

## Future expectations in COPD: measures of success

P.M.A. Calverley

*Future expectations in COPD: measures of success. P.M.A. Calverley. ©ERS Journals Ltd 2004.*

**ABSTRACT:** Chronic obstructive pulmonary disease (COPD) has a dramatic impact on patients' health-related quality of life and physical and emotional wellbeing. Patient expectations of COPD management include improvements in symptoms, exercise tolerance, health status, exacerbations and mortality. Even small improvements in care may have significant and important benefits for patients. Therefore, measuring the success of COPD management strategies from the patients' perspective is crucial.

A prerequisite of any chronic obstructive pulmonary disease management strategy is to include patient-recognised outcomes in order to measure accurately the effect of therapeutic intervention. In terms of therapy, in the absence of currently available, clinically effective disease-modifying pharmacological agents, patients may benefit from multi-modal individualised programmes, incorporating existing therapies and nonpharmacological interventions.

*Eur Respir Rev 2004; 13: 88, 22–27.*

Chronic obstructive pulmonary disease (COPD) has a dramatic impact on patients' health-related quality of life (HRQL), sometimes called health status, and on their physical and emotional wellbeing [1, 2]. Given the disabling and serious nature of the disease, patients have a right to expect compassion and access to diagnostic tests and management strategies that enable them to feel as well as possible. Evidence-based guidance on how best to do this is now available from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [3]. GOLD is an international initiative designed to raise awareness of the disease and improve its diagnosis, management and prevention. Regional and national guidelines are also being developed, such as those proposed jointly by the American Thoracic Society and the European Respiratory Society, which address issues specific to clinical practice in these geographical areas.

From the patients' perspective, there are certain expectations of COPD management. These expectations concern improving symptoms, exercise tolerance, health status, exacerbations and mortality. The goal of any intervention, be it pharmacological or nonpharmacological, should address these expectations. As a consequence, GOLD has proposed several objectives of COPD management to reflect the needs of patients (table 1).

This paper will discuss the measures of success of current COPD management strategies viewed from a patient's perspective and how these strategies can be refined in order to further improve outcomes.

### Measuring the success of current management strategies

COPD patients are often neglected because of a lack of health initiatives to help them manage their symptoms and a lack of resources to fund the care that they need [4]. As a result, a rather fatalistic attitude towards COPD has been adopted by both doctors and patients. However, small improvements in care can

Department of Medicine, University Hospital of Aintree, Liverpool, UK

Correspondence: P.M.A. Calverley  
Department of Medicine  
Clinical Sciences  
University Hospital Aintree  
Longmoor Lane  
Liverpool, L9 7AL  
UK  
Fax: 44 151 5295812  
Email: pmacal@liverpool.ac.uk

Keywords: Budesonide/formoterol in a single inhaler, COPD, exacerbation, health-related quality of life, outcome

have significant and important benefits for patients, highlighting the need to define appropriate outcomes by which the success of therapeutic interventions can be measured from a patient's perspective.

Although improving lung function is an important goal of COPD management, patients do not complain of poor lung function *per se* and it is unlikely that they would see this as an important outcome by itself. Instead, determinants such as exacerbations, symptoms, exercise tolerance and mortality are more readily appreciated outcomes by which patients determine whether treatment has been successful.

### Exacerbations

Exacerbations of COPD, which can be defined in various ways [1], have a dramatic adverse effect on patients' lung function, daily activities and HRQL [5, 6] and can significantly increase the risk of hospitalisation and death [7]. HRQL is worse in patients who have frequent exacerbations [6]. Hospitalisations for exacerbations have a huge impact on the healthcare costs associated with COPD [1, 8–10], while the economic impact is greater with increasing disease severity [8].

Table 1. – Global Initiative for Chronic Obstructive Lung Disease (GOLD) objectives for the management of patients with COPD

---

Prevent disease progression
Relieve symptoms
Improve exercise tolerance
Improve health status
Prevent and treat exacerbations
Prevent and treat complications
Reduce mortality
Minimise side effects of treatment

---

Table modified with permission from [3].

COPD management strategies that reduce the frequency of exacerbations have a profound positive impact on HRQL [11]. Thus, prevention and treatment of exacerbations are of paramount importance in any COPD management strategy [1].

### *Symptoms*

Symptoms of COPD cause a significant degree of disability, emotional disturbance and restriction of normal daily and social activities [12–15]. These symptoms can be assessed relatively easily using patient diaries. The most frequent complaint from COPD patients, and probably the most prominent symptom limiting health status and activities of daily living, is dyspnoea during customary activity [3, 16–18].

The severity of dyspnoea is often under-estimated. According to the Confronting COPD International Survey of >3,000 COPD patients across North America and Europe performed in 2000; a significant disparity was evident between patients' perception of disease severity and the degree of severity as indicated using a more objective breathlessness scale [19]. More than two-thirds of patients with the most severe breathlessness, which rendered them unable to get dressed or leave the house, described their condition as only mild or moderate. These patients had adapted their lifestyles to their symptoms over time. Some patients, as a consequence of adapting their behaviour to suit their symptoms, may appear to be free of symptoms. However, the goal of any management strategy should be to enable patients to carry out normal, simple daily tasks while controlling their symptoms.

Other chronic symptoms (cough, sputum production, night-time awakenings) associated with COPD have an important effect on the daily lives of patients and their families [3]. Sleep disturbance is a common complaint among patients, particularly the elderly, with chronic airway diseases [20]. According to the British Lung Foundation's 'Breathe Easy' survey of COPD patients in the UK, 31% of respondents woke up every night because of their COPD, while 72% claimed their illness affected their ability to take a holiday [21].

### *Exercise tolerance*

Exercise tolerance is beginning to gain recognition as an important non-invasive patient-centred outcome. There is a close association between dyspnoea and exercise tolerance, and both influence patients' health status, regardless of disease severity [22–25]. Validated instruments, such as the Transitional Dyspnoea Index (TDI) and the 6-minute walking test, are responsive to changes in dyspnoea and exercise capacity [22, 26] in relation to disease progression or therapeutic intervention. Exercise tolerance can also be measured by recording end-expiratory and end-inspiratory lung volume before, during and after physical exertion. A recent study in patients with symptomatic but stable COPD found that some individuals developed dynamic hyperinflation during exercise, *i.e.* their end-expiratory lung volume rose; the expected physiological abnormality in advanced COPD [27]. However, in the remaining patients, exercise was accompanied by a fall in end-expiratory lung volume, which mimicked the normal change in healthy people, while there was no tendency towards dynamic hyperinflation. These differing patterns of response to exercise in COPD

patients may reflect diverse disease mechanisms, although all mechanisms have similarly disabling consequences. More importantly, they may require different treatment strategies to obtain maximum benefit for the patient.

### *Health-related quality of life*

Most measures of COPD, symptoms, exacerbations and lung function, are associated with, and impact on, HRQL [6, 11]. Changes in HRQL are apparent to patients with COPD [16] and even small improvements that enable patients to become more active may be meaningful to the individual, allowing him or her to live a more normal, independent life. Setting patient goals (*e.g.* walking to the shops, being able to do the gardening) may be important to measure the success of interventions on an individual basis. As a consequence of the effect of COPD on daily activities, HRQL affects the psychological and emotional status of individuals. Validated instruments, such as the St George's Respiratory Questionnaire (SGRQ), may be used effectively to quantify changes in HRQL [12, 28].

### *Mortality*

In 2000, COPD was the fourth leading cause of mortality worldwide [29]. One of the objectives of any future COPD management strategy, according to GOLD recommendations, should be to reduce mortality [3]. Mortality rates can be reduced with effective management of the disease. In a retrospective analysis of patients receiving inhaled corticosteroids (ICS) following discharge from hospital, mortality rates were decreased by 29% and readmission rates were reduced by 24% compared with patients who did not receive ICS [30]. Pharmaco-epidemiological studies suggest a reduction in mortality with ICS/long-acting  $\beta_2$ -agonist (LABA) combinations compared with a reference population and patients receiving ICS or LABA alone [31, 32]. A large, prospective randomised clinical study, Towards a Revolution in COPD Health (TORCH), is underway to determine whether adding an ICS to a LABA increases survival in patients with moderate to severe COPD (GOLD stages II/III) [33]. The study, which spans a period of 3 yrs, includes patients randomised to receive a combination of ICS and LABA, ICS alone, LABA alone or placebo.

Future COPD management strategies should be expected not only to measure accurately the effect of treatment on these outcomes, but also to reduce the number of patients who are affected by the debilitating aspects of the disease.

### **Improving patients' daily lives**

Probably the most important intervention in COPD is smoking cessation; however, this on its own is not sufficient to manage the disease once lung damage and symptoms have developed [34] and patients should be made aware of this. Management of COPD should involve several different treatment approaches, all directed at controlling symptoms, improving exercise capacity, preventing exacerbations and thereby improving health status and wellbeing [34].

Despite a lack of disease-modifying interventions, it is clear

that there are drug therapies and nonpharmacological measures (e.g. smoking cessation, pulmonary rehabilitation, supplementary oxygen self-management and noninvasive positive pressure ventilation) that can benefit patients, especially in terms of reducing exacerbations and improving HRQL [3]. The role of ICS as maintenance therapy in COPD is not yet clearly defined [35]; however, they do provide a benefit in terms of reducing exacerbations [36–39].

Airflow obstruction is a persistent characteristic of COPD; therefore, a reasonable approach to managing stable disease is to try to maintain effective and continuous bronchodilation [34]. Bronchodilators are essential to the management of COPD, and are given to relieve or prevent symptoms, reduce dynamic hyperinflation and improve lung function [40]. The main classes of bronchodilators used in COPD include  $\beta_2$ -agonists (short- and long-acting), anticholinergics (e.g. tiotropium and ipratropium) and theophylline [35, 41]. Combination therapies, including ICS and LABA (e.g. budesonide/formoterol in a single inhaler and fluticasone/salmeterol), have been shown to reduce effectively the frequency and severity of exacerbations and have a beneficial effect on symptoms [38, 39, 42, 43], such as night-time awakenings (figure 1). This, in turn, has a beneficial impact on lung function and HRQL [11, 39, 44].

Optimal treatment of COPD relies on a greater understanding of the mechanisms underlying COPD and COPD exacerbations and the impact of the disease on health outcomes [1].

### Improving the management of COPD

It is clear that an improvement in the management of COPD is needed to help patients feel more positive about their illness. Pharmacological therapies (e.g. ICS/LABA combinations) are available that reduce symptoms and the number of exacerbations, improve HRQL and possibly decrease mortality [4, 11, 31, 32, 38, 44]; however, in order to improve disease management, these therapies need to be used optimally.

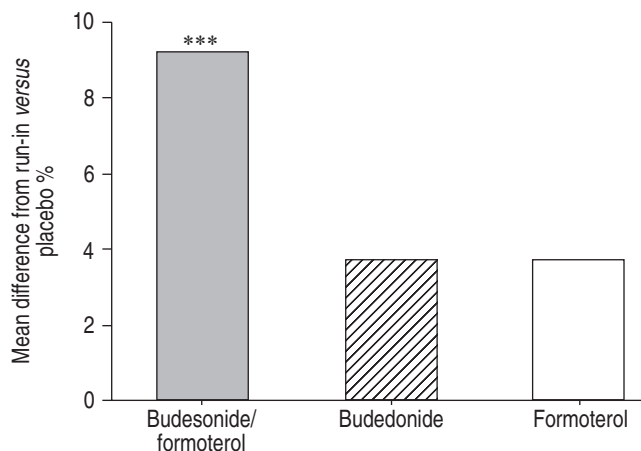


Fig. 1. – Data presented as mean difference from run-in of budesonide/formoterol (■); budesonide (▨); or formoterol (□) versus placebo. Use of combination therapy with budesonide/formoterol in a single inhaler increases the number of nights without awakenings when compared with budesonide and formoterol given alone in patients with chronic obstructive pulmonary disease (COPD).  $p < 0.05$  for combination therapy versus budesonide or formoterol given alone. \*\*\*:  $p < 0.001$  versus placebo. Data taken from a 12-month, randomised, placebo-controlled, double-blind study involving 1,022 patients with COPD (GOLD stage III–IV) [44].

### Early intervention of therapy

One possibility for more effective management of COPD is early therapeutic intervention mediated by early diagnosis. Early diagnosis may benefit patients since they may receive effective therapy at an earlier stage of disease as well as being made aware of the importance of avoiding irritants that aggravate their lung disease and the need to stop smoking [45]. Prompt and accurate diagnosis of COPD depends on the use of spirometry to detect airflow obstruction and lung disease [46, 47]. Although defined as the method of choice for the diagnosis of COPD [3], spirometry is sometimes not used in general practice [4]. Clinical symptoms and signs, such as abnormal shortness of breath and increased forced expiratory time, can be used to help with the diagnosis, as can patient characteristics, such as age and smoking habit [3]. Some symptoms associated with COPD, such as a low peak flow, have poor specificity, since they can also be caused by other lung diseases [3].

It is likely that patients would experience significant benefits through early intervention of therapy. For example, early intervention with prophylactic, nonpharmacological interventions that can prevent or delay the time to exacerbations, will clearly have benefits for the patient in terms of the decline in lung function and health status. As mentioned previously, an important aspect of COPD management is smoking cessation. Further to this, however, is the maintenance of a healthy lifestyle with regular exercise and good nutrition, which should help to maintain a healthy weight [48].

### Predicting exacerbations

It is important to understand the triggers and mechanisms of exacerbations to predict their onset [1]. Several factors are linked to exacerbations of COPD and may possibly be useful for predicting their occurrence [1]. Changes in symptoms that patients can detect may appear to be useful predictors of exacerbations in populations of patients, but their variability within individual patients makes them unreliable on a patient-by-patient basis [1].

### Adjustable dosing

Therapy that allows for adjustable dosing has proven effective in the management of asthma and it may be feasible to extrapolate these results to the COPD setting. For example, adjustable maintenance dosing with budesonide and formoterol in a single inhaler has been shown to improve asthma symptom severity, reduce the number of asthma exacerbations and reduce healthcare costs [49–52]. If proven effective, adjustable dosing in COPD could form part of a self-management programme.

### Design of clinical studies

Well-designed clinical studies are essential for the accurate evaluation of therapies. For instance, in some clinical studies it can be difficult to determine whether the improvement observed in patient-centred outcomes, such as health status, is due to closer attention from healthcare professionals or is a result of the treatment itself. A study by CALVERLEY *et al.* [44]

was designed with the intention of minimising such ambiguity by using symptom-control measures. In this study of budesonide/formoterol combination therapy *versus* placebo and monocomponents, COPD patients received intensified treatment with inhaled formoterol and oral steroids for two weeks before entering into the study [44]. Thus, a more realistic comparison was possible between the effect of treatment on health status. Differences between treatment groups were more pronounced in this study: in particular, the additional clinical benefit of budesonide/formoterol in a single inhaler in terms of time to first exacerbation requiring medical intervention and HRQL (qualified using the SGRQ) (fig. 2) were greater compared with placebo and budesonide or formoterol given alone.

The design of clinical studies in the future should perhaps include more accurate questionnaires, so that a more precise interpretation of the extent to which study treatment is effective, or otherwise, can be made. The use of data collated from diary cards completed by patients may be of great importance. These data have both clinical and statistical validity, since changes in health status are often reflected in symptom-based information given by patients.

A prerequisite of any future COPD management strategy is to include the most appropriate outcomes in order to measure accurately the effect of therapeutic intervention. Patient-centred outcomes may be appropriate measures of quantifying the efficacy of therapy as these are outcomes that patients can recognise. Such outcomes include symptoms, exercise tolerance, HRQL, exacerbations and ability to perform activities of daily living [53, 54]. A holistic approach to COPD management may be required to further improve outcomes.

Defining outcomes in clinical studies should also reflect the severity of disease in recruited patients. Some outcomes, for instance exacerbations, are only documented in patients with

more severe disease; therefore, the effect of therapy in patients with less severe disease may not be measured accurately unless other outcomes are considered. Data from CALVERLEY *et al.* [38] suggest that symptoms in patients with less severe disease are improved with the use of a combination of ICS and a LABA.

### New therapies

Better utilisation of existing therapies, as outlined above, would improve the benefits of existing drugs in preventing and reducing the signs and symptoms of COPD, and in reducing the number and severity of exacerbations. However, there are currently no therapies available to control the inflammatory processes underlying the disease.

Research into the inflammatory processes involved in the airways of COPD patients has led to the discovery of new potential ‘disease modifying’ therapeutic agents, including cytokine and chemokine inhibitors [41, 55, 56]. A number of these potentially promising therapies are currently in clinical development [57]. Increased levels of cytokines, including interleukin (IL)6 and tumour necrosis factor (TNF)- $\alpha$  have been measured in the sputum of COPD patients [58] and some of these molecules may be the target of therapy. For instance, IL-5 and IL-13 inhibitors both show promise as therapies for chronic airway diseases [56]. Inhibition of TNF- $\alpha$  may be useful for treating severe COPD with systemic features [56]. Several small molecule inhibitors of chemokine receptors are in clinical development, including CXCR2 antagonists, which block neutrophil and monocyte chemotaxis [56].

Interestingly, phosphodiesterase-IV inhibitors also show potential for the treatment of inflammatory airways diseases, such as COPD [59] and research into their impact on clinical measures of COPD is underway. Matrix metalloproteinase (MMP) inhibitors are another group of compounds that are under investigation for the treatment of COPD. MMP-9 (gelatinase) is an MMP that is present in low quantities in the healthy adult lung, but is much more abundant in several lung diseases, including asthma and COPD [60].

### Future management of COPD exacerbations

Management of COPD exacerbations in the future is likely to involve more programmes that care for patients in the community, such as the ‘hospital at home’ concept [61]. The ‘hospital at home’ programme in the study by DAVIES *et al.* [61] included a specialist nurse escorting the patient home from the hospital; prescription of nebulised ipratropium bromide and salbutamol with a compressor, oral prednisolone for 10 days and antibiotics for 5 days; visits by nurses both morning and evening for 3 days and thereafter at the discretion of the nurse; and evening and night cover provided by district nurses. This type of management relies on accurate assessment of patients in the hospital accident and emergency department in order to identify patients who would be eligible for care at home rather than in hospital. For instance, patients with a history of asthma, an impaired level of consciousness, acute changes on radiography or an electrocardiogram, or who required intravenous therapy may not be eligible for outpatient care and should be admitted to hospital [61, 62]. Evidence suggests that patients are comfortable with this type of outpatient management [61,

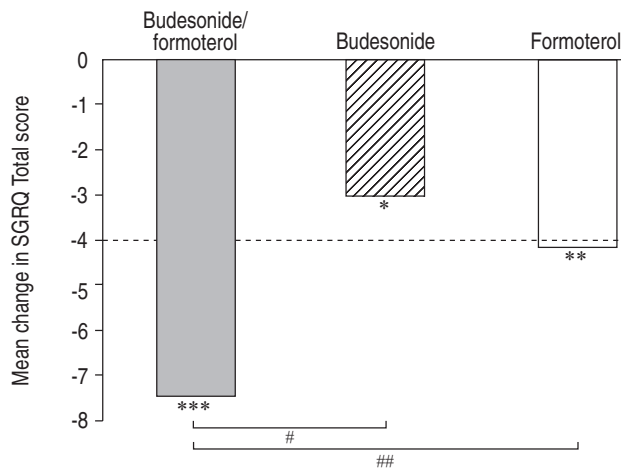


Fig. 2.— Data presented indicates the mean change in St George’s Respiratory Questionnaire (SGRQ) total score *versus* placebo for budesonide/formoterol (■), budesonide (▨) or formoterol (□). Management of chronic obstructive pulmonary disease (COPD) with the use of budesonide/formoterol in a single inhaler provides an additional clinical benefit in terms of health status compared with budesonide or formoterol given alone or placebo. Health status was quantified by measuring change in St George’s Respiratory Questionnaire (SGRQ) total score from randomisation *versus* placebo in a 12-month, randomised, placebo-controlled, double-blind study involving 1,022 patients with COPD (GOLD stage III–IV) ([43, 44]). ----- : clinically important difference relevant to the patient; \*:  $p < 0.05$  *versus* placebo; \*\*:  $p < 0.01$  *versus* placebo; \*\*\*:  $p < 0.001$  *versus* placebo; #:  $p = 0.014$ ; #:  $p = 0.001$ .

62]. However, although this represents an effective and practical alternative to hospitalisation in selected patients, the exact criteria for eligibility to this type of management are uncertain [3]. The role of self-management for COPD exacerbations remains unclear [2].

### Conclusions

The future of care for COPD patients in terms of pharmacological interventions lies with disease-modifying agents. However, these will not be available for a number of years. In the meantime, patients may benefit from multi-modal individualised programmes including existing therapies and non-pharmacological interventions. Combination therapy with ICS and LABA has been shown to offer the greatest benefits for patients with regard to patient-centred outcomes (reduction in exacerbations, sustained and clinically relevant improvements in HRQL, and rapid and sustained relief of symptoms).

Improvements in education, for both patients and healthcare providers, and access to and utilisation of existing interventions may enhance the management of COPD and provide the opportunity for patients to manage their own symptoms, allowing them to remain at home and maintain their independence.

It is possible to improve our patients' lives with current therapies and allow them to achieve daily goals that are important to them. Using appropriate patient-centred measures of success in current clinical studies is likely to pave the way for improvements in the administration of future therapies, which will be based on individual patient needs.

### References

- Vestbo J. What is an exacerbation of COPD? *Eur Respir Rev* 2003; 88: 6–13.
- Partridge MR. Living with COPD: the patients' perspective. *Eur Respir Rev* 2003; 88: 1–5.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda, MD: National Institutes of Health. (NIH Publication No. 2701); 2003.
- Partridge MR. Patients with COPD: do we fail them from beginning to end? *Thorax* 2003; 58: 373–375.
- Anto JM, Vermeire P, Vestbo J, Sunyer J. Epidemiology of chronic obstructive pulmonary disease. *Eur Respir J* 2001; 17: 982–994.
- Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1418–1422.
- Patil SP, Krishnan JA, Lechtzin N, Diette GB. In-hospital mortality following acute exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med* 2003; 163: 1180–1186.
- Andersson F, Borg S, Jansson SA, *et al.* The costs of exacerbations in chronic obstructive pulmonary disease (COPD). *Respir Med* 2002; 96: 700–708.
- Miravittles M, Murio C, Guerrero T, Gisbert R, DAFNE Study Group. Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. *Chest* 2002; 121: 1449–1455.
- Wouters EF. Economic analysis of the Confronting COPD survey: an overview of results. *Respir Med* 2003; 97 (Suppl. C): S3–S14.
- Jones PW, Ståhl E. Reducing exacerbations leads to a better health-related quality of life in patients with COPD. *Eur Respir J* 2003; 22: Suppl. 45, 238S.
- Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; 145: 1321–1327.
- McSweeney AJ, Grant I, Heaton RK, Adams KM, Timms RM. Life quality of patients with chronic obstructive pulmonary disease. *Arch Intern Med* 1982; 142: 473–478.
- Ketelaars CA, Schlosser MA, Mostert R, *et al.* Determinants of health-related quality of life in patients with chronic obstructive pulmonary disease. *Thorax* 1996; 51: 39–43.
- Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Comparison of discriminative properties among disease-specific questionnaires for measuring health-related quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 785–790.
- Murdoch I, Ståhl E, Ahlström L, Löfdahl CG. Understanding patients' needs: the impact of COPD. *Eur Respir J* 2003; 22: Suppl. 45, 69S.
- Mahler DA, Faryniarz K, Tomlinson D, *et al.* Impact of dyspnea and physiologic function on general health status in patients with chronic obstructive pulmonary disease. *Chest* 1992; 102: 395–401.
- Elias Hernandez MT, Ortega Ruiz F, Sanchez Riera H, Otero Candelera R, Sanchez Gil R, Montemayor Rubio T. Role of dyspnea in quality of life of the patient with chronic obstructive pulmonary disease. *Arch Bronconeumol* 1999; 35: 261–266.
- Rennard S, Decramer M, Calverley PM, *et al.* Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. *Eur Respir J* 2002; 20: 799–805.
- Bellia V, Catalano F, Scichilone N, *et al.* Sleep disorders in the elderly with and without chronic airflow obstruction: the SARA study. *Sleep* 2003; 26: 318–323.
- Breathing fear: the COPD effect. Report commissioned by Allen & Hanburys and the British Lung Foundation, September 2003.
- Oga T, Nishimura K, Tsukino M, Hajiro T, Ikeda A, Mishima A. Relationship between different indices of exercise capacity and clinical measures in patients with chronic obstructive pulmonary disease. *Heart Lung* 2002; 31: 374–381.
- Berry MJ, Rejeski WJ, Adair NE, Zaccaro D. Exercise rehabilitation and chronic obstructive pulmonary disease stage. *Am J Respir Crit Care Med* 1999; 160: 1248–1253.
- Stavem K, Boe J, Erikssen J. Health status, dyspnea, lung function and exercise capacity in patients with chronic obstructive pulmonary disease. *Int J Tuberc Lung Dis* 1999; 3: 920–926.
- Hajiro T, Nishimura K, Tsukino M, Ikeda A, Oga T. Stages of disease severity and factors that affect the health status of patients with chronic obstructive pulmonary disease. *Respir Med* 2000; 94: 841–846.
- Carter R, Holiday DB, Nwasuruba C, Stocks J, Grothues C, Tjep B. 6-minute walk work for assessment of functional capacity in patients with COPD. *Chest* 2003; 123: 1408–1415.
- Aliverti A, Stevenson N, Dellacà RL, Lo Mauro A, Pedotti A, Calverley PMA. Regional chest wall volumes during exercise in chronic obstructive pulmonary disease. *Thorax* 2004 (In press).
- Ståhl E, Jansson S-A, Jonsson A-C, Svensson K, Lundbäck B, Andersson F. Health-related quality of life, utility, and productivity outcomes instruments: ease of completion by subjects with COPD. *Health Qual Life Outcomes* 2003; 1: 18.
- Murray CJL, Lopez AD, Mathers CD, Stein C. The Global Burden of Disease 2000 Project: global programme on evidence for health policy discussion, paper number 36. Geneva: WHO, 2001.
- Sin DD, Tu JV. Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 580–584.

31. Soriano JB, Vestbo J, Pride NB, Kiri V, Maden C, Maier WC. Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice. *Eur Respir J* 2002; 20: 819–825.
32. Soriano JB, Kiri VA, Pride NB, Vestbo J. Inhaled corticosteroids with/without long-acting  $\beta$ -agonists reduce the risk of rehospitalization and death in COPD patients. *Am J Respir Med* 2003; 2: 67–74.
33. Calverley PMA, Celli B, Ferguson G, *et al.* Baseline characteristics of the first 5,000 COPD patients enrolled in the TORCH survival study. *Eur Respir J* 2003; 22: Suppl. 45, 578S.
34. Calverley PMA, Walker P. Chronic obstructive pulmonary disease. *Lancet* 2003; 362: 1053–1061.
35. Van Schayck OCP, Rabe KF, Rudolf M. COPD: The role of primary care in effective diagnosis, treatment and management. *Prim Care Respir J* 2003; 12: 16–20.
36. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group. *Lancet* 1998; 351: 773–780.
37. Burge PS, Calverley PMA, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive airways disease: the ISOLDE trial. *BMJ* 2000; 320: 1297–1303.
38. Calverley P, Pauwels R, Vestbo J, *et al.* Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; 361: 449–456.
39. Szafranski W, Cukier A, Ramirez A, *et al.* Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003; 21: 74–81.
40. Pauwels RA, Buist AS, Calverley PMA, Jenkins CR, Hurd SS on behalf of the GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary. *Am J Respir Crit Care Med* 2001; 163: 1256–1276.
41. Di Maria G, Spicuzza L, Mazzarella G. Future treatment of chronic obstructive pulmonary disease. *Monaldi Arch Chest Dis* 2002; 57: 200–205.
42. Chapman KR. Seretide for obstructive lung disease. *Expert Opin Pharmacother* 2002; 3: 341–350.
43. Marchand E. Survival in COPD patients after regular use of fluticasone propionate and salmeterol. *Eur Respir J* 2003; 21: 559–560.
44. Calverley PMA, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H on behalf of study group. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 22: 912–919.
45. Blanchard AR. Treatment of COPD exacerbations. Pharmacologic options and modification of risk factors. *Postgrad Med* 2002; 111: 65–75.
46. Petty TL. Scope of the COPD problem in North America: early studies of prevalence and NHANES III data: basis for early identification and intervention. *Chest* 2000; 117 (Suppl. 2): 326S–331S.
47. Doherty DE. Early detection and management of COPD. What you can do to reduce the impact of this disabling disease. *Postgrad Med* 2002; 111: 41–44.
48. Hunter MH, King DE. COPD: Management of acute exacerbations and chronic stable disease. *Am Fam Physician* 2001; 64: 603–612.
49. Sears MR, McIvor A, Becker A, *et al.* Budesonide/formoterol adjustable maintenance dosing effectively improves asthma symptom severity: a multicentre Canadian study. *Eur Respir J* 2003; 22: Suppl. 45, 258S.
50. FitzGerald M, Boulet LP, McIvor A, *et al.* Adjustable maintenance dosing with budesonide/formoterol reduces asthma exacerbations compared with fixed dosing – a 5-month study in Canada. *Eur Respir J* 2003; 22: Suppl. 45, 411S.
51. Ställberg B, Olsson P, Jörgensen LA, Lindarck N, Ekström T. Budesonide/formoterol adjustable maintenance dosing reduces asthma exacerbations *versus* fixed dosing. *Int J Clin Pract* 2003; 57: 656–661.
52. Olsson P, Karlsson G, Ekström T, Lindarck N. Adjustable dosing with budesonide/formoterol in a single inhaler reduces costs compared with a conventional fixed-dosing regimen. *Eur Respir J* 2003; 22: Suppl. 45, 411S.
53. Van der Molen T, Pieters W, Bellamy D, Taylor R. Measuring the success of treatment for chronic obstructive pulmonary disease - patient, physician and healthcare payer perspectives. *Respir Med* 2002; 96 (Suppl. C): S17–S21.
54. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J* 2002; 19: 398–404.
55. Friedman M. Future treatment strategies for COPD. *Clin Cornerstone* 2003; 5: 45–51.
56. Barnes PJ. Cytokine-directed therapies for the treatment of chronic airway diseases. *Cytokine Growth Factor Rev* 2003; 14: 511–522.
57. Blease K, Raymon HK. Small molecule inhibitors of cell signalling: novel future therapeutics for asthma and chronic obstructive pulmonary diseases. *Curr Opin Investig Drugs* 2003; 4: 544–551.
58. Chung KF. Cytokines in chronic obstructive pulmonary disease. *Eur Respir J* 2001; 18: Suppl. 34, 50s–59s.
59. Gamble E, Grootendorst DC, Brightling CE, *et al.* Anti-inflammatory effects of the phosphodiesterase-4 inhibitor cilomilast (Ariflow) in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; 168: 976–982.
60. Atkinson JJ, Senior RM. Matrix metalloproteinase-9 in lung remodelling. *Am J Respir Cell Mol Biol* 2003; 28: 12–24.
61. Davies L, Wilkinson M, Bonner S, Calverley PMA, Angus RM. “Hospital at home” *versus* hospital care in patients with exacerbations of chronic obstructive pulmonary disease: prospective randomised controlled trial. *BMJ* 2000; 321: 1265–1268.
62. Skwarska E, Cohen G, Skwarski KM, *et al.* Randomised controlled trial of supported discharge in patients with exacerbations of chronic obstructive pulmonary disease. *Thorax* 2000; 55: 907–912.

# Instructions to authors

THE EUROPEAN RESPIRATORY REVIEW, the official journal of the European Respiratory Society. Clinical and experimental work dealing with the whole field of respiratory medicine, including cell biology, epidemiology, immunology, pathophysiology, paediatric pneumology, occupational medicine, intensive care, sleep medicine, and thoracic surgery, will be published.

Presentation of manuscripts should conform with the **Uniform Requirements for Manuscripts Submitted to Biomedical Journals**, (see *N Engl J Med* 1997; 336: 309–315).

**Manuscript with illustrations should be e-mailed to:**  
**Sherwood Burge**

c/o Vicky Huggins at [vicky.huggins@heartsol.wmids.nhs.uk](mailto:vicky.huggins@heartsol.wmids.nhs.uk)

**Electronic copies of manuscripts can be mailed to: P.S. Burge, Respiratory Medicine, Birmingham Heartlands Hospital, Bordesley Green East, BIRMINGHAM, UK.**

**The journal does not hold itself responsible for loss or damage to mailed manuscripts.**

Authors submitting a paper do so on the understanding that the work has not been published before nor has it been submitted to another scientific journal or is being considered for publication elsewhere. The work has been approved by all co-authors, if any. Submission of the manuscript also implies that if and when it is accepted for publication the authors automatically agree to transfer the copyright to the publisher.

The copyright protection implies that the publishers holds the exclusive right to reproduction (including publication in another language) and distribution of any of the articles in the journal. Material published in this journal may only be stored on microfilm, video discs and in electronic database etc. and be reproduced photographically with a prior written permission of the publisher.

Each manuscript will be reviewed by an Associate Editor and reviewers.

## ■ Conflicts of interest

Any conflict of interest for a given manuscript must be dealt with according to the statement of the International Committee of Medical Journal Editors (the "Vancouver Group") as published in the *Lancet* 1993; 341: 742. The editors and reviewers of the European Respiratory Review must disclose to the Chief Editor any personal or financial relationship that could bias their opinion and decision in the peer review process. Every author of each manuscript is responsible for recognizing and disclosing financial and other conflicts of interest related to their study or to the subject of their review or editorial article. The authors have to acknowledge in a manuscript all financial support for the work and other financial or personal connections to the work. In case of single- or multi-centre trials with blinded intervention, the code must have been broken at the end of the study in the presence of the responsible investigator of each centre. The code and the data will then be available to each participating centre. The first author makes provisions that, if needed, the code and the data are available to the European Respiratory Review for independent statistical analysis.

## ■ Preparation of manuscripts

The text should be typewritten with an electronic typewriter or letter quality computer printer. The format must be in numbered pages with double line spacing, on one side of the paper only, and with wide margins.

Abbreviations or unusual terms should be described at the first time of use. Symbols as defined by the *ad hoc* working group of the Commission of the European Communities (see *Eur Respir J* 1993; 6: Suppl. 16) are recommended. Système International (SI) units are recommended.

The presentation should have the following components on separate pages:

## ■ Title page

It should contain:

(1) a concise informative title, not longer than 90 letters; (2) name(s) of author(s); (3) name of department(s)/institution(s); (4) corresponding author's name, address, telephone and fax numbers, including country code; (5) a running head of not more than 45 letters and spaces; (6) keywords using, where possible, terms of the Medical Subjects Headings list from Index Medicus.

## ■ Abstract

Provide an Abstract of not more than 200 words, which is easily understood without reference to the text (see *Ann Intern Med* 1987; 106: 598–604). The Abstract **must** have 4 separate paragraphs for the **question of the study, materials/patients and methods, results, and the answer to the question**. Include one or two sentences of background information before the question, if necessary. The question and answer should be the same as those in the text. Include only a few important values. Avoid using abbreviations and reporting detailed statistics.

## ■ Introduction

State the question you asked (or hypothesis to be tested) and your considerations leading to the formulation of the question. Give only pertinent references.

## ■ Material and Methods

### *Study subjects or animals*

Describe the selection of subjects or experimental animals, including controls (for animals, see *Laboratory Animals* 1985; 19: 106–108). All work involving studies on human subjects is expected to have received approval from local Ethical Committees. Animal experimentation must be performed according to the Helsinki convention for the use and care of animals. The Editors reserve the right to refuse work which does not conform to acceptable ethical criteria.

### *Study design*

Provide a brief overview of the tests or experiments, that is the strategy for answering the question(s). In this subsection, include the independent variable(s) manipulated, the dependent variable(s) measured and all controls. Do not include details of methods.

### *Methods*

Describe methods and apparatus in sufficient detail to allow other workers to evaluate or reproduce the tests/experiments. For methods that have been published, provide only a reference or a reference and a brief description. Identify drugs and chemicals, including generic name, dosage and route of administration.

### *Analysis*

Define the variables clearly. Use statistical analysis that is appropriate for the study. Give sample size estimation, particularly if a type II error may be involved. Describe clearly the statistical methods you used for each analysis: give references for tests that are not well known. For guidance, see *BMJ* 1983; 286: 1489–1493, *BMJ* 1986; 292: 746–750 and *BMJ* 1986; 292: 810–812. Use proper analysis for repeatability (*Lancet* 1986; i: 307–310).

## ■ Results

Include only important results, that is, results that help answer the question. Present most data in figures or tables, not in the text. In the text emphasize or summarize the most important observations. Describe the prestudy condition of patients or animals in Methods, not in Results. Keep the Results section brief.

## ■ Discussion

At the beginning of the Discussion summarize the main results, the answer to the question asked in the introduction (check that the results answer the question) and briefly support the answer with the relevant results. Then, as necessary, explain or defend the answer, explain contradictory or unexpected results and discrepancies with

previous findings, describe limitations of the methods, and discuss possible implications. Emphasize the new and important aspects of the study. Make sure that the conclusions at the end are pertinent to the question and the answer.

#### ■ Acknowledgements

All acknowledgements should be grouped into one paragraph placed after Discussion. Acknowledge only persons who have made substantial contributions to the study.

#### ■ References

Number references consecutively in the order in which they first appear in the text, using Arabic numerals in parentheses. All authors cited and only these must be included in the reference list. For original articles we suggest limiting the number of references to 30. References should conform to the style used in Index Medicus (Vancouver Style) as shown in the following examples:

1. Gelb AF, Zamel N. Lung recoil and density dependence of maximum expiratory flow in emphysema. *Bull Eur Physiopathol Respir* 1981; 17: 793–798.

2. Hyatt RE, Mead J, Rodarte JR, Wilson TA. Changes in lung mechanics. Flow-volume relationships. In: Macklem PT, Permutt S, eds. *The lung in transition between health and disease*. New York, NY, USA, Dekker, 1979; pp. 73–112.

Work, which has not yet been accepted for publication, and personal communications should not appear in the reference list.

#### ■ Tables

Tables should be numbered consecutively with Arabic numerals. Units should be presented in one row. Limit decimals to a sensible number. Type each table on a separate sheet with a self-explanatory title and concise footnotes. Large tables should be avoided. The Editors may recommend that additional tables containing important back-up

data be deposited with the National Auxiliary Publication Service or other permanent organisations; such a deposition should be noted in the text.

#### ■ Figures

Provide a legend to each figure. Photomicrographs must have internal scale markers (linear scale), since the size and magnification may be altered by the publisher. Figures should be professionally drawn, planning for reduction to column width, with words and numerals large enough to retain their clarity; preferably provide glossy photographs; computer and artist drawn graphs are also acceptable. Colour illustrations must be paid for by the authors. Ask the Production Office for a quotation before you decide.

In general, figures to be reduced to one column width should be drawn with the abscissae two columns wide (16 cm). Do not crowd the figures or axes with too many numerals or words. Label the figures on the back with the author's name and figure number, and indicate the top of the figure.

Reproduction is normally black and white. Colour is available through discussion with the Journals Manager.

#### ■ Proofs and reprints

A proof will be sent by express mail delivery or fax to the corresponding author. It should be corrected and returned to the ERJ Production Office within 48 h by fast mail or fax (for address and number, see below). Late return will delay publication. Modification to proofs should be limited to typographical errors only.

#### ■ Further information and enquiries

Copies of these instructions can be obtained from:

**The European Respiratory Society Journals Ltd, Suite 2.4, Hutton's Building, 146 West Street, Sheffield S1 4ES, UK. Tel: 44 1142-780498. Fax: 44 1142-780501.**