chronic obstructive pulmonary disease (COPD) has been regarded, at least by doctors, as a rather dull and unrewarding illness. The reasons for this perception are complex and different factors are probably important to different people. However, prominent reasons include the longstanding arguments about the definition of the disease,<sup>1,2</sup> uncertainties about its natural history, and, rather perversely, a belief that COPD could be a self-limiting problem because a fall in the number of people smoking and improvements in urban air quality would lead to a gradual reduction in the number of cases. The frequency of the illness defined objectively by spirometry has now been appreciated,<sup>3,4</sup> although overinterpretation of the term irreversible airflow obstruction has encouraged the view that nothing can be done to improve it. In fact, some physicians seem to believe that even a modest degree of improvement in lung function in patients with COPD must be because of underlying asthma—since by definition the disease cannot improve. Unsurprisingly, researchers have little enthusiasm to do small, not to mention large, clinical treatment trials. The past 10 years, however, have seen a substantial shift in our approach to COPD, as many of the aforementioned views have been challenged.

A clear cohort effect is seen in people who smoke heavily, although the number of deaths due to COPD in any given age group is not falling as rapidly as those due to lung cancer.<sup>5,6</sup> However, fewer people now die from serious illnesses like ischaemic heart disease early in life than they did 20 years ago, and so there is more opportunity to develop clinically important COPD as the population ages.<sup>7</sup> Moreover, COPD is progressive. Although smoking cessation early in the disease slows progression, cessation after the disease has progressed

probably has less benefit. In most people, even with smoking cessation, lung function will decline over time. The economic effect of COPD, especially on acute medical care, has been well documented with more than €38.6 billion spent on COPD in Europe and US\$32.1 billion in the USA in 2002. COPD is now recognised as a major and growing public-health problem.<sup>8</sup> Although present treatments have limited effects, the benefit of even modest improvements in lung function in people with severe disease is now recognised.<sup>9</sup> This understanding has encouraged investment in large clinical trials, the analysis of which has in turn changed our perceptions of what can be achieved for patients with COPD. In this Review, we discuss some important changes in management resulting from large clinical trials of drug treatments. Inevitably, such an overview is selective but we have tried to highlight data that are generalisable and which aspects of disease continue to be controversial, and thus will shape our future understanding of COPD.

## What is a large COPD trial?

Although most studies in the past 10 years have been funded by the health-care industry or with some Government sponsorship, the first studies defining the clinical course of COPD were entirely funded by governments. Thus, the landmark study of Fletcher and colleagues<sup>10</sup> in a stratified random sample of 792 British men was supported by the British Medical Research Council. They tested the hypothesis that the presence of cough and sputum identified patients with a worse natural history of disease compared with those without cough or sputum production.<sup>10</sup> The unexpected conclusion, that the degree of airflow obstruction determined disease progression, has affected the subsequent definition of COPD and provided a clear

	Duration	Outcome
MRC domiciliary oxygen trial, <sup>16</sup> 1981 (n=89)	Up to 5 years	Domiciliary oxygen prolongs life in patients with hypoxaemic COPD
NHLBI nocturnal oxygen therapy trial, <sup>17</sup> 1980 (n=203)	19.3 months*	Continuous oxygen therapy is better than nocturnal oxygen therapy in patients hypoxaemic COPD
NHLBI intermittent positive pressure breathing (IPPB) trial, <sup>18</sup> 1983 (n=985)	33 months*	No difference in lung function, mortality, or quality of life when bronchodilators were given by intermittent positive pressure breathing
Antibiotic therapy in exacerbations of COPD, <sup>22</sup> 1987 (n=173)	3–5 years	Exacerbations associated with worsening dyspnoea, sputum production, and purulence respond to antibiotics
Lung Health Study, <sup>13</sup> 1994 (n=5887)	5 years	Smokers with mild or moderate COPD and who quit, improve their lung function. Subsequent follow-up confirmed recorded benefit of a smoking cessation programme on decline in lung function and mortality <sup>14,15</sup>

\*Reported mean follow-up.

**Table 1: Large randomised controlled treatment trials done before 1997**

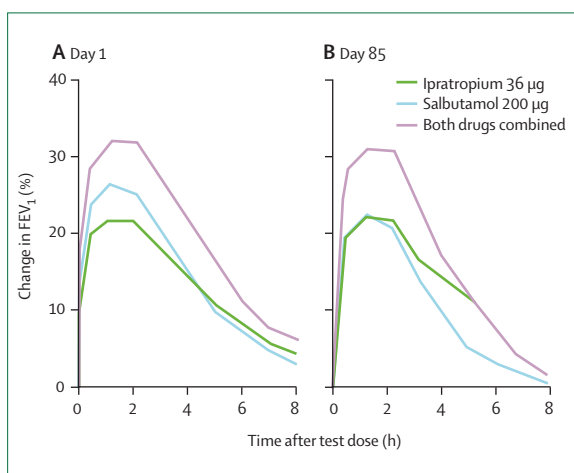
rationale for the role of spirometry in diagnosis. This study also led directly to a difficult therapeutic target, namely the slowing of the decline in lung function over time, which has subsequently been studied in detail. Results in other general populations have supported the longitudinal findings of Fletcher and Peto<sup>11,12</sup> about the association of decline in lung function with tobacco smoking, but the US National Heart Lung and Blood Institute (NHLBI)-supported Lung Health Study in nearly 6000 North American smokers with mild COPD showed beyond doubt that smoking cessation, and treatment in a smoking cessation programme had beneficial effects on lung function decline<sup>13,14</sup> and other important outcomes such as mortality.<sup>15</sup>

Before the Lung Health Study, the British Medical Research Council's long-term oxygen trial in 89 patients with hypoxaemic COPD<sup>16</sup> and the NHLBI nocturnal oxygen therapy trial, in 203 patients<sup>17</sup> were thought to be large studies. Each of these studies lasted for 3 years with a clear endpoint of all-cause mortality. At about the

same time, the NHLBI funded the intermittent positive pressure breathing trial in 985 patients to establish whether this way of delivering bronchodilator drugs was most effective. Although this study had negative results,<sup>18</sup> it led to many important findings about the natural history of COPD,<sup>19,20</sup> not least about the pathological changes of COPD and inflammation in the smaller airways.<sup>21</sup> Table 1 shows data for some of these important early studies.

Although exacerbations of COPD, especially those defined as being infectious, are quite frequent, the number of randomised placebo-controlled trials of antibiotics is surprisingly small. The largest reported study included 173 people<sup>22</sup> with the smallest recruiting only 30 participants. Data from the first trial, which was reported in 1987, have dominated subsequent thinking and meta-analyses, and are at the core of recommendations about the use of antibiotics in present treatment guidelines.<sup>23</sup> Specifically, the data suggest that the only patients to improve with antibiotic treatment are those reporting an increase in breathlessness, increased sputum volume, and purulence before treatment. In view of the frequency of COPD exacerbations, that these simple observations have not been revisited using present methods is surprising. Unfortunately, the criteria used to approve antibiotics are largely based on bacteriological cure rates, often with non-inferiority as an endpoint. As a result, the many antibiotic trials for exacerbations of COPD have done little to advance understanding or improve clinical care.

Other trials designed to improve symptoms in stable COPD have focused on bronchodilator drugs originally developed for the management of asthma. The number of participants needed to show a small but significant degree of bronchodilation is quite small. A well established assessment method used by US and European regulators includes the serial measurement of forced expiratory volume in 1 min (FEV<sub>1</sub>) to define the duration of drug action, then 12 weeks of regular treatment compared with a placebo or active comparator,



**Figure 1: Assessment of bronchodilators in COPD**

Serial spirometry is done to define the course of action of the bronchodilator drug before (A) and after (B) regular treatment with the test agent and either a placebo or an active comparator. Redrawn from reference 24.

then a further FEV<sub>1</sub> assessment. Figure 1 shows a study of the combination of a short-acting inhaled  $\beta$  agonist and anticholinergic bronchodilator.<sup>24</sup> However, effective management of COPD needs more than small changes in lung function, and to study this disease effectively, complex trial designs have emerged.

Clinical trials have been used to test specific hypotheses and to identify clinically important effects beyond spirometrical change. The best studied mechanisms include exercise physiology, for which trial designers have moved from individual investigators doing crossover studies of 12–20 patients<sup>25,26</sup> to multicentre randomised placebo-controlled studies using complex exercise physiology assessments in 100–200 patients.<sup>27,28</sup> Yet, the question of how well such

changes relate to everyday activity remains unanswered.<sup>29</sup> Even larger studies than those mentioned are needed to assess parameters that change slowly, for instance reduction in lung function, or that are intermittent (eg, exacerbations needing medical attention). Table 2 shows examples of such large studies. Assessment of these important endpoints has been a real logistical challenge. Data resulting from such trials, however, have taught us practical lessons about who should be included in clinical studies, and how they should be assessed, and have greatly advanced our understanding of COPD.

### Improving trial design and interpretation

Although that the results of a clinical trial only apply to the population under study seems obvious, small

	Duration	Outcome
<b>Do inhaled corticosteroids reduce the rate of FEV<sub>1</sub> decline?</b>		
Vestbo, <sup>30</sup> 1999 (n=290)	3 years	In patients with mild COPD (FEV <sub>1</sub> =86% of predicted)* budesonide 800 $\mu$ g daily had no effect
Pauwels, <sup>31</sup> 1999 (n=1277)	3 years	In patients with moderate COPD (FEV <sub>1</sub> =77% of predicted) budesonide 800 $\mu$ g daily had no effect
Lung Health Investigators, <sup>32</sup> 2000 (n=1116)	3 years	In patients with moderate COPD (FEV <sub>1</sub> = 30–90% of predicted*) triamcinolone 1200 $\mu$ g daily did not affect rate of FEV <sub>1</sub> decline but reduced symptoms and physical visits
Burge, <sup>33</sup> 2000 (n=751)	3 years	In patients with moderately severe COPD (FEV <sub>1</sub> =50% of predicted*) fluticasone did not affect FEV <sub>1</sub> decline, but reduced the number of exacerbations and improved health status
<b>Can a long-acting inhaled bronchodilator modify endpoints not usually associated with bronchodilation?</b>		
Casaburi, <sup>34</sup> 2002 (n=921)	12 months	In patients with severe or very severe COPD (FEV <sub>1</sub> =38% of predicted) tiotropium improved lung function and health status, and reduced exacerbations compared with placebo
Vincken, <sup>35</sup> 2002 (n=535)	12 months	In patients with severe or very severe COPD (FEV <sub>1</sub> =42% of predicted) tiotropium was better than ipratropium
Brusasco, <sup>36</sup> 2003 (n=1207)	6 months	In patients with severe or very severe COPD (FEV <sub>1</sub> =38% of predicted) tiotropium reduced exacerbations significantly and both tiotropium and salmeterol improved health status and lung function compared with placebo
<b>Does combining an inhaled corticosteroid with a long-acting beta-agonist have clinical benefit?</b>		
Calverley, <sup>37</sup> 2003 (n=1465)	12 months	In patients with moderately severe COPD (FEV <sub>1</sub> =44% of predicted) salmeterol with fluticasone reduced exacerbations and improved health status, as did either drug on its own compared with placebo
Szafrański, <sup>38</sup> 2003 (n=812)	12 months	In patients with severe or very severe COPD (FEV <sub>1</sub> =36% of predicted) budesonide 800 $\mu$ g formoterol 9 mg daily improved lung function and exacerbations compared with placebo and or formoterol on its own
Calverley, <sup>39</sup> 2003 (n=1022)	12 months	In patients with severe COPD (FEV <sub>1</sub> =36% of predicted) who had previous oral corticosteroid and formoterol treatment, budesonide with formoterol improved health status and reduced exacerbations compared with placebo or either drug on its own
Calverley, <sup>40</sup> 2007 (n=6112)	3 years	In patients with moderate or very severe COPD (FEV <sub>1</sub> =44% of predicted*) salmeterol with fluticasone combination did not reduce mortality significantly compared with placebo. Significantly fewer exacerbations, admissions to hospital, and better health status were recorded with this therapy. Pneumonia was more commonly seen with inhaled corticosteroid treatment than with salmeterol and fluticasone
<b>Does phosphodiesterase-4 inhibition improve lung function and clinical outcomes?</b>		
Rennard, <sup>41</sup> 2006 (n=647)	24 weeks	In patients with moderately severe COPD (FEV <sub>1</sub> =50% of predicted) cilomilast 15 mg twice daily increased FEV <sub>1</sub> by mean 40 mL and reduced the number of exacerbations compared with placebo
Rabe, <sup>42</sup> 2005 (n=1411)	24 weeks	In patients with moderately severe COPD (FEV <sub>1</sub> =51% of predicted) FEV <sub>1</sub> after bronchodilator increased by 97 mL with 500 mg roflumilast and exacerbations needing bronchodilator treatment were reduced
Calverley, <sup>43</sup> 2007 (n=1513)	12 months	In patients with severe or very severe COPD (FEV <sub>1</sub> =41% of predicted) roflumilast 500 mg increased FEV <sub>1</sub> by 41 mL, but did not improve health status or number of exacerbations. More patients withdrew because of drug intolerance with roflumilast than with placebo
<b>Does the antioxidant drug acetylcysteine reduce the rate of decline of FEV<sub>1</sub>?</b>		
Decramer, <sup>44</sup> 2005 (n=523)	3 years	In patients with moderate or severe COPD (FEV <sub>1</sub> =57% of predicted) 600 mg oral acetylcysteine did not change the decline in FEV <sub>1</sub> , but reduced exacerbations in patients who were not taking inhaled corticosteroids
*FEV <sub>1</sub> , after taking bronchodilator.		
<b>Table 2: Large randomised controlled treatment trials done after 1997</b>		

differences in recruitment criteria can substantially affect outcome variables and restrict how results are generalised. This difficulty could help to explain conflicting results between seemingly similar studies. COPD is heterogeneous, both clinically and pathologically, but this heterogeneity is not the same for the pathological and clinical aspects of the disease. Thus, definition of reliable phenotypes on the basis of a patient having mostly emphysema or airways disease, or presence or absence of specific symptoms has, to date, proven extremely difficult. Similarly, the failure to establish a surrogate endpoint for many clinically important outcomes (eg, admissions to hospital or mortality), has led to the need for large studies of long duration in patients who are sick enough for the events of interest to take place. Further work to establish the association between potentially important surrogate measurements, whether physiological or biochemical, is urgently needed if clinical trials are to be shorter and more discriminating than at present. Several other issues have been identified that have effects well beyond clinical trial design.

#### Bronchodilator reversibility

Bronchodilator reversibility (panel) in COPD as conventionally defined is not a useful marker in patients with established disease. One of the main concerns in the management of COPD and in the identification of treatment effects has been to avoid confusion between COPD and bronchial asthma. Asthma is characterised by variable airway calibre, either spontaneously or in response to treatment. Thus, an improvement in some measure of lung function, usually FEV<sub>1</sub>, after taking a bronchodilator drug, either a  $\beta$  agonist or an anticholinergic, would seem to be a good way of distinguishing asthma from COPD. The definition of COPD based on clinical presentation and FEV<sub>1</sub> before taking bronchodilator led to some early confusion because inhaled corticosteroids seemed to have notable effects that many experts would have attributed to the presence of individuals with asthma in the study populations.<sup>45</sup> Subsequently, and especially in Europe where these data originated, a bronchodilator response was redefined to try to overcome the inadvertent inclusion of asthmatic participants<sup>46</sup> and this change emphasised that COPD was irreversible. In fact, a COPD phenotype based on the presence or absence of small increases in lung function after bronchodilator (panel) does not allow for spontaneous variation in airway smooth muscle tone, and the ability of bronchodilator drugs to reduce this tone in both health and disease.<sup>47</sup>

If baseline lung function is relatively well preserved, small changes in FEV<sub>1</sub> after taking bronchodilator will probably not meet the threshold relative to baseline for patients to be reclassified as having asthma. When lung function is severely reduced in advanced COPD, similar

#### Panel: Definitions used in COPD trials

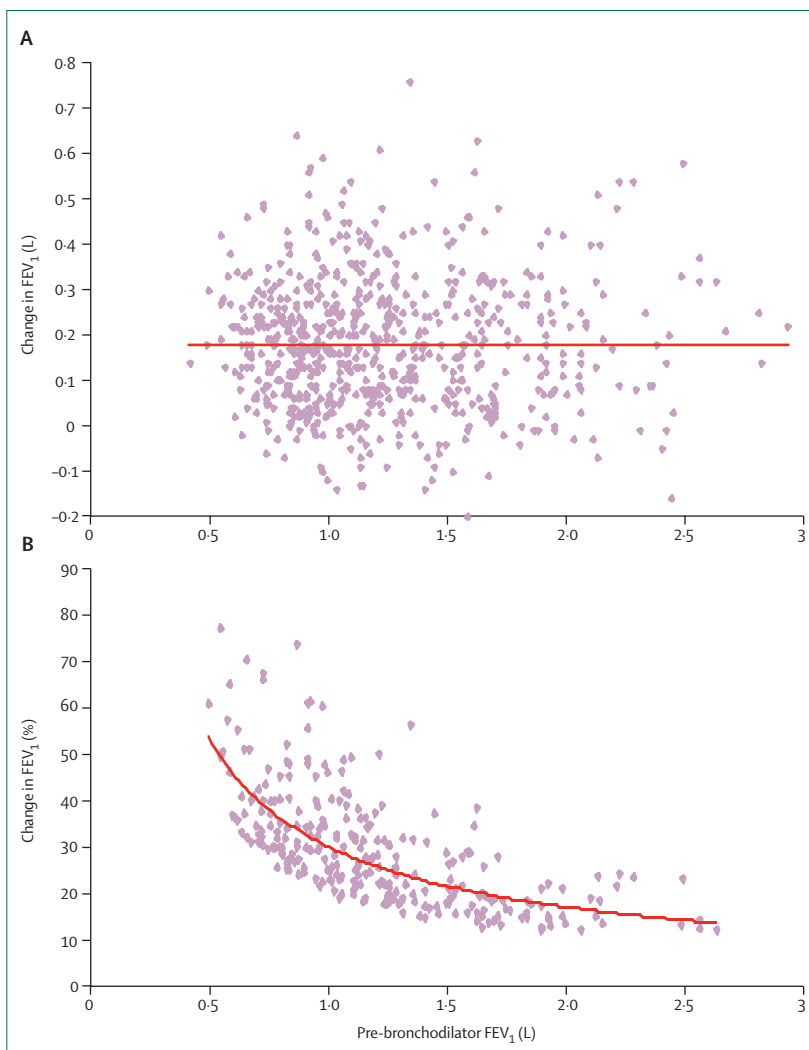
##### Bronchodilator reversibility

American Thoracic Society and GOLD criteria: a change in FEV<sub>1</sub> that is greater than 12% of baseline and encompasses an absolute change of 200 mL

European Respiratory Society criteria: a change in FEV<sub>1</sub> that is greater than 9% of the value predicted for that person

##### COPD exacerbation

An event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea and cough or sputum, or both, that is beyond normal day-to-day variations, is acute in onset, and might warrant a change in the patient's regular medication



**Figure 2: The relationship between bronchodilator response and FEV<sub>1</sub> before bronchodilator** (A) The change in FEV<sub>1</sub> after 400  $\mu$ g salbutamol and 80  $\mu$ g ipratropium given by metered-dose inhaler. Data are expressed as absolute change in FEV<sub>1</sub>. (B) Shows similar data expressed as a percentage of the baseline value. Data were obtained from 600 patients with stable COPD. Although the absolute change in FEV<sub>1</sub> after these drugs is unrelated to baseline, the degree of reversibility seems to increase as lung function falls. Redrawn from data from reference 48.

changes in lung function can lead to an erroneous diagnosis of asthma (figure 2). Confusion about this point led to different requirements for drug regulators on either side of the Atlantic, with the European regulators insisting that the diagnosis of COPD needed the patient to have some bronchodilator response, but the US Food and Drug Administration did not regard such a response as an essential feature of COPD, if lung function after taking bronchodilator remained abnormal.

As a result of these differing criteria, clinical trials in the US showed larger improvements in lung function than was seen in Europe for the same drugs in similar patients.<sup>49,50</sup> Some of this confusion was resolved by analysis of bronchodilator data from the ISOLDE<sup>48,51</sup> study and in the Lung Health Study.<sup>52</sup> In both studies, the most symptomatic patients did not show any relation between the size of bronchodilator response and clinical outcomes such as exacerbation frequency or health status. Both studies showed that patients had significant day-to-day variability in airflow. Thus, the classification of an individual by some criteria would have changed on different days. Moreover, the number of people classified as having reversible disease was affected by the number of drugs tested. Taken together with the other problems of bronchodilator testing, such as its reproducibility, firm recommendations about using bronchodilator reversibility as a criterion for diagnosis, staging, and drug treatment in routine clinical practice are clearly undesirable—a view supported by subsequent national and international guidance.<sup>23,53</sup>

Large changes in lung function (ie, two standard deviations beyond the spontaneous variability of the measurement; about 400 mL) probably identify individuals who have an asthmatic clinical syndrome. Such individuals should be carefully assessed because they could have COPD. Proper prospective studies are needed in this small but important group of patients. The identification of so-called isolated volume responders, who show a clinically important reduction in forced expiratory vital capacity (FVC) with a small change in FEV<sub>1</sub>, is an attractive notion, but thus far we know little about how predictive such results are or how they can be reproduced. To date, bronchodilator response has been a poor predictor of short-term improvement in exercise ability or of other clinical outcomes such as exacerbation frequency or health status.<sup>52,54</sup>

#### Withdrawal from trials

Differences in withdrawal of patients from the two (or more) groups in a randomised clinical trial is a sign of treatment effect and not merely a statistical headache. Large studies of patients with COPD have investigated the rate of decline in lung function over time and most of these have studied the effects of inhaled

corticosteroids.<sup>30–32</sup> In studies in which most patients had more than 60% of predicted FEV<sub>1</sub> and few symptoms, the dropout rate for the active treatment group was not different from the placebo group.<sup>30–34</sup> However, in subsequent studies of inhaled glucocorticoids in severe COPD, in patients who generally had less than 50% of predicted FEV<sub>1</sub>, many patients had already been taking inhaled corticosteroids. As a result, participants assigned placebo were significantly more likely to have disease-related adverse events and to withdraw than were those assigned active treatment.<sup>33,55</sup> The higher dropout rate in the placebo group creates a bias against the active intervention for outcomes such as exacerbations that take time to occur. Similar findings have been seen in long-term studies of bronchodilator drugs (with or without inhaled corticosteroids) lasting at least 1 year.<sup>37–38,56</sup> This effect has been exploited in trials in which patients have been assigned to continue or stop their inhaled corticosteroids.<sup>57,58</sup>

Differing withdrawal between patients assigned placebo or active treatments tends to narrow the difference in results, because the sickest patients are those most likely to withdraw. This result was seen in ISOLDE,<sup>48</sup> in which patients with the most rapid deterioration in health status and in FEV<sub>1</sub> withdrew quickest.<sup>43</sup> Differing rates of withdrawal can compromise primary outcomes as was seen in TORCH,<sup>40</sup> BRONCUS,<sup>44</sup> and OPTIMAL.<sup>56</sup> In these studies, the reasons for withdrawal have been categorised in a standard way that permits further analysis. Exacerbations and patient dissatisfaction with treatment are major explanations for the differences in dropouts. Recognition that these factors can create both bias and logistical issues in long-term studies of patients with COPD is important for clinical study design. Moreover, informative dropout from a randomised blinded study can be viewed as a marker of overall treatment effectiveness—whether patients withdraw from placebo or because of treatment intolerance.<sup>59</sup>

#### Assessment of health status

One innovation in drug trials for COPD is the use of disease-specific health status questionnaires, which ask for data that is not strongly affected by the severity of airflow obstruction. Both the Chronic Respiratory Disease Questionnaire and the St George's Respiratory Questionnaire are used in treatment trials. The first questionnaire tends to detect small changes<sup>60,61</sup> but the second has a useful summary score and an identified minimum clinical difference.<sup>62</sup> However, recruitment into a clinical trial seems to have a positive effect on the health status of patients with COPD.<sup>37,44,63</sup> This result might be a Hawthorne effect (ie, better care resulting from participation in the trial), or the expected consequence of previous exacerbations, following which health status can continue to improve for more than 12 weeks.<sup>64</sup> These effects help to explain why the

health status of people assigned to placebo without other interventions commonly improves, at least for some months, although not by as much as those on active therapy.<sup>40</sup> As noted previously, patients who leave a clinical trial tend to be those who are sickest at the beginning, leaving a healthy survivor population and affecting health status measurements. One way to overcome this drawback is to give intensive treatment with oral corticosteroids or additional long-acting beta-agonists, or both before randomisation.<sup>33,39</sup> In these trials, no spontaneous improvement was seen in patients allocated to placebo.

### Definition of exacerbation

The ISOLDE study looked at the number of episodes of symptomatic deterioration during its 3-year follow-up. An event was defined as contact with a health-care professional that resulted in a change in treatment, specifically a course of antibiotics or oral corticosteroids, or both.<sup>33,65</sup> This definition has been developed further in the most recent version of the guidelines by the Global initiative for Obstructive Pulmonary Disease (GOLD).<sup>66</sup> Careful study of daily diary cards showed that episodes of symptomatic deterioration persisting for many days occur more commonly than is seen with a definition based on use of health care.<sup>67</sup> The importance of these episodes is unclear, neither their duration nor their cause has been robustly defined. However, data from both randomised controlled trials and observational studies show that health status is significantly worse in those who have more of them.<sup>68,69</sup> Identification of exacerbations by daily diary cards is complex, but the high number of events recorded improves statistical power. Additionally, this method does not depend much on the availability of health care or on patterns of local clinical practice, which are important factors in international trials. Hopefully the EXACT-PRO initiative, which was started through a collaboration of the FDA, industry, and academics, can resolve many of these issues.

### Statistical analysis of infrequent events

COPD exacerbations do not occur at regular intervals, nor do all patients have them. As a result, recruitment of individuals with frequent exacerbations might be seen as an advantage, but in a study of long duration many such patients could drop out early. Sufficient time must pass for an adequate number of exacerbations to take place, and most studies of 6 months or shorter are not usually large enough for such dropout to become a problem. Approaches include reporting the number of patients experiencing an exacerbation in each group or the time to first occurrence.<sup>36,70</sup> However, clinicians want a sense not just of whether a treatment reduces the frequency of an event or of a statistical derivative, such as the time to first exacerbation, but they also would like an idea of the size of the change.

Parametric statistics are clearly not appropriate for expression of exacerbation rates, but reporting data as a median can also be misleading, because of the very skewed distribution of exacerbations between individuals. To overcome this problem, complex statistical analyses such as Poisson distribution and the negative binomial approach have been done.<sup>37,59,71</sup> These analyses model exacerbation rates for the whole population and give an idea of the size of an effect, but they are not literal representations of the number of events that have taken place. Pooling of cited data in meta-analyses can be misleading if exacerbations are the outcome, and caution is needed for interpretation of the reported exacerbation rates in earlier treatment trials.<sup>72</sup>

Previous exacerbation history is a determinant of the likelihood of having further events,<sup>73</sup> but, as the TORCH study<sup>40</sup> showed, patients without exacerbations in the preceding year can subsequently have an exacerbation, and treatment in this subgroup can also be beneficial. Exacerbation analysis is further complicated by differential withdrawal as mentioned above, thus it is a difficult outcome to deal with, but one that is nonetheless important to patients and clinicians. However, care should be taken not to overinterpret the results of statistical modelling. The present approach probably gives an acceptable estimate of the effect of treatment on these events, if not for an individual, at least for a population of patients.

### Underpowered studies

The expense and complexity of COPD trials is daunting, but as has been the case with cardiovascular disease, evidence that large and long-term studies are most informative is increasing. The effect of differences in patient recruitment, variations in initial treatment, differences in the natural history of each individual's disease, not to mention previous and present smoking status (which as an outcome variable has made remarkably little difference to treatment effects reported in COPD trials) are all reduced as sample size increases. Large studies are more robust in the face of logistical problems, such as withdrawal of patients. Additionally, large trials allow for reasonable analysis of secondary hypotheses. Failure to account for these factors can raise uncertainty about the outcome of carefully designed studies.<sup>40,56</sup>

### Different trial designs give different answers

Randomised controlled trials have some important drawbacks when studying a disease such as COPD, in which change develops slowly. The criteria required for a patient to enter a randomised study, whether overtly stated or applied by investigators keen to recruit patients who will probably complete the trial, mitigate against the inclusion of patients with substantial comorbidities and those who are sickest. The availability of

computerised medical records documenting health-care consultations, diagnoses, and treatment should overcome these problems. Much research to validate such databases and investigate them has already been undertaken. However, database analyses have other forms of bias. Patients in databases are not necessarily from the same population as those in a clinical trial.<sup>56,74</sup> Most importantly, these patients are not assigned to a treatment, but are given a therapy because an individual doctor believes it to be appropriate. Beneficial effects could be a direct result of treatment. However, outcomes could also be affected by other factors such as the organisation of health-care systems, or a physician giving other treatments, or selection bias because the patient has visited the physician. The creation of control populations to measure the effect of treatment is equally difficult. Untreated patients are those with mild disease who might not be directly comparable with treated individuals. The potential for time bias in database studies has been clearly identified.<sup>75</sup> In view of the different limitations of these study methods, we should not be surprised that database studies and prospective randomised trials sometimes reach different conclusions.

### What we have learned from clinical trials

Large clinical trials have prespecified primary outcomes and usually test a number of secondary hypotheses. Their results have substantial effects on treatment guidance, which for COPD is updated annually by GOLD.<sup>76</sup> Smoking cessation early in the natural history of COPD undoubtedly has benefits for disease progression and risk of death, although at 14.5 years after randomisation in the Lung Health Study<sup>13</sup>, few deaths were of a respiratory nature and most were related to cardiovascular disease and cancer.<sup>15</sup> Smoking cessation can be helped with nicotine replacement therapy,<sup>77</sup> and the antidepressant drug bupropion, which is associated with successful attempts to stop in COPD patients.<sup>78</sup> Varenicline has proven more effective than nicotine replacement or bupropion in healthy volunteers<sup>79-81</sup> and data for its effects in COPD are awaited.

Bronchodilator drugs, whether  $\beta$  agonists or anticholinergics, give small but consistent improvements in FEV<sub>1</sub>, irrespective of baseline airway calibre.<sup>34,82-84</sup> A combination of bronchodilator drugs is generally better than using one on its own,<sup>24,85</sup> and a long duration of action of inhaled drugs is associated with greater clinical benefit than short-acting medications.<sup>35</sup> Existing combinations of inhaled corticosteroids and long-acting inhaled  $\beta$  agonists result in greater improvement than either alone with generally acceptable side-effects.<sup>37,40,86,87</sup> Long-acting drugs given by inhalation are preferred to short-acting ones, because they give important improvements not only in spirometry but also in health status and

frequency of exacerbations.<sup>50</sup> Adding an inhaled corticosteroid could result in additional clinical gains.<sup>38-40</sup> Improvements in symptoms of COPD, especially exercise performance is related more to changes in lung capacity than to changes in expiratory flow.<sup>27,54,88</sup> The improvement in vital capacity under resting conditions is probably due to a reduction in residual volume, a change which also occurs when high doses of bronchodilators are given during exacerbations.<sup>89,90</sup> Additionally, bronchodilator drugs and bronchodilator-corticosteroid combinations reduce both the degree of dynamic hyperinflation seen during exercise and increase the duration of endurance exercise. These effects add to those of pulmonary rehabilitation or ambulatory oxygen,<sup>91-93</sup> giving a clear rationale for combining different therapeutic approaches in the management of stable COPD.

Although still disputed by some researchers, most data suggest that inhaled corticosteroids reduce the number of exacerbations and improve the health status of patients. However, the TORCH study<sup>40</sup> suggests that inhaled corticosteroids are associated with additional reports of pneumonia. This effect has been seen data from Canada.<sup>94</sup> Both large clinical trials and database studies suggest a mortality benefit with bronchodilators or bronchodilator and corticosteroid combinations, but a beneficial effect of inhaled glucocorticoids was seen only in the database studies, not in the TORCH trial.

Different meta-analyses with slightly different datasets have given conflicting estimates of the effect of inhaled corticosteroids and of the rate of reduction in lung function.<sup>95,96</sup> Using many of the same studies and also incorporating data from studies lasting 1 year, a recent report suggests that such an effect seems absent.<sup>97</sup> A preliminary report of a subanalysis<sup>98</sup> of TORCH data suggests a positive effect on rate of decrease in lung function with all active treatments in 4000 patients studied prospectively. The UPLIFT study is comparing tiotropium with placebo on rate of reduction in lung function.<sup>99</sup> The study is powered to detect a difference in rate of decline of 15 mL per year between treatment groups, a difference similar to that suggested by TORCH data. A smaller effect size than 15 mL per year reduction in lung function, would have needed an even larger or longer trial, than the 6000 participants and 3 years of follow-up in the TORCH trial.

### Outcomes we did not anticipate

Large COPD trials have taught us much about aspects of COPD that we understood poorly or not at all before the studies. The limited usefulness of bronchodilator reversibility testing and the unexpected occurrence of pneumonia with inhaled corticosteroids have already been discussed. As also noted, patients who enter studies in COPD are often not as sick as many who attend their doctor's office. Patients with substantial

comorbidities such as ischaemic heart disease, congestive heart failure, or known cancers are mostly excluded from clinical trials. The prevalence of these comorbidities in COPD patient populations has been described in epidemiological studies.<sup>100</sup> However, even in trial participants, comorbidity is common. Thus in TORCH,<sup>40</sup> which did not exclude individuals with comorbidities that were not expected to be rapidly fatal, more than a quarter of the subsequent deaths were thought to be from cardiovascular causes and 20% were from a tumour, with half of these being lung cancer. Additionally, more than 50% of the 654 TORCH participants who underwent measurement of bone mineral density showed osteoporosis or osteopenia at the time they were allocated to treatment. Moreover, their baseline disease was a much stronger predictor of subsequent outcome for bone-mineral density than of any identified effect of treatment.

The heterogeneity of COPD has been recognised for decades. Although not a drug trial, the National Emphysema Treatment trial (NETT)<sup>101</sup> was the first to show a different response to treatment based on the phenotype of COPD. Specifically, in participants with upper-lobe emphysema seen by CT, and whose exercise performance did not improve after rehabilitation, surgical intervention resulted in large benefits on mortality and health status. By contrast, those with diffuse disease had greater mortality than those with localised disease. A specific group of responders to any drug treatment has not been identified, but might be identified in future treatment trials.

Treatment does not always do what we expect. Thus, a bronchodilator drug such as a long-acting  $\beta$  agonist should result in larger changes in lung function than any inhaled corticosteroid, but in several trials, the changes in lung function were surprisingly similar over at least a year of follow-up. Moreover, bronchodilator drugs might be expected to improve exercise performance, but their ability to substantially reduce exacerbations has challenged existing thinking. This has been shown clearly with tiotropium, which had no recognised anti-inflammatory effects before studies were done, and has led to a reassessment of the role of anticholinergics in inflammation. These studies have also challenged us to rethink the pathophysiology of an exacerbation. The many stimuli producing an exacerbation result in similar changes in lung physiology. Bronchodilators probably prevent exacerbation by reducing the operating lung volumes of the patient, and so improving their functional reserve. Understanding of how exacerbations are triggered and how the way in which we measure them relates to the biological processes within the lung is an important future challenge.

So far our approaches to modification of intrapulmonary inflammation in stable COPD have been disappointing. By applying the methods of clinical trials

to understand how drug treatment affects the nature of the inflammatory change in the large airways in COPD we have established that inhaled corticosteroids are not very effective at modifying this change<sup>102,103</sup> although both a combination of corticosteroids and a  $\beta$  agonist and inhibition of phosphodiesterase-4 can reduce the number of inflammatory cells in endobronchial biopsies.<sup>104,105</sup> This action could explain some of the benefits seen with these drugs. Studies with phosphodiesterase-4 inhibitors<sup>42</sup> have shown consistent improvements in lung function over 6 months<sup>41</sup> but these improvements have not been as notable in severe disease and have not affected frequency of exacerbations, except perhaps in patients with very severe disease.<sup>59</sup> Additional data are needed to assess patient acceptability of these oral treatments because treatment-related nausea can be a drawback. Other approaches to anti-inflammatory therapy include the use of monoclonal antibodies against tumour necrosis factor- $\alpha$ , which, despite a good theoretical basis, has so far proved disappointing.<sup>106</sup>

### Future clinical trials

Large clinical trials have led to a substantial improvement in our understanding of COPD and of its management. Treatment strategies are now evidence-based and we can estimate the number of patients who need to be treated to prevent an event of interest taking place. The effect of this information will vary with the frequency with which a particular outcome occurs in a specific population of patients with COPD. We still do not have good algorithms to predict which patients will benefit from specific treatments. To develop these, we need to better define the clinical heterogeneity of this disease and establish how it relates to the symptoms of patients or their disease progression, or both. The search continues for validated intermediate outcome variables that will act as surrogates for treatment and so reduce the expense and delay inherent in clinical studies with agents unlikely to be of clinical benefit. Advances in CT and the identification of biochemical and cellular biomarkers hold great promise to help to address these needs. Application of these methods will be key in trials of new treatments such as retinoid drugs for emphysema.<sup>107</sup>

The presence of comorbidities including cardiac disease, osteoporosis, muscle weakness, depression, and anaemia is being recognised as part of COPD rather than as separate medical disorders. This notion, which is supported by the increased risk of these non-pulmonary disorders in patients with COPD compared with similarly aged smokers without COPD, suggests a pathophysiological link. It also suggests that these disorders can be endpoints for COPD trials, which is a substantial diversion from the usual framework, in which patients with COPD who have important comorbidities are excluded from large clinical trials.

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Inclusion of such individuals as study participants will not only allow results to be generalised, but will also offer opportunities to assess aspects of COPD that have thus far been poorly assessed. Additionally, trials of non-respiratory drugs such as angiotensin-2 inhibitors have been done, although results have so far been negative.<sup>108</sup> Database studies suggest that patients with COPD who use statins have a better prognosis than those who do not,<sup>109–111</sup> therefore the role of statins might be a useful area for future prospective study. Data like these are needed if we are to address the reasonable request for guidance about holistic management of patients.<sup>112</sup>

Traditional randomised placebo-controlled trials have limitations as a practical instrument to establish treatment efficacy in a disease in which symptoms continue and complications such as exacerbations are distressing. The issues of differential withdrawal from studies, especially when the treatment under study is already available and licensed for another indication, have already been noted. Patients who are willing to participate might not be representative of the disease in the community and so findings can underestimate or overestimate how useful the treatment will be in general medical practice. The use of administrative databases to generate treatment hypotheses continues to be a reasonable way forward, but, as data for the use of inhaled corticosteroids and mortality from COPD show, they can generate findings opposing those from randomised controlled trials. We will probably follow the cardiologists in increasing the complexity of our treatment regimens, because future trials will investigate whether a new treatment augments or can be substituted for existing treatment, rather than showing efficacy compared with treatment with short-acting bronchodilators.

Perhaps the greatest challenge for future trials in a slowly progressive condition such as COPD will be the development of a robust and transparent funding model allowing the benefits of these large and costly studies done by industry to be retained, yet at the same time guaranteeing an independent role for investigators interested in the outcome for clinical rather than commercial reasons; traditionally, large trials in COPD have been sponsored by both industry and government. Generally, industry trials have focused on the effects of new products. Government trials, by contrast, have assessed both the effects of drugs and non-pharmaceutical interventions (eg, NETT, oxygen) and, to a lesser extent, have investigated the biology of the disease. However, several industry-funded trials in collaboration with academic centres now look at basic questions about genetics, natural history, and disease heterogeneity. As interactions between industry, academia, and government become more complex, the organisational structure that permits these studies and the regulatory policies that govern them need to

evolve. Many of the studies discussed in this Review have helped us toward achievement of this goal, and as a result have greatly informed clinical practice, leading us to rethink the biology of COPD and to pose more specific questions relevant to our patients' needs.

#### Conflict of interest statement

PMAC has received laboratory and industry grants from Altana, BOC, Chiesi, and GlaxoSmithKline; has served as a consultant to or on advisory boards of Almirall, Altana, AstraZeneca, BOC, Chiesi, Dey, Novartis, GlaxoSmithKline, Roche, Schering-Plough, and Pfizer; and has been paid for speaking for Altana, AstraZeneca, BOC, Boehringer-Ingelheim, Chiesi, and GlaxoSmithKline. SIR has received laboratory and industry grants from Almirall, Altana, Astellas, Centocor, GlaxoSmithKline, Nabi, Novartis, and Pfizer; has served as a consultant to or on advisory boards of Adams, Almirall, Altana, AstraZeneca, Bend, Biolipox, Centocor, Critical Therapeutics, Dey, GlaxoSmithKline, ICOS, Johnson & Johnson, Novartis, Ono Pharma, Parengenix, Pfizer, Roche, Sankyo, Sanofi, Schering-Plough, and Talecris; and has been paid for speaking for AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Otsuka, and Pfizer.

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