National Clinical Guideline Centre

Chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care

Update guideline

All update work added to the original guideline is highlighted in pink

Note to stakeholders:

The Guideline Development Group wish to point out that this is a partial update of an existing guideline, with the integration of new sections into the old publication. This has inevitably led to inconsistencies in style, particularly where new tables and forest plots have been inserted alongside old-style evidence statements, and also where new recommendations (without any gradings) have been added to, or replaced, existing recommendations which do have gradings.

The expanded section on Inhaled Therapy (which now incorporates the previous separate sections on Inhaled Bronchodilators, Inhaled Corticosteroids and Inhaled Combination Therapy) now concludes with a number of new recommendations which have all been grouped together for ease of reference, although this has necessitated their being somewhat removed from their supporting evidence.

The guideline was first published in February 2004 and updated and published in June 2010.

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Contents

NOTE: the evidence tables are in separate files.

Preface to original guideline

COPD is common but for many years it was largely ignored on the (false) grounds that little could be done. However in the last 10 years there has been a surge in research interest and several new treatment options. The first Guidelines on the Management of COPD (published by the British Thoracic Society in Jan 1997) led to significant improvements in the recognition and care of COPD. Since then new treatment possibilities including long-acting bronchodilator drugs, respiratory rehabilitation services, and non-invasive ventilation in respiratory failure, have meant that a revision is overdue.

The guideline was commissioned from NICE and the scope for the project was developed by National Collaborating Centre with input from all the stakeholders registered with NICE. The agreed final project scope advises that since it is aimed at the NHS, the guideline should concentrate on the health aspects of COPD. However it should also include the need for support from other agencies including social services, and should set out the interface with such services but not discuss their detailed provision.

There are other national and international guidelines for COPD but this is the first to systematically bring together and examine all the evidence in the published literature. The systematic nature of the approach provides an explicit audit trail of what has and has not been identified and how it was treated. Because the project scope was so wide ranging, even with an extremely hard working and dedicated team, it has not been possible to examine every paper on every question. Pragmatic choices have had to be made. Thus we searched first for the best quality research studies and if several were found that provided a strong evidence base, we did not continue to search for papers of lesser quality. The searching for, and systematic critical appraisal of, studies has been done using standard techniques and all searches will be available to future researchers. We believe it is unlikely that important papers have been missed either by the technical team in their searches or by the expertise of the guideline groups.

The guideline had to cover all aspects of the disease so that local care pathways could be defined using the document. Where there were gaps between the evidence, these have been filled with best practice recommendations based on a formal consensus of the experts on our guideline groups.

In each section of the document the level of supporting evidence is made clear on the understanding that the stronger the evidence the greater likelihood that the recommendations based on it are sound. However the reader should not equate level of evidence with strength of recommendation - some of the most important recommendations with greatest consequences for the health service or for people with COPD have been made by group consensus because there was inadequate evidence. This is what the experts believe to be best practice i.e. what they would recommend for their patients or relatives.

While the detail of local implementation of this guideline may vary (according to local facilities and geography), the main aims ought to be common across England and Wales and if adopted should lead to better standards of care and thus better outcomes from this often distressing condition. But implementation will depend on both clinicians and managers working together to ensure that resources and patient needs are matched. COPD is a common disease with many different facets to management that varies with the stages of disease and with individual patient circumstance. The evidence of the last 6 years since the first British guideline is that it is possible to work together and to improve care.

There are some recommendations that either may seem to challenge the international COPD guidelines or may rankle with individual clinicians. Our guideline group believe their recommendations to be the best advice for patient care – and hope that any who disagree will feel challenged to produce and publish evidence to either confirm or refute what this guideline sets out.

It is therefore a pleasure to welcome you to this Guideline on the management of COPD. We hope that all those involved in health care (those that commission care, those that deliver care, and the patient and carer groups) ensure that these guidelines are used and to that end we commend the audit/implementation criteria set out in the final section as ways of measuring the implementation process. Those with COPD deserve no less.

Dr Mike Pearson

Director, National Collaborating Centre - Chronic Conditions

Preface to NEW 2010 update guideline

It is over six years since the original NICE COPD guideline was published, and it is essential to note that this 2010 version is only a partial update, concentrating on specific issues relating to diagnosis, clinical assessment, the management of stable disease with inhaled therapies, and the timing of pulmonary rehabilitation. Other important aspects such as the management of acute exacerbations were specifically excluded from the scope of the guideline revision. Whilst the Guideline Development Group have gone to great lengths to make as obvious as possible which parts of the guideline are new and which are not, it is important to emphasise that many of the 2004 recommendations (for example those relating to smoking cessation and the crucial role of multidisciplinary teams) remain just as important and relevant now as they did when the original guideline was produced. Indeed many of the 2004 recommendations still remain key priorities for implementation.

The revision of the section on diagnosis has provided an opportunity to ensure that the classification of severity of airflow obstruction is now in line with other international guidelines. It was always difficult to rationalise why, for example, a patient with “severe” airflow obstruction in North America had it classified as only “moderate” in the U.K. This welcome realignment will lead to some patients having their severity stage re-classified; such patients will need reassurance that their actual clinical condition and need for appropriate therapy remain unchanged.

A recurring theme of the guideline update is the emphasis on the clinical features of the disease and not over-reliance on spirometry. Many of the new recommendations for treatment are based on the persistence of symptoms (including exacerbations) and not on arbitrary levels of lung function. The guideline emphasises that the realigned gradation of spirometric impairment refers purely to the degree of airflow obstruction and not the clinical severity of the disease, for which a far more comprehensive assessment needs to be made. There is an important research recommendation that simple and practical multi-dimensional assessment tools (some of which were in development during the period of the guideline production) need to be assessed and validated in primary care settings.

A major component of the guideline revision is the new section relating to inhaled therapies. A number of complex inter-locking recommendations are all summarised in a novel clinical algorithm which is intended to provide clarity regarding the clinical and cost-effective use of these drugs. In addition to these new recommendations about pharmacological therapy, there is also an important new recommendation relating to the use of pulmonary rehabilitation following hospitalisation for an acute exacerbation.

This full version of the guideline provides all the evidence, carefully evaluated, on which the update has been based. It is inevitable that not everyone will agree with all of the recommendations. Nevertheless,

taken in conjunction with the research recommendations and the key priorities for implementation, they do provide a sound basis for reassessing the management of people with COPD and ensuring continuing improvements in the standards of care that our patients deserve.

Michael Rudolf,

Chair, NICE COPD Guideline Development Group.

1 Introduction

1.1 Definition of chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is characterised by airflow obstruction. The airflow obstruction is usually progressive, not fully reversible and does not change markedly over several months. The disease is predominantly caused by smoking.

- Airflow obstruction is defined as a reduced post-bronchodilator FEV_1/FVC ratio (where FEV_1 is forced expiratory volume in 1 second and FVC is forced vital capacity), such that FEV_1/FVC is less than 0.7.
- If FEV_1 is ≥ 80% predicted normal, a diagnosis of COPD should only be made in the presence of respiratory symptoms e.g. breathlessness or cough.
- The airflow obstruction is due to a combination of airway and parenchymal damage.
- The damage is the result of chronic inflammation that differs from that seen in asthma and which is usually the result of tobacco smoke.
- Significant airflow obstruction may be present before the individual is aware of it.
- COPD produces symptoms, disability and impaired quality of life which may respond to pharmacological and other therapies that have limited or no impact on the airflow obstruction.
- COPD is now the preferred term for the conditions in patients with airflow obstruction who were previously diagnosed as having chronic bronchitis or emphysema.
- Other factors, particularly occupational exposures, may also contribute to the development of COPD.

There is no single diagnostic test for COPD. Making a diagnosis relies on clinical judgement based on a combination of history, physical examination and confirmation of the presence of airflow obstruction using spirometry. These issues are discussed in more detail in the diagnosis section (Section 6).

1.2 Clinical context

An estimated three million people are affected by COPD in the UK. About 900,000 have been diagnosed with COPD and an estimated two million people have COPD which remains undiagnosed[1]. The symptoms of the disease usually develop insidiously, making it difficult to determine the incidence of the disease. Most patients are not diagnosed until they are in their fifties.

1.2.1 Prevalence

Because it is defined by airflow obstruction, questionnaire surveys cannot be used to identify patients with COPD. In the last 20 years, only one national study has measured airway function in patients aged 18-65 in the UK. Overall 10% men and 11% women had an abnormally low FEV_1 [2]. A postal study[3] with hospital assessment in Manchester in patients aged 45 and over suggested prevalence of non-reversible chronic airflow obstruction in 11%. Half of these individuals had not previously been diagnosed.

In a primary care population aged 45 and over in the UK, screened opportunistically, the prevalence of an abnormal FEV_1 and respiratory symptoms was around 9%[4]. Prevalence increases with increasing age[5] and there are significant geographic variations in the prevalence of COPD.

Unlike many other common chronic diseases the prevalence of COPD has not declined in recent years. Prevalence rates appear to be increasing steadily in women but have reached a plateau in men[6].

The rate of COPD in the population is estimated at between 2% and 4%, representing between 982,000 and 1.96 million people in England[1]. The diagnosed prevalence of COPD is 1.5% of the population in 2007/08 according to the Quality Outcome Framework (QOF) statistical bulletin[1].

Approximately 835,000 people in England have been diagnosed with COPD in 2008-9[7]. However it is currently estimated that over 3 million people have the disease and that an estimated 2 million have undiagnosed COPD, among whom it is considered that 5.5% will have COPD at the mild end of the spectrum[8]

Estimates of the prevalence of COPD in the UK vary widely, depending on the criteria that are used. Data from the Quality and Outcomes Framework (QOF)[9] for GPs suggest that the majority of general practices can produce a register of patients with COPD amounting to 710,000 people on COPD, although these registers may be incomplete.

COPD is closely associated with levels of deprivation - rates of COPD are higher in more deprived communities[1,10].

Estimates based on pre-bronchodilator lung function measurements, as reported from the HSE 2001 data set, are likely to represent an overestimate of the prevalence of COPD in the population. This overestimate will be more evident in the mild and moderate severity stages, with little difference in estimates for prevalence in the severe and very severe COPD groups.

1.2.2 Mortality

It is difficult to be certain of the true mortality rate due to COPD. Some patients die with the disease rather than because of it. Others will die of causes related to COPD, but their death may be certified as being due to these complications[11]. Analysis of trends in death rates is also complicated by changes in the diagnostic labels.

Chronic obstructive lung disease, mainly chronic obstructive pulmonary disease, is the third largest cause of respiratory death, accounting for more than one fifth (23%) of all respiratory deaths[12].

COPD accounts for approximately 30,000 deaths each year in the UK, with more than 90% of these occurring in the over 65 age group in 2004[1,10,12-14]. The rate of mortality for respiratory disease in the UK is almost double the European average. The Health Development Agency estimated in 2004 that around 85% of COPD related deaths could be attributed to smoking.

In men, age standardized mortality rates from COPD have fallen progressively since the 1970s, but in women there has been a small but progressive increase[6]. All cause mortality is increased in patients with COPD[15].

The inpatient mortality rate in 2008 was 7.7% compared with 7.5% in 2003[16]. The overall mortality rate at 90 days was 13.9% in 2008 indicating a reduction from 15.5% in 2003. Of those patients dying within 90 days of admission, fewer succumbed from COPD or its consequences in 2008 (65%) compared to 2003 (71%). Mortality varies between hospitals and is higher in those with fewer respiratory consultants and in those serving more deprived communities. It is thought that up to 25% of patients die within a year[1,17,18].

Mortality from COPD in England shows a strong urban rural gradient with high mortality rates in the large conurbations in the North of England[19]. Mortality reflects social inequalities with men aged 20-64 employed in unskilled manual occupations being 14 times more likely to die from chronic obstructive pulmonary disease than those in professional occupations[12]. People in urban and deprived areas are more likely to be at risk[20].

Cause of death was recorded as COPD in 65% of those who died, a reduction from the 71% observed in 2003[16]. Information on COPD deaths from death certificates significantly under-estimate the burden of disease[16,21].

COPD is an important co-morbidity in those dying from other smoking related diseases, most commonly ischaemic heart disease and lung cancer[12,22]. COPD is the fifth leading cause of death in the UK and fourth worldwide[21,23]. Moreover, due to an aging population, increases in its prevalence and mortality are expected in the coming decades. COPD is set to become the third leading cause of death worldwide by the year 2020, surpassed only by heart disease and stroke[24].

Five year survival from diagnosis is 78% in men and 72% in women with clinically mild disease defined as not requiring continuous drug therapy, but falls to 30% in men and 24% in women with severe disease defined as requiring oxygen or nebulised therapy. The mean age of death of patients with severe COPD is 74.2 years compared with 77.2 years in patients with mild disease and 78.3 years in individuals who did not have COPD[15].

1.2.3 Morbidity

An average general practice in the UK which cares for about 7,000 people will have up to 200 people with COPD on its practice list, for many of whom the condition will be undiagnosed. This equates to around 1.4 million consultations with GPs each year, up to four times more than the number of consultations for angina[1]. COPD patients admitted to hospital are frequent users of primary care in the 12 months prior to their admission.

Three quarters (74%) of admitted patients make contact with their general practice in the month before admission and nearly a third (31%) have 3 or more contacts in those 4 weeks. Although patients make a median of 12 contacts with general practice in the 12 months prior to the audited admission, and have a median of 3 exacerbations, 51% have no contact with out-of-hours services[16].

The National COPD Audit 2008 patient survey noted that the majority (83%) of patients report frequent exacerbation of their COPD. Two thirds (68%) of patients reported a respiratory infection or flu-like symptoms in the month prior to admission, about half (57%) noticed a change in colour/volume of phlegm before admission, often 2-5 days before (46%), but with one quarter (26%) having noticed this 6 or more days before. Although 25% of patients admitted with COPD said this was their first admission, 60% had also been admitted to hospital with COPD in the previous 12 months[16].

Although only a small proportion of people with COPD are admitted to hospital each year, one in eight (130,000) emergency admissions to hospital is for COPD, making it the second largest cause of emergency admission in the UK, and one of the most costly inpatient conditions treated by the National Health Service (NHS)[21]. Respiratory disease accounts for 5.2 million bed days, nearly 10% of all hospital

bed days. One fifth (21%) of bed days used for respiratory disease treatment are due to chronic obstructive lung disease, such that COPD accounts for more than one million 'bed days' each year in hospitals in the UK[10,12].

COPD is the most common reason for emergency admission to hospital due to respiratory disease, accounting for the most finished consultant episodes of care (80% of them in those aged over 60 years of age) and is second only to pneumonia in total bed-days per year[13] . About 30% of patients admitted with COPD for the first time will be readmitted within three months[12].

Admission rates have risen in all age groups since 1994 except in the under 45s. The highest rises have occurred in the over 85s in which rates have almost doubled from 1994 to 2005. www.laia.ac.uk/copd1994-2005.html

Rates of admission to hospital vary by up to five times in different parts of England, reflecting differences in the prevalence of COPD as well as wide variations in the quality of care that is provided in the community[1]. Risk of hospital admission for the disease varies greatly between regions and within regions.

COPD admissions also show some seasonality and are more common in the winter months[25].

The median length of stay in 2008 was 5 days (interquartile range 3-10 days) compared with 6 days in 2003. There has been an increase from 26% to 34% in the proportion of patients having a shorter stay of at most 3 days since 2003. The readmission rate in 2008 was 33%, increased from 31% in 2003. The median time to readmission was 38 days.

There has been an increase in the proportion of admissions that are female so that COPD is now a disease of equal importance in both men and women. The mean age of admissions in 2008 was 73 years for men (increased from 72 years in 2003), and 72 years for women.

90% of patients still live at home, 36% on their own. 39% of patients received some form of personal care at home, whether paid or unpaid. The median % predicted forced expiratory volume in 1 second (FEV_1) for those patients with spirometry recorded in the last 5 years was 38%. 67% of recorded Medical Research Council (MRC) dyspnoea scores are Grade 4-5 in the steady state prior to admission the number of current smokers was 33% in 2008 compared with 41% in 2003[16].

1.2.4 Comorbidities

COPD coexists with other diseases that share tobacco smoking as a risk factor, of which the most common are heart disease and lung cancer[26].

Advances in the understanding of COPD have stressed the importance of co-morbidities[27]. COPD increases the risk for lung cancer, and a recent meta-analysis found a strong inverse relationship between level of lung function and risk of lung cancer. For the same marginal decrease in FEV_1, adjusted for smoking, women were twice as likely as men to develop lung cancer[28,29].

The National COPD audit showed a very high level of co-morbidity, the association with cardiovascular disease being particularly strong. 51% of the patients had been admitted for COPD within the preceding 24 months[16].

The cost and complexity of care escalates with the number of co-morbid conditions[30]. There is a high frequency of chronic conditions in older adults[24,31,32].

1.2.5 Economic impact

The total annual cost of COPD to the NHS in 2000-1 was estimated to be £491,652,000 for direct costs only and £982,000,000 including indirect costs (See Section 14).

Broken down by disease severity according to guidelines at that time, the cost p.a. was

- Mild £149.68
- Moderate £307.74
- Severe £1,307.10

The average cost per patient p.a. was £819.42, of which 54.3% was due to inpatient hospitalisation, 18.6% for treatment, 16.4% for GP and specialist visits, 5.7% for accident and emergency visits and unscheduled contacts with the GP or specialist and 5% for laboratory tests[33].

The Chief Medical Officer has reported COPD accounts for more than £800 million in direct health care costs[10]. The direct cost of COPD to the UK healthcare system has been estimated to be between £810-£930m to a year[34].More than half of these costs relate to the provision of care in hospital. COPD is among the most costly inpatient conditions treated by the NHS.

The indirect costs of COPD are substantial with an impact on annual productivity amounting to an estimated 24 million lost working days per annum[1,10,35]. There is little UK data available to quantify other indirect costs such as carer time and inability to carry out non-occupationally related activities[13].

Assuming the above estimates for the 'cost of caring' is referring to the NHS cost and not the societal cost associated with informal carers, recent DH analysis has estimated the direct cost associated with COPD by disease severity.

GOLD Stage I ($FEV_1 \geq 80\%$ predicted): £120 - £130

GOLD Stage II (FEV_1 50% to 79% predicted): £270 - £290

GOLD Stage III (FEV_1 30% to 49% predicted): £910 - £980

GOLD Stage IV ($FEV_1 \leq 30\%$ predicted): £3,000 - £3,200

(see section 6.9, table 6.7)

The estimated cost of an acute episode (exacerbation) in 2004, using the severity classification at that time, ranges from:

- £8 to £15 for a person with mild COPD
- £23 to £95 for a person with mild to moderate COPD
- £1,400 to £1,600 for a person with severe COPD[10]

As well as these costs, it has been estimated that 21.9 million working days were lost in 1994-5. In a recent survey of a random sample of patients with COPD 44% were below retirement age and 24% reported that they were completely prevented from working by their disease. A further 9% were limited in their ability to work and patients' carers also missed time from work [33].

The symptoms of the disease usually develop insidiously, making it difficult to determine the incidence of the disease. Most patients are not diagnosed until they are in their fifties.

1.3 Original guideline aims

This guideline offers best practice advice on the identification and care of patients with COPD. It aims to define the symptoms, signs and investigations required to establish a diagnosis of COPD. It also aims to define the factors that are necessary to assess its severity, provide prognostic information and guide best management. It gives guidance on the pharmacological and non-pharmacological treatment of patients with stable COPD, and on the management of exacerbations. The interface with surgery and intensive therapy units (ITU) are also discussed.

1.4 Patient choice

Whenever recommendations are made, it is recognised that informed patient choice is important in determining whether or not an individual patient chooses to undergo the investigation or accept treatment that is recommended.

1.5 Underlying guideline principles

The main principles behind the development of this guideline were that it should:

- Consider all issues that are important in the management of people with COPD
- Use published evidence wherever this is available
- Be useful and usable to all professionals
- Take full account of the perspective of the person with COPD and their carers
- Indicate areas of uncertainty or controversy needing further research.

1.6 Structure of the original guideline

The document is divided into sections, which cover a set of related topics. For each topic the layout is similar.

The **background** to the topic is provided in one or two paragraphs that simply set the recommendations in context.

Then the **evidence statements** are given and these summarise the evidence, which is detailed in the **evidence tables.** In addition there is an evidence statement about the health economic evidence where this is available. These evidence statements and tables aim to provide context and aid the reader's understanding of why each recommendation was made.

The evidence statements are followed by **consensus statements** agreed by the guideline development group. These statements have been made when there is a lack of evidence or where the guideline development group felt that there were important issues which needed commenting on but which lay beyond or outside the current evidence base.

The main **recommendations** follow. These are graded to indicate the strength of the evidence behind the recommendation.

1.7 Updating a NICE guideline

The National Clinical Guideline Centre for Acute and Chronic Conditions (NCGC-ACC) undertook a review for update three years after publication of the original COPD guideline in concordance with the NICE Guidelines Manual 2007[36]. Literature searches (based upon the original guideline searches) were re-run.

New evidence that had implications for changing recommendations was ascertained. This review of the evidence and the views of healthcare professionals and patients led to NICE commissioning an 18 month partial update of the COPD guideline. The remit and scope of the update are available in appendix G.

The guideline update 2010 has attempted to maintain, as far as possible, the structure and content of the original NICE COPD guideline 2004. Superseded sections have been removed to an appendix K and new sections have been clearly marked and inserted. GRADE methodology was used to assess the quality of clinical research studies for the first time in a NICE update guideline.

Sections and recommendations from the 2004 guideline which have remained unchanged have maintained the old hierarchy of evidence and recommendation grading system in use at that time.

The development of this evidence-based clinical guideline (partial update) draws upon the methods described by the NICE Guidelines Manual[36] specifically developed by the NCGC-ACC for each acute and chronic condition guideline.

1.8 Update aim

The aim of the NCGC-ACC is to provide a user-friendly, clinical, evidence-based guideline for the National Health Service (NHS) in England and Wales that:

- Offers best clinical advice for the management and treatment of COPD in adults in primary and secondary care
- Is based on best published clinical and economics evidence, alongside expert interpretation
- Takes into account patient choice and informed decision-making
- Defines the major components of NHS care provision for COPD
- Details areas of uncertainty or controversy requiring further research
- Provides a choice of guideline versions for different audiences.

1.9 Scope

The guideline was developed in accordance with the partial update scope, which detailed the remit of the guideline originating from the Department of Health and specified those aspects of COPD care to be included and excluded.

Prior to the commencement of the guideline development, the scope was subjected to stakeholder consultation in accordance with processes established by NICE in the guidelines manual[37]. The full update scope is shown in appendix G.

1.10 Audience

The guideline is intended for use by the following people or organisations:

- All healthcare professionals
- People with COPD and their carers
- Patient support groups
- Commissioning organisations
- Service providers.

1.11 Involvement of people with COPD

The NCGC-ACC was keen to ensure the views and preferences of people with COPD and their carers informed all stages of the guideline. This was achieved by:

- Having a person with COPD as a patient representative on the guideline development group (GDG)
- Consulting with the Patient and Public Involvement Programme (PPIP) housed within NICE during the pre-development (scoping) and final validation stages of the guideline.
- Inclusion of patient groups as registered stakeholders for the guideline.
- Securing patient organisation representation from the British Lung Foundation on the guideline development group.

1.12 Guideline limitations

These include:

- NICE clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the Department of Health).
- NICE is primarily concerned with Health Services and so recommendations are not provided for Social Services and the voluntary sector. However, the guideline may address important issues related to the interface of NHS clinicians with these sectors.
- Generally, the guideline does not cover rare, complex, complicated or unusual conditions.

It is not possible in the development of a clinical guideline to complete extensive systematic literature review of all pharmacological toxicity. NICE expect the guidelines to be read alongside the Summaries of Product Characteristics.

The guideline usually makes recommendations within medication licence indications. Exceptionally, where there was clear supporting evidence, recommendations, outside the licensed indications have been included. As far as possible where this is the case it is indicated.

1.13 Other work relevant to the guideline

Related NICE guidance:

National Institute for Clinical Excellence. Guidance on the use of zanamivir, amantadine and oseltamivir for the treatment of influenza. NICE technology appraisal guidance. TA58, 2003. This guidance has been replaced by TA168 Influenza - zanamivir, amantadine and oseltamivir (review).

National Collaborating Centre for Acute Care. Nutrition support in adults: Oral nutrition support, enteral tube feeding and parenteral nutrition. National Clinical Guideline Number 32. London: National Collaborating Centre for Acute Care. 2006. http://guidance.nice.org.uk/CG32

National Institute for Health and Clinical Excellence. Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. NICE clinical guideline 43 (2006). http://www.guidance.nice.org.uk/CG43

National Institute for Health and Clinical Excellence. Anxiety (amended): management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care. NICE clinical guideline 22 (2007). http://www.guidance.nice.org.uk/CG22

National Institute for Health and Clinical Excellence. Varenicline for smoking cessation. TA 123 (2007). Clinical Introduction. http://www.guidance.nice.org.uk/TA123

National Institute for Health and Clinical Excellence. Influenza (prophylaxis) - amantadine, oseltamivir and zanamivir. TA 158 (2008). http://guidance.nice.org.uk/TA158

National Institute for Health and Clinical Excellence. Smoking cessation services: guidance. London: UK: National Institute for Health and Clinical Excellence. PH 10 (2008). http://guidance.nice.org.uk/PH10

National Institute for Health and Clinical Excellence. Influenza - zanamivir, amantadine and oseltamivir (review). 2009. http://guidance.nice.org.uk/TA168

National Institute for Health and Clinical Excellence. Depression: the treatment and management of depression in adults (update). London: UK: National Institute for Health and Clinical Excellence. 2009. http://guidance.nice.org.uk/CG90

National Institute for Health and Clinical Excellence. Depression in adults with a chronic physical health problem: treatment and management. NICE clinical guideline 91 (2009). http://www.nice.org.uk/guidance/CG91

The developer's role and remit is summarised below:

National Clinical Guidelines Centre for Acute and Chronic Conditions (NCGC-ACC)	The NCGC-ACC was set up in 2009 and is housed within the Royal College of Physicians (RCP). The NCGC-ACC undertakes commissions received from the National Institute for Health and Clinical Excellence (NICE).
NCGC-ACC Technical Team	The technical team met approximately two weeks before each GDG meeting and comprised the following members: GDG chair, GDG clinical advisor, Information Scientist, Research Fellow, Health Economist and Project Manager.
Guideline Development Group	The GDG met monthly and comprised a multi disciplinary team of health professionals and a person with COPD, who were supported by the technical team. The GDG membership details including patient representation and professional groups are detailed in the GDG membership table at the front of this guideline.
Guideline Project Executive (PE)	The PE was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the DH remit and NICE scope. The PE comprised of: NCGC-ACC Clinical Director; NCGC-ACC Operations Director; NICE Commissioning Manager; Technical Team.
Formal consensus	At the end of the guideline development process the GDG met to review and agree the guideline recommendations.

2 Methodology

2.1 The process of guideline development (for a partial update)

The basic steps in the process of producing a guideline update are:

- Identifying areas of existing guidance that need updating
- Developing clinical questions
- Developing the review protocol
- Systematically searching for the evidence
- Critically appraising the evidence
- Undertaking new health economic analysis
- Distilling and synthesising the evidence and writing recommendations
- Agreeing the recommendations
- Structuring and writing the guideline
- Updating the guideline.

2.1.1 Identifying areas of existing guidance that need updating

The NCGC-ACC conducted a preliminary search for new evidence using the search strategies from the original guideline. The views of healthcare professionals and patients were also sought to identify any change in practice or additional relevant published evidence. Key areas that would directly result in changes to recommendations were highlighted for updating.

2.1.2 Developing evidence based questions

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refined and approved these questions, which are shown in appendix H.

2.1.3 Developing the review protocol

For each clinical question, the Information Scientist and the Research Fellow (with input from the technical team) prepared a review protocol. This protocol explained how the review was to be carried out (see table 2.1), in order to formulate a plan of how to review the evidence, limit the introduction of bias, and for the purpose of reproducibility. A health economic literature review protocol was also developed. All review protocols can be found in appendix I.

Table 2.1 Components of the review protocol

Component	Description
Review question	The review question as agreed by the GDG.
Objectives	Short description; for example 'To estimate the effects and cost effectiveness of…' or 'To estimate the diagnostic accuracy of…'.
Criteria for considering studies for the review	Using the PICO (population, intervention, comparison and outcome) framework. Including the study designs selected.
How the information will be searched	The sources to be searched and any limits that will be applied to the search strategies; for example, publication date, study design, language. (Searches should not necessarily be restricted to RCTs.)
The review strategy	The methods that will be used to review the evidence, outlining exceptions and subgroups. Indicate if meta-analysis will be used.

2.1.4 Searching for the evidence

The Information Scientist developed a search strategy for each question. Key words for the search were identified by the GDG. A separate health economic search strategy was developed looking for economic studies in COPD. Papers that were published in peer-reviewed journals (including e-publications ahead print where identified) were considered as evidence by the GDG. Conference paper abstracts and non-English language papers were excluded from the searches. Where it was deemed appropriate and where there was lack of evidence in the literature on an area of clinical importance, the GDG decided to initiate a 'call for evidence' asking all registered stakeholders to submit any relevant unpublished evidence. Where this occurred this is detailed within the guideline write-up.

Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. The research fellow or health economist identified relevant titles and abstracts for each clinical question from the search results and full papers were obtained. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. See appendices I and J for review protocols and literature search details.

2.1.5 Appraising the evidence

The research fellow or health economist, as appropriate, critically appraised the full papers. In general, no formal contact was made with authors. However there were ad hoc occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper.

For non-observational studies, where possible this included meta-analysis of data and synthesis of data into a GRADE 'evidence profile'. The evidence profile shows for each outcome an overall assessment of both the quality of the evidence as a whole (low, moderate or high), as well as an estimate of the size of effect. For observational and qualitative studies, a narrative summary (evidence statements) was written summarising the results.

For economic studies, an economic 'evidence profile' was constructed. The economic evidence profile shows, for each economic study, an assessment of applicability (directly applicable, partially applicable or not applicable) and methodological quality (minor limitations, potentially serious limitations, very serious limitations) with footnotes indicating the reasons for the assessment. It also shows incremental costs, incremental outcomes (e.g. QALYs) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis. In this guideline results are presented for the comparison specified in the clinical question irrespective of whether or not the comparison was 'appropriate' in the analysis being reviewed (that is where an intervention is compared with the next most expensive non-dominated option – a clinical strategy is said to 'dominate' the alternatives when it is both more effective and less costly). Footnotes indicated if a comparison was 'inappropriate' in the analysis.

A research fellows or health economist, as appropriate, undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with the NICE methodology as detailed in the 'Guideline Development Methods – Information for National Collaborating Centres and Guideline Developers' Manual[36].

2.1.6 Undertaking new health economic analysis

Priority areas for new health economics modelling were agreed by the GDG after the formation of the clinical questions and consideration of available health economic evidence.

The Health Economist performed supplemental literature searches to obtain additional data for modelling. Assumptions, data and structures of the models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions. See appendix M for details of the modelling undertaken for the guideline.

2.1.7 Distilling and synthesising the evidence and developing recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into an evidence

profile and evidence statements before being presented to the GDG. The results of health economic modelling undertaken for the guideline were also presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations.

Evidence tables are available at http://guidance.nice.org.uk/CG101/EvidenceTables/pdf/English.

2.1.8 Agreeing the recommendations

The GDG employed formal consensus techniques to:

- Ensure that the recommendations reflected the evidence-base
- Approve recommendations based on lesser evidence or extrapolations from other situations
- Reach consensus recommendations where the evidence was inadequate
- Debate areas of disagreement and finalise recommendations.

The GDG also reached agreement on the following:

- Recommendations as key priorities for implementation
- Future research recommendations
- Algorithms

In prioritising key priorities for implementation, the GDG took into account the following criteria:

- High clinical impact
- High impact on reducing variation in practice
- More efficient use of NHS resources
- Allowing the patient to reach critical points in the care pathway more quickly.

2.1.9 Structuring of the updated sections of the guideline

The guideline is divided into sections for ease of reading. For each section the layout is similar and contains:

- **Clinical introduction**

  This sets a succinct background and describes the current clinical context. It includes which section of the original guideline has been updated and why, and what the existing guideline recommends.

- **Methodological introduction**

  This section outlines the a priori agreement of the GDG in relation to the inclusion and exclusion criteria together with the outcomes of interest.

- **GRADE Evidence profiles and forest plots**

  The GRADE evidence profiles provide a synthesis of the evidence-base, the quality and describe what the evidence showed in relation to the outcomes of interest (including effect sizes). Forest plots showing meta-analysis results are also provided for outcomes where appropriate.

- **Evidence statements**

  Provide a bottom-line narrative summary.

- **Health economics**

  Presents, where appropriate, an overview of the cost effectiveness evidence-base, or any economic modelling.

- **From evidence to recommendations**

  This section sets out the Guideline Development Group (GDG) decision-making rationale providing a clear and explicit audit trail from the evidence to the evolution of the recommendations.

- **Recommendations**

  Provides stand-alone, action-orientated recommendations and details which of the original guideline recommendations have been amended or deleted and any new recommendations that have been added. Unlike the original guideline, recommendations made in this partial update are no longer graded on the strength of evidence, in keeping with the guidelines manual 2009.

- **Evidence tables**

  The evidence tables are not published as part of the full guideline but are available on-line. These describe comprehensive details of the primary evidence that was considered during the writing of each section.

2.1.10 Writing the guideline

The first draft version of the guideline was drawn up by the technical team in accordance with the decisions of the GDG, incorporating contributions from individual GDG members in their expert areas and edited for consistency of style and terminology. The guideline was then submitted for a formal public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed on the NICE website www.nice.org.uk. Editorial responsibility for the full guideline rests with the GDG.

The original guideline evidence tables from February 2004 are available at http://thorax.bmj.com/content/59/suppl_1

The following versions of the guideline are available:

Full version:	Details the recommendations, the supporting evidence base and the expert considerations of the GDG. Published by the NCGC-ACC. Available from http://guidance.nice.org.uk/CG101/Guidance/pdf/English
NICE version:	Documents the recommendations without any supporting evidence. Available from http://guidance.nice.org.uk/CG101/NICEGuidance/pdf/English http://guidance.nice.org.uk/CG101/NICEGuidance/doc/English
"Quick reference guide":	An abridged version. Available from http://guidance.nice.org.uk/CG101/QuickRefGuide/pdf/English
"Understanding NICE guidance":	A lay version of the guideline recommendations. Available from http://guidance.nice.org.uk/CG101/PublicInfo/pdf/English

2.2 Re-run evidence

Literature searches were repeated for all of the evidence based questions at the end of the GDG development process allowing any relevant papers published up until 20th August 2009 to be considered. Future guideline updates will consider evidence published after this cut-off date. Further updates will take place in concordance with the specifications outlined in the NICE guidelines manual.

2.3 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The NCGC-ACC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

2.4 Funding

The NCGC-ACC was commissioned by NICE to undertake the work on this guideline.

3 Hierarchy of evidence and grading of recommendations

Please note the hierarchy of evidence and grading of recommendations was used for the original COPD guideline and hence still stands for those areas not covered by the 2010 COPD update.

Each recommendation has been allocated a grading which directly reflects the hierarchy of evidence upon which it is based. Please note that the hierarchy of evidence and the recommendation grading relate to the strength of the literature **not** to clinical importance.

The grading is as follows:

Hierarchy of Evidence		**Grading of Recommendations**	
Ia	Evidence from systematic reviews or meta-analysis of randomised controlled trials	A	Based on hierarchy I evidence
Ib	Evidence from at least one randomised controlled trial		
IIa	Evidence from at least one controlled study without randomisation	B	Based on hierarchy II evidence or extrapolated from hierarchy I evidence
IIb	Evidence from at least one other type of quasi experimental study		
III	Evidence from non experimental descriptive studies, such as comparative studies, correlation studies and case control studies	C	Based on hierarchy III evidence or extrapolated from hierarchy I or II evidence
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities	D	Directly based on hierarchy IV evidence or extrapolated from hierarchy I, II or III evidence.
DS	Evidence from diagnostic studies	DS	Evidence from diagnostic studies
NICE	Evidence from NICE guidelines or Health Technology Appraisal programme	NICE	Evidence from NICE guidelines or Health Technology Appraisal programme
HSC	Evidence from Health Service Circulars	HSC	Evidence from Health Service Circulars

4 Glossary of terms

Term	Definition
ACBT	Active Cycle of Breathing Technique
ACCP	American College of Chest Physicians
ACE inhibitor	Angiotensin-Converting Enzyme inhibitor
ADL	Activities of Daily Living
Ads	Advanced Directives
Adverse event	Usually in relation to treatment and sometimes known as side-effects. Adverse events are any event that is not to the benefit of the person.
Allied health professionals	Healthcare professionals, other than doctors and nurses, directly involved in the provision of healthcare. (Also known as professions allied to medicine or PAMs.)
Anticholinergic drugs	Anticholinergic drugs are also referred to as muscarinic antagonists e.g. short-acting muscarinic antagonist (SAMA) in the update guideline
Appraisal of evidence	Formal assessment of the quality of research evidence and its relevance to the clinical question or guideline under consideration, according to predetermined criteria.
ARDS	Acute Respiratory Distress Syndrome
ARF	Acute Respiratory Failure
ARR	Adjusted risk ratio
ASA Scoring System	American Society of Anaesthesiologists
ATBC	Alpha-Tocopherol and Beta-Carotene Supplementation
ATS	American Thoracic Society
AUC	Area under the curve
BD	Bronchodilator
BMI	Body Mass Index
BORG	Tool for measuring dyspnoea or the state of being short of breath
BTS	British Thoracic Society
Case-control study (CCT)	A study that starts with the identification of a group of individuals sharing the same characteristics and a suitable comparison (control) group. All participants

Term	Definition
	are then assessed with respect to things that happened to them in the past.
CEN	European Committee for Standardization
CES-D	Centre for Epidemiological Studies Depression Scale
CI	Confidence Interval
CLD	Chronic Lung Disease
Clinical audit	A systematic process for setting and monitoring standards of clinical care.
Clinical effectiveness	How well a drug, treatment or package of care works to produce good outcomes for patients?
Clinician	A health care professional providing patient care, e.g. doctor, nurse, physiotherapist.
CMC	Clinically Meaningful Change
CNS	Clinical Nurse Specialist
Cochrane Library	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews. The Cochrane Library is available on CD-ROM and the Internet.
Cochrane review	Reviews of randomised controlled trials prepared by the Cochrane Collaboration.
Cohort study	A cohort study takes a group of patients, follows them forward in time and measures their outcome (e.g. disease or mortality rates). Patient subgroups are identified from the information collected, and these groups are compared with respect to outcome.
Concordance	Concordance is a concept reflecting agreement between clinicians and patient on the best course of managing a disease, and adherence to that course until alternatives are agreed on and adopted.
COPD	Chronic Obstructive Pulmonary Disease
COPM	Canadian Occupational Performance Measure
Cost-effectiveness	Comparative analysis of the costs and health benefits of a treatment or care pathway.
CRG	Consensus Reference Group

Term	Definition
CRQ / CRDQ	Chronic Respiratory Diseases Questionnaire
CT scan	Computed Tomography
CXR	Chest X-Ray
Dco	Diffusing Capacity of Carbon Dioxide
DDD	Defined Daily Dosage
Diagnostic study	Any research study aimed at evaluating the utility of a diagnostic procedure.
DLCO	Carbon Monoxide Diffusing Capacity
DPI	Dry Powdered Inhaler
DPTC	Disabled Person's Tax Credit
ECCS	European Coal & Steel Community
ECG	Electrocardiogram
ERS	European Respiratory Society
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Evidence-based	The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.
Experimental study	A research study designed to test if a treatment or intervention has an effect on the course or outcome of a condition or disease.
FET	Forced Expiratory Time
FEV_1	Forced Expiratory Volume in 1 second
FFM	Fat Free Mass Index
FFMPIBW	Fat-Free Mass as a Percentage of Ideal Body Weight
FVC	Forced Vital Capacity
GDG	Guidelines Development Group
GI	Gastrointestinal

Term	Definition
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Grade of recommendation	A code (e.g. A, B, C) linked to a guideline recommendation, indicating the strength of the evidence supporting that recommendation.
HADS	Hospital Anxiety and Depression Scale
HAM-D	Hamilton Depression Rating Scale
Health technology	Health technologies include medicines, medical devices, diagnostic techniques, surgical procedures, health promotion and other therapeutic interventions.
Health Technology Appraisal (HTA)	A focused review of evidence around a newly emerging health technology, produced by NICE.
Hierarchy of evidence	An established hierarchy of study types, based on the degree of certainty that can be attributed to the conclusions of a well-conducted study. Well-conducted randomised controlled trials (RCTs) are at the top of this hierarchy. (Several large statistically significant RCTs which are in agreement represent stronger evidence than say one small RCT.) Well-conducted studies of patients' views and experiences would appear at a lower level in the hierarchy of evidence.
HR	Hazard Ratio
HRQL	Health Related Quality of Life
IBW	Ideal Body Weight
ICS	Inhaled corticosteroid
ICU	Intensive Care Unit
ILI	Influenza Like Illness
IPPV	Intermittent Positive Pressure Ventilation
IQR	Inter Quartile range
IRR	Incident Rate Ratio
ITT	Intention to Treat Analysis
ITU	Intensive Care Unit
KPa	Kilopascal – A unit of pressure
LABA	Long-acting $beta_2$ agonist

Term	Definition
LAMA	Long-acting muscarinic antagonist
LCADL	London Chest Activity of Daily Living scale
Level of evidence	A code (e.g. 1a, 1b) linked to an individual study, indicating where it fits into the hierarchy of evidence and how well it has adhered to recognised research principles.
Literature review	A process of collecting, reading and assessing the quality of published (and unpublished) articles on a given topic.
LTOT	Long Term Oxygen Therapy
LVRS	Lung Volume Reduction Surgery
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question to produce a summary result.
MID	Minimally important difference
MRADL	Manchester Respiratory Activities of Daily Living
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
Muscarinic antagonist drugs	Muscarinic antagonists e.g. long-acting muscarinic antagonists (LAMA) are also referred to as Anticholinergic drugs in the original guideline.
MV	Mechanical Ventilation
NAC	N-acetylcysteine
NCC-CC	The National Collaborating Centre for Chronic Conditions. Set up in 2000 to undertake commissions from the National Institute for Clinical Excellence to develop clinical guidelines for the National Health Service
NCEPOD	National Confidential Enquiry into Perioperative Deaths
NICE	National Institute for Clinical Excellence
NIV	Non Invasive Ventilation
NNT	Number Needed to Treat
Non-experimental study	A study based on participants selected on the basis of their availability, with no attempt having been made to avoid problems of bias.

Term	Definition
NRT	Nicotine Replacement Therapy
NSF	National Service Framework
OR	Odds Ratio
Palliative care	Care aimed at alleviating symptoms, pain and distress, and hence improving quality of life, rather than at curing or slowing progression of a disease or condition. It is often associated with, but is actually not limited to, the end of life
$PaCO_2$	Arterial Carbon Dioxide Tension
PEF	Peak Expiratory Flow
Pemax	Maximal Expiratory Pressure
PEP	Positive Expiratory Pressure
PIBW	Percent Ideal Body Weight
PICO	Population, intervention, comparison, outcome
Pimax	Maximum Inspiratory Pressure
Placebo	A pill, medicine, or other treatment that has no physiological effect and is used as a dummy treatment.
pMDI	Patient Administered Metered Dose Inhalers
Ppa	Pulmonary Artery Pressure
Prevalence	The proportion of a population of people who are experiencing a condition or disease at a given time.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen.
P-value	P values indicate whether an effect can be regarded as statistically significant or not. By convention, where the value of P is below 0.05 the result is seen as statistically significant. Where the value of P is 0.001 or less, the result is seen as highly statistically significant.
Quality-Adjusted Life Year (QALY)	A measure of health outcome
Quasi experimental study	This is a study in which the treatment comparison groups are not assigned by

Term	Definition
	randomisation.
Randomised controlled trial (RCT)	A trial in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was.
RCP	Royal College of Physicians
RD	Risk Difference
RR	Risk Ratio
RV	Residual Volume
SABA	Short-acting $beta_2$ agonist
SAMA	Short-acting muscarinic antagonist
SaO_2	Oxygen saturation – The % of oxygen present in the haemoglobin present in arterial blood
SEK	Swedish Krona unit of monetary currency
SGRQ	St George's Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
Six MD / 6MWT	Six minute distance or six minute walking test – 6MD / 6MWT
SMD	Standard Mean Difference
Stakeholder	Any national organisation, including patient and carers' groups, healthcare professionals and commercial companies with an interest in the guideline under development.
Systematic review	Research that summarises the evidence on a clearly formulated question using systematic and explicit methods to identify, select and appraise relevant primary studies, and to extract, collate and report their findings. By following this process it becomes a proper piece of research. It may or may not use statistical meta-analysis.
TAG	Technology Appraisal Guidance
TDI	Transition Dyspnoea Index

Term	Definition
TLC	Total Lung Capacity
T_LCO	Transfer Factor for Carbon Monoxide
TNF-α	Tumour Necrosis Factor – alpha
Trial of treatment	A planned period during which a patient receives a treatment to find out if it will be of benefit to them as individuals.
TSF	Triceps Skin Fold
VAS	Visual Analogue Scale
VC	Vital Capacity
VMT	Ventilatory Muscle Training
VO_2	Oxygen Uptake
WMD	Weight Mean Difference

5 Summary of key priorities for implementation, algorithms and audit criteria

5.1 Key priorities for implementation

The National Clinical Guidelines for COPD makes nearly 200 specific recommendations concerning the management of COPD. These deal with diagnosis and assessment, management of stable COPD and management of exacerbations. The recommendations about managing stable COPD cover all aspects of the disease and include pharmacological and non-pharmacological approaches. An individual patient will not experience all the problems, but there is no predictable pattern or progression, and some may experience several problems. Some exacerbations can be managed at home whilst others require hospital treatment. In each of these settings there is more uniformity in the management but individual patients may still have specific problems, such as respiratory failure. The heterogeneity of COPD makes it difficult to choose the most important recommendations.

Exacerbations (see section 8.2) are important events for patients and the NHS. Patients experiencing frequent exacerbations have a worse prognosis and much of the cost of caring for COPD results from managing exacerbations. Strategies to reduce the frequency and impact of exacerbations are essential.

The guideline development groups have identified seven key areas where it was felt that recommendations were likely to have the biggest impact on the management of COPD

These seven key areas were selected against two criteria:

- That they would make a large difference to patients and the NHS
- That they benefit a large number of people.

The key messages eventually chosen:

- Reflect the stated concerns of many people with COPD;
- Are largely patient-centred; **and**
- Are all derived from the full guideline, but are newly written to combine issues with a common theme that are dealt with in separate but related recommendations.

The wording of the key priorities is derived from the recommendations in the main text. It was our intention to make them short, clear and comprehensive. If further detail is needed then reference should be made to the original recommendations.

The order of the key priorities given here is arbitrary and does not reflect their relative importance.

The following recommendations have been identified as priorities for implementation:

Diagnose COPD

- A diagnosis of COPD should be considered in patients over the age of 35 who have a risk factor (generally smoking) and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter 'bronchitis' or wheeze.
- The presence of airflow obstruction should be confirmed by performing post-bronchodilator spirometry. All health professionals involved in the care of people with COPD should have access to spirometry and be competent in the interpretation of the results.

Stop smoking

- Encouraging patients with COPD to stop smoking is one of the most important components of their management. All COPD patients still smoking, regardless of age should be encouraged to stop, and offered help to do so, at every opportunity.

Promote effective inhaled therapy

NEW 2010 UPDATE RECOMMENDATION 5 (U5)

In people with stable COPD who remain breathless or have exacerbations despite use of short-acting bronchodilators as required, offer the following as maintenance therapy:

- if $FEV_1 \geq 50\%$ predicted: either long-acting $beta_2$ agonist (LABA) or long-acting muscarinic antagonist (LAMA)
- if $FEV_1 < 50\%$ predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or LAMA.

NEW 2010 UPDATE RECOMMENDATION 7 (U7)

Offer LAMA in addition to LABA+ICS to people with COPD who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV_1.

Provide pulmonary rehabilitation for all who need it

NEW 2010 UPDATE RECOMMENDATION 11 (U11)

Pulmonary rehabilitation should be made available to all appropriate people with COPD including those who have had a recent hospitalisation for an acute exacerbation.

Use non-invasive ventilation

Non-invasive ventilation (NIV) should be used as the treatment of choice for persistent hypercapnic ventilatory failure during exacerbations not responding to medical therapy. It should be delivered by staff trained in its application, experienced in its use and aware of its limitations.

- When patients are started on NIV, there should be a clear plan covering what to do in the event of deterioration and ceilings of therapy should be agreed.

Manage exacerbations

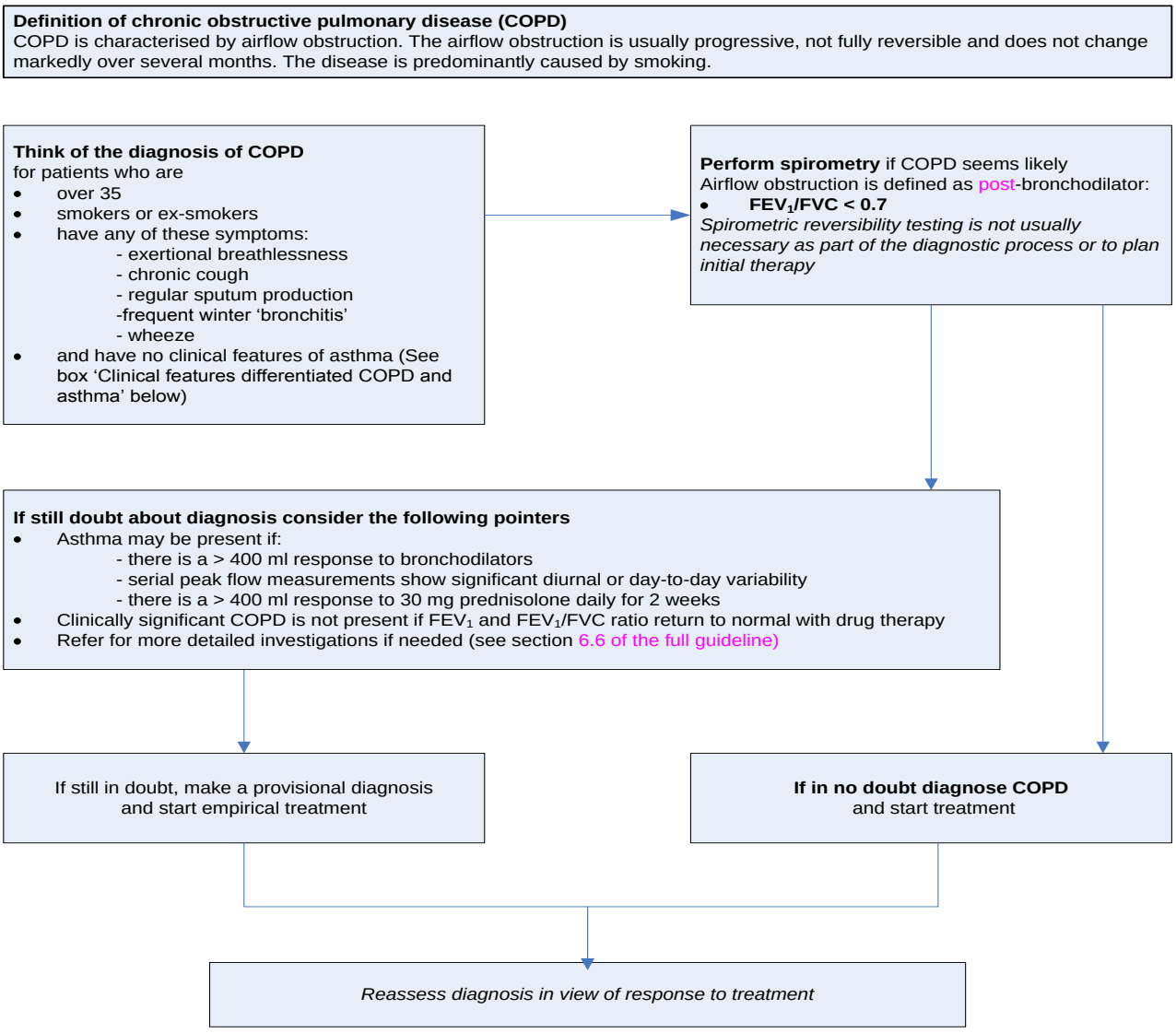
- The frequency of exacerbations should be reduced by appropriate use of inhaled corticosteroids and bronchodilators, and vaccinations.
- The impact of exacerbations should be minimised by:
    - giving self-management advice on responding promptly to the symptoms of an exacerbation
    - starting appropriate treatment with oral steroids and/or antibiotics
    - use of non-invasive ventilation when indicated
    - use of hospital-at-home or assisted-discharge schemes.

Ensure multidisciplinary working

- COPD care should be delivered by a multidisciplinary team.

5.2 Algorithms

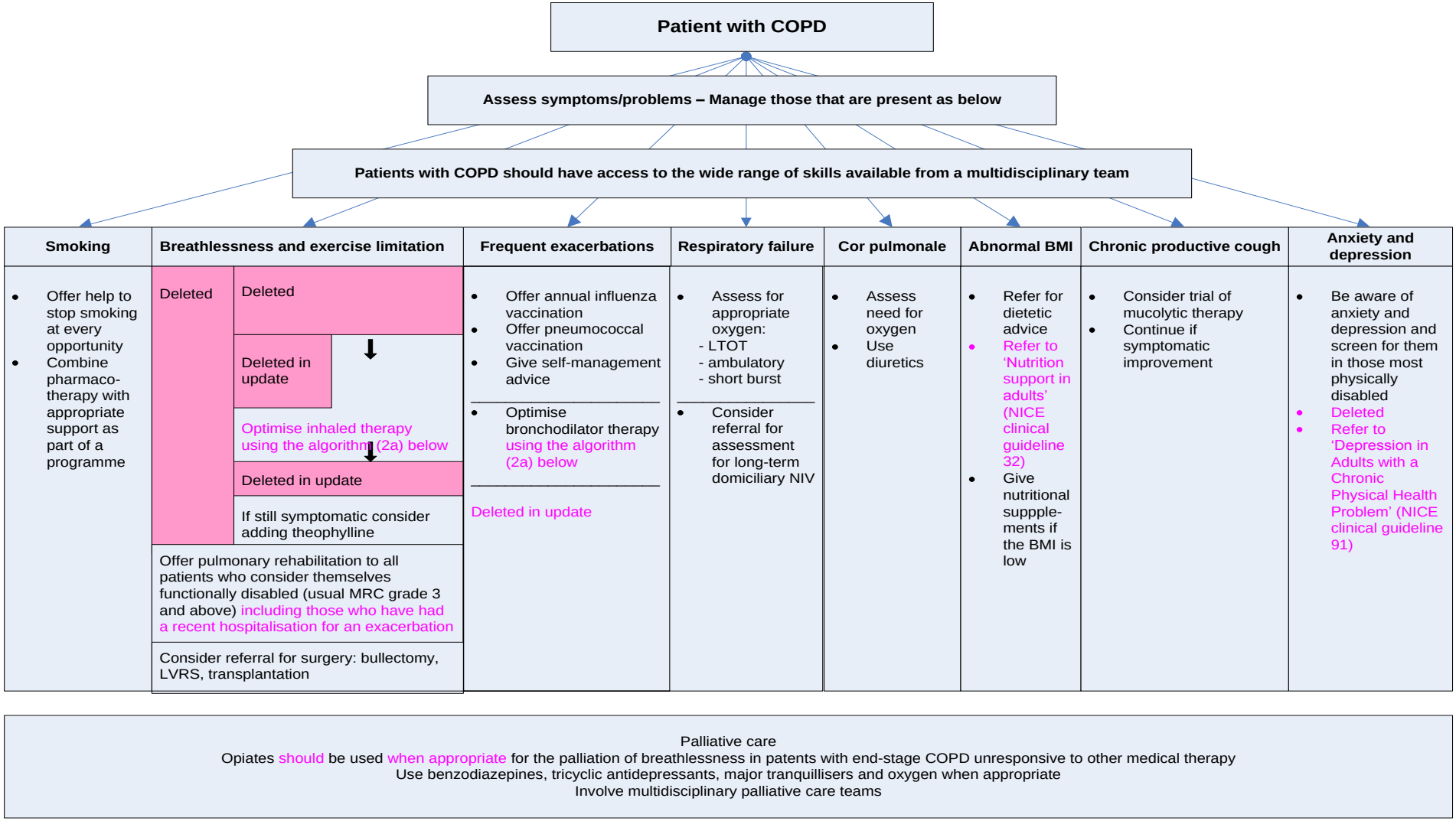
Algorithm 1: Diagnosing COPD



Clinical features differentiating COPD and asthma

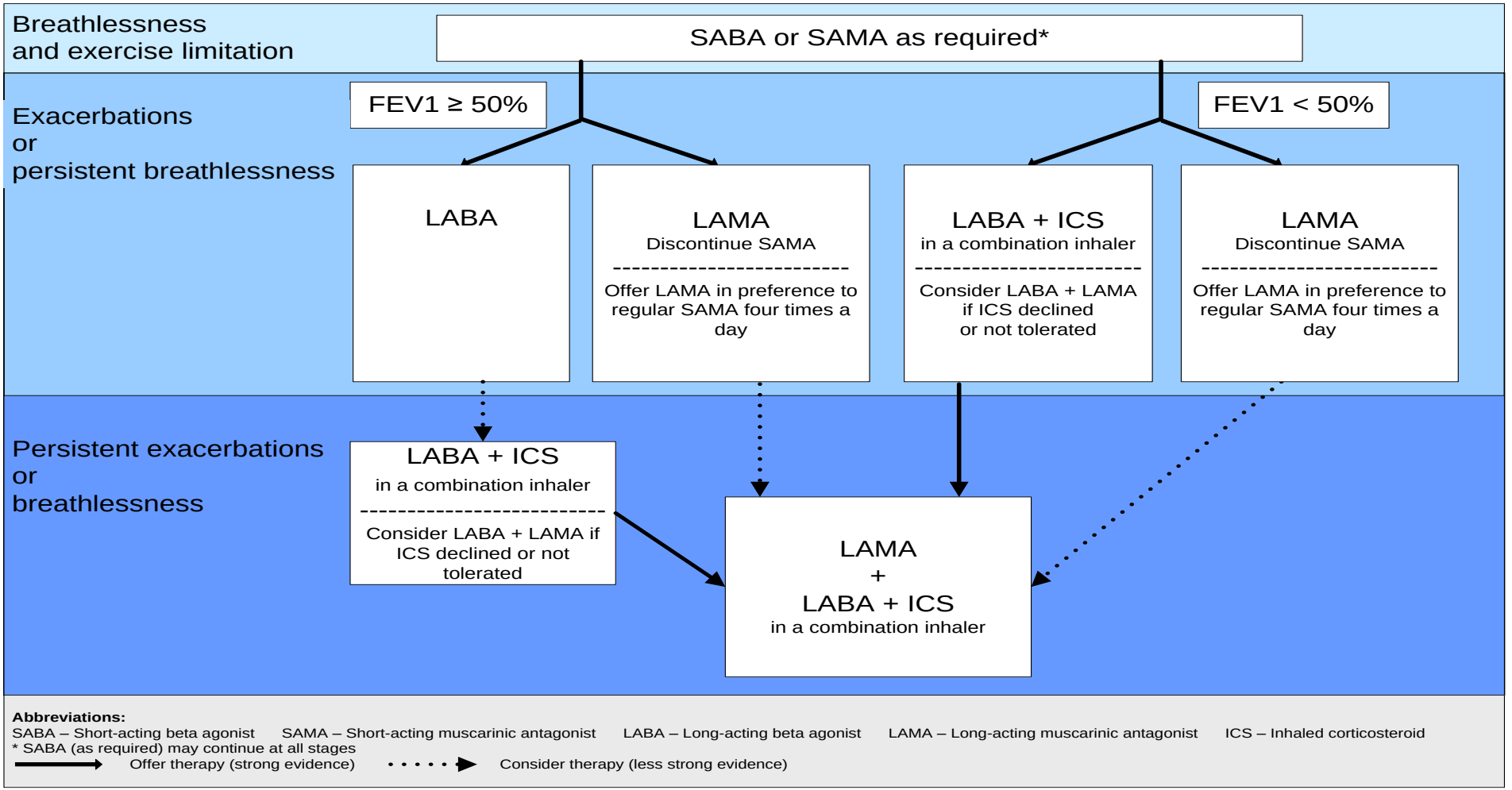
	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Symptoms under age 35	Rare	Often
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Night- time waking with breathlessness and or wheeze	Uncommon	Common
Significant diurnal or day-to-day variability of symptoms	Uncommon	Common

Algorithm 2: Management of stable COPD



Algorithm 2a: Use of inhaled therapies

Please note: This algorithm should be used within the wider context of the management of COPD, including algorithms 1, 2 and 3



NEW 2010 UPDATE 2a ALGORITHM

Algorithm 3: Managing exacerbations of COPD

Exacerbations of COPD can be associated with increased:
Dyspnoea/sputum purulence/sputum volume/cough

Initial management
- Increase frequency of bronchodilator use - consider giving via a nebuliser
- Oral antibiotics if purulent sputum
- Prednisolone 30 mg daily for 7 – 14 days – for all patients with significant increase in breathlessness, and all patients admitted to hospital, unless contraindicated

Decide where to manage (see table below)

Hospital
Investigations
- Chest X-ray
- Arterial Blood gases (record inspired oxygen concentration)
- ECG
- Full blood count and urea and electrolytes
- Theophylline level if patient on theophylline at admission
- Sputum microscopy and culture if purulent

Further management
- Deleted
- If necessary, oxygen should be given to keep the SaO_2 within the individualised target range*
- Assess need for non-invasive ventilation:
  - consider respiratory stimulant if NIV not available
  - assess need for intubation
- Consider intravenous theophyllines if poor response to nebulised bronchodilators

Consider hospital-at-home or assisted-discharge scheme

Before discharge
- Establish on optimal therapy
- Arrange multidisciplinary assessment if necessary

*Readers should refer to local protocols for oxygen therapy

Factors to consider when deciding where to manage patient

Factor	Favours treatment at home	Favours treatment in hospital
Able to cope at home	Yes	No
Breathless-ness	Mild	Severe
General condition	Good	Poor - deteriorating
Level of activity	Good	Poor/ confined to bed
Cyanosis	No	Yes
Worsening peripheral oedema	No	Yes
Level of consciousness	Normal	Impaired
Already receiving LTOT	No	Yes
Social circumstances	Good	Living alone/ Not coping
Acute confusion	No	Yes
Rapid rate of onset	No	Yes
Significant comorbidity (particularly cardiac and insulin dependent diabetes)	No	Yes
SaO_2 < 90%	No	Yes
Changes on the chest radiograph	No	Present
Arterial pH level	≥ 7.35	< 7.35
Arterial PaO_2	≥ 7kPa	< 7kPa

Home
Investigations
- Sputum culture not normally recommended
- Pulse oximetry if severe exacerbation

Further management
- Arrange appropriate review
- Establish on optimal therapy
- Arrange multidisciplinary assessment if necessary

Abbreviations:
LTOT – long-term oxygen therapy
SaO_2 – oxygen saturation of arterial blood
PaO_2 – partial pressure of oxygen in arterial blood

5.3 Suggested audit criteria for implementation

Key Priority	Criterion	Exception
1. Diagnose COPD A diagnosis of COPD should be considered in patients over the age of 35 who have a risk factor (generally smoking) and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter 'bronchitis' or wheeze. The presence of airflow obstruction should be confirmed by performing spirometry. All health professionals managing patients with COPD should have access to spirometry and they must be competent in the interpretation of the results.	a) percentage of smokers over the age of 35 consulting with a chronic cough and/or breathlessness who have had spirometry performed b) percentage of patients with a diagnosis of COPD who have had spirometry performed	Inability to perform spirometry, for example because of facial paralysis
2. Stop smoking Encouraging patients with COPD to stop smoking is one of the most important components of their management. All COPD patients still smoking, regardless of age should be encouraged to stop, and offered help to do so, at every opportunity.	Percentage of patients with COPD who are current smokers recorded in the general practice records as having been offered smoking cessation advice and or therapy	
3. Give effective inhaled therapy Long-acting inhaled bronchodilators should be used in people with COPD who remain symptomatic (e.g. breathlessness or exacerbations) despite the use of short-acting drugs. A long-acting beta-agonist or a long-acting muscarinic antagonist should be used in people with COPD and $FEV_1 \geq 50\%$ predicted who continue to experience problems despite the use of short-acting drugs. Either a long-acting beta-agonist and inhaled corticosteroid in a	Appropriateness of inhaled steroid therapy	Patient choice

combination inhaler, or a long-acting muscarinic antagonist should be used in patients with an FEV_1 < 50% predicted who continue to experience problems despite the use of short-acting drugs. Additional treatment with a long-acting muscarinic antagonist should be used in people with COPD who remain symptomatic despite taking a long-acting beta-agonist and inhaled steroid in a combination inhaler, irrespective of their FEV_1.		
4. Provide pulmonary rehabilitation for all who need it Pulmonary rehabilitation should be offered to all patients who consider themselves functionally disabled by COPD. Pulmonary rehabilitation programmes must meet clinical needs in terms of access, location and availability.	Percentage of patients with COPD who have undergone pulmonary rehabilitation	Patient choice
5. Use non-invasive ventilation Non-invasive ventilation (NIV) is the treatment of choice for persistent hypercapnic respiratory failure during exacerbations after optimal medical therapy. It should be delivered by staff trained in its application, experienced in its use and aware of its limitations. When patients are started on NIV there should be a clear management plan in the event of deterioration and ceilings of therapy agreed.	Percentage of patients presenting with acute hypercapnic ventilatory failure who have received non-invasive ventilation	Patient choice
6. Manage exacerbations The frequency of exacerbations should be reduced by appropriate use of inhaled corticosteroids and bronchodilators, and vaccinations. The impact of exacerbations should be minimised by:	Frequency and appropriateness of oral steroid and antibiotic therapy	Patient choice

• giving self-management advice on responding promptly to the symptoms of an exacerbation • starting appropriate treatment with oral steroids and or antibiotics • use of non-invasive ventilation when indicated • use of hospital-at-home or assisted-discharge schemes		

Sentinel events audit

The recommendations above concern monitoring services as routinely delivered. A second approach to audit is to use adverse events to highlight particular areas of low quality service. This requires identification of agreed 'sentinel events'. In people with COPD readmission to hospital with one month of an admission with an exacerbation of COPD may represent such an event.

Criterion

Percentage of patients readmitted to hospital with an exacerbation of COPD within 28 days of discharge.

Patient-centred audit

Finally it is recommended that health care commissioning organizations should consider using a patient-centred audit approach intermittently, to investigate the totality of services and identify particular areas that need further development

6 Diagnosing COPD

6.1 Introduction

The diagnosis of COPD depends on thinking of it as a cause of breathlessness or cough. The diagnosis is suspected on the basis of symptoms and signs and supported by spirometry.

A multidimensional assessment is important (taking into account symptoms such as breathlessness, exercise limitation and exacerbations). The principal differential diagnosis is asthma and this can usually be distinguished on clinical grounds.

COPD is a heterogeneous disease that affects different patients in different ways. Assessment of the clinical features that are present in an individual helps guide appropriate management.

Spirometry can be used to assess the severity of airflow limitation and together with other investigations it can help predict the prognosis. Any tabulation of spirometry is purely a way of documenting airflow obstruction and should not be indicative of the overall severity of the disease. Different guidelines have previously had varying ways of grading severity of airflow obstruction (section 6.9, table 6.7).

6.2 Symptoms

In the early stages COPD may produce minimal or no symptoms [11] and as the disease progresses the symptoms in individual patients vary.	IV
Individual patients rank the importance of different symptoms differently; however, in general, breathlessness is the symptom which causes them most concern.	IV
Individual symptoms in isolation are not useful in excluding or making the diagnosis of COPD.	IV

Recommendations

R1	A diagnosis of COPD should be considered in patients over the age of 35 who have a risk factor (generally smoking) and who present with one or more of the following symptoms: • exertional breathlessness • chronic cough • regular sputum production • frequent winter "bronchitis" • wheeze.	**Grade D**
R2	Patients in whom a diagnosis of COPD is considered should also be asked about the presence of the following factors: • weight loss • effort intolerance • waking at night • ankle swelling • fatigue • occupational hazards • chest pain • haemoptysis. NB These last two symptoms are uncommon in COPD and raise the possibility of alternative diagnoses.	**Grade D**
R3	One of the primary symptoms of COPD is breathlessness. The Medical Research Council (MRC) dyspnoea scale (see table 6.1) should be used to grade the breathlessness according to the level of exertion required to elicit it.	**Grade D**

Table 6.1 MRC dyspnoea scale

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after walking about 100 metres or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing or undressing

Adapted from Fletcher CM et al (1959)[38])

6.3 Signs

Individual clinical signs are not helpful in making a diagnosis of COPD and in some patients there may be no abnormal physical signs.

The following signs may be present:

- hyperinflated chest
- wheeze or quiet breath sounds
- purse lip breathing
- use of accessory muscles
- paradoxical movement of lower ribs
- reduced crico-sternal distance
- reduced cardiac dullness on percussion
- peripheral oedema
- cyanosis
- raised JVP
- cachexia.

6.4 Spirometry

6.4.1 Performing Spirometry

Demonstration of the presence of airflow obstruction is critical to making the diagnosis of COPD. Spirometry is the only accurate method of measuring the airflow obstruction in patients with COPD. Peak expiratory flow measurement may significantly underestimate the severity of the airflow limitation. All hospitals have access to spirometry and many primary care practices now have a spirometer.

GDG consensus statements

Spirometry is fundamental to making a diagnosis of COPD and a confident diagnosis of COPD can only be made with spirometry.	IV
A diagnosis of airflow obstruction can be made if the $FEV_1/FVC < 0.7$ (i.e. 70%) and $FEV_1 < 80\%$ predicted.	IV
In individual patients peak expiratory flow (PEF) rates have not been validated for the diagnosis of COPD and a normal PEF rate does not exclude significant airflow obstruction [39].	IV
Spirometry is a poor predictor of disability and quality of life in COPD [40].	IV
Spirometry predicts prognosis in COPD [41,42].	IV
Spirometry contributes to the assessment of the severity of COPD.	IV
Spirometry alone cannot separate asthma from COPD.	IV
Changes in the flow volume loop may give additional information about mild airflow obstruction.	IV
Measurement of the slow vital capacity may allow the assessment of airflow obstruction in patients who are unable to perform a forced manoeuvre to full exhalation.	IV

Clinical Introduction

Current clinical practice in primary care in the UK has been driven by the Quality Outcome Framework (QOF) which initially advocated bronchodilator reversibility testing (i.e. measurement of both pre and post-bronchodilator values (see section 6.7)) as a diagnostic tool. The 2009 QOF[9] requires the diagnosis to be confirmed by post bronchodilator spirometry. The 2004 COPD guideline did not specify whether spirometry measurements should be made pre or post bronchodilator. This was identified as an area for clarification in the 2010 partial update.

The GDG posed the following question:

DIAG1: How does post bronchodilator FEV_1 (forced expiratory volume in one second) compare with pre bronchodilator FEV_1 in terms of: a) sensitivity / specificity of FEV_1 for diagnosis; b) classification of severity of disease?

The literature was searched from 2003-20/8/09 for studies that compared pre and post bronchodilator (BD) FEV_1 values to a clinical diagnosis of COPD (based on symptoms). Very few papers defined COPD in this way; i.e. without including FEV_1 as part of the definition of COPD. Several studies were excluded because pre and post BD FEV_1 values were compared to identify COPD defined according to GOLD criteria (post bronchodilator $FEV_1/FVC < 0.70$). By definition, post bronchodilator FEV_1 would correlate better with a definition of COPD that is based on post bronchodilator FEV_1.

Two studies[43,44] were identified that addressed this issue.

The PLATINO study [43] was a cross sectional study of adults in Latin America defined as either at low risk or high risk for COPD (based on questionnaires and medical histories). The low risk group (N=1895) lacked significant exposures, cough, dyspnoea, wheezing and did not refer a medical diagnosis of asthma or COPD. The remaining participants (N=3288) were considered as having a high risk for COPD. The study compared pre bronchodilator (BD) with post BD FEV_1 to identify people with COPD defined as either an $FEV_1/FVC < 0.70$ or an $FEV_1/FVC < 5^{th}$ percentile. This study was included because it compared the FEV_1 measures in a high and low risk group. It should be noted that there is no accepted gold standard d iagnostic test for COPD against which to compare the FEV_1 indices.

It was unclear if the assessors were blinded to whether the FEV_1 measurements were pre or post BD. The pre and post BD FEV_1 measurements were performed close together and all patients received both FEV_1 measurements (pre and post bronchodilator).

A case series study [44] assessed the utility of reversibility testing in people with a clinical diagnosis and symptoms compatible with non-asthmatic COPD (N=660). People whose FEV_1 improved post BD by > ten percent of their predicted FEV_1 were excluded. This study was included because it measured FEV_1 pre and post bronchodilator and calculated an interclass correlation coefficient, giving some indication of repeatability of the pre and post bronchodilator measurements.

There were no studies comparing pre with post BD FEV_1 to classify the severity of COPD.

Evidence summary

Prevalence of COPD: Pre versus post bronchodilator FEV_1

In the PLATINO study [43], the prevalence of airway obstruction defined according to $FEV_1/FVC < 0.70$ was less when FEV_1 was measured post BD than pre BD (17.4% versus 26.2%) in the group at high risk of COPD. In the low risk group, the prevalence of airway obstruction defined according to $FEV_1/FVC < 0.70$ was also less when FEV_1 was measured post BD than pre BD (8.2% versus 13.8%).

When airway obstruction was defined as $FEV_1/FVC < 5^{th}$ percentile, the prevalence of airway obstruction in the high risk group was lower when FEV_1 was measured post BD versus pre BD (13.8% versus 14.5%); and was also lower in the low risk group (5.6% versus 6.2%).

To discriminate between high and low risk for COPD, the likelihood ratio of pre BD tests to detect $FEV_1/FVC < 0.70$ was 1.899. The likelihood ratio of post BD tests to detect $FEV_1/FVC < 0.70$ was higher at 2.122.

To discriminate between high and low risk for COPD, the likelihood ratio of pre BD tests to detect $FEV_1/FVC < 5^{th}$ percentile was 2.339. Again the likelihood ratio was higher for post BD tests at 2.464.

Sensitivity and specificity are not provided by the authors but the likelihood ratio combines both these parameters and provides a direct estimate of how the odds of having a disease will increase with a positive test (or decrease with a negative test).

Reproducibility of measurement: Pre versus Post BD FEV_1

Intraclass correlation coefficient

The mean post-bronchodilator FEV_1 was reproducible between visits (interclass correlation coefficient 0.93). The intraclass correlation coefficient for mean pre-BD FEV_1 was slightly less (interclass correlation coefficient 0.91) compared with post BD FEV_1. [44]

Health economic evidence

No relevant economic analyses were identified that compared COPD diagnosis or severity classification using post-bronchodilator FEV_1 with pre-bronchodilator FEV_1.

Evidence to recommendations

This question looked at evidence relating to pre and post bronchodilator spirometry as stand-alone measurements in terms of confirming a diagnosis of COPD, noting that this is different issue from reversibility testing, which is still not deemed to be a necessary routine diagnostic procedure.

The GDG considered the potential clinical and health economic implications of changes in COPD severity grading if a change is made to use post-bronchodilator spirometry in COPD diagnosis. The potential benefit of using post-bronchodilator FEV_1 to improve accuracy of diagnosis is offset by a small cost implication compared to using pre-bronchodilator FEV_1 since a post-bronchodilator test necessarily takes longer.

The GDG considered that there would, however, be minimal increase in resource use as reversibility testing is currently undertaken to fulfil QOF criteria, and patients do not need detailed observation while awaiting the post-bronchodilator FEV_1 measurement.

It was noted that the draft National Strategy for COPD makes no recommendation regarding restaging people unless there was a clinical indication.

In terms of quality assessment, it was noted that there are no measurements other than spirometry which have been used to confirm a diagnosis of COPD. Most studies use either pre or post bronchodilator FEV_1 as part of the definition of COPD, making it impossible to assess the independent value of the measurements in diagnosis. Furthermore no studies were found which allowed consideration of sensitivity and specificity.

Data in the PLATINO study [43] was from a non-UK population without robust predicted reference values. The data compared pre and post bronchodilator FEV_1 in groups at high and low risk for COPD and showed that post-bronchodilator measurements discriminated slightly better between the two groups. In the second study [44] post-bronchodilator measurements proved to be slightly more repeatable than pre-bronchodilator measurements, although the GDG noted that over time, between day variation in participant stability is often as important as the between day variation in measurement.

No evidence was found comparing pre FEV_1 and post FEV_1 over time for mortality outcome.

The GDG therefore discussed this question without the benefit of robust evidence, although the limited data available favoured post-bronchodilator values. They agreed to recommend use of post bronchodilator measurement, noting also that this would harmonise with international guidelines, the Quality Outcome Framework, and the National Strategy for COPD.

Evidence was not reviewed for what exactly constitutes a post bronchodilator test (in terms of precise recommendations for performing the test), and no recommendation was felt possible based upon evidence not examined, and with potential health-economic implications.

Finally the GDG noted that virtually all the evidence around treatment recommendations is based upon clinical trials where criteria for entry into the trial were pre bronchodilator measurements, but did not feel that this historical fact should prevent them from recommending the alternative.

6.4.2 Interpreting Spirometry

Clinical introduction

The values for the post-bronchodilator forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) must be compared with the predicted normal values which depend on the individual's age height and sex. Various tables of predicted normal values have been published but the ones most widely used in Europe and most relevant for patients in the UK are those published by the European Coal & Steel Community (ECCS) [45].

A controversial area of spirometry interpretation relates to whether a fixed ratio or an age dependent lower limit of normal (LLN) should be used to define air flow obstruction.

International GOLD guidelines note that specific spirometric cut-points (e.g., post-bronchodilator FEV_1/FVC ratio < 0.70 or FEV_1 < 80,50, or 30% predicted) are used for purposes of simplicity, but that these cut-points have not been clinically validated[46].[3] The process of aging affects lung volumes, and the FEV_1/FVC ratio is dependent on age, height and sex, such that the use of a fixed ratio might result in over diagnosis of COPD in older people, and under diagnosis in younger people[47-64]. It has therefore been proposed that confirmation of obstructive lung disease should be based on an FEV_1/FVC ratio below the LLN, classifying the bottom 5% of the healthy population as abnormal[45,48,65,66]. In principle, all programmable spirometers could do this calculation if reference equations for the LLN of the ratio were available. However, reference equations using post-bronchodilator FEV_1 and longitudinal studies to validate the use of the LLN are not available and urgently needed[46].

The GDG felt it appropriate to review the current guideline recommendation noting increasing availability of computerised spirometry and expertise in conducting studies, and the potential impact on accuracy of diagnosis, treatment and costs.

The GDG posed the following question:

DIAG2: In individuals where the diagnosis of COPD is considered and spirometry is conducted, what are the sensitivity and specificity of a fixed ratio FEV_1/FVC compared with the lower limit of normal FEV_1/FVC ratio to diagnose COPD?

Methodological introduction

Four cross-sectional studies[52,56,67,68] were found that compared FEV_1/FVC ratio (fixed vs. lower limit of normal [LLN]) with a physician's diagnosis of COPD. There is no GRADE profile for diagnostic studies.

In all the studies, the definition of the fixed ratio was from GOLD or equivalent definition (FEV_1/FVC < 70%) and all measurements were post-bronchodilator (except for Celli et al)[52]. The definition of 'physician's diagnosis' in all the studies was based on a self-reported diagnosis of COPD (patients filled in a questionnaire). It is important to note that the results for the physician's diagnosis in the studies probably underestimated the true percentage of patients who had COPD.

Evidence statements

FEV_1/FVC ratio (fixed vs. LLN) vs. physician's diagnosis

The two largest studies [52,68] showed that FEV_1/FVC (fixed ratio) was most similar to the physician's diagnosis. The two smaller studies [56 67] showed that the FEV_1/FVC (LLN) was most similar to the physician's diagnosis. (See summary table 6.2).

Celli et al [52] also showed that for persons aged < 50 years, the LLN produced the highest rate estimates; whereas for persons aged ≥ 55 years, the fixed ratio produced the highest rate estimates. For the older population (aged 75-80 years) GOLD IIA (defined as FEV_1/FVC < 0.70 and FEV_1 < 80% predicted) identified fewer patients than the LLN, and was nearer to the physician's diagnosis. GOLD IIA therefore gave a more conservative estimate. The GOLD Stage IIA definition for all age-groups produced lower estimates than the other definitions (LLN and fixed ratio) and was more similar to the physician diagnosis than the other definitions.

Table 6.2 Summary of studies assessing FEV_1/FVC ratio (fixed vs. LLN) vs. physician's diagnosis

Reference	Patients with diagnosis of COPD			
	N	**Physician diagnosis**	**FEV_1/FVC (fixed ratio)**	**FEV_1/FVC (LLN)**
Celli et al. [52]	9838	**77.3** cases/1000 population	**167.8** (fixed) **78.7** (fixed, GOLD stage IIA) cases per 1000 population	**142.1** cases per 1000 population
Ko et al. [67]	1008	**3.6%**	**25.9%** Poor agreement with physician diagnosis	**12.4%** Poor agreement with physician diagnosis
Roche et al. [68]	4764	**8.4%**	**8.7%**	**6.4%** (ERS definition using ECCS equations) **7.96%** (ERS definition using study population equations)
Shirtcliffe et al [56]	749	**10.6%**	**15.5%** Poor agreement with physician diagnosis (K coefficient)	**10.4%** Poor agreement with physician diagnosis (K coefficient)

Health economic evidence

No relevant economic analyses were identified that compared COPD diagnosis using a fixed ratio FEV_1/FVC compared with the lower limit of normal FEV_1/FVC ratio.

Evidence to recommendations

The GDG noted that papers which compared each of these two spirometric criteria for COPD diagnosis with clinical correlates of COPD varied in use of pre and post bronchodilator spirometry values. There are currently no reference ranges for post bronchodilator values. Physician diagnosis of COPD was limited as a gold standard as current diagnostic criteria include spirometric indices by definition.

One study [52] showed that use of pre bronchodilator values of FEV_1/FVC ratio < 70% and FEV_1 < 80% predicted derived almost identical sensitivity to use of FEV_1/FVC ratio of < 5% below the LLN. Both criteria produced the same prevalence of COPD but did not necessarily identify the same people.

Diagnosis of COPD by FEV_1/FVC ratio below LLN was considered an attractive option which may in time supersede current practice as a more precise measurement. Currently however, use of LLN was considered impractical due to lack of predictive equations and reference values for post bronchodilator FEV_1 and FVC values.

The GDG noted that the lack of normal ranges for certain ethnic populations could also create diagnostic difficulties which might merit specialist advice being sought. This was a very complicated area for which there were uneven data at the time. The GDG was aware that international research into reference values was ongoing. Whilst these data were awaited, no specific recommendation was made.

Caution was advised regarding the risk of failure to diagnose COPD in some younger people with symptomatic COPD, and the risk of inappropriate management in older people in whom symptoms do not fit the clinical pattern of COPD but in whom spirometry records FEV_1/FVC ratio < 70%. Specialist advice should be sought in such cases, (recommendation U2).

Recommendations

R4	Spirometry should be performed: • at the time of diagnosis • to reconsider the diagnosis, if patients show an exceptionally good response to treatment.	**Grade D**
U1	**NEW 2010 UPDATE RECOMMENDATION 1 (U1)** Measure post-bronchodilator spirometry to confirm the diagnosis of COPD.	
U2	**NEW 2010 UPDATE RECOMMENDATION 2 (U2)** Consider alternative diagnoses or investigations in: • older people without typical symptoms of COPD where the FEV_1/FVC ratio is < 0.7 • younger people with symptoms of COPD where the FEV_1/FVC ratio is ≥ 0.7.	
R5	All health professionals involved in the care of people with COPD should have access to spirometry and be competent in the interpretation of the results.	**Grade D**
R6	Spirometry can be performed by any health care worker who has undergone appropriate training and who keeps his or her skills up to date.	**Grade D**
R7	Spirometry services should be supported by quality control processes.	**Grade D**
R8	It is recommended that ERS 1993[45] reference values are used but it is recognised that these values may lead to under-diagnosis in older people and are not applicable in black and Asian populations. NB Definitive spirometry reference values are not currently available for all ethnic populations. The GDG was aware of on-going research in this area.	**Grade D**

6.5 Differential diagnosis

None of the symptoms discussed above are specific to COPD, and several other disorders may present with similar symptoms, signs and spirometry results (Table 6.3). As well as mimicking COPD these conditions may also coexist in a patient with COPD.

Table 6.3 Conditions presenting with similar symptoms

NB Elderly patients are particularly likely to have a number of concomitant medical problems.

Other conditions that may present with similar symptoms	
Common	Less common
• asthma	• obliterative bronchiolitis
• bronchiectasis	• bronchopulmonary dysplasia
• congestive cardiac failure	
• carcinoma of the bronchus	

6.6 Further investigations

As well as spirometry a number of other investigations are helpful in the initial assessment of patients at the time of diagnosis. Further investigations are also indicated in selected patients depending on the clinical findings.

Recommendations

R9 At the time of their initial diagnostic evaluation in addition to spirometry all patients should have: **Grade D**

- a chest radiograph to exclude other pathologies
- a full blood count to identify anaemia or polycythaemia
- body mass index (BMI) calculated.

R10 Additional investigations should be performed to aid management in some circumstances (see Table 6.4). **Grade D**

Table 6.4 Additional investigations

Investigation	Role
Serial domiciliary peak flow measurements	To exclude asthma if diagnostic doubt remains
Alpha-1 antitrypsin	If early onset, minimal smoking history or family history
Transfer factor for carbon monoxide (T_LCO)	To investigate symptoms that seem disproportionate to the spirometric impairment
CT scan of the thorax	To investigate symptoms that seem disproportionate to the spirometric impairment To investigate abnormalities seen on a chest radiograph To assess suitability for surgery
ECG	To assess cardiac status if features of cor pulmonale
Echocardiogram	To assess cardiac status if features of cor pulmonale

Pulse oximetry	To assess need for oxygen therapy If cyanosis, or cor pulmonale present, or if FEV_1 < 50% predicted
Sputum culture	To identify organisms if sputum is persistently present and purulent

R11 Patients identified as having alpha-1 antitrypsin deficiency should be offered the opportunity to be referred to a specialist centre to discuss the clinical management of this condition. **Grade D**

6.7 Reversibility testing

COPD is defined by the presence of airflow limitation that is "not fully reversible and does not change markedly over several months" (See Section 1.1). The GDG is aware that in the past there have been concerns about both the under and over diagnosis of COPD in the absence of an objective diagnostic test. Traditionally measurement of the degree of reversibility using bronchodilators or corticosteroids has been used to confirm the diagnosis and in particular to try to separate patients with asthma from those with COPD.

In the 2010 update, post-bronchodilator spirometry measurement is recommended in assessment of COPD for reasons discussed in the previous section. This measurement should not be confused with or equated with reversibility testing.

While post-bronchodilator FEV_1/FVC and FEV_1 measurements are recommended for the diagnosis and assessment of severity of COPD, the degree of reversibility of airflow limitation (e.g., change in FEV_1 after bronchodilator or glucocorticosteroids) is not recommended for diagnosis, or for predicting the response to long-term treatment with bronchodilators or glucocorticosteroids[46,69,70].

There are many difficulties with this approach. The degree of reversibility that has been regarded as significant was arbitrarily defined and varied from 10% to 20% in different settings. To overcome spurious results in patients with a low FEV_1 a minimum absolute value for the increase (e.g.200 ml) has also been recommended. In practice, there is considerable variability in the change in FEV_1 in response to the same stimulus from day to day. This makes it virtually impossible to interpret the response to an individual reversibility test unless the response is very large (e.g. an increase in FEV_1 of more than 400 ml).

Reversibility testing was promoted in previous national and international guidelines [BTS[71] & GOLD[72]], but is not recommended in the latest guidelines produced jointly by the American Thoracic Society and the European Respiratory Society.

The BTS/SIGN[73] guidelines on the management of asthma recommend that objective test are used "*to try to"* confirm the diagnosis. In this section they discuss the fact that significant variability in PEF can be used to identify asthma and suggest that a 20% or greater variability in amplitude is highly suggestive. However, they highlight that many patients will show less variability than this and they conclude that the test is "reasonably specific but insensitive". The guidelines also mention that increases of 15% or 200ml in FEV_1 after inhalation of short-acting $beta_2$ agonists or oral prednisolone can also be seen in asthma, but these guidelines do not deal specifically with the differentiation of asthma from COPD.

In most cases the diagnosis of COPD is suggested by the combination of the clinical history, signs and baseline spirometry. Reversibility testing does not add any additional information. It is also generally possible to identify patients who have asthma rather than COPD on the basis of the clinical picture and again reversibility testing does not add additional information.

Reversibility testing has also been advocated as a means of identifying the most appropriate therapies for individual patients. There is now evidence that the clinical response to bronchodilators or inhaled corticosteroids cannot be predicted by response to a reversibility test.

Evidence statements

There is considerable variation in the magnitude of change in FEV_1 following inhalation of a bronchodilator between individuals and within individuals tested on different days [44,74].	IIb
A number of different methods for assessing the response to bronchodilators have been proposed [75-78].	IIb IIb Ib IIb
A change in FEV_1 of at least 160 ml is required to exclude changes within the natural variability in of FEV_1 in people with obstructive ventilatory defects [79].	IIb
A study of patients with fixed airflow obstruction diagnosed as having COPD or asthma on the basis of the clinical history[80] has shown that the clinical diagnosis was correct as assessed by the basis of the pattern of inflammation seen on bronchial biopsies and the differential cell counts in induced sputum findings. Reversibility testing was unable to differentiate the two groups.	III
Bronchodilator tests performed with different inspiratory manoeuvres before and after bronchodilator administration provide differing results[81].	IIb
The response to a short course of oral steroids does not predict the response to long-term therapy [82].	Ib

Recommendations

R12 In most patients routine spirometric reversibility testing is not necessary as a part of the diagnostic process or to plan initial therapy with bronchodilators or corticosteroids. It may be unhelpful or misleading because: **Grade D**

- repeated FEV_1 measurements can show small spontaneous fluctuations **Grade B**
- the results of a reversibility test performed on different occasions can be inconsistent and not reproducible **Grade B**
- over-reliance on a single reversibility test may be misleading unless the change in FEV_1 is greater than 400 ml **Grade B**
- the definition of the magnitude of a significant change is purely arbitrary **Grade B**
- response to long-term therapy is not predicted by acute reversibility testing. **Grade A**

R13 COPD and asthma are frequently distinguishable on the basis of history (and examination) in untreated patients presenting for the first time. Features from the history and examination (such as those listed in table 6.5) should be used to differentiate COPD from asthma whenever possible. **Grade D**

Table 6.5 Clinical features differentiating COPD and asthma

	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Symptoms under age 35	Rare	Often
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable

Night time waking with breathlessness and/or wheeze	Uncommon	Common
Significant diurnal or day-to-day variability of symptoms	Uncommon	Common

R14 Longitudinal observation of patients (whether using spirometry, peak flow or symptoms) should also be used to help differentiate COPD from asthma. **Grade D**

R15 To help resolve cases where diagnostic doubt remains, or both COPD and asthma are present, the following findings should be used to help identify asthma: **Grade D**

- a large (> 400 ml) response to bronchodilators
- a large (> 400 ml) response to 30 mg oral prednisolone daily for 2 weeks
- serial peak flow measurements showing 20% or greater diurnal or day-to-day variability.

Clinically significant COPD is not present if the FEV_1 and FEV_1/FVC ratio return to normal with drug therapy.

R16 If diagnostic uncertainty remains, referral for more detailed investigations, including imaging and measurement of T_LCO, should be considered. **Grade D**

R17 If patients report a marked improvement in symptoms in response to inhaled therapy, the diagnosis of COPD should be reconsidered. **Grade D**

6.8 Assessment of severity and prognostic factors

6.8.1 Multidimensional assessment

COPD is heterogeneous, so no single measure can give an adequate assessment of the true severity of the disease in an individual patient. Severity assessment is, nevertheless, important because it has implications for therapy and relates to prognosis.

Other guidelines have used spirometry to classify the severity of the disease, but using spirometry alone may underestimate the impact of the disease in some patients and overestimate it in others. Nevertheless, spirometry can be used to assess the severity of *airflow obstruction* and can be used to guide therapy and predict prognosis. Different thresholds for defining mild, moderate and severe airflow obstruction have been recommended. Thresholds of 80%, 50% and 30% are used to define the boundaries as these have implications both for therapy and prognosis and harmonise with the values recommended in the[46] GOLD and the ATS/ERS guidelines. National Institutes of Health NHLaBI. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007. Available from: URL: http://www.goldcopd.com/.

BMI and exercise capacity also reflect the impact of the disease in an individual and predict prognosis.

Clinical introduction

The NICE guidelines in 2004 stated that a true assessment of severity in COPD should include assessment of the degree of airflow obstruction and disability, the frequency of exacerbations and a range of prognostic factors. Since that time, a range of clinical indices have been compared with FEV_1 in assessment of COPD outcomes[83-97]. Clinical indices including exercise capacity have been used in conjunction with spirometry to provide a multi-dimensional index and further studies have assessed whether such indices can provide a better predictor of clinical outcomes than FEV_1 alone[98-102].

There is a need to assess whether a practical multi-dimensional assessment can be used in routine practice to assist in predicting clinically relevant outcomes including exacerbations, hospitalisations, and mortality in people with stable COPD.

For example the BODE index comprises measures of BMI, airflow obstruction (FEV_1 % predicted), dyspnoea (modified MRC score) and exercise tolerance (6 minute walking distance).

The GDG posed the following question:

MULTI: Is routine assessment using multidimensional severity assessment indices (e.g. BODE) more predictive of outcomes compared with FEV_1 alone?

Methodological introduction

Studies were included if they compared FEV_1 with a multidimensional index to predict exacerbations, mortality, or hospitalisation in people with stable COPD. Exclusion criteria were retrospective studies, univariate analyses, and multivariate analyses if they did not adjust for age and smoking. Any index that was not multidimensional (i.e. it must include measures of different outcome combinations such as quality of life plus symptoms, not just multiple dimensions of one type of outcome measure such as quality of life) was also excluded.

One prospective cohort study [101] and three prospective case-series [98,102,103] were found that assessed the prognostic ability of FEV_1 vs. multidimensional indices to predict outcomes (mortality, hospitalisations and exacerbations) in stable COPD patients.

All of the studies [98,101-103] compared FEV_1 with the BODE index in people with COPD.

Evidence statements

- 1 study [102] found that the BODE index was a better predictor of the likelihood of COPD exacerbations at 5.1 years (mean follow-up) than FEV_1 and also predicted the time to first exacerbation.

- 1 study [98] found that the BODE index was a better predictor of hospitalisation (number of admissions) at 16.2 years (mean follow-up) than FEV_1.

- 3 studies [98,101,103] found that the BODE index was a better predictor of mortality than FEV_1 (at 16.2 months,[98] 28 months[103] and 36 months[101] mean follow-up). Two studies [101,103]

assessed risk of death and one study [98] assessed time until death.

Table 6.6 Summary of studies assessing multidimensional indices vs. FEV_1 as predictors of COPD outcomes

Reference	Multidimensional index	FEV_1 (% predicted)
Outcome: number of hospital admissions		
Ong et al.[98]	**BODE index** IRR 1.20, 95% CI 1.15 to 1.25, p<0.001	FEV_1 IRR 0.08, 95% CI 0.04 to 0.16, p<0.001
Outcome: time to exacerbation		
Marin et al.[102]	**BODE index vs. FEV_1** P<0.01 (values not given); BODE predicts onset of exacerbations better than FEV_1 (values not given).	
Outcome: Mortality		
Ong et al.[98]	**BODE index** Time until death HR 1.30, 95% CI 1.08 to 1.56, p=0.006	**FEV_1** Time until death HR 0.41, 95% CI 0.03 to 5.57, p=0.5
de Torres et al.[101]	**BODE index** Risk of death HR 1.41, 95% CI 01.22 to 1.61, p<0.001	**FEV_1** Risk of death HR 0.96, 95% CI 0.94 to 0.98, p=0.001
Celli et al.[103]	**BODE index** Risk of death **C-statistic 0.74**	**FEV_1** Risk of death **C-statistic 0.65**

When BODE scores were divided into quartiles, the BODE index was a better predictor of hospital admissions than the GOLD Staging system (based on FEV_1). Using quartiles of BODE as the predictor of hospital admissions, the pseudo r^2 was 0.16, as compared with 0.04 for stages of severity based on FEV_1 (GOLD; p value not given).[98]

Additionally, Kaplan-Meier analysis of survival showed that each quartile increase in BODE score was associated with increased mortality ($p < 0.001$); the highest quartile (BODE score 7-10) was associated with a mortality rate of 80% at 52 months.[103]

Health economic evidence

No relevant economic analyses were identified that assessed severity assessment using multidimensional severity assessment indices.

Evidence to recommendation

The GDG considered the evidence to be of high methodological quality.

Multidimensional indices were considered potentially useful as an index of prognosis in primary and secondary care, with the potential to enable prediction of outcomes and targeting of resources to high risk patients.

The BODE index was considered better than FEV_1 alone with regard to prognostic stratification. One study [103] included people with COPD undergoing assessment for pulmonary rehabilitation or lung volume reduction surgery and who were likely to have relatively severe COPD and were more likely to die from respiratory disease than the general population of people with COPD. The study conclusion could not therefore be extrapolated to a general or primary care COPD population. However, three further studies produced a similar conclusion in people with COPD in a general outpatient setting.

It was noted that measurement of the BODE index offered additional prognostic information. However it was not felt that this information was sufficiently advantageous to justify the additional time and cost of routinely performing 6 MWT in all patients, and noted the difficulty of making this measurement in a primary care setting. The GDG concluded that it would be useful to calculate the BODE index where the component information was available or when it was considered necessary to have a more accurate prognosis (e.g. consideration for lung surgery).

The GDG felt that in most cases this would lead to a cost-neutral recommendation.

The GDG was aware of other indices e.g. DOSE, CAT, ADO but these were published after the literature search cut off date.

Recommendations

R18

Deleted.

U3

NEW 2010 UPDATE RECOMMENDATION 3 (U3)

Be aware that disability in COPD can be poorly reflected in the FEV_1. A more comprehensive assessment of severity includes the degree of airflow obstruction and disability, the frequency of exacerbations and the following known prognostic factors:

- FEV_1
- T_LCO
- Breathlessness (MRC scale)
- Health status
- Exercise capacity (for example, 6-minute walk test)
- BMI
- Partial pressure of oxygen in arterial blood (PaO_2)
- Cor pulmonale.

Calculate the BODE index (BMI, airflow obstruction, dyspnoea and exercise capacity) to assess prognosis where its component information is currently available.

6.9 Assessment and classification of severity of airflow obstruction

Although the categorisation of impairment of airflow obstruction was not part of a specific question for review, the GDG felt it important that health care professionals who look after people with COPD should be aware that a number of different classifications were being used by various international guideline groups (see section 6.9, table 6.7). The GDG was aware that the forthcoming National Strategy for COPD would be referring to GOLD stages. The GDG felt the NICE 2010 categorisation of airflow obstruction should align with GOLD spirometric cut-offs in line with international consensus.

It was felt important to emphasise that the severity of COPD from a clinical patient perspective depended upon far more than the degree of impairment of spirometry (e.g. symptoms of breathlessness, exercise limitation, frequency of exacerbations) and that more attention should be paid to the multidimensional assessment of impairment in COPD (see section 6.8.1) than to purely categorising disease severity in terms of lung function impairment.

The GDG considered that the clinical diagnosis of COPD in people with mild airflow obstruction ($FEV_1 \geq$ 80% predicted) should require the presence of respiratory symptoms as symptomatic but not asymptomatic GOLD stage 1 COPD has been associated with faster decline in FEV_1, increased respiratory care utilisation and a lower quality of life compared with people with normal lung function[104]. This expands the NICE 2004 definition of airflow obstruction to include the group of people with an FEV1 $\geq$ 80% predicted (with an FEV1/FVC ratio < 0.7). It also expands the clinical diagnosis of COPD to include patients in this mild airflow obstruction group who are also symptomatic.

It was also noted that all of the new recommendations relating to drug treatment in this guideline update made reference to FEV_1 being above or below 50% and made no mention of GOLD stages or the terms mild, moderate or severe.

The GDG was conscious of the potential economic impact of this change but felt that in people with mild COPD the primary course of action would be to encourage smoking cessation which is known to cost-effective even in those without COPD. As other treatments are provided in response to symptoms, which will generally be less in patients with less severe disease, it was considered that the impact would be likely to be modest in relation to the potential benefits conferred by encouraging smoking cessation earlier.

R19 The severity of airflow obstruction should be assessed according to the reduction in FEV_1 as shown in table 6.7

NEW 2010 UPDATE TABLE

Table 6.7 Gradation of severity of airflow obstruction

		NICE clinical guideline 12 (2004)[105]	ATS/ERS[69] (2004)	GOLD (2008)[23]	NICE update clinical guideline 101 (2010)
Post-bronchodilator FEV_1/FVC	**FEV_1 % predicted**	**Severity of airflow obstruction**			
			Post-bronchodilator	Post-bronchodilator	Post-bronchodilator
< 0.7	≥ 80%		Mild	Stage 1 – Mild	Stage 1 – Mild*
< 0.7	50-79%	Mild	Moderate	Stage 2 – Moderate	Stage 2 – Moderate
< 0.7	30-49%	Moderate	Severe	Stage 3 – Severe	Stage 3 – Severe
< 0.7	< 30%	Severe	Very severe	Stage 4 – Very severe**	Stage 4 – Very severe**

* Symptoms should be present to diagnose COPD in people with mild airflow obstruction (see R1)

**or FEV_1 < 50% with respiratory failure

6.10 Identification of early disease

In the early stages airflow limitation may be present without producing symptoms. Even if it does produce symptoms, such as breathlessness on exertion or chronic cough, these may not be recognised as being abnormal by the individual. Smoking cessation has the most to offer such patients as it slows the rate of decline in lung function.

See section 2 for the methodology underpinning the evidence statements.

Evidence statements

COPD can be present in the absence of symptoms [11].	III
COPD can be detected by opportunistic case finding in primary care [4,106] and in patients aged 65 and over discharged from hospital.	III
Opportunistic case finding has a high uptake, reaches most of the target group and has a high yield [4].	III
In a study of opportunistic case finding Van Schayck et al. found that 27% of patients who were aged over 35 years, were current or ex-smokers and had a chronic cough had reduced FEV_1 [107].	III
Early diagnosis of abnormal lung function as part of a motivational package, significantly affects the success of smoking cessation therapy [108,109].	Ib

GDG consensus statements

Opportunistic case finding should be based on the presence of risk factors (age and smoking) and symptoms. The diagnosis should be confirmed using spirometry.	IV

Health economics

The GDG was interested in the cost effectiveness of opportunistic case finding using spirometry linked to smoking cessation therapy. They were interested in whether the extra resources involved in testing for airflow obstruction and the subsequent intervention of smoking cessation was worth the additional expected benefits. A simple cost effectiveness model was therefore built to look at this issue. This is discussed in detail in appendix B.

In summary, the model showed that opportunistic case finding in primary care is a relatively cost effective strategy. Key parameters are the prevalence of undetected COPD and the smoking cessation success rate. It should be noted that the model is quite sensitive to some of the parameters and the results must be interpreted with this in mind.

Recommendations

R20	Spirometry should be performed in patients who are over 35, current or ex-smokers, and have a chronic cough.	**Grade D**
R21	Spirometry should be considered in patients with chronic bronchitis. A significant proportion of these will go on to develop airflow limitation [110].	**Grade B**

6.11 Referral for specialist advice

A specialist opinion may be helpful at any stage of the disease. Referral may be to establish the diagnosis, to exclude other pathology, to reassure the patient, to reinforce the need to stop smoking, to optimise treatment, or to assess the need for the more complex and expensive therapies appropriate to severe COPD. The principal reasons are based upon original work from the BTS Statement[111] and have been augmented with consensus from the COPD Guideline Development Group. See section 2 for the methodology underpinning this section. The reasons for referral for specialist advice are summarised below:

Recommendations

R22 It is recommended that referrals for specialist advice are made when clinically indicated. Referral may be appropriate at all stages of the disease and not solely in the most severely disabled patients (see table 6.8).

Grade D

Table 6.8 Reasons for referral include

Reason	Purpose
There is diagnostic uncertainty	Confirm diagnosis and optimise therapy
Suspected severe COPD	Confirm diagnosis and optimise therapy
The patient requests a second opinion	Confirm diagnosis and optimise therapy
Onset of cor pulmonale	Confirm diagnosis and optimise therapy
Assessment for oxygen therapy	Optimise therapy and measure blood gases
Assessment for long-term nebuliser therapy	Optimise therapy and exclude inappropriate prescriptions
Assessment for oral corticosteroid therapy	Justify need for long-term treatment or supervise withdrawal
Bullous lung disease	Identify candidates for surgery
A rapid decline in FEV_1	Encourage early intervention
Assessment for pulmonary rehabilitation	Identify candidates for pulmonary rehabilitation
Assessment for lung volume reduction surgery	Identify candidates for surgery
Assessment for lung transplantation	Identify candidates for surgery
Dysfunctional breathing	Confirm diagnosis, optimise pharmacotherapy and access other therapists

Onset of symptoms under 40 years or a family history of alpha 1-antitrypsin deficiency	Identify alpha$_1$-antitrypsin deficiency, consider therapy and screen family
Uncertain diagnosis	Make a diagnosis
Symptoms disproportionate to lung function deficit	Look for other explanations including cardiac impairment, pulmonary hypertension, depression and hyperventilation
Frequent infections	Exclude bronchiectasis
Haemoptysis	Exclude carcinoma of the bronchus

R23 Patients who are referred do not always have to be seen by a respiratory physician. In some cases they may be seen by members of the COPD team who have appropriate training and expertise. **Grade D**

7 Managing stable COPD

7.1 Introduction

COPD is a heterogeneous disease that affects different patients in different ways. Some patients may be more troubled by breathlessness, others may develop ankle swelling and others may be experiencing frequent hospital admissions. The management of an individual patient's disease should be guided by the symptoms and disability that they experience. At different times in the natural history of their disease different features may predominate and their management will change to reflect this. COPD also has effects outside the lung for example on peripheral muscles and may lead to mood or cognitive changes which should also be assessed.

This section presents statements and recommendations about the efficacy and role of therapies in stable COPD. Section 8 presents statements and recommendations about the efficacy and role of therapies in managing exacerbations of COPD.

The assessment of a patient's symptoms should take into account the presence of the symptoms listed in section 6.2, the clinical signs listed in section 6.3, the results of spirometry and the frequency of exacerbations. Using the algorithm in section 5.2, the results of the assessment can be used to identify therapies that are appropriate for that individual at that time.

7.2 Smoking cessation

Getting patients with COPD to stop smoking is one of the single most important interventions. Stopping smoking slows the rate of decline in FEV_1 with consequent benefits in terms of progression of symptoms and survival.

The GDG reviewed the smoking cessation evidence for both pharmacological and non-pharmacological approaches as they related specifically to COPD. Studies were rejected either because they were non-specific to COPD or due to small sample size.

One Cochrane systematic review by van der Meer et al was identified[112] which was specific to chronic obstructive pulmonary disease and contained five studies[113-117]. The review authors highlighted that only two of the five studies were of high quality and hence these were reviewed on an individual basis[113,117]. An additional two trials were identified[118 119] and one NICE Technology Appraisal [53] met our quality appraisal criteria. Three studies [113,118,119]were all part of the Lung Health Study.

The guideline remit was to consider smoking cessation approaches as they relate specifically to COPD. However the project Scope also highlighted that the NICE Technology Appraisal on "Smoking cessation treatments and nicotine replacement therapy", which is non-specific to COPD, should inform the COPD guideline.

Since the publication of the original guideline in February 2004, NICE has:

Published PH10 – Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities

Published TA123 Smoking cessation – varenicline

Replaced TA39 Smoking cessation – bupropion and nicotine replacement therapy with PH10

7.2.1 Benefits of stopping smoking

Evidence statements

The Lung Health Study showed that participants in the two smoking intervention groups showed significantly smaller declines in **FEV_1** than did those in the control group. Average decreases from baseline to 5 years were 267ml for the control group, 209ml for the smoking intervention group without study bronchodilator and 184ml with study bronchodilator. ($p<0.002$)[118,113]. Ib

Kanner, as part of the Lung Health Study evaluated the effects on **symptoms** of chronic cough, chronic phlegm production, wheezing and shortness of breath. The prevalence of each of the four symptoms in the two intervention groups was significantly less than in the usual care group ($p<0.0001$). Smokers with early COPD who were assigned to a smoking cessation intervention had fewer respiratory symptoms after 5 years of follow-up [119]. Ib

7.2.2 Smoking cessation therapy

Tashkin investigated the effect of sustained release **bupropion** compared to placebo in promoting abstinence from smoking in patients with mild to moderate COPD. This study specifically focused on a COPD population [117]. Ib

Continuous smoking abstinence rates from wk 4 to 7 were significantly higher in participants receiving bupropion than those receiving placebo (28% vs. 16%, $p=0.003$). Weeks 4 to 12 (18% vs. 10%) and weeks 4 to 26 (16% vs. 9%) smoking cessation was also higher in participants receiving bupropion than those taking placebo ($p<0.05$).

The National Institute of Health and Clinical Excellence guidance focuses on pharmacological approaches (nicotine replacement therapy and bupropion) to smoking cessation (although not specifically COPD)[12053]. NICE

Nicotine Replacement Therapy (NRT)

There is currently insufficient evidence to conclude that one form of NRT is more effective than another. In the small number of studies

undertaken with specific subgroups (pulmonary disease) results were generally inconclusive on an individual study basis, but in aggregate were consistent with the overall pooled results.

Bupropion

From a meta-analysis of ten RCTs the odds ratio for smoking cessation of bupropion vs. placebo was 2.16 (1.51 to 3.10) for 6 and 12 months. In terms of percentages of smokers quitting, the average over all trials shows that about 9% had not smoked for the 12 months following placebo therapy and about 19% had not smoked following bupropion therapy. The results for specific subgroups (pulmonary disease) were generally consistent with the overall pooled results. *Bupropion should be used in conjunction with appropriate support.*

Bupropion vs. NRT

There have been only two RCTs of bupropion vs. nicotine replacement therapy. For bupropion vs. patch, the odds ratio at 12 months for continuous abstinence was 2.07 (1.22 to 3.53) in favour of bupropion, and for bupropion plus patch versus bupropion it was 1.28 (0.82 to 1.99). In the second study, which compared bupropion to NRT gum, there was no significant difference between the groups in quit rates.

Combination of NRT and bupropion

In the single study so far conducted, the result was in favour of the combination of NRT and bupropion against bupropion alone, but the difference was not statistically significant.

Health Economic Evidence

A HTA report [121] contains a review of the economic evidence of smoking cessation interventions in the UK and a decision analytic model built by the authors. Although all of this is for smoking cessation in general and not specific to COPD, most of the literature and the model suggest that smoking cessation is a reasonably cost effective intervention.

Smoking cessation interventions, including the use of nicotine replacement therapy and/or bupropion SR are relatively cost effective in terms of the of the cost per life year saved.[121]

Recommendations

R24	An up-to-date smoking history, including pack years smoked (number of cigarettes smoked per day, divided by 20, multiplied by the number of years smoked), should be documented for everyone with COPD.	**Grade D**
R25	All COPD patients still smoking, regardless of age, should be encouraged to stop, and offered help to do so, at every opportunity.	**Grade A**
R26	Unless contraindicated, offer NRT, varenicline or bupropion, as appropriate, to people who are planning to stop smoking combined with an appropriate support programme to optimise smoking quit rates for people with COPD[a].	
R27	Deleted and replaced by PH10 'Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities' (NICE public health guidance 10). [120]	

[a] See also 'Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities' (NICE public health guidance 10). [120]

TA123

TA123 Smoking cessation – varenicline

The following two recommendations are from 'Varenicline for smoking cessation' (NICE technology appraisal guidance 123)[122].

- Varenicline is recommended within its licensed indications as an option for smokers who have expressed a desire to quit smoking.
- Varenicline should normally be prescribed only as part of a programme of behavioural support.

7.3 Inhaled therapy

NICE COPD guidelines in 2004 made specific recommendations regarding the use of inhaled long-acting bronchodilators and inhaled steroids separately and in combination, but newer studies have assessed these drugs singly and in combination over longer periods of time. The GDG felt it appropriate to restructure the updated guidelines to reflect this new information. The discussion of evidence to recommendation for comparison of inhaled long-acting bronchodilators with inhaled long-acting bronchodilator and steroid combinations is discussed at the end of this section. The expanded section on Inhaled Therapy (which now incorporates the previous separate sections on Inhaled Bronchodilators, Inhaled Corticosteroids and Inhaled Combination Therapy) now concludes with a number of new recommendations. The recommendations have all been grouped together for ease of reference, although this has necessitated their being somewhat removed from their supporting evidence.

Although COPD is characterised by substantially irreversible airflow obstruction, bronchodilators have been the mainstay of pharmacotherapy [71,123]. The structural changes in the airways prevent bronchodilators returning airway calibre to normal. Clinically relevant improvements in FEV_1 may be too small to identify against the background day to day variation in an individual patient. Inhaled agents are preferred to oral because of the reduction in systemic side effects. $Beta_2$ agonists act directly on bronchial smooth muscle to cause bronchodilation whereas anticholinergics act by inhibiting resting broncho-motor tone. As well as improving breathlessness through their direct bronchodilator effects, both classes of drugs also appear to work by reducing hyperinflation (both static and dynamic). This probably explains why clinical benefits may be seen without clear changes in the FEV_1.

7.3.1 Short-acting beta$_2$ agonists (SABA)

Beta$_2$ agonists act directly on bronchial smooth muscle to cause bronchodilation. They are the most widely used bronchodilators for COPD. The dose response relationship for salbutamol in patients with largely or completely irreversible COPD is almost flat[124,125]. The time to peak response is slower than in patients with asthma and the side-effect to benefits ratio is such that there is little benefit in giving more than 1 mg salbutamol. Their effects on airway calibre last for up to 4 hours and can be used on a regular, or as required, basis. Short-acting beta$_2$ agonists are the most commonly used short-acting bronchodilators in COPD.

One systematic review was found looking at their efficacy[126]. The review comprised of 13 RCTs[127-139], however 4 of these were from the same cohort of patients[128-130,132]. All the RCTs were of a crossover design and had variable washout periods, 7 being undocumented whilst the rest ranged from washout periods of 10 hours to 2 weeks. The majority of evidence for short-acting beta$_2$ agonist comes from older (date range 1975 to 1991), short-term (1 to 8 weeks duration), small studies (sample size range N=5 to N=48), some of which used older compounds (interventions included isoproterenol, metaproterenol, salbutamol and terbutaline)[57].

The 2010 partial update did **not** update the section on short-acting beta$_2$ agonists compared with placebo.

Evidence statements

SABA versus placebo

Ia

Daily **breathlessness** scores were reduced with the use of short-acting beta$_2$ agonists (SMD 1.33, 95% CI 1.01 to 1.65, p<0.0001)[126].

Ib

One study [128] measured the effects of short-acting beta$_2$ agonist changes on **health related quality of life**. This study was included in the

systematic review referred to above[126] however the data was not available for meta-analysis, N=32. The study showed significant improvements in the dyspnoea (p=0.003) and fatigue (p=0.0003) domains using the Chronic Respiratory Disease Questionnaire (CRQ).

Short-acting beta$_2$ agonists improve **FEV$_1$** (WMD 0.140 L, 95% CI 0.04 to 0.25, p=0.008)[126]. Ia

Short-acting beta$_2$ agonists appear to be as effective when used on an **as needed basis** as when used regularly on a background of other bronchodilators[140]. Ib

7.3.2 Short-acting beta$_2$ agonists (SABA) and short-acting muscarinic antagonists (SAMA)

Cholinergic nerves are the main neural bronchoconstrictor pathway in the airways and the resting tone is increased in patients with COPD [141]. Anticholinergic drugs cause bronchodilatation by blocking this bronchoconstrictor effect. Cholinergic effects on the airway are mediated by muscarinic receptors and these also mediate effects on mucus secretion.

Anticholinergic drugs are also referred to as muscarinic antagonists (e.g. short-acting muscarinic antagonist (SAMA)).

There were no systematic reviews comparing short-acting anticholinergics in comparison to placebo or other bronchodilating drugs. In view of the availability of data from longer term studies several trials were rejected due to small sample size [142-144] or short trial duration [145]. Four trials [146-149] had methodological limitations, which precluded making recommendations based upon the papers findings. Trials also used a variety of differing endpoint outcome measures.

The 2010 partial update did **not** update the section on short-acting anticholinergics compared with placebo.

Evidence statements

SAMA versus placebo

Three studies [150-152] demonstrated significant increases in **FEV_1** with the use of short-acting anticholinergic drugs when compared to placebo, p<0.001, p<0.026 and p<0.001 respectively.	Ib
One study [152] found that **dyspnoea** measured by the Transition Dyspnoea Index (TDI) was significantly improved with short-acting anticholinergics compared to placebo.	Ib
Two other studies found no significant differences for **symptoms** [151] or **dyspnoea** [150] or **walking distance** [150] with the use of short-acting anticholinergics compared to placebo.	Ib
One study [152] found that health related **quality of life** (measured using the Chronic Respiratory Disease Questionnaire (CRDQ)) was significantly higher for short-acting anticholinergics compared to placebo (p=0.007).	Ib
Two studies [150,151] found no significant differences between short-acting anticholinergics and placebo groups for **quality of life**.	Ib
Three studies looked at the need for **rescue medication** [150-152]. Two trials [150,152] found a decrease in use of rescue medication, p<0.047 [152]. One study [151] found no significant difference in use of rescue medication use when using short-acting anticholinergic compared to placebo.	Ib

Recommendation

R28	Short-acting bronchodilators, as necessary, should be the initial empirical treatment for the relief of breathlessness and exercise limitation.	**Grade B**

7.3.3 Long-acting beta$_2$ agonists (LABA)

The bronchodilator effects of long-acting beta$_2$ agonists are similar to the short-acting agents but their duration of action is around 12 hours. There are two long-acting beta$_2$ agonists: salmeterol and formoterol. These drugs have quite different molecular structures and there are thought to be different mechanisms responsible for the longer duration of action of these two molecules.

We found one systematic review[153] comparing long-acting beta$_2$ agonists with placebo. This deals predominantly with salmeterol, as there were few published studies of the effects of formoterol at the time it was undertaken. The review comprised of eight RCTs[152,154-160], six were of a parallel group design of 12-16 weeks duration. Two were cross over studies [156,159]. Appleton et al highlights two important points. Firstly, that there was variation in the methodological quality of the included studies and secondly that few of the results could be combined in meta analyses due to differences in methods of reporting outcomes.

One of the studies included in the systematic review [155] has only been published in abstract form and it includes data published by Mahler et al [152]. Therefore this study is not included in the table below.

Shukla et al (2002)[161] in a Canadian Health Technology Assessment included nine trials, all but one (which is Russian) are taken into account within the Appleton systematic review[153].

In addition to the trials included in the systematic review, seven other trials were identified[151,162-167].

As well as this, Mahler et al[165], Calverley et al[167] and Szanfranski et al[166] were identified as three separate studies that had single salmeterol or formoterol compared to placebo comparative arms within studies reporting on the use of combination drugs and hence these were included.

Because of the variability in the results of the trials of these drugs they have been summarised in Table 7.1.

This section was **not** updated in the 2010 partial COPD guideline update, but new recommendations were made concerning comparison of LABA and LAMA based on newer health economic assessments and the use of LABA + ICS combinations in the section on combination inhaled therapies – see section 7.3.6.

Table 7.1 Summary of results of studies on long-acting beta$_2$ agonists

Trial	Sample size	Duration (weeks)	Drug	Dose (µg)	FEV_1	FVC	Diary symptoms	Night	Rescue	Dyspnoea	Ex test	HRQL	Exacerbations	Reference
v Placebo														
Rennard 2001 (a)	405	12	S	50	↑	↑	NS	NS	↑	NS	NS	NS	NS	[150]
Van Noord 2000	144	12	S	50	↑	NS	↑	NS	↑	-	-	-	NS	[160]
Mahler 1999	411	12	S	50	↑	↑	NS	NS	↑	↑	-	↑	↑	[152]
Boyd 1997 (b)	674	16	S	50	↑	-	↑	↑	↑	↑	NS	(a)	NS	[154]
Boyd 1997 (b)	674	16	S	100	↑	-	↑	↑	↑	↑	NS	(a)	NS	[154]
Grove 1996	29	4	S	50	↑	NS	-	-	-	↑	NS		-	[156]

Ulrik 1995	63	4	S	50	NS	NS	↑	↑	↑	-	-	-	-	[159]
Donohue 2002	623	26	S	50	↑	↑	-	-	↑	NS	-	NS	-	[168]
Albers 2002 (c)	687	12	F	6	↑	-	↑	NS	↑	NS	NS	-	NS	[162]
Albers 2002 (c)	687	12	F	12	↑	-	↑	NS	↑	NS	NS	-	NS	[162]
Albers 2002 (c)	687	12	F	24	↑	-	↑	↑	↑	↑	NS	-	NS	[162]
Rossi 2002	854	52	F	12	↑	↑	NS	-	↑	-	-	↑	↑	[163]
Rossi 2002	854	52	F	24	↑	↑	NS	-	↑	-	-	↑	↑	[163]
Dahl 2001	780	12	F	12	↑	-	↑	-	↑	-	-	↑	NS	[151]
Dahl 2001	780	12	F	24	↑	-	↑	-	↑	-	-	↑	NS	[151]
Brusasco 2003 (d)	1207	26	S	50	↑	-	-	-	-	↑	-	NS	NS	[164]
Mahler 2002	691	24	S	50	↑	-	-	↑	↑	NS	-	NS	-	[165]
Calverley 2003	1465	52	S	50	-	-	NS	NS	↑	-	-	NS	↑	[167]
Szanfranski 2003	812	52	F	12	↑	↑	-	-	-	-	-	-	NS	[166]
Rutten Van Molken 1999 (e)	144	12	S	50								NS		[158]
Jones 1997 (f)	283	16	S	50								↑		[157]
Jones 1997 (f)	283	16	S	100								NS		[157]

v Ipratropium														
Rennard 2001 (a)	405	12	S	50	NS	NS	NS	NS	NS	NS	NS	NS	NS	[150]
Dahl 2001	780	12	F	12	↑	-	↑	-	↑	-	-	↑	NS	[151]
Dahl 2001	780	12	F	24	↑	-	NS	-	↑	-	-	↑	NS	[151]
v Tiotropium – **this section has been updated**														
Donohue 2002	623	26	S	50	↓	↓	-	-	↓	↓	-	NS	-	[168]
Brusasco 2003 (d)	1207	26	S	50	↓	-	-	-	-	NS	-	NS	NS	[164]

N.B. ↑ denotes statistically significant superiority versus comparator group (e.g. increased FEV_1, reduced symptoms scores etc), NS denotes no statistically significant benefits versus comparator group, ↓ denotes statistically significant inferiority versus comparator group, - denotes not assessed.

Drugs: S = salmeterol, F = formoterol

(a) Over 77% of patients in this study showed at least 12% or 200ml reversibility to salbutamol

(b) An inclusion criterion for this trial was an increase in FEV_1 of 5-15% 15 minutes after the inhalation of salbutamol

(c) 23% of patients in this trial showed an increase of at least 10% in FEV_1 after terbutaline

(d) This study includes patients reported in the study by Donohue et al. but includes additional outcome measures.

(e) This trial reports the health related quality of life outcomes in a sub-group of the patients in the study by van Noord et al. 2000 [160].

(f) This trial reports the health related quality of life outcomes in a sub-group of the patients in the study by Boyd et al. 1997[154].

Evidence statements

Long-acting beta$_2$ agonists compared to placebo in stable COPD

There was variation in the results within the systematic review [84] for **symptom scores** across four studies [152,154,159,160]. The largest of the trials [154] demonstrated that long-acting beta$_2$ agonists reduce symptom scores. Day time (p=0.01). Night time (p=0.001). Ia

There were three subsequent randomised controlled trials [151,162,163]. Using standard therapeutic doses only one trial [151] found that **symptom scores** were reduced (p<0.001). Ib

With regard to the reduction of **breathlessness**, five trials within the systematic review [84] found no significant differences between long-acting beta$_2$ agonist and placebo. One trial with the largest sample size (n= 674) [154] demonstrated that long-acting beta$_2$ agonist reduce the degree of breathlessness produced by exercise. Ia

There were two subsequent randomised controlled trials [162,164] with large sample sizes that demonstrated a statistically significant difference with the use of long-acting beta$_2$ agonists in **reducing dyspnoea** (p=0.002 and p<0.05 respectively). Ib

In addition to this Brusasco[164] found that for **TDI** focal score a higher percentage of patients achieved a change of at least one unit with salbutamol (41.2%) than with placebo (29.8%) p < 0.01. Ib

Mahler et al[165] showed a significant reduction in overall **use of supplemental** albuterol after treatment with salmeterol compared with placebo ($p \leq 0.045$). Ib

A significant increase in the overall percentage of **nights with no awakenings** requiring albuterol was observed for salmeterol compared with placebo ($p < 0.001$).

Long-acting beta$_2$ agonists have no proven effect on **walking distance**[153]. Ia

The systematic review[153] demonstrated that there was variation in trial results for **health related quality of life** (HRQL) and hence the trial results are looked at on an individual basis for this outcome. Ia

Three studies [151,157,163] showed that long-acting beta$_2$ agonists significantly improved **HRQL** using the St George's Respiratory Questionnaire (SGRQ). $P < 0.01$, $p = 0.030$, $p = 0.01$ respectively. Ib

Four other studies also looked at **health related quality of life**[150,152,158 164] two[150,152] of which used the Chronic Respiratory Diseases Questionnaire (**CRDQ**), one[164] used the SGRQ to measure HRQL and one used the SGRQ and CRQ[158]. Ib

Rutten van Molken [158] and Brusasco [164] did not find any statistically significant differences.

Rutten van Molken[158] also found no significant difference in the proportion of patients achieving clinically relevant improvements (13% in the salmeterol and 12% in the placebo groups using the **CRDQ** and 24% of the salmeterol and 23% of the placebo groups using the **SGRQ)**.

Mahler et al[152] found that at week 12 the mean **CRDQ** overall score was significantly higher for salmeterol ($p = 0.007$) than for placebo. The proportion of patients who achieved an increase of ≥ 10 points in overall score (the minimum change indicative of an important difference) was significantly higher at week 12 in the salmeterol (46%, p = d0.002) than in the placebo group (27%) in non-reversible patients.

Rennard et al[150] using the **CRDQ** showed that the proportion of patients who achieved a clinically significant change of 10 from the baseline was 46% in the salmeterol group and 38% in the placebo group.

Brusasco[164] found that the percentage of patients achieving a **SGRQ** improvement of at least 4 units was 43.2% in the salmeterol group and 39.3% in the placebo group.

The systematic review [84] found that long-acting beta$_2$ agonists compared to placebo did not significantly affect the incidence of COPD **exacerbations**, however this meta-analysis was only based upon two RCTs [154,160]. Ia

One cross over study [159] n = 63, not combined in the meta-analysis but also included in the systematic review [84] found no significant difference in **exacerbations**. Ib

Two subsequent trials by Dahl [151] and Brusasco [164] also found no significant difference in **exacerbations**. Ib

However, two trials[163,167] found significant differences favouring long-acting beta$_2$ agonists compared to placebo for **exacerbations**. Ib

Rossi et al[163] in a large multicentre trial over one year found that formoterol was significantly superior to placebo for the mean percentages of bad days defined as "**mild COPD exacerbation**" $p \leq 0.008$. Ib

A large (n = 1465) multicentre RCT[167] showed that compared with placebo, salmeterol significantly reduced the number of **exacerbations** per patient per year and the number of exacerbations that needed treatment with oral corticosteroids. The rate of exacerbations fell by 20% (p = 0.0027) in the salmeterol group compared to placebo. Ib

Acute episodes of symptom exacerbation that required oral corticosteroids were reduced by 29% in the salmeterol group (p=0.0003) compared with placebo.

7.3.4 Long-acting anticholinergics (long-acting muscarinic antagonists or LAMA)

Tiotropium is currently the only long-acting anticholinergic bronchodilator available. Its duration of action is such that it can be given once daily.

In 2004 there were no systematic reviews comparing tiotropium with placebo, short-acting drugs or long-acting $beta_2$ agonists. Because of the existence of larger longer-term studies on anticholinergic drugs it was felt unnecessary to include the shorter-term studies. There were a number of randomised controlled trials comparing these drugs. Two publications compare the effects of long-acting anticholinergics with long-acting $beta_2$ agonists and placebo. One of these [164] includes patients described in the earlier paper [168] but a potential limitation of this paper is the fact that it does not explicitly cite the earlier study or provide specific information on the other trial that is included. However, whenever possible the paper with the largest sample has been used to formulate the evidence statements.

The results of these have been summarised in (Table 7.2).

Table 7.2 Summary of results of studies on long-acting anticholinergics

Trial	Sample size	Duration (weeks)	Drug	Dose (µg)	FEV_1	FVC	Diary Symptoms		Rescue medication use	Dyspnoea	Ex test	HRQL	Exacerbations	Reference
							Day	Night						
v Placebo														
Littner 2000	169	4	T	4.5	↑	↑	-	-	-	-	-	-	-	169
Littner 2000	169	4	T	9	↑	↑	-	-	-	-	-	-	-	169
Littner 2000	169	4	T	18	↑	↑	-	-	-	-	-	-	-	169
Littner 2000	169	4	T	36	↑	↑	-	-	-	-	-	-	-	169
Casaburi 2000	470	13	T	18	↑	↑	↑	↑	↑	-	-	-	-	170
Casaburi 2002	921	52	T	18	↑	↑	↑	-	↑	↑	-	↑	↑	171
Donohue 2002	623	26	T	18	↑	↑	-	-	↑	↑	-	↑	-	168
Brusasco 2003 (a)	1207	26	T	18	↑	-	-	-	-	↑	-	↑	↑	164

v Ipratropium														
Vincken 2002	535	52	T	18	↑	↑	-	-	↑	↑	-	↑	↑	[172]
v Salmeterol – this section has been updated														
Donohue 2002	623	26	T	18	↑	↑	-	-	↑	↑	-	NS	-	[168]
Brusasco 2003 (a)	1207	26	T	18	↑	-	-	-	-	NS	-	NS	NS	[164]

NB ↑ denotes statistically significant superiority versus comparator group (e.g. increased FEV_1, reduced symptoms scores etc), NS denotes no statistically significant benefits versus comparator group, ↓ denotes statistically significant inferiority versus comparator group, - denotes not assessed.

Drugs: T = tiotropium

(a) This study includes patients reported in the study by Donohue et al. [168] but includes additional outcome measures.

Evidence statements

Long-acting anticholinergics compared to placebo in stable COPD

Four studies [164,169-171] demonstrated a significant increase in **FEV_1 and FVC** in favour of long-acting anticholinergics compared to placebo. p<0.001 [170], p<0.01[171] and p=0.001 [164]. Ib

A one year clinical trial[171] found that long-acting anticholinergic significantly improved morning and evening **PEFR** compared to placebo (p<0.005). Ib

Three studies [164,170,171] used differing measures for assessing **symptoms**. Casaburi [170,171] found that symptom scores for wheezing and shortness of breath were significantly improved (p<0.01[170] and p<0.05 [171]) for long-acting anticholinergics compared to placebo. Ib

Two studies [164,171] measured dyspnoea using the Transition Dyspnoea Index (**TDI**) and both found that long-acting anticholinergic was superior to placebo (p<0.001 respectively).

In addition, Brusasco et al[164] and Casaburi et al[171] found that the proportion of patients achieving a change of at least 1 unit in TDI focal scores for long-acting anticholinergic compared to placebo were significantly higher (p=<0.01 respectively).

Two studies [164,171] measured HRQL using the St George's Respiratory Questionnaire (SGRQ). Both found significant improvements with the use of long-acting anticholinergic over placebo. p<0.05 and p<0.01 respectively. Ib

Brusasco [164] also found that the proportion of patients with a clinically meaningful change (CMC) in the **SGRQ** score (of at least 4 Units) was

superior in the long-acting anticholinergic group (48.9%) compared to the placebo group (39.3%), p<0.05.

Two studies [164,170] looked at the amount of **rescue medication** required and found that it was used less often in the long-acting anticholinergic group compared to placebo. p<0.001 and p<0.0001 respectively. Ib

Two studies measured **exacerbation rates** [164,171]. Casaburi[171] found that the proportion of patients experiencing exacerbation was lower in the long-acting anticholinergic group (36%) compared to the placebo group (42%), with a reduction of 14% and a p value of <0.05. Ib

Brusasco [164]found that patients treated with long-acting anticholinergic had significantly fewer exacerbations per patient year than the placebo group (p<0.05).

There was no significant difference in the proportion of patients having at least one **exacerbation**, but long-acting anticholinergic delayed the time to the first exacerbation ($p \leq 0.001$) compared to placebo.

Long-acting muscarinic antagonists (LAMA) compared to short-acting muscarinic antagonists (SAMA) in stable COPD

Clinical introduction

In the 2010 partial update of the guideline, the GDG did not look for new evidence comparing LAMA with placebo.

The NICE guidance 2004 relating to use of long-acting bronchodilators in patients who remain symptomatic on short-acting bronchodilators was based on currently available clinical and health economic data.[172.] The guideline development group was however made aware of some reluctance to fund or prescribe clinically appropriate use of a long-acting muscarinic antagonist (anticholinergic) in preference to regular use of short-acting

muscarinic antagonist (anticholinergic), on the basis of greater drug cost. It was therefore considered that a review of the evidence was necessary to address this issue.

DRUG8: LAMA vs SAMA (question 8)

The GDG revisited the evidence comparing LAMA with SAMA and posed the following question:

What is the clinical and cost effectiveness of long-acting muscarinic antagonists compared to short-acting muscarinic antagonists in the management of people with stable COPD?

Methodological introduction:

The literature was searched from 2003 onwards for RCTs and systematic reviews comparing treatment with long-acting muscarinic antagonists with short-acting muscarinic antagonists. RCTs with a minimum follow-up of 6 months were included. Outcomes of interest were mortality, exacerbations, hospitalisations, decline in FEV_1, change in health related quality of life (measured with total SGRQ), adverse events (MI or acute arrhythmia), and change in breathlessness score (measured with TDI).

There was no new evidence. One double blind RCT comparing tiotropium with ipratropium was appraised in the original guideline and the original evidence statements are presented again[172].

Long-acting anticholinergics compared to short-acting anticholinergics in stable COPD

One study[172] looked at the effects on **FEV_1 and FVC** and found that long-acting anticholinergic was superior to short-acting anticholinergic, $p<0.05$. Ib

In a one year clinical trial[172] long-acting anticholinergic significantly improved morning and evening **PEFR** compared to short-acting Ib

anticholinergic, p<0.01.

Only one study [172] measured **dyspnoea**. TDI focal score for long-acting anticholinergic was superior to short-acting anticholinergic, p<0.05. Ib

Only one study [172] measured **HRQL** using SGRQ. There were significant improvements in the SGRQ total and impact scores with long compared to short-acting anticholinergic. SGRQ Impacts mean difference score -4.28+/- 1.32; 95% CI -6.87 to –1.68; p=0.001. SGRQ Total mean difference score –3.30 +/- 1.13; 95% CI -5.51 to -1.09; p=0.004. Ib

One study [172] looked at **rescue medication** and found that it was used less often in the long compared to short-acting anticholinergic group, p<0.05. Ib

Vincken [172] found that the proportion of patients who experienced **exacerbations** was significantly lower in the long (35%) compared to short (46%) acting anticholinergic group during the trial, p=0.014). Ib

Health economic evidence: LAMA vs. SAMA

Economic methodological introduction

The literature was searched from 2003 onwards for economic evaluations comparing treatment with long-acting muscarinic antagonists with short-acting muscarinic antagonists.

Two cost-utility studies (that is, using QALYs as the health outcome measure) were identified from the update search that included the relevant comparision[173,174]. These are summarised in the economic evidence profile below. Two studies that evaluated the relevant comparison were excluded due to the availability of better quality or more applicable studies; one based on data from a 3-month study (the clinical review excluded studies with less than 6-month follow-up) and one that did not use QALYs[175,176].

No studies were identified in the original guideline search.

Update 2010: Economic evidence profile

Economic evidence: LAMA vs. SAMA

Study	*Limitations**	*Applicability***	*Other comments*	*Incremental‡ cost (£)*	*Incremental‡ effects*	*ICER‡*	*Uncertainty*
Oostenbrink et al (2005)[173] - Netherlands	Potentially serious limitations[b]	Partially applicable[c]	Based on 1-year morbidity estimated by a Markov model of moderate, severe, and very severe COPD using data from tiotropium RCTs. Treatment effect applied on disease progression and exacerbations. LAMA vs. SAMA relative treatment effect based on Vincken et al[172]. Moderate = FEV_1 50%-79% predicted	-£118[d]	0.026 QALYs	Dominant[e]	Tiotropium was always the most cost-effective option (highest net benefit at a £20,000/QALY threshold) in base case PSA and sensitivity analyses.
Oostenbrink et al (2005)[173] - Canada	Potentially serious limitations	Partially applicable[f]		£2[g]	0.026 QALYs	£77/QALY gained[h]	None of the sensitivity analyses found SAMA to be the preferred option at a threshold of £20,000/QALY[i].

[b] Key limitation: modelling incorporates a difference between treatments in COPD progression determined by FEV_1 status and exacerbations, inclusion of the former treatment effect by this method was considered potentially to be inappropriate by GDG based on current evidence (this was however explored in a sensitivity analysis where this effect was removed and only the exacerbation effect included); Minor limitations: 1-year time horizon but chronic condition – longer term model may be more appropriate, impact not tested in sensitivity analysis. The study is funded by the tiotropium sponsor.

[c] Some uncertainty over applicability of Netherlands resource use and unit costs to UK.

[d] Converted from 2001 Dutch Euros using 2001 Purchasing Power Parities[177].

[e] LABA also included in analysis. LAMA dominated SAMA and LABA based on mean costs and outcomes from base case probabilistic analysis. LAMA had the highest probability of being cost-effective of the three options.

[f] Some uncertainty over applicability of Canadian resource use and unit costs to UK.

[g] Converted from 2001 Canadian dollars using 2001 Purchasing Power Parities[177] (Euros reported in paper converted to Canadian dollars using exchange rate reported in paper).

[h] LABA was also included in analysis. SAMA was dominated by LABA based on mean costs and outcomes from base case probabilistic analysis, therefore making the comparison of LAMA vs SAMA an inappropriate one in the analysis. LAMA vs LABA was cost-effective (see LAMA vs LABA question)

[i] LABA was also included in analysis. At a threshold of £20,000 per QALY gained, SAMA was never the most cost-effective option (highest net benefit) of the three options in sensitivity analysis. LAMA was the most cost-effective option in most analyses. LABA was the most cost-effective option in a sensitivity analysis where disease progression was held constant and only a difference in exacerbation rate was applied between treatments (see LAMA vs LABA question).

			Severe = FEV_1 30%-49% predicted Very severe = FEV_1 <30% predicted				
Rutten et al (2007)[174]	Potentially serious limitations[j]	Partially applicable[k]	Based on 5-year morbidity and mortality estimated by a Markov model using data from tiotropium RCTs (builds on Oostenbrink model above) and epidemiological data. Treatment effect applied on disease progression and exacerbations. LAMA vs. SAMA relative treatment effect based on Vincken et al[172].	£1,051[l]	0.15 QALYs	£6,895 /QALY gained[m]	The ICER ranged from £5,263 to £13,217 in sensitivity analyses.

*Very serious limitations/Potentially serious limitations/Minor limitations; ** Directly applicable/Partially applicable/Not applicable; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; ‡ LAMA – SAMA; dominant = LAMA is cost saving with better outcomes; dominated = LAMA increases costs with worse outcomes

[j] Key limitation: modelling incorporates a difference between treatments in COPD progression determined by FEV_1 status and exacerbations, inclusion of the former treatment effect by this method was considered potentially to be inappropriate by GDG based on current evidence (this was not explored in sensitivity analysis); Minor limitations: As mortality is impacted in the model a lifetime horizon would be most appropriate – not examined in sensitivity analysis. The study is funded by the tiotropium sponsor.

[k] Some uncertainty over applicability of Spanish resource use, unit costs, utilities and epidemiological data to UK. Discount rates used for costs and outcomes not those currently recommended by NICE.

[l] Converted from 2005 Spanish Euros using 2005 Purchasing Power Parities[177]

[m] LABA also included in analysis but was ruled out by extended dominance

Economic evidence statements

Two economic evaluations found tiotropium to be cost-effective compared with ipratropium[173,174]. Both studies used data from the Vinken et al. study identified in the clinical review to inform the relative treatment effects of LAMA and SAMA. Both studies were judged partially applicable due to their non-UK perspectives.

Evidence to recommendations

The GDG noted that this question was specifically looking at the evidence for the use of a LAMA versus a SAMA in patients who require maintenance bronchodilator therapy for their COPD, and specifically whether the clinical and health economic evidence favoured once-daily tiotropium over four-times-daily ipratropium.

The GDG acknowledged that a recent literature search found no new clinical evidence; however new health economic evaluations supported the clinical use of LAMA over regular SAMA.

The clinical evidence favoured the use of LAMA in preference to SAMA and this preference was cost-effective. In addition patient and carer representatives on the GDG strongly supported the use of a once daily therapy as likely to improve treatment adherence. This evidence links to recommendation U4.

Long-acting muscarinic antagonist compared to long-acting beta$_2$ agonists in stable COPD

Clinical Introduction

The NICE COPD guideline 2004 recommendation that long-acting bronchodilators should be given to people with more than two exacerbations each year was felt to need review in the light of recent large studies of combination therapies with stratification by lung function.

Health economic studies on long-acting bronchodilator therapies have been published since the NICE COPD 2004 guideline. The GDG felt that a comparative clinical and health economic review of long-acting beta$_2$ agonists and long-acting muscarinic antagonists may be helpful in guidance on sequencing of long-acting bronchodilator therapies and combinations of long-acting bronchodilators with inhaled steroids.

The GDG posed the following question:

What is the clinical and cost effectiveness of long-acting muscarinic antagonists compared with long-acting beta$_2$ agonists in the management of people with stable COPD?

Methodological introduction

The literature was searched for RCTs (with a minimum follow-up of 6 months) and systematic reviews from 2003 onwards.

Two RCTs with 6 months follow-up compared tiotropium (18 microgram once daily) with formoterol (10 microgram twice daily) [178] or salmeterol (50 microgram twice daily) [164] in people with COPD. The Brusasco et al RCT combined the results of two 6-month RCTs comparing tiotropium with salmeterol in people with COPD. The Brusasco et al RCT was appraised in the original guideline.

The Brusasco et al and Vogelmeier et al RCTs provided data that could be pooled for two outcomes: exacerbations and exacerbations requiring hospitalisations.

In Brusasco et al exacerbations were defined as new respiratory symptoms lasting at least three days and usually associated with a therapeutic intervention. The number of patients experiencing exacerbations included people who were hospitalised (personal

communication with V. Bruasaco)[164]. In the Vogelmeier et al RCT "exacerbations requiring further treatment" was defined as COPD adverse events (coded as COPD, COPD exacerbated, cough, dyspnoea, lower respiratory infection, chronic bronchitis, bronchospasm, bronchial obstruction) requiring additional therapy, where additional therapy was any COPD therapy reported being used to treat an exacerbation other than a rescue bronchodilator. This group of people also included people who had been hospitalised for an exacerbation (personal communication with C. Vogelmeier). [178]

The GRADE evidence profile summarises the results and study quality. The clinically important relative risk reduction (RRR) for mortality was 15%, exacerbations (20%), hospitalisation (20%), change in SGRQ (- 4 points), FEV_1 (100 ml), and TDI (1 unit). For further forest plots, please see appendix O.

Evidence Profile: LAMA versus LABA

Question: Should tiotropium vs. long-acting beta$_2$ agonists be used for stable COPD?

Bibliography: Vogelmeier C, Kardos P, Harari S et al. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study. Respiratory Medicine. 2008; 102(11):1511-1520. Ref ID: 2521 Brusasco, V., Hodder, R., Miravitles, M., Korducki, L., Towse, L., Kesten, S. (2003). Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax, 58, 399-404.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	tiotropium	long-acting beta 2 agonists	Relative (95% CI)	Absolute		
Number of people who had exacerbations requiring additional therapy (includes people who had been hospitalised) (follow-up 6 months)												
2[1]	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	68/623 (10.9%)	73/615 (11.9%)	RR 0.92 (0.68 to 1.26)	10 fewer per 1000 (from 38 fewer to 31 more)	⊕OOO VERY LOW	
Number of people who had exacerbations requiring hospitalisations (follow-up 6 months)												
2[1]	randomised trial	serious[4]	serious[5]	no serious indirectness	very serious[6]	none	17/623 (2.7%)	21/615 (3.4%)	RR 0.81 (0.43 to 1.52)	6 fewer per 1000 (from 19 fewer to 18 more)	⊕OOO VERY LOW	

[1] Vogelmeier et al; Brusasco et al

[2] trials had unclear allocation concealment; one trial (Vogelmeier et al) was open label and the other trial (Brusasco) was double blind; both were ITT.

[3] very wide 95% CI that crosses the MID twice

[4] both trials had unclear allocation concealment; one trial (Vogelmeier et al) was open label and the other trial (Brusasco) was double blind; both were ITT.

[5] significant heterogeneity (I2 = 69.6%)

[6] wide 95% CI that cross the MID twice; few events

Evidence statements

LAMA versus LABA

Brusasco [164] compared long-acting anticholinergic to long-acting beta$_2$ agonist. The **FEV$_1$** measures were statistically significant in favour of long-acting anticholinergic compared to long-acting beta$_2$ agonist ($p < 0.05$).

Ib

There was no significant difference in the TDI **dyspnoea** focal score [164].

Ib

There were no statistically significant outcomes for **HRQL** measured using the SGRQ when comparing long-acting anticholinergic to long-acting beta$_2$ agonist [164].

Ib

There were no statistically significant differences between the two groups for **rescue medication** use [168].

Ib

Evidence statements

There was no significant difference between tiotropium or long-acting beta$_2$ agonists (salmeterol or formoterol) for the proportion of people who had exacerbations requiring :

- additional therapy (this included people who were hospitalised for an exacerbation of COPD) (very low quality evidence)
- hospitalisations (very low quality evidence).

Health economic evidence

Economic methodological introduction

The literature was searched from 2003 onwards for economic evaluations comparing treatment with long-acting muscarinic antagonists with long-acting beta$_2$ agonists.

Two cost-utility studies (that is using QALYs as the health outcome measure) were identified from the update search that included the relevant comparison[173,174]. These are summarised in the economic evidence profile below. One study was excluded due to a combination of methodological limitations and a US perspective that meant it was considered of limited use to decision making[175].

No studies were identified in the original guideline search.

Update 2010: Economic evidence profile

Economic evidence: LAMA vs LABA							
Study	***Limitations****	***Applicability***	***Other comments***	***Incremental cost (£)***[‡]	***Incremental effects***[‡]	***ICER***[‡]	***Uncertainty***
Oostenbrink et al (2005)[173] - Netherlands	Potentially serious limitations[n]	Partially applicable[o]	Based on 1-year morbidity estimated by a Markov of moderate, severe, and very severe COPD using data from tiotropium RCTs. Treatment effect applied on disease progression and exacerbations. LAMA vs. LABA relative treatment effect based on Brusasco 2003 et al[164]. Moderate = FEV_1 50% -79%	-£29[p]	0.021 QALYs	LAMA dominant[q]	Tiotropium was always the most cost-effective option (highest net benefit at a £20,000/QALY threshold) in base case PSA and sensitivity analyses.
Oostenbrink et al (2005)[173] - Canada	Potentially serious limitations[n]	Partially applicable[r]		£3[s]	0.021 QALYs	£134/QALY[t]	Dominant to £36,403/QALY[u] (ICER range in variety of sensitivity analyses).

[n] Key limitations: LAMA vs LABA treatment effect s based on 1 of the 2 studies identified by clinical review – effect on exacerbations attenuated with pooled estimate; modelling incorporates a difference between treatments in COPD progression determined by FEV_1 status and exacerbations, inclusion of the former treatment effect by this method was considered potentially to be inappropriate by GDG based on current evidence (this was however explored in a sensitivity analysis where this effect was removed and only the exacerbation effect included). Minor limitations: 1-year time horizon but chronic condition – longer term model may be more appropriate, impact not tested in sensitivity analysis. The study is funded by the tiotropium sponsor.

[o] Some uncertainty over applicability of Netherlands resource use and unit costs to UK.

[p] Converted from 2001 Dutch Euros using 2001 Purchasing Power Parities[177].

[q] SAMA also included in analysis. LABA dominated SAMA based on mean costs and outcomes from base case probabilistic analysis. LAMA had the highest probability of being cost-effective of the three options.

[r] Some uncertainty over applicability of Canadian resource use and unit costs to UK.

[s] Converted from 2001 Canadian dollars using 2001 Purchasing Power Parities[177] (Euros reported in paper converted to Canadian dollars using exchange rate reported in paper)

[t] SAMA also included in analysis. LABA dominated SAMA based on mean costs and outcomes from base case probabilistic analysis. LAMA had the highest probability of being cost-effective of the three options in the base case analysis.

[u] £34,403/QALY result was for analysis where treatment effect on disease progression was held constant (so did not vary between treatments) and only exacerbation effect applied. In this analysis LABA was the most cost-effective option at a threshold of £20,000 per QALY gained.

			predicted Severe = FEV_1 30%-49% predicted Very severe <30% predicted				
Rutten et al (2007)[174] – Spain	Potentially serious limitations[v]	Partially applicable[w]	Based on 5-year morbidity and mortality estimated by a Markov model using data from tiotropium RCTs (builds on Oostenbrink model above) and epidemiological data. Treatment effect applied on disease progression and exacerbations. LAMA vs. LABA relative treatment effect based on Brusasco 2003 et al[164].	£469[x]	0.14 QALYs	£3,481/QALY[y]	Tiotropium was always the most cost-effective option (highest net benefit at a £20,000/QALY threshold) in base case PSA and sensitivity analyses.

*Very serious limitations/Potentially serious limitations/Minor limitations; ** Directly applicable/Partially applicable/Not applicable; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; ‡ LAMA – LABA, dominant = LAMA is cost saving with better outcomes, dominated = LAMA increases costs with worse outcomes

[v] Key limitations: LAMA vs LABA treatment effect s based on 1 of the 2 studies identified by clinical review – effect on exacerbations attenuated with pooled estimate; modelling incorporates a difference between treatments in COPD progression determined by FEV_1 status and exacerbations, inclusion of the former treatment effect by this method was considered potentially to be inappropriate by GDG based on current evidence (this was not explored in sensitivity analysis); Minor limitations: As mortality is impacted in the model a lifetime horizon would be most appropriate – not examined in sensitivity analysis. The study is funded by the tiotropium sponsor.

[w] Some uncertainty over applicability of Spanish resource use, unit costs, utilities and epidemiological data. Discount rates used for costs and outcomes not those currently recommended by NICE.

[x] Converted from 2005 Spanish Euros using 2005 Purchasing Power Parities[177]

[y] SAMA was also included in analysis. LABA was ruled out by extended dominance by LAMA based on mean costs and outcomes from base case probabilistic analysis, therefore making the comparison of LAMA vs LABA an inappropriate one in the analysis. LAMA was cost-effective vs SAMA, at a threshold of £20,000 per QALY gained (see LAMA vs SAMA).

Economic evidence statements

Two cost-effectiveness studies presenting three analyses found tiotropium to be cost effective compared with salmeterol in patients with COPD[173,174]. One of the analyses found use of tiotropium to be cost saving as well as improving outcomes, with any increase in drug costs completely offset by reduced healthcare resource use. The other two analyses found that increased drug costs were partially offset by reduced healthcare resource use. All analyses were judged partially applicable due to their non-UK perspectives.

Both studies based relative treatment effect of LAMA vs. LABA on the Brusasco et al. study[164]. The clinical review identified another study (Vogelmeier et al.[178]) and pooled estimates of effect showed less difference between treatments in terms of exacerbations than Brusasco alone. As all studies included a treatment effect on exacerbations this would potentially impact all the cost-effectiveness results.

Both studies were based on the same underlying model and both incorporated a treatment effect on disease progression (as well as on exacerbation rate) based on data from the Brusasco et al. study. Removal of the disease progression effect in a sensitivity analysis in the Oostenbrink et al. analysis found that LABA became the cost-effective option in the Canadian perspective, although not in the Netherlands perspective[173]. This was not tested in sensitivity analysis in the Rutten et al. analysis[174].

Evidence to recommendation

LAMA vs. LABA

The GDG agreed that both classes of drugs are clinically effective and there was no strong evidence to favour one over the other. The GDG noted considerable limitations in the studies, noting insufficient numerical data, inappropriateness of using mean FEV_1 and lack of detail in adverse event data.

The cost-effectiveness studies appear to show LAMA to be cost-effective compared to LABA. However the GDG had serious concerns about this in part due to the limitations of the Brusasco study on which the analysis is based. Moreover, the superiority of tiotropium seems highly likely to be over-stated based on our pooled data, combining information from the two RCTs and the modelling approach taken[164 178].

The GDG therefore felt that there was insufficient evidence to distinguish between the two classes of drugs and agreed that it could not make a recommendation in favour of one class of long-acting bronchodilator over another where their use as monotherapy was indicated.

The GDG therefore felt it appropriate to recommend either LABA or LAMA for initial maintenance bronchodilator therapy, although subsequently modified this recommendation for people with an FEV_1 < 50% when reviewing evidence for other treatment options.

This evidence links to recommendation U5.

7.3.5 Inhaled corticosteroids (ICS)

Inhaled steroids as monotherapy was not in the scope of the update guideline. However the GDG felt that the recent evidence reviewed in section 7.3.6 relating to combination therapy of ICS+LABA superseded the previous advice about inhaled steroids.

There is little evidence that inhaled steroids have any effects on the inflammatory cells present in COPD: neutrophils, unlike eosinophils are relatively insensitive to the effects of steroids. Even high doses of inhaled steroids do not reduce the number of inflammatory cells or the levels of cytokines [179,180]. Currently up to 70% of patients with COPD are prescribed an inhaled steroid and approximately 5% are prescribed oral steroids [33 181]. The rationale for this is unclear and at least some of this prescribing may have been based on an extrapolation from the effects of these drugs in asthma and their effects at the time of an exacerbation (see section 8.11.3).

A systematic literature search, limited to a research design of systematic reviews and RCTs, yielded a hit rate of 260 potential papers applicable to inhaled steroids and stable COPD. Because the GDG was interested in the long-term effects of inhaled steroids and long-term data are available, together with the fact that the results of shorter studies may be affected by changes in lung function seen in the first six months, the evidence statements in this section are based on studies of at least 36 months duration. The evidence for the effects of inhaled corticosteroids when combined with long-acting beta$_2$-agonists is considered in section 7.3.6

The GDG identified one systematic review [182]; this systematic review did however include studies with duration of 6 to 40 months. However, there was significant heterogeneity between the longer term studies included in this systematic review, possibly due to the severity of COPD in the patients recruited. In addition to critically appraising the systematic review, the studies of ≥ 36 months duration were independently critically appraised and these included ISOLDE[183], duration 36 months, The Lung Health Study[184], duration 40 months, Vestbo 1999 [185], duration 36 months and EUROSCOP [186], duration 36 months). The rationale for this was the need to ascertain further outcomes (not presented in the systematic review) and hence the need to ensure the quality aspects of these primary papers prior to presenting evidence statements for inhaled steroids. The systematic review looked at the outcomes for exacerbation, adverse events and mortality [182].

A systematic review (van Grunsven PM et al 1999)[187] was excluded, as the durations of the studies were 24 to 30 months but only data up to 24 months was used in the meta-analysis. The Derenne et al (1995)[188] study (contained within the meta-analysis) was only published in abstract form however >80% of the patients in the meta-analysis were from this study.

In addition to the included papers identified above, one additional paper was found[189], which was an analysis of the EUROSCOP [186] trial and pertained to the effects of treatment on bone mineral density in patients with COPD treated with inhaled steroids. One *post hoc* analysis of the ISOLDE data was also identified which looked at the correlation between the response to oral steroids and the response to inhaled steroids [82] and a further *post hoc* analysis which looked at effects on exacerbation rates according to the severity of airflow obstruction [190].

The GDG was also aware of two quasi-experimental database studies looking at the relationship between prescription of inhaled steroids and mortality[191,192] and one looking at the effect of dose[193]. All of these have methodological limitations, particularly the lack of randomisation.

The four identified RCTs [183-186] were all placebo-controlled trials of inhaled steroids.

Vestbo 1999 [185] (N=290) and Burge 2000 [183] (N=751) included a systemic steroid run in phase. The Lung Health Study [184] (N=1116) and EUROSCOP [186] (N=1277) did not have a systemic steroid run in phase.

Issues for consideration include a variety of differing inhaled steroid drugs and dosages which included budesonide 400ug twice daily [186], budesonide 800ug a.m. and 400ug p.m. for six months followed by 400ug twice daily for 30 months [185], and fluticasone propionate 500ug twice daily [183] and triamcinolone acetonide 600ug twice daily (100ug per inhalation) for each group six inhalations twice daily were prescribed resulting in a dose of 1200ug per day for the triamcinolone group [184]. The Renkema et al (1996)[194] study contained within the systematic review[182] administered budesonide 1600ug a day whilst Paggiaro et al (1998)[195] also in the systematic review by Alsaeedi[182] gave fluticasone 1000ug per day. The primary outcomes also varied for each trial and as such secondary outcomes may have been underpowered. Recruitment strategies differed between trials, Vestbo et al. [185] recruiting participants from an already on-going epidemiological study whilst EUROSCOP [186] undertook a mass media recruitment campaign. Severity of COPD and definitions of exacerbations varied between trials whilst ages ranged between the trials from 30 to 75 years.

Evidence statements

A study in patients with mild COPD (defined as FEV_1 > 50% and FEV_1/FVC ratio < 70%) showed no effect on **exacerbation rates** [185].	Ib
A study in patients with more severe COPD (mean FEV_1 of 50% predicted) showed a 25% reduction in **exacerbation rates** from 1.32 per year on placebo to 0.99 per year on fluticasone [183].	Ib
A *post hoc* analysis has shown that this effect is most marked in patients with an FEV_1 < 50% predicted [190] (having a median of 1.47 exacerbations per year).	Ib
A further study [184] in a group of patients with a similar mean FEV_1 also showed a significant reduction in visits to a physician for respiratory illness (1.2 v 2.1 per 100 patient years, p=0.03).	Ib
Vestbo [185], Pauwels[186] Burge[183] and the Lung Health Study[184] found no significant differences in annual **rate of FEV_1 decline**.	Ib

The systematic review [182] found no significant differences between inhaled steroids and placebo on **mortality** rates. Ia

The systematic review [182] showed that inhaled steroid therapy compared to placebo was associated with increased rates of: Ia

Oropharyngeal candidiasis (RR 2.1; 95% CI 1.5 to 3.1)

Skin bruising (RR 2.1; 95%CI 1.6 to 2.8).

Alsaeedi[182] highlights that the definitions of adverse events were not uniform over the trials. Ia

There were no significant differences for **cataract or fracture rates** [182] for the drug dosages used, however the follow-up was generally of short duration. The drug dosages for the trials referred to in the Alsaeedi systematic review[182] are quoted under issues for consideration in the introduction to inhaled corticosteroids.

The systematic review [182] found the results of **bone mineral density** variable between studies. Ia

The Lung Health Study[184], in a subgroup analysis of N=328 participants found significantly lower bone density measurements in the lumbar spine and femur ($p<0.01$) in patients treated with inhaled steroids. Ib

However the EUROSCOP study [186] and a separate paper utilising the same study population was subsequently published [189] exploring bone mineral density in N=192 patients with mild COPD (defined as $FEV_1 > 50\%$ and FEV_1/FVC ratio $< 70\%$). There were no significant changes in bone mineral density at any site or fracture rates in the inhaled steroid group compared with the placebo group over the 3-year duration. Ib

Burge et al [183] compared inhaled steroid to placebo in patients with moderate to severe COPD over a 36-month duration. The total **SGRQ** score was not significantly different between the groups over the first 6 months of the trial. However the SGRQ score deteriorated at a faster rate by 3.2 units/year on placebo and 2.0 units/year in the inhaled steroid group (p=0.0043).	Ib
Vestbo et al [185] looked at inhaled steroids compared to placebo in mild and moderate COPD as then defined, over a 36-month duration. Although **symptoms** decreased during the study period there were no statistically significant differences between the two groups.	Ib
The Lung Health Study [184] found that the "incidence of respiratory symptoms over the preceding 12 months measured by the ATS Division of Lung Disease questionnaire at the 36 month visit, did not differ significantly between the treatment groups with the exception of dyspnoea, which was more frequent in the placebo group (p=0.02)".	Ib
The response to inhaled steroids could not be predicted by the response to a short course of oral steroids [82].	Ib

GDG consensus statements

The GDG was aware of additional, quasi-experimental data in large populations that suggest that the use of inhaled steroids may be associated with reductions in mortality.	IV
The benefits of inhaled steroids have been shown in studies using a variety of doses of varying steroid molecules.	IV

There is insufficient evidence to establish the minimum dose of inhaled steroid required to achieve the proven benefits.	IV
There is limited experience of doses higher than 1000 μg fluticasone per day (or equivalent) and no evidence of superiority.	IV

Health economic Evidence statements

Four papers were identified. One had already been reviewed under bronchodilators. Two papers were excluded, as they did not have a follow up period greater than 36 months. The paper by Dragonetti et al[196] demonstrated that because the use of inhaled corticosteroids has no effect in patients with mild COPD (FEV_1 > 50%), it is an unnecessary cost to prescribe steroids for this patient group.

Evidence to recommendation

The update did not look at ICS in isolation. The scope included assessment of ICS in combination with LABA for which new evidence was available, such that there was a need to review earlier recommendations. In respect of safety data, new evidence was available regarding osteoporosis. This is discussed in the Inhaled Combination LABA+ICS section 7.3.6.

Recent evidence from better long term randomised trials is reassuring with regard to data on safety and mortality related to inhaled corticosteroid therapy[197]. A small increased risk of pneumonia was noted in people given inhaled steroid therapy, and it is important that clinicians inform patients appropriately. Data suggest that there may be differences between specific inhaled steroids with regard to risk of pneumonia and this is discussed in the section on combination inhaled therapy. The incidence of osteoporosis and cataracts is a significant fear for people with COPD, but osteoporosis appears to be related to the underlying COPD rather than inhaled steroid therapy[198].

The GDG was aware of the data in the recently published Sin paper[199], in which pneumonia was not noted in some studies of less than one year duration, but were unable to determine whether the risk of pneumonia was a class effect for inhaled steroids or related to treatment duration. The GDG felt that this recommendation should point out the small but real risk of non-fatal pneumonia that has been identified in some studies.

Recommendations

None of the inhaled corticosteroids currently available are licensed for use alone in the treatment of COPD. The following recommendations therefore include usage outside licensed indications, and prescribers need to remember that responsibility for such prescribing lies with them.

R38	Oral corticosteroid reversibility tests do not predict response to inhaled corticosteroid therapy and should not be used to identify which patients should be prescribed inhaled corticosteroids.	**Grade A**
R39	Deleted.	
R40	Deleted.	
U9	**NEW UPDATE RECOMMENDATION 9 (U9)** Be aware of the potential risk of developing side effects (including non-fatal pneumonia) in people with COPD treated with inhaled corticosteroids and be prepared to discuss with patients.	

7.3.6 Inhaled combination therapy

Since beta$_2$-agonists, anticholinergic drugs and ICS affect airway calibre and lung function through different mechanisms combining drugs of these classes may potentially give clinical benefits to patients. An additional advantage of this approach is the ability to limit potential side effects of the drugs by avoiding having to use individual drugs near the top of their dose response curves.

Clinical Introduction

The NICE 2004 guideline identified several types of inhaled combination therapy which included regular use of *inhaled* short-acting antimuscarinic antagonists (SAMA). The regular use of SAMA as maintenance therapy is not recommended in 2010 update and therefore all evidence statements related to use of SAMA in this way have been deleted.

Since publication of the NICE guidance in 2004, a number of large randomised controlled trials have been published and these may assist in stratification and relative positioning of drugs.

It remains unclear whether greater benefit is obtained from use of a triple combination of two bronchodilators from different classes with an inhaled steroid, or use of a combination of two long-acting bronchodilators from different classes, compared with use of a single long-acting bronchodilator alone.

Since the publication of the NICE COPD guideline in 2004, one study has been published which allows comparison of concurrent use of two long-acting bronchodilators with one long-acting bronchodilator and another study has compared the effect of two long-acting bronchodilators with a combination of a long-acting bronchodilator and inhaled steroid[178,200]. A call to stakeholders for unpublished subgroup data from published trials which might address this question led to consideration of data from a subgroup analysis of the UPLIFT RCT [201].

The evidence was reviewed for the following combinations and comparisons based on prioritisation by the GDG:

- LABA + ICS versus LABA
- LABA + ICS versus LAMA
- LABA + LAMA versus LABA
- LABA + LAMA versus LAMA
- LABA + LAMA versus LABA + ICS
- LAMA + ICS versus LABA
- LAMA + ICS versus LAMA
- LABA + ICS + LAMA versus LABA + ICS
- LABA + ICS + LAMA versus LAMA
- LABA + ICS + LAMA versus LABA + LAMA

Other comparisons were deemed of lower priority and were not included in the update review.

For all the listed drug questions please see appendix H

Sections 7.3.6.1 to 7.3.6.4 below summarise the evidence for the above comparisons from the literature and the call for evidence. Section 7.3.6.5 summarises the new health economic analysis that was undertaken as part of the update. Section 7.3.6.6 discusses the evidence and the resulting recommendations regarding inhaled combination therapy.

Combinations of inhaled and oral therapies were considered in the 2004 guideline and are presented separately from either oral therapies alone or inhaled therapies (given as monotherapy or in combination) in this partial update.

7.3.6.1 Long-acting beta$_2$ agonists (LABA) and inhaled corticosteroids (ICS)

The GDG posed the following two questions:

1. LABA + ICS vs. LABA alone (questions 3a)

What is the clinical and cost effectiveness of long-acting beta$_2$ agonists plus inhaled corticosteroids compared to long-acting beta$_2$ agonists in the management of people with stable COPD?

2. LABA + ICS vs. LAMA alone (question 3b)

What is the clinical and cost effectiveness of long-acting beta$_2$ agonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists in the management of people with stable COPD?

Methodological introduction

The literature was reviewed from 2003 onwards for systematic reviews and RCTs comparing long-acting beta$_2$ agonists plus inhaled corticosteroids with either long-acting beta$_2$ agonists alone or long-acting muscarinic antagonists alone in people with COPD. RCTs were included if there was a minimum 6 month follow-up period and the population consisted of adults with stable COPD characterised by no recent infections, exacerbations or hospitalisations in the previous month and a minimum of 10 smoking pack years. Outcomes of interest included all-cause mortality, exacerbations, hospitalisations, decline in FEV1, change in SGRQ, and adverse events (pneumonia, bone fractures, MI, arrhythmia, congestive heart failure).

Drug 3a LABA + ICS versus LABA alone

The evidence profile below summarises the quality of the evidence and outcome data from an updated systematic review [202] comparing long-acting beta$_2$ agonists plus inhaled corticosteroids with long-acting beta$_2$ agonists. RCTs with less than six month follow-up were excluded from the Nannini et al systematic review.

An additional report from the TORCH RCT [203] that assessed fractures in people with COPD receiving salmeterol or salmeterol plus fluticasone was added to the Nannini et al meta-analysis. The outcome of changes in bone mineral density was not incorporated as the comparator was placebo and not salmeterol.

In addition, three recently published double blind RCTs [204] [205,206]were added to the Naninni et al meta-analysis. One of these RCTs [204] compared treatment with salmeterol (50 microgram) versus salmeterol/fluticasone (50 microgram/250 microgram) in people with COPD (N=782; follow-up 1 year). Two different RCTs [205,206] compared budesonide/formoterol pMDI (320/9 microgram b.i.d.) with formoterol DPI (9 microgram b.i.d.) for either 6 months [206] or 1 year [205]. These studies also compared a lower dose of budesonide/formoterol pMDI (160/9 microgram b.i.d.) with formoterol DPI (9 microgram b.i.d.); however this comparison was not added to the meta-analysis as all the other studies of formoterol plus budesonide used the higher dose (320/9 microgram).

To explore sources of heterogeneity, the studies were stratified by either length of follow-up (6 months, up to 1 year, > 1 year) or by the type of run-in prior to randomisation (drug therapy removed, drug therapy optimised in order to stabilise the trial recruits). The clinically important relative risk reduction (RRR) for mortality was 15%, exacerbations (20%), hospitalisation (20%), pneumonia (15%), fractures (15%), cataracts (15%), change in SGRQ (-4 points), FEV_1 (100 ml), and TDI (1 unit).

A posthoc subgroup analysis of TORCH [207] was identified that compared salmeterol plus fluticasone with salmeterol or placebo or fluticasone in people with COPD stratified by GOLD severity (stage II, III, or IV). This study focussed on the comparison of salmeterol plus fluticasone with placebo. There was little statistical analysis for the relevant comparison of salmeterol plus fluticasone versus salmeterol. Nevertheless, there was mortality data for the comparison of salmeterol plus fluticasone versus salmeterol in people with GOLD stage II (baseline post-bronchodilator $FEV_1 \geq 50\%$; N= 1084); GOLD stage III (baseline post-bronchodilator FEV_1 30% to < 50%; N= 1467); and GOLD stage IV (baseline post-bronchodilator FEV_1< 30%; N= 503). This posthoc subgroup analysis should be treated with caution as TORCH was not designed to test for differences between GOLD stages or

differences between treatment arms within GOLD stages. The number of people in each GOLD stage was different; the study is probably underpowered for most comparisons. A summary of this posthoc analysis is presented in a separate evidence profile and evidence statements below. For further forest plots, please see appendix O.

Evidence profile: Drug 3a LABA+ICS vs. LABA

Question: Should LABA + ICS vs. LABA be used in adults with stable COPD?

Bibliography: Nannini LJ, Cates CJ, Lasserson TJ et al. Combined corticosteroid and long-acting beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease. [Review] [32 refs]. Cochrane Database of Systematic Reviews. 2007 ;(4):CD006829. Ferguson GT, Anzueto A, Fei R et al. Effect of fluticasone propionate/salmeterol (250/50mug) or salmeterol (50mug) on COPD exacerbations. Respiratory Medicine. 2008; 102(8):1099-1108. ; Tashkin DP, Rennard SI, Martin P et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. Drugs. 2008; 68(14):1975-2000; Rennard SI, Tashkin DP, McElhattan J et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. Drugs. 2009; 69(5):549-565.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	LABA + ICS	LABA	Relative (95% CI)	Absolute		
Change from baseline in post dose FEV_1 (follow-up 24-156 weeks; measured with: Litres; range of scores: -; Better indicated by more)												
5[1]	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3188	3132	-	0.04 (0.03 to 0.05)	⊕⊕⊕O MODERATE	
Exacerbations (rate ratio) (follow-up 52 - 156 weeks)												
6[3]	randomised trial	serious[4]	serious[5]	no serious indirectness	no serious imprecision	none	3251	3221	rate ratio 0.83 (0.79 to 0.88)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	
Mean rate of exacerbations per participant per year (follow-up 1 years; range of scores: -; Better indicated by less)												
3[6]	randomised trial	serious[7]	serious[8]	no serious indirectness	no serious imprecision	none	820	828	-	WMD -0.16 (-0.3 to -0.02)	⊕⊕OO LOW	

Number of participants with one or more exacerbation (follow-up 24-52 weeks)												
4[9]	randomised trial	serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	none	506/1245 (40.6%)	545/1213 (44.9%) 5% 60%	RR 0.91 (0.83 to 0.99)	40 fewer per 1000 (from 4 fewer to 76 fewer) 4 fewer per 1,000 53 fewer per 1,000	⊕⊕⊕O MODERATE	
Exacerbations requiring hospitalisation (follow-up 52-156 weeks)												
2[11]	randomised trial	serious[12]	serious[13]	no serious indirectness	serious[14]	none	2040	2008	rate ratio 0.86 (0.56 to 1.31)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	
Change from baseline in TDI (follow-up 24 weeks; measured with: TDI; range of scores: -; Better indicated by more)												
2[15]	randomised trial	very serious[16]	serious[17]	no serious indirectness	no serious imprecision	none	341	336	-	MD 0.47 (-0.02 to 0.96)	⊕OOO VERY LOW	
Change from baseline in SGRQ (total score) (follow-up 24-156 weeks; measured with: SGRQ; range of scores: 0-100; Better indicated by less)												
6[18]	randomised trial	very serious[19]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3156	3094	-	MD -1.63 (-2.21 to -1.06)	⊕⊕OO LOW	
Mortality (follow-up 24-156 weeks)												
9[20]	randomised trial	very serious[21]	no serious inconsistency	no serious indirectness	serious[14]	none	228/4557 (5%)	244/4522 (5.4%) 0.5% 13.4%	RR 0.93 (0.78 to 1.1)	4 fewer per 1000 (from 12 fewer to 5 more) 0 fewer per 1,000 9 fewer per 1,000	⊕OOO VERY LOW	

pneumonia (follow-up 24-156 weeks)												
10[22]	randomised trial	very serious[23]	no serious inconsistency	no serious indirectness	no serious imprecision	none	390/4691 (8.3%)	266/4692 (5.7%)	RR 1.46 (1.26 to 1.69)	26 more per 1000 (from 15 more to 39 more)	⊕⊕OO LOW	
								0%		0 more per 1,000		
								13.3%		61 more per 1,000		
Cataracts (follow-up 156 weeks)												
1[24]	randomised trial	serious[25]	no serious inconsistency	no serious indirectness	very serious[14]	none	14/52 (26.9%)	6/41 (14.6%)	RR 1.84 (0.78 to 4.37)	123 more per 1000 (from 32 fewer to 492 more)	⊕OOO VERY LOW	
Fractures (follow-up 156 weeks)												
1[24]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[14]	none	78/1546 (5%)	61/1542 (4%)	RR 1.28 (0.92 to 1.77)	11 more per 1000 (from 3 fewer to 31 more)	⊕⊕⊕O MODERATE	

[1] Kardos et al; SCO 100470; TORCH; Tashkin et al; Rennard et al

[2] 3/5 RCTs had unclear allocation concealment, all double blinded, 3/5 have dropout rates >=20% ; and all conducted ITT. The largest study TORCH which comprised most of the weight of the meta-analysis was double blinded, had adequate allocation concealment, and performed ITT; however TORCH also had a dropout rate of 34% (LABA + ICS) and 37% (LABA) over 3 years

[3] TORCH, TRISTAN, Calverley et al, Szafranski et al, Kardos et al, Ferguson et al

[4] 1/6 unclear allocation concealment, all double blind, 5/6 have dropout rates >20%, all conducted ITT. The largest study TORCH which comprised almost half of the weight of the meta-analysis was double blinded, had adequate allocation concealment, and performed ITT; however TORCH also had a dropout rate of 34% (LABA + ICS) and 37% (LABA).

[5] overall has significant heterogeneity (I2 = 72.3%) and this is not explained by further sub grouping (length of follow-up or type of run-in)

[6] Calverley et al, Szafranski et al, TRISTAN

[7] 1/3 RCTs had unclear allocation concealment, all double blind, all trials had dropout rates > 20%; all performed ITT.

[8] Significant heterogeneity (I2=78.1%) not explained by stratifying studies by type of run-in

[9] Mahler et al, Hanania et al, Kardos et al, Ferguson et al

[10] 2/4 unclear allocation concealment, all double blinded, 3/4 have dropout rate >20% (similar in each arm) and 3/4 conducted ITT

[11] TORCH; Kardos et al

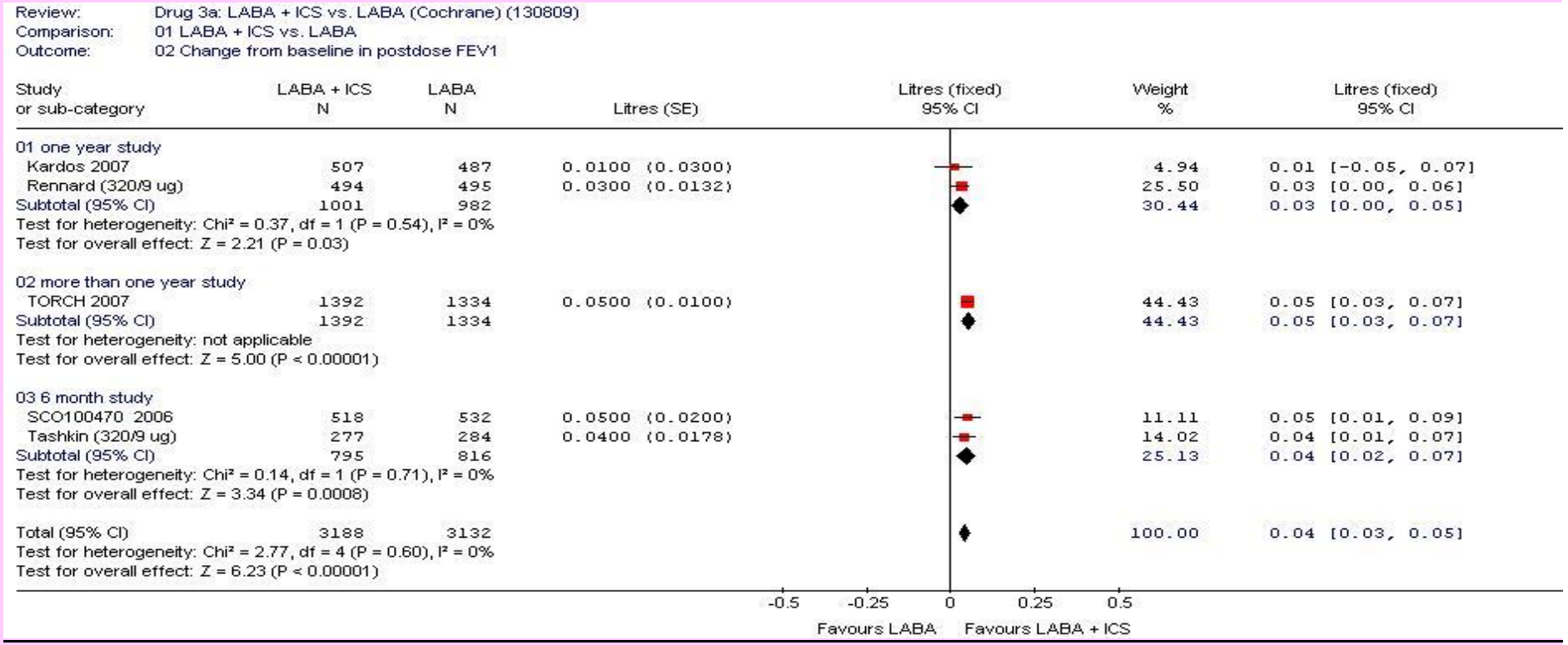
[12] Both studies have adequate allocation concealment, are double blinded, and both conducted ITT. The larger study TORCH has dropout rates >20% over 3 years.

[13] significant heterogeneity (I2 = 70.8%)

[14] wide 95% CI that crosses MID
[15] Hanania et al; Mahler et al
[16] Both have unclear allocation concealment, both double blind, both have dropout rates >20% (similar in both arms) and 1/2 is unclear if ITT was conducted
[17] Significant heterogeneity (I2= 76.6%)
[18] TRISTAN;TORCH; Kardos et al; SCO100470; Tashkin et al; Rennard et al
[19] 3/6 RCTs had unclear allocation concealment, all double blind; all performed ITT; 4/6 studies had dropout rates > 20% .
[20] TORCH; TRISTAN; SCO100470; Kardos et al; Calverley et al; Szafranski et al; Ferguson et al; Tashkin et al; Rennard et al
[21] 4/9 RCTs had unclear allocation concealment; all double blind; all performed ITT, 7/9 had dropout rates > 20%
[22] TORCH; TRISTAN; Mahler et al; Hanania et al; SCO100470; Calverley et al; Kardos et al; Ferguson et al; Tashkin et al; Rennard et al
[23] 6/10 studies have unclear allocation concealment, all studies are double blinded, all have dropout rates >20% , and 1/8 was unclear if ITT was performed.
[24] TORCH
[25] not ITT for this outcome; dropout rate > 20% at 3 years; double blind

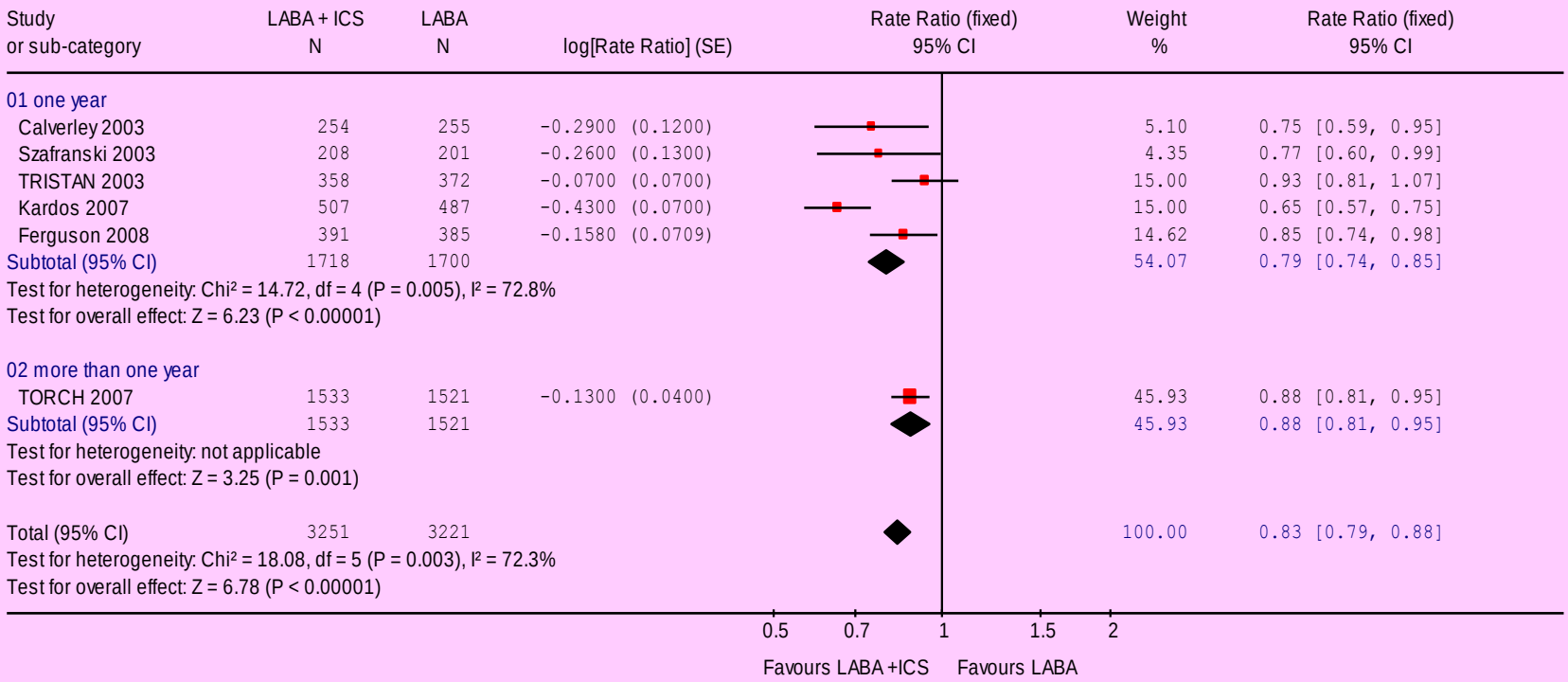
Forest Plots: Drug 3a LABA + ICS versus LABA

Change from baseline in post dose FEV_1



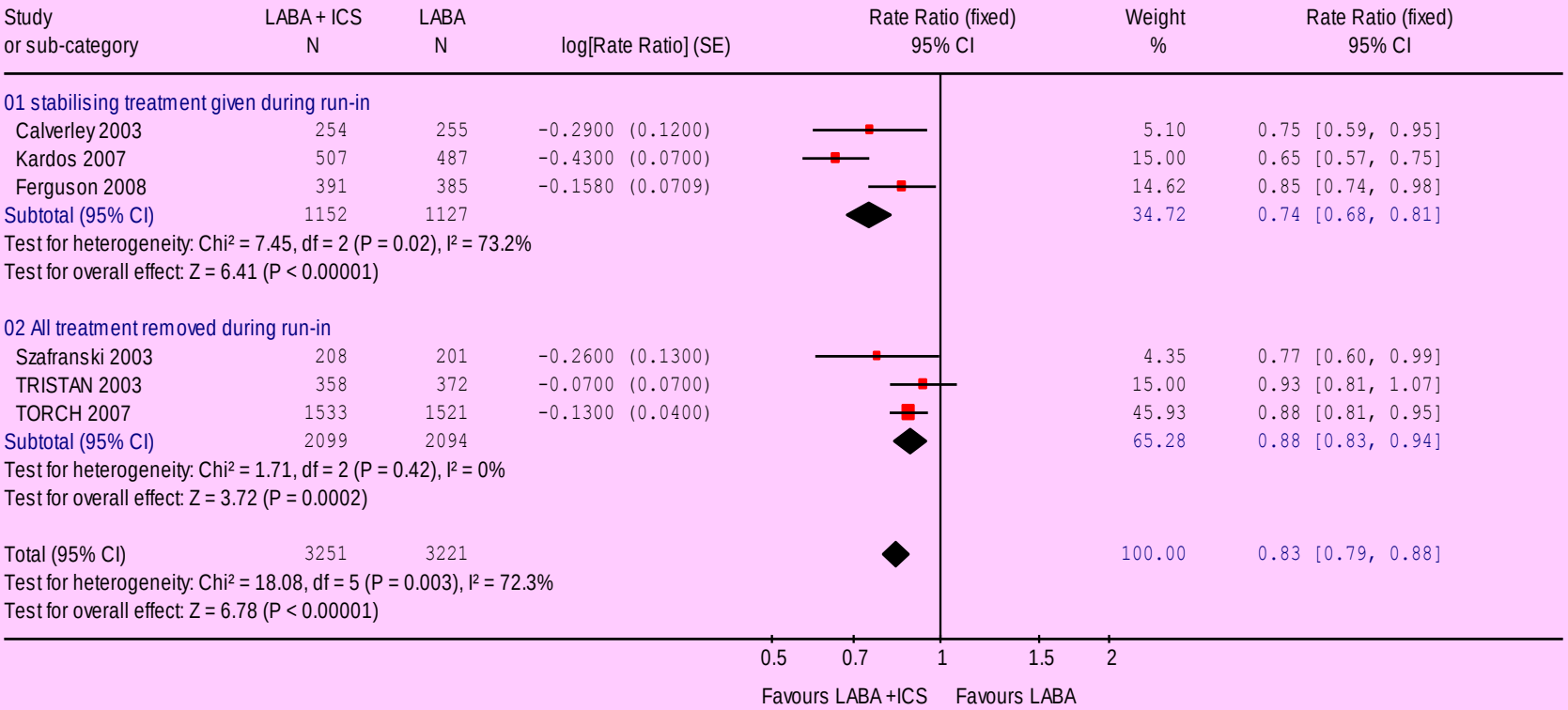
Exacerbations (expressed as a rate ratio)

Review: Drug 3a: LABA + ICS vs. LABA (Cochrane) (latest 300309)
Comparison: 01 LABA + ICS vs. LABA
Outcome: 03 Exacerbations (rate ratio) - duration of study split



Exacerbations (expressed as rate ratio)

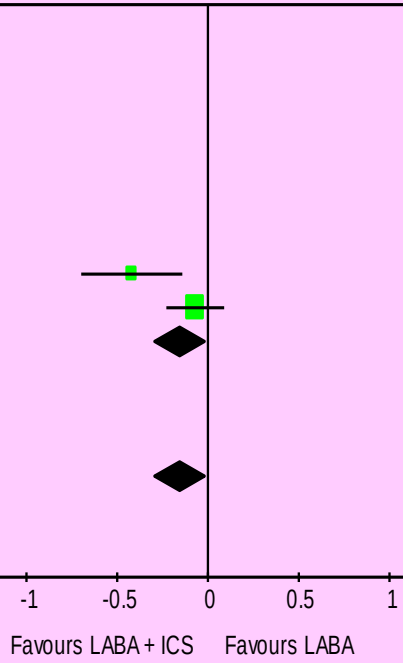
Review: Drug 3a: LABA + ICS vs. LABA (Cochrane) (latest 300309)
Comparison: 01 LABA + ICS vs. LABA
Outcome: 04 Exacerbations (rate ratio) - run in split



Mean number of exacerbations per person per year

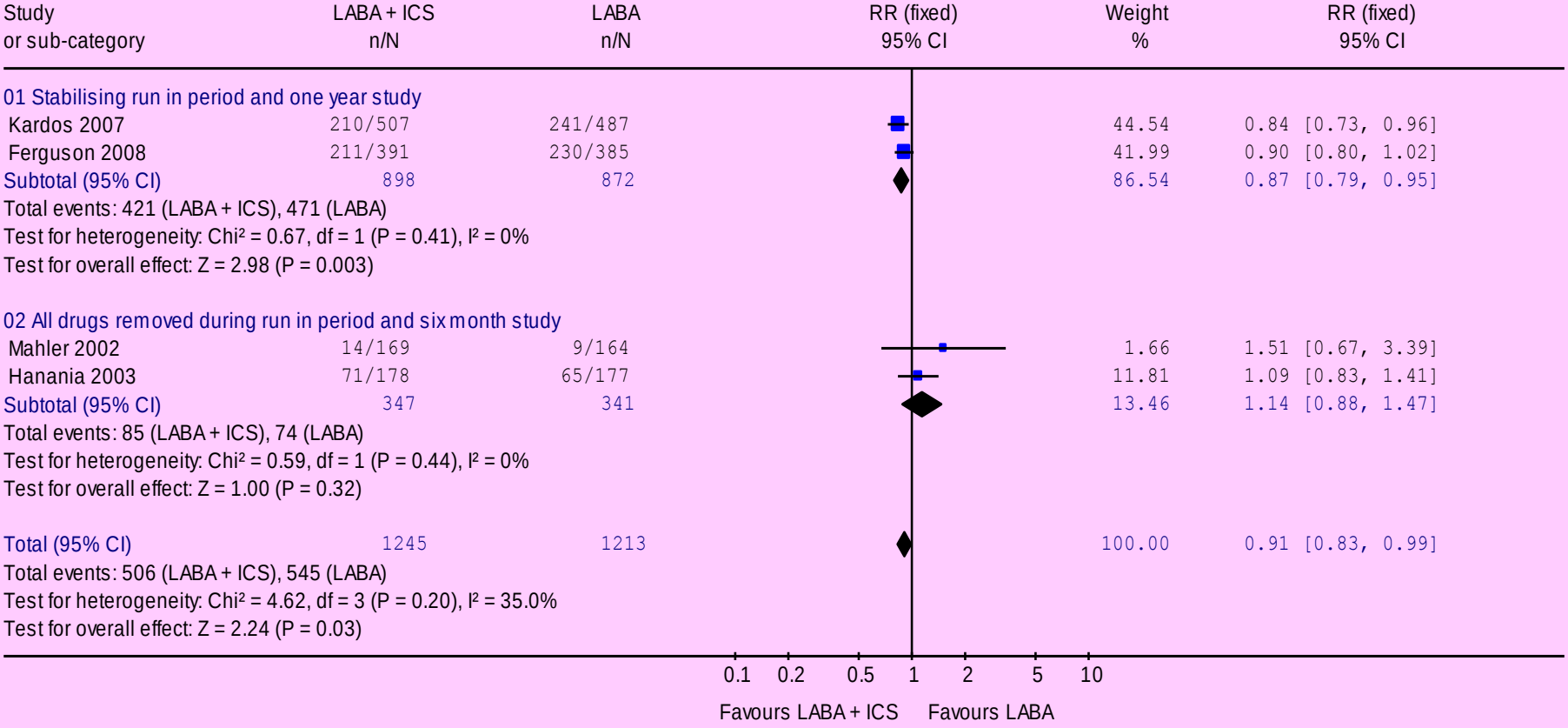
Review: Drug 3a: LABA + ICS vs. LABA (Cochrane) (latest 300309)
Comparison: 01 LABA + ICS vs. LABA
Outcome: 05 Mean number of exacerbations per participant per year - run in split

Study or sub-category	LABA + ICS N	LABA + ICS Mean (SD)	LABA N	LABA Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 All treatment removed during run in							
Calverley 2003	254	1.38 (0.00)	255	1.85 (0.00)			Not estimable
Subtotal (95% CI)	254		255				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
02 stabilising treatment given during run in							
Szafranski 2003	208	1.42 (1.49)	201	1.84 (1.38)		24.77	-0.42 [-0.70, -0.14]
TRISTAN 2003	358	0.97 (1.10)	372	1.04 (1.10)		75.23	-0.07 [-0.23, 0.09]
Subtotal (95% CI)	566		573			100.00	-0.16 [-0.30, -0.02]
Test for heterogeneity: Chi² = 4.57, df = 1 (P = 0.03), I² = 78.1%							
Test for overall effect: Z = 2.22 (P = 0.03)							
Total (95% CI)	820		828			100.00	-0.16 [-0.30, -0.02]
Test for heterogeneity: Chi² = 4.57, df = 1 (P = 0.03), I² = 78.1%							
Test for overall effect: Z = 2.22 (P = 0.03)							

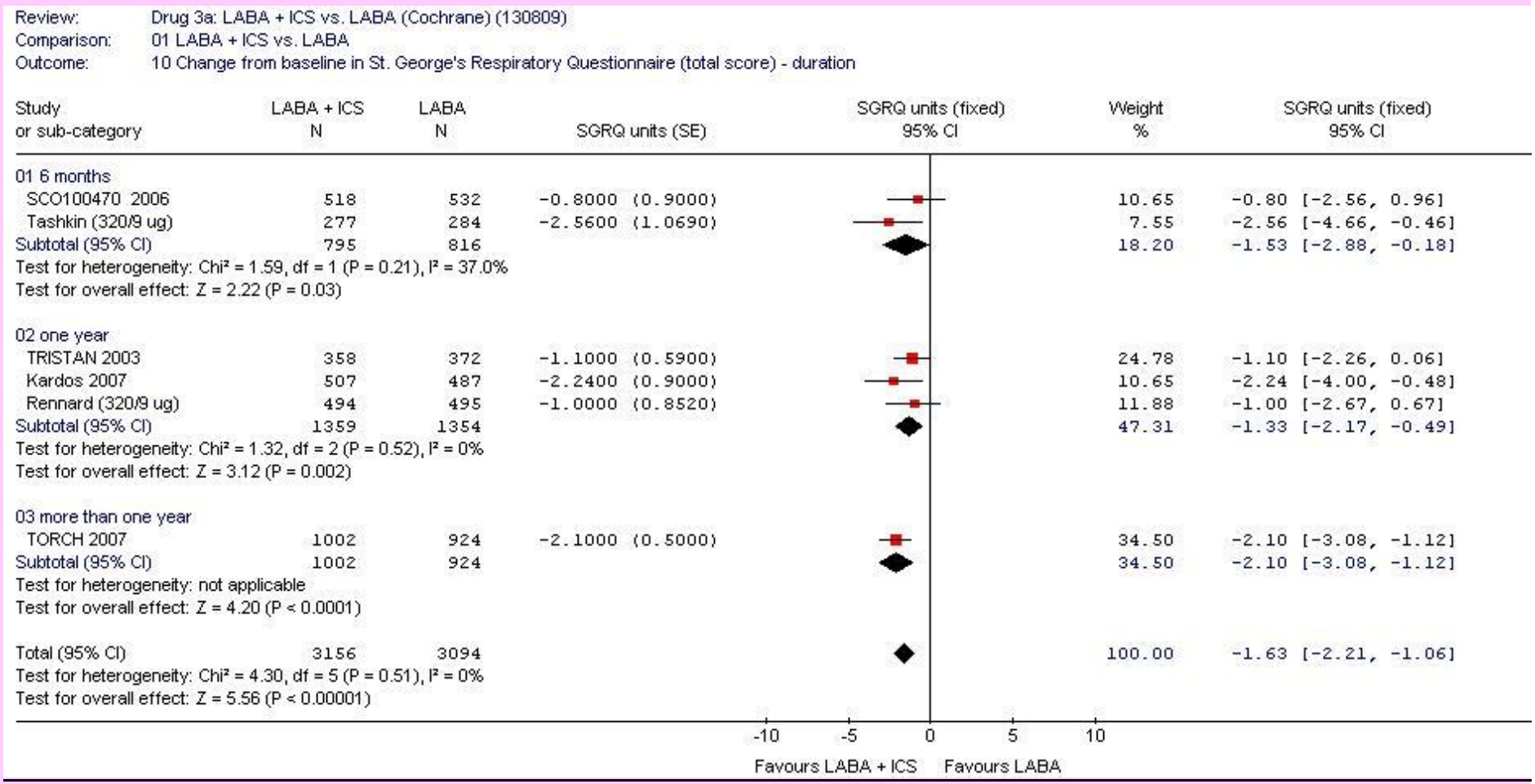


Number of participants with one or more exacerbation

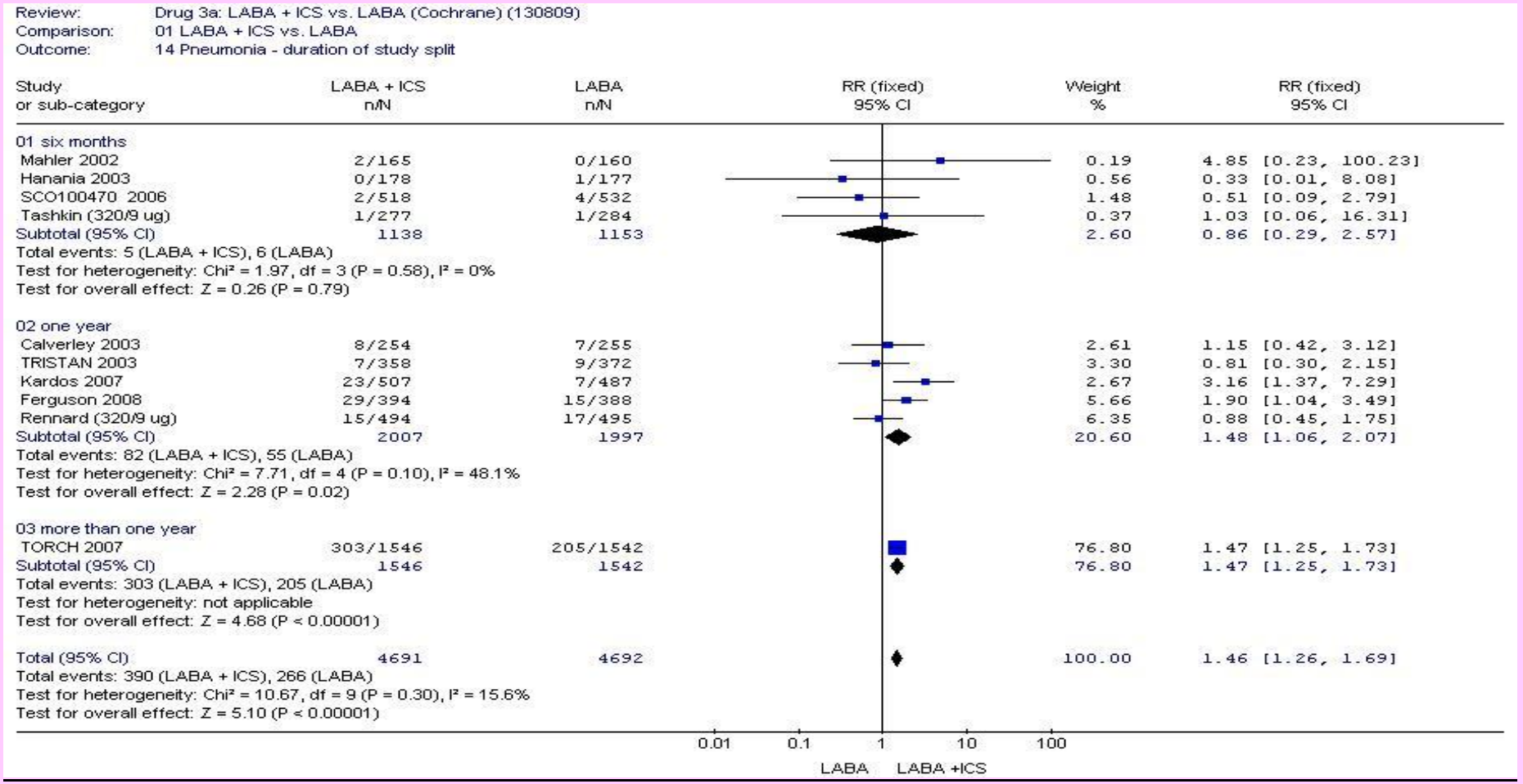
Review: Drug 3a: LABA + ICS vs. LABA (Cochrane) (latest 300309)
Comparison: 01 LABA + ICS vs. LABA
Outcome: 06 Number of participants with one or more exacerbation



Change from baseline in health related quality of life (total SGRQ score)



Pneumonia


Review: Drug 3a: LABA + ICS vs. LABA (Cochrane) (130809)
Comparison: 01 LABA + ICS vs. LABA
Outcome: 14 Pneumonia - duration of study split
Study or sub-category
LABA + ICS n/N
LABA n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
01 six months
Mahler 2002 2/165 0/160 0.19 4.85 [0.23, 100.23]
Hanania 2003 0/178 1/177 0.56 0.33 [0.01, 8.08]
SCO100470 2006 2/518 4/532 1.48 0.51 [0.09, 2.79]
Tashkin (320/9 ug) 1/277 1/284 0.37 1.03 [0.06, 16.31]
Subtotal (95% CI) 1138 1153 2.60 0.86 [0.29, 2.57]
Total events: 5 (LABA + ICS), 6 (LABA)
Test for heterogeneity: Chi² = 1.97, df = 3 (P = 0.58), I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)
02 one year
Calverley 2003 8/254 7/255 2.61 1.15 [0.42, 3.12]
TRISTAN 2003 7/358 9/372 3.30 0.81 [0.30, 2.15]
Kardos 2007 23/507 7/487 2.67 3.16 [1.37, 7.29]
Ferguson 2008 29/394 15/388 5.66 1.90 [1.04, 3.49]
Rennard (320/9 ug) 15/494 17/495 6.35 0.88 [0.45, 1.75]
Subtotal (95% CI) 2007 1997 20.60 1.48 [1.06, 2.07]
Total events: 82 (LABA + ICS), 55 (LABA)
Test for heterogeneity: Chi² = 7.71, df = 4 (P = 0.10), I² = 48.1%
Test for overall effect: Z = 2.28 (P = 0.02)
03 more than one year
TORCH 2007 303/1546 205/1542 76.80 1.47 [1.25, 1.73]
Subtotal (95% CI) 1546 1542 76.80 1.47 [1.25, 1.73]
Total events: 303 (LABA + ICS), 205 (LABA)
Test for heterogeneity: not applicable
Test for overall effect: Z = 4.68 (P < 0.00001)
Total (95% CI) 4691 4692 100.00 1.46 [1.26, 1.69]
Total events: 390 (LABA + ICS), 266 (LABA)
Test for heterogeneity: Chi² = 10.67, df = 9 (P = 0.30), I² = 15.6%
Test for overall effect: Z = 5.10 (P < 0.00001)
0.01
0.1
1
10
100
LABA
LABA +ICS

Evidence statements DRUG 3a LABA + ICS versus LABA alone

Overall, compared with LABA alone, people in the LABA + ICS group had a significant:

- Increase from baseline in post dose FEV_1 (litres) (moderate quality evidence).
- Decrease in the rate ratio of exacerbations (low quality evidence).
- Decrease in the mean rate of exacerbations per patient per year (low quality evidence).
- Decrease in the proportion of people experiencing one or more exacerbation (moderate quality evidence).
- Increase in the risk of pneumonia (low quality evidence).
- Improvement in health related quality of life (measured as change from baseline in SGRQ total score) (low quality evidence).

There was no significant difference between LABA+ICS and LABA alone for:

- Exacerbations that require hospitalisation (expressed as a rate ratio) (very low quality evidence). [studies were not powered to look at this outcome].
- Change from baseline in TDI (breathlessness) (very low quality evidence).
- Mortality (very low quality evidence)
- Cataracts (very low quality evidence)

- Fractures (moderate quality evidence)

In general, studies that only had six months follow-up yielded non-significant results for most outcomes assessed. The effect of type of run-in on the outcomes assessed was unclear.

Evidence Profile: Posthoc subgroup analysis of TORCH

Question: Should salmeterol/fluticasone vs. salmeterol be used for people with COPD stratified by GOLD severity?
Bibliography: Jenkins C, Jones P, Calverley P et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. *Respiratory Research.* 2009; 10(1):59. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	salmeterol/fluticasone	salmeterol	Relative (95% CI)	Absolute		
mortality - people with baseline post BD FEV_1 < 30% (follow-up 3 years)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	43/243 (17.7%)	64/260 (24.6%)	RR 0.72 (0.51 to 1.01)	69 fewer per 1000 (from 121 fewer to 2 more)	⊕OOO VERY LOW	
mortality - people with baseline post BD FEV_1 30% to < 50% (follow-up 3 years)												
1	randomised trial	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	106/728 (14.6%)	93/739 (12.6%)	RR 1.16 (0.89 to 1.5)	20 more per 1000 (from 14 fewer to 63 more)	⊕OOO VERY LOW	

mortality - people with baseline post BD FEV_1 greater than or equal to 50% (follow-up 3 years)												
1	randomised trial	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	44/562 (7.8%)	48/522 (9.2%)	RR 0.85 (0.58 to 1.26)	14 fewer per 1000 (from 39 fewer to 24 more)	⊕OOO VERY LOW	

[1] posthoc subgroup analysis of TORCH; very high withdrawal rate in this subgroup (GOLD stage IV) over 3 years (53% in salmeterol vs. 42% in SFC groups).

[2] wide 95% CI that crosses MID

[3] posthoc subgroup analysis of TORCH; high withdrawal rate in this subgroup (GOLD stage III) over 3 years (38% in salmeterol vs. 35% in SFC groups).

[4] posthoc subgroup analysis of TORCH; high withdrawal rate in this subgroup (GOLD stage II) over 3 years (27% in salmeterol vs. 27% in SFC groups).

[5] wide 95% CI that crosses MID twice

Evidence statements: Posthoc subgroup analysis of TORCH

In the posthoc subgroup analysis of TORCH[207], there was no significant difference between salmeterol plus fluticasone compared with salmeterol for:

- Death in people with baseline post-bronchodilator FEV_1 < 30% (very low quality evidence)
- Death in people with baseline post-bronchodilator FEV_1 30% to < 50% (very low quality evidence)
- Death in people with baseline post-bronchodilator FEV_1 ≥ 50% (very low quality evidence).

Health economic methodological introduction: LABA+ICS vs. LABA

The literature was searched from 2003 onwards for economic evaluations comparing treatment with combined long-acting $beta_2$ agonists and ICS versus long-acting $beta_2$ agonists alone. This comparison was also subject to a call for unpublished evidence.

Four studies were included that included the relevant comparison[208-211]. These are summarised in the economic evidence profile below. Two studies that based differences in LABA+ICS and LABA on the TORCH study and took a US perspective were excluded because a more applicable analysis (from a Western European perspective) based on TORCH, with higher methodological quality, was available[212,213]. Four studies examining this comparison were excluded due to being US retrospective database analyses, as other more relevant data was available based on RCT evidence[214-217].

No studies were identified in the original guideline search.

Health economic evidence profile

Economic evidence: LABA+ICS vs. LABA							
Study	***Limitations****	***Applicability***	***Other comments***	***Incremental cost (£)***[‡]	***Incremental effects***[‡]	***ICER***[‡]	***Uncertainty***
Dal Negro et al (2007)[208] – Italy ***SF vs. S***	Potentially serious limitations[z]	Partially applicable[aa]	Literature based lifetime Markov model of COPD natural history. Treatment effect on exacerbations applied in GOLD stage 3 and 4 (FEV_1 <50%) – data from Calverley 2003 (SF)[218] and Szafranski (FB)[166]	£496[bb]	0.98 exacerbations avoided	£505 per exacerbation avoided[cc]	Not reported[dd]
As above ***FB vs. S***				£427[c]	0.41 exacerbations avoided	£1033 per exacerbation avoided[cc]	Not reported[dd]

[z] Key limitations: Sensitivity analysis is very limited and no results are reported or discussed for the comparisons of interest. No discounting is reported. Minor limitations: Based on single study when another was identified in clinical review – exacerbation rate ratios very similar however. The study is funded by LABA+ICS sponsor (GlaxoSmithKline Italia).
[aa] Some uncertainty over the applicability of Italian resource use, costs and epidemiological data to UK. QALYs not used – inhibits interpretation of results.
[bb] Converted from 2005 Italian Euros using 2005 Purchasing Power Parities[177].
[cc] Study included placebo and ICS alone as well as SF, FB and S. Placebo and ICS were both dominated by S.
[dd] Study undertook one way sensitivity but only reported SF vs placebo results.

Lofdahl et al (2005)[209] – Sweden ***FB vs. F***	Potentially serious limitations[ee]	Partially applicable[ff]	1 year analysis of resource use and outcomes in Calverley 2003 [218] RCT (GOLD stage 3 and 4 - FEV_1 <50% predicted)	-£691[gg]	Reduction in exacerbations[hh]	LABA+ICS dominant[ii]	LABA+ICS dominant in >95% bootstrap replications Alternative cost analyses were all cost-saving with LABA+ICS
Mayers et al. (2007)[210] – Canada ***LABA+ICS (sev patients) vs. LABA***	Potentially serious limitations[jj]	Partially applicable[kk]	Literature based lifetime Markov model of COPD natural history. Treatment effect on exacerbations applied to different patient group – data from Calverley 2003[218], Szafranski[166] and TRISTAN[167].	£53[ll]	0.01187 QALYs	£4,497/QALY	PSA found LABA+ICS highly likely to be cost-effective in severe, or moderate and severe patients, and highly unlikely to be cost-effective in all patients at a threshold of £20,000.
As above			Mild = FEV_1 >50% predicted	£236[ll]	0.024 QALYs	£9833/QALY	

[ee] Key limitation: By design based on a single study and so doesn't incorporate all clinical evidence available for LABA+ICS – exacerbation rate ratio used more favourable than the new pooled estimate based on all available evidence with LABA+ICS vs LABA. Minor limitations: Resource use may be influence by trial setting; 1-year time horizon but chronic condition – longer term model may be appropriate, not estimated or discussed; study is funded by the LABA+ICS sponsor (Astrazeneca).

[ff] Some uncertainty over the applicability of international resource use and Swedish costs to UK – authors indicate that conclusions did not change when UK costs applied although details are not reported. QALYs not used – however as costs are reduced and outcomes improved an ICER does not need to be calculated.

[gg] Converted from 2001 Swedish Kroner using 2001 Purchasing Power Parities[177] (Swedish Kroner are back-calculated from Euros reported in paper by apply exchange rate used to convert to Euros in paper).

[hh] Improvements in FEV1 and SGRQ also reported.

[ii] Study included placebo and ICS alone as well as LABA+ICS and LABA. LABA+ICS dominated all.

[jj] Treatment effect based on pooled estimate that is now out of date as new studies have been published - exacerbation rate ratio used more favourable than the new pooled estimate based on all available evidence with LABA+ICS vs LABA.

[kk] Some uncertainty over the applicability of Canadian resource use, costs and epidemiological data to UK.

[ll] Converted from 2004 Canadian dollars using 2004 Purchasing Power Parities[177].

LABA+ICS (mod&sev patients) vs. LABA			Moderate = FEV_1 35-50% predicted Severe = FEV_1 < 35% predicted			[mm]	
As above ***LABA+ICS (all) patients vs. LABA***				£1971[ll]	0.037 QALYs	£52,270/QALY [nn]	
Briggs et al. (2009)[211] ***SF vs S*** Western Europe	Potentially serious limitations[oo]	Partially applicable[pp]	3-year analysis of resource use and health outcomes (mortality and EQ-5D utility) collected in TORCH[197] RCT (FEV_1<60% predicted)	£677[qq]	0.078 QALYs	£8655/QALY [rr]	ICER CI: £5659-£22,038. Bootstrap analysis found LABA+ICS to be preferred option at £20,000/QALY threshold ~70% and LABA alone <5%.[ss]

*Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; ‡ LABA+ICS – LABA alone; Dominant = LABA+ICS is cost saving with improved outcomes; SF = salmeterol/fluticasone; FB = formoterol/budenoside; S = salmeterol alone

[mm] Study does not report this comparison – more appropriate to compare use in moderate and severe patients to just using in severe patients (see table below).
[nn] Study does not report this comparison – more appropriate to compare use in all patients with use in just moderate and severe patients (see table below).
[oo] Key limitation: by design based on a single study and so doesn't incorporate all clinical evidence available for LABA+ICS – exacerbation and hospitalisation rate ratios in TORCH are more conservative that pooled estimate from all available data. Minor limitations: Unit costs used aren't reported. Resource use may be influenced by trial setting. Time horizon is 3 years – longer term extrapolation may be appropriate; authors discuss and conclude that longer time horizon would improve ICERs.
[pp] Some uncertainty regarding applicability of Western European resource use and costs to UK. Note that other perspectives were reported but Western Europe subgroup results deemed most applicable.
[qq] Converted from 2007 US dollars using 2007 Purchasing Power Parities[177].
[rr] Study also included an ICS (F) alone arm and a placebo arm. When all comparators considered, based on mean costs and QALYs, LABA is ruled out by extended dominance, as is ICS, and the most appropriate ICER in analysis is LABA+ICS vs placebo. LABA+ICS vs placebo ICER: Western Europe £16,112/QALY (CI: £10,120-£37,351).
[ss] ICS <5%; placebo ~25%.

Economic evidence: LABA+ICS (severe patients only) vs. LABA+ICS (severe and moderate patients only)

Study	*Limitations**	*Applicability***	*Other comments*	*Incremental‡ cost (£)*	*Incremental‡ effects*	*ICER‡*	*Uncertainty*
Mayers et al. (2007)[210] – Canada	Potentially serious limitations[jj]	Partially applicablekk	Literature based lifetime Markov model of COPD natural history. Treatment effect on exacerbations applied – data from Cal;verley 2003[218], Szafranski[166] and TRISTAN[167] Mild = FEV_1 >50% predicted Moderate = FEV_1 35-50% predicted Severe = FEV_1 < 35% predicted	£182[ll]	0.01217 QALYs	£14,931 per QALY gained	PSA found LABA+ICS to be highly likely to be cost-effective in severe, or moderate and severe patients, and highly unlikely to be cost-effective in all patients at a threshold of £20,000.

*Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; ‡ LABA+ICS – LABA alone

Economic evidence: LABA+ICS (severe and moderate patients only) vs. LABA+ICS (all patients)							
Study	***Limitations****	***Applicability***	***Other comments***	***Incremental[‡] cost (£)***	***Incremental[‡] effects***	***ICER[‡]***	***Uncertainty***
Mayers et al. (2007)[210] – Canada	Potentially serious limitations[jj]	Partially applicable[kk]	Literature based lifetime Markov model of COPD natural history. Treatment effect on exacerbations applied – data from Calverley 2003[218], Szafranski[166] and TRISTAN[167]}. Mild = FEV_1 >50% predicted Moderate = FEV_1 35-50% predicted Severe = FEV_1 < 35% predicted	£1735[ll]	0.01323 QALYs	£131,165 per QALY gained	PSA found LABA+ICS to be highly likely to be cost-effective in severe, or moderate and severe patients, and highly unlikely to be cost-effective in all patients at a threshold of £20,000.

*Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; [‡] LABA+ICS – LABA alone

Health economic Evidence statements

Three economic studies identified found LABA+ICS to be cost-effective compared with LABA alone in people with COPD with FEV_1 < 50% predicted or < 60% predicted (depending on the analysis)[209-211]. These were judged partially applicable due to their non-UK setting. Between them they used data from TRISTAN[167], Szafranski 2003[166], Calverley 2003[218] and TORCH[197]. One of the three studies found use of LABA+ICS to be cost saving as well as improving health outcomes with the additional cost of treatment offset by saving in healthcare resource use. The TORCH analysis was based on outcomes, resource use and EQ5D utility data collected prospectively within the trial[197].

One of the six studies only reported costs per exacerbation avoided and so was difficult to interpret[208].

One study examined cost-effectiveness of different strategies for using LABA+ICS and found that use of LABA+ICS in all people with COPD was not cost-effective compared to giving it only to people with an FEV_1 < 50% predicted (those not receiving LABA+ICS received LABA alone)[210].

DRUG 3b LABA + ICS versus LAMA alone

The evidence profile below summarises the quality of the evidence and outcome data from one double blinded RCT (INSPIRE)[219] comparing salmeterol/fluticasone propionate (50 microgram/500 microgram) with tiotropium bromide (18 microgram) in adults with stable COPD (N=1323; follow-up 2 years).

Evidence Profile DRUG 3B: LABA+ICS vs. LAMA

Question: Should salmeterol/fluticasone propionate vs. tiotropium bromide be used in adults with stable COPD?
Bibliography: Wedzicha JA CPSTH. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008; 177(1):19-26.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	salmeterol/fluticasone propionate	tiotropium bromide	Relative (95% CI)	Absolute		
Mean exacerbations (rate ratio) requiring use of oral corticosteroids and/or antibiotics or hospitalisation (follow-up 2 years)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	658 (1.28 mean exacerbations/year)	665 (1.32 mean exacerbations /year)	rate ratio 0.97 (0.84 to 1.12)[3]	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O MODERATE	
Mean exacerbations (rate ratio) requiring antibiotics (follow-up 2 years)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	658 (0.97 mean exacerbations/year)	665 (0.82 mean exacerbations/year)	rate ratio 1.19 (1.02 to 1.38)[5]	0 more per 1000 (from 0 more to 0 more)	⊕⊕OO LOW	

Mean exacerbations (rate ratio) requiring oral corticosteroids (follow-up 2 years)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	658 (0.69 mean exacerbation/year)	665 (0.85 mean exacerbation/year)	rate ratio 0.81 (0.67 to 0.99)[6]	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	
Mean exacerbations (rate ratio) requiring hospitalisation (follow-up 2 years)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	658	665	rate ratio 1.08 (0.73 to 1.59)[8]	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	
Mean change from baseline in Quality of Life (follow-up 2 years; measured with: SGRQ total score; range of scores: 0-100; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	658	665	-	MD -2.07 (-4.02 to -0.12)[9]	⊕⊕OO LOW	
Change from baseline in post bronchodilator FEV_1 (follow-up 2 years; range of scores: -; Better indicated by more)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	658	665	-	MD -0.02 (-0.06 to 0.01)	⊕⊕⊕O MODERATE	
All-cause mortality (follow-up 2 years)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	21/658 (3.2%)	38/665 (5.7%)	RR 0.56 (0.33 to 0.94)	25 fewer per 1000 (from 3 fewer to 38 fewer)	⊕⊕OO LOW	

Pneumonia (follow-up 2 years)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50/658 (7.6%)	24/665 (3.6%)	RR 2.11 (1.31 to 3.38)	40 more per 1000 (from 11 more to 86 more)	⊕⊕⊕O MODERATE	
Bone disorder (follow-up 2 years)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[10]	very serious[11]	none	17/658 (2.6%)	12/665 (1.8%)	RR 1.43 (0.69 to 2.97)	8 more per 1000 (from 6 fewer to 35 more)	⊕OOO VERY LOW	

[1] double blind, ITT performed, however possible attrition bias as dropout rates were high: 35% in the salmeterol/fluticasone propionate group versus 42% tiotropium group; p<0.005. The GDG thought the dropout rate was not unexpected in a 2 year study of people with decreased lung function. The GDG thought that the difference in dropouts between the two arms could have been a treatment effect.

[2] population consisted of people with COPD who had history of exacerbation of COPD; history of ≥ 10 pack years; score ≥ 2 modified MRC dyspnoea score and post bronchodilator FEV_1 < 50% predicted value

[3] 1.28 mean exacerbations/year in SFC group versus 1.32 mean exacerbations /year in tio group

[4] wide 95% CI that crosses MID

[5] 0.97 mean exacerbations/year in SFC group versus 0.82 exacerbations/year in tio group

[6] 0.69 mean exacerbation/year in SFC group versus 0.85 mean exacerbations/year in tio group

[7] wide 95% CI that crosses MID

[8] Rate ratio provided by investigators. This analysis accounts for differing lengths of time in the study among patients and adjusts for baseline factors (smoking status, age, sex, baseline disease severity, BMI, the number of moderate/severe exacerbations reported in the 12 months prior to screening).

[9] adjusted mean change at 2 years was -1.70 units in SFC and + 0.37 units in tio group

[10] bone disorder not defined

[11] wide 95% CI that crosses MID twice

Evidence statements: DRUG 3b LABA + ICS versus LAMA alone

There was no significant difference between salmeterol/fluticasone propionate versus tiotropium alone for:

- The primary outcome: mean exacerbations requiring oral corticosteroids or antibiotics or hospitalisations (expressed as a rate ratio) [moderate quality evidence]

Compared with tiotropium alone, salmeterol/fluticasone propionate significantly:

- Increased mean exacerbations requiring antibiotics (expressed as rate ratio) [low quality evidence]
- Decreased mean exacerbations requiring oral corticosteroids (expressed as rate ratio) [low quality evidence]
- Improved health related quality of life (expressed as the mean change from baseline in total SGRQ score) [low quality evidence]
- Decreased risk of all-cause mortality [low quality evidence]
- Increased risk of pneumonia [low quality evidence]

There was no significant difference between salmeterol/fluticasone propionate versus tiotropium alone for:

- Mean exacerbations requiring hospitalisation (expressed as rate ratio) [low quality evidence]
- Change from baseline in post-bronchodilator FEV_1 [moderate quality evidence]
- Bone disorders [very low quality evidence]

Health economic evidence LABA+ICS vs. LAMA

Health economic methodological introduction

The literature was searched from 2003 onwards for economic evaluations comparing treatment with combined long-acting beta$_2$ agonists and ICS versus long-acting muscarinic antagonists alone. This comparison was also subject to a call for unpublished evidence.

No studies were identified in the update search or in the original guideline search.

Health economic modelling

Note that this comparison was included in a health economic analysis undertaken as part of this update. The GDG were interested in the following question: Is LAMA, LABA+ICS or triple therapy more cost-effective as initial therapy in COPD patients with an FEV_1 <50% predicted (severe to very severe COPD)?

The results of this analysis are summarised later in this section of the guideline, following the review of the clinical and economic literature. The full report in included in Appendix M.

7.3.6.2 Long-acting beta$_2$ agonists (LABA) and inhaled corticosteroids (ICS) and long-acting muscarinic antagonist (LAMA)

Methodological introduction

The literature was searched for systematic reviews and RCTs (with a minimum follow-up of 6 months) conducted in people with stable COPD that compared triple therapy (long-acting muscarinic antagonists plus long-acting beta$_2$ agonists plus inhaled corticosteroids) with either:

a) long-acting beta$_2$ agonists plus inhaled corticosteroids

b) long-acting muscarinic antagonists alone

c) long-acting beta$_2$ agonists plus long-acting muscarinic antagonists

DRUG 6a: LAMA + LABA + ICS vs. LABA + ICS (question 6a)

The GDG posed the following question:

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists plus inhaled corticosteroids compared to long-acting beta$_2$ agonists plus inhaled corticosteroids in the management of people with stable COPD?

There were no published RCTs identified for this treatment strategy.

A 'Call for Evidence', in which registered stakeholders were invited to submit unpublished data, was conducted in the hope of identifying some evidence that could inform this drug comparison. Boehringer Ingelheim Ltd. submitted an unpublished post hoc subgroup analysis of the UPLIFT trial that compared people with COPD randomised to placebo or tiotropium (18 µg once daily) in which both arms had LABA plus ICS at baseline (N=2926).[201]. Although the two arms were similar at baseline, it is important to note that only placebo and tiotropium were randomised; the background LABA + ICS was not randomised. This subgroup had predominantly moderate to severe COPD (GOLD stage II [42%] and GOLD stage III [46%]).

Call for Evidence: tiotropium + baseline LABA + baseline ICS versus placebo + baseline LABA + baseline ICS (DRUG 6a)

A GRADE profile is presented for this subgroup analysis comparing tiotropium + baseline LABA+baseline ICS with placebo + baseline LABA + baseline ICS.

Evidence Profile Call for Evidence Drug 6a: tiotropium + baseline LABA + baseline ICS versus placebo + baseline LABA + baseline ICS

Question: Should tiotropium + LABA (at baseline) + ICS (at baseline) vs. placebo + LABA (at baseline) + ICS (at baseline) be used in people with COPD?
Bibliography: Unpublished Data from UPLIFT RCT (Boehringer)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	tiotropium + LABA (at baseline) + ICS (at baseline)	placebo + LABA (at baseline) + ICS (at baseline)	Relative (95% CI)	Absolute		
Mean post bronchodilator FEV_1 at 1 year (follow-up 1 years; range of scores: -; Better indicated by more)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1210	1129	-	MD 0.060 (0.042 to 0.077)[2]	⊕⊕OO LOW	
Mean post bronchodilator FEV_1 at 4 years (follow-up 4 years; range of scores: -; Better indicated by more)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	858	752	-	MD 0.053 (0.03 to 0.076)[2]	⊕⊕OO LOW	
Quality of Life at 1 year (follow-up 1 years; measured with: mean total SGRQ score; range of scores: 0-100; Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1193	1101	-	MD -2.751 (-3.725 to -1.778)[2]	⊕⊕OO LOW	
Quality of Life at 4 years (follow-up 4 years; measured with: mean total SGRQ score; range of scores: 0-100; Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	854	750	-	MD -1.932 (-3.284 to -0.579)[2]	⊕⊕OO LOW	

Number of patients with COPD exacerbations (follow-up 4 years)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1052/1464 (71.9%)	1066/1462 (72.9%)	HR 0.86 (0.79 to 0.93)[3]	54 fewer per 1000 (from 26 fewer to 85 fewer)	⊕⊕OO LOW	
Number of patients hospitalised for COPD exacerbations (follow-up 4 years)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	398/1464 (27.2%)	442/1462 (30.2%)	HR 0.80 (0.7 to 0.92)[5]	52 fewer per 1000 (from 20 fewer to 79 fewer)	⊕OOO VERY LOW	
Mean COPD exacerbations per patient year (expressed as rate ratio) (follow-up 4 years)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1464 (0.85 [SE 0.03] exacerbations/patient year)	1462 (1.00 [SE 0.03] exacerbations/patient year)	rate ratio 0.85 (0.78 to 0.92)[6]	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	
Mean hospitalisations for COPD exacerbations per patient per year (expressed as rate ratio) (follow-up 4 years)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1464 (0.16 [SE 0.01] hospitalisations/patient year)	1462 (0.18 [SE 0.01] hospitalisations/patient year)	rate ratio 0.89 (0.75 to 1.07)[7]	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	
Mortality (adjudicated on treatment and vital status censoring at 1470 days) (follow-up 1470 days)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	205/1464 (14%)	220/1462 (15%)	HR 0.91 (0.76 to 1.15)[8]	13 fewer per 1000 (from 34 fewer to 20 more)	⊕OOO VERY LOW	

[1] UPLIFT trial: people randomisation to placebo or tiotropium. This is a post hoc subgroup analysis of people taking LABA + ICS at baseline; unclear allocation concealment; not true ITT; dropouts in this subgroup not reported; double blind. LABA + ICS was not randomised between the two groups.

[2] the mean, standard error, 95% CI, and p value are based on least squares mean estimate using repeated measures ANOVA model, adjusted for baseline values

[3] HR and p value are based on Cox regression with treatment, baseline LABA/ICS use, and baseline LABA/ICS use by treatment interaction as covariates.
[4] wide 95% CI that crosses MID
[5] HR based on Cox regression with treatment, baseline LABA use, and baseline LABA use by treatment interaction as covariates
[6] The Poisson with Pearson overdispersion model adjusting for treatment exposure was used to estimate the number of exacerbations per patient year and the ratio between tiotropium and placebo. Mean COPD exacerbations per patient year for triple therapy was 0.85 (SE 0.03) and for LABA + ICS was 1.00 (SE 0.03).
[7] The Poisson with Pearson overdispersion model adjusting for treatment exposure was used to estimate the number of hospitalisations per patient year and the ratio between tiotropium and placebo. Mean hospitalisations for exacerbations per patient year for triple therapy were 0.16 (SE 0.01) and for LABA + ICS were 0.18 (SE 0.01)
[8] The p value and HR are based on Cox regression with treatment, baseline LABA/ICS use, and baseline LABA/ICS use by treatment as covariates. Observations are censored at 1470 days for patients still in the risk set at that time

Evidence statements for Call for Evidence DRUG 6a: tiotropium + baseline LABA + baseline ICS versus placebo + baseline LABA + baseline ICS

Compared with people in the placebo + baseline LABA + baseline ICS group, the tiotropium + baseline LABA + baseline ICS group experienced a significantly

- Higher mean post bronchodilator FEV_1 at 1 or 4 years [low quality evidence]
- Better health related quality of life (mean total SGRQ score) at 1 or 4 years [low quality evidence]
- Decreased risk of exacerbations [low quality evidence]
- Lower rate of COPD exacerbations (expressed as exacerbations per patient year) [low quality evidence]
- Decreased risk of hospitalisation for COPD exacerbations [very low quality evidence]

There was no significant difference between the groups for:

- Rate of exacerbations requiring hospitalisations (expressed as hospitalisations per patient year) [low quality evidence]
- All-cause mortality [very low quality evidence]

Health economic evidence: LAMA+LABA+ICS vs. LABA+ICS

Health economic methodological introduction

The literature was searched from 2003 onwards for economic evaluations comparing treatment with triple therapy versus combined long-acting $beta_2$ agonists and ICS. This comparison was also subject to a call for unpublished evidence.

No studies were identified in the update search or in the original guideline search.

Health economic modelling

Note that this comparison was included in a health economic analysis undertaken as part of this update. The GDG were interested in the following question: Is LAMA, LABA+ICS or triple therapy more cost-effective as initial therapy in COPD patients with an FEV_1 <50% predicted (severe to very severe COPD)?

The results of this analysis are summarised later in this section of the guideline, following the review of the clinical and economic literature. The full report in included in appendix M.

Drug 6b: LAMA + LABA + ICS vs. LAMA alone (question 6b)

The question posed was:

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists alone in the management of people with stable COPD?

In the double blind OPTIMAL RCT [200] people with moderate to severe COPD (N=449; follow-up 1 year) were randomised to one of three arms: tiotropium (18 microgram once daily) plus placebo inhaler (two puffs twice daily) or tiotropium (18 microgram once daily) plus salmeterol (25 microgram/puff; 2 puffs; twice daily) or tiotropium (18 microgram once daily) plus fluticasone-salmeterol (250/50 microgram/puff, 2 puffs twice daily).

The evidence profile below summarises the quality of the evidence and outcome data for the OPTIMAL RCT [200] comparing triple therapy (tiotropium plus fluticasone/salmeterol) with tiotropium plus placebo in people with moderate to severe COPD.

Evidence Profile DRUG 6B: triple therapy versus tiotropium + placebo

Question: Should tiotropium + salmeterol/fluticasone vs. tiotropium + placebo be used in people with stable COPD?
Bibliography: Aaron SD, Vandemheen KL, Fergusson D et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2007; 146(8):545-555.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	tiotropium + salmeterol/fluticasone	tiotropium + placebo	Relative (95% CI)	Absolute		
Primary outcome: Number of people with 1 or more acute exacerbations (assuming all patients lost to follow-up did not have exacerbations; these include people who were hospitalised) (follow-up 1 years; blinded assessor)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	87/145 (60%)	98/156 (62.8%)	RR 0.96 (0.8 to 1.14)	25 fewer per 1000 (from 126 fewer to 88 more)	⊕⊕⊕O MODERATE	
Primary outcome: Number of people with 1 or more acute exacerbations (assuming all patients lost to follow-up had exacerbations; these include people who were hospitalised) (follow-up 1 years; blinded assessor)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	none	96/145 (66.2%)	117/156 (75%)	RR 0.88 (0.76 to 1.02)	90 fewer per 1000 (from 180 fewer to 15 more)	⊕⊕OO LOW	

Primary outcome: Number of people with 1 or more acute exacerbations (assuming all patients lost to follow-up had exacerbations at same rate as those who remained in the study; these include people who were hospitalised) (follow-up 1 years; blinded assessor)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	none	93/145 (64.1%)	112/156 (71.8%)	RR 0.89 (0.76 to 1.04)	79 fewer per 1000 (from 172 fewer to 29 more)	⊕⊕OO LOW	
Mean exacerbations/patient-year (expressed as rate ratio) (follow-up 1 years; blinded assessor)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	145 (1.37 mean exacerbations/patient year)	156 (1.61 mean exacerbations/patient year)	rate ratio 0.85 (0.65 to 1.11)[4]	0 fewer per 1,000	⊕⊕⊕O MODERATE	
Mean hospitalisation for acute exacerbation per patient year (expressed as rate ratio) (follow-up 1 years)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	145 (0.19 mean hospitalisations/patient year)	156 (0.355 mean hospitalisations/patient year)	rate ratio 0.53 (0.33 to 0.86)[5]	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕O MODERATE	
Change from baseline in health related quality of life (follow-up 1 years; measured with: total SGRQ score; range of scores: 0-100; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision[6]	none	145	156	-	MD -4.1 (0 to 0)[7]	⊕⊕⊕O MODERATE	
Change from baseline in mean pre-bronchodilator FEV_1 (follow-up 1 years; range of scores: 0-; Better indicated by more)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision[6]	none	145	156	-	MD 0.059 (0 to 0)[8]	⊕⊕⊕O MODERATE	

mean difference in breathlessness score (follow-up 1 years; measured with: Transitional Dyspnoea Index; range of scores: -9-+9; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	none	145	156	-	MD 0.06 (-0.84 to 0.96)	⊕⊕OO LOW	
All-cause mortality (follow-up 1 years)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	very serious[9]	none	6/145 (4.1%)	4/156 (2.6%)	RR 1.61 (0.46 to 5.6)	16 more per 1000 (from 14 fewer to 120 more)	⊕OOO VERY LOW	
Adverse event: Pneumonia leading to mechanical ventilation or death (follow-up 1 years)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	very serious[9]	none	1/145 (0.7%)	0/156 (0%)	RR 3.23 (0.13 to 78.56)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	
Adverse event: MI or acute arrhythmia (follow-up 1 years)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	very serious[9]	none	2/145 (1.4%)	2/156 (1.3%)	RR 1.08 (0.15 to 7.54)	1 more per 1000 (from 11 fewer to 85 more)	⊕OOO VERY LOW	

[1] large differences in loss to follow-up: tio + placebo =47% versus tio + salmeterol/fluticasone = 25% (p<0.001 with tio + placebo arm)

[2] inclusion criteria: people with post bronchodilator FEV_1 < 65%; FEV1/FVC < 0.70 and who had ≥ 1 exacerbation of COPD requiring antibiotic or systemic steroids within previous 12 months.

[3] wide 95% CI that crosses MID

[4] mean exacerbations/patient year were 1.37 (triple therapy) and 1.61 (tiotropium + placebo)

[5] mean hospitalisations/patient year were 0.19 (triple therapy) and 0.355 (tiotropium + placebo)

[6] unable to assess precision as 95% CI were not provided

[7] change in SGRQ was -4.5 points in tiotropium + placebo versus -8.6 points in tiotropium + salmeterol/fluticasone, p=0.01

[8] change in mean FEV1 was 0.086 litres (tiotropium + salmeterol/fluticasone) and 0.027 litres (tiotropium + placebo) , p=0.049

[9] wide 95% CI that cross MID twice; study not powered for this outcome

Evidence statements DRUG 6B: LAMA + LABA + ICS vs. LAMA + placebo

At one year, there was no significant difference between triple therapy (tiotropium + fluticasone/salmeterol) and tiotropium + placebo for:

- proportion of people with 1 or more acute exacerbations (these include people who were hospitalised) [low quality evidence]
- Mean exacerbations per patient year (expressed as a rate ratio) [moderate quality evidence]
- Breathlessness score at one year (measured with TDI) [low quality evidence]
- All cause mortality [very low quality evidence]
- Pneumonia leading to mechanical ventilation or death [very low quality evidence]
- MI or acute arrhythmia [very low quality evidence]
- Change from baseline in mean pre bronchodilator FEV_1 [moderate quality evidence]

Compared with tiotropium + placebo, triple therapy with tiotropium + fluticasone/salmeterol significantly reduced:

- Mean hospitalisations for acute exacerbations per patient year (expressed as a rate ratio) [moderate quality evidence]

Triple therapy with tiotropium + fluticasone/salmeterol was significantly better than tiotropium + placebo for:

- Change from baseline in health related quality of life (measured with total SRGQ score) at one year [moderate quality evidence]

Health economic methodological introduction: LAMA+LABA+ICS vs. LAMA

The literature was searched from 2003 onwards for economic evaluations comparing treatment with triple therapy versus long-acting muscarinic antagonists. This comparison was also subject to a call for unpublished evidence.

One study was identified in the update search that included the relevant comparison[220]. This is summarised in the economic evidence profile below.

No studies were identified in the original guideline search.

Health economic modelling

Note that this comparison was included in a health economic analysis undertaken as part of this update. The GDG were interested in the following question: Is LAMA, LABA+ICS or triple therapy more cost-effective as initial therapy in COPD patients with an FEV_1 < 50% predicted (severe to very severe COPD)?

The results of this analysis are summarised later in this section of the guideline, following the review of the clinical and economic literature. The full report in included in appendix M.

Health economic evidence profile

Economic evidence: Triple vs. LAMA (drug 6b)

Study	*Limitations**	*Applicability***	*Other comments*	*Incremental‡ cost (£)*	*Incremental‡ effects*	*ICER‡*	*Uncertainty*
Najafzadeh et al (2008)[220] – Canada	Potentially serious limitations[tt]	Partially applicable[uu]	1 year analysis of resource use and health outcomes (SGRQ – mapped to EQ-5D utility) in Optimal RCT[200] (FEV_1<65% predicted)	£731[vv]	0.0056 QALYs[ww]	£130,308/ QALY	LAMA cost-effective >90% of bootstrapping/ imputation simulations in base case, at threshold of £20,000/QALY. One-way sensitivity analyses ICER range £30,620 to £78,103/QALY.

*Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable; ICER = incremental cost-effectiveness ratio; ‡ Triple – LAMA

[tt] Key limitations: GDG concerns re clinical trial; LABA+ICS drug costs based on 250/50 microgram/puff inhaler, x2 puffs, twice daily – in UK this would cost £260 more than using the 500/50 microgram/puff inhaler x1puff, twice daily (not included in sensitivity analysis); one patient in triple arm had a 215 day hosp stay (included in base case although excluded in a sensitivity analysis). Minor limitations: Resource use may be influenced by trial setting. Time horizon is 1 year – investigations of impact of longer term extrapolation may be appropriate – authors consider this unlikely to impact results greatly.

[uu] Some uncertainty over the applicability of Canadian resource use and unit costs to UK.

[vv] Converted from 2006 Canadian dollars using 2006 Purchasing Power Parities[177]

[ww] Reduced exacerbations reported also (primary analysis)

Health economic evidence statements

One study[220] found triple therapy not to be cost-effective compared to LAMA alone. The study was judged to be partially applicable due to its non UK setting. This analysis was based on resource use and health outcomes collected within the OPTIMAL trial[200]. The study did not however collect utility data (required to calculate QALYs) – the analysis is based on mapping of SGRQ data to EQ-5D utility.

Within the base case analysis triple therapy was highly non-cost-effective with a cost-effective ratio of £130,308 per QALY gained, compared to LAMA. The likelihood triple therapy was cost-effective was estimated at <10%. The base case however was based on costs for triple therapy that included a patient with a hospital stay of 215 days. When this patient was excluded the cost-effectiveness ratio fell considerably to £78,103 per QALY gained. Other one way sensitivity analyses also improved cost-effectiveness of triple therapy.

LABA+ICS costs in the analysis were based on costs for fluticasone/salmeterol 250/25 microgram/puff, two puffs twice daily, as this was the trial protocol dosing. However, the recommended UK dosing for LABA+ICS is fluticasone/salmeterol 500/50 microgram/puff, one puff twice daily and using this would result in lower drug cost of approximately £260 which would also improve cost-effectiveness[221,222].

Drug 6c) LAMA + LABA + ICS vs. LABA + LAMA

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists plus inhaled corticosteroids compared to long-acting beta$_2$ agonists plus long-acting muscarinic antagonists in the management of people with stable COPD?

The evidence profile below summarises the quality of the evidence and outcome data for the double blind OPTIMAL RCT [200] comparing triple therapy tiotropium [18 microgram once daily] plus fluticasone-salmeterol [250/50 microgram/puff, 2 puffs twice daily]) with tiotropium (18 microgram once daily) plus salmeterol (25 microgram/puff; 2 puffs; twice daily) in people with moderate to severe COPD. It should be noted that the OPTIMAL RCT was not designed or powered to compare tiotropium plus fluticasone/salmeterol with tiotropium plus salmeterol.

Evidence Profile Drug 6C : triple therapy versus LABA + LAMA

Question: Should tiotropium + salmeterol/fluticasone vs. tiotropium + salmeterol be used in people with stable COPD?
Bibliography: Aaron SD, Vandemheen KL, Fergusson D et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2007; 146(8):545-555.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	tiotropium + salmeterol/fluticasone	tiotropium + salmeterol	Relative (95% CI)	Absolute		
Primary outcome: Number of people with 1 or more acute exacerbations (assuming all patients lost to follow-up did not have exacerbations; these include people who were hospitalised) (follow-up 1 years; blinded assessor)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	none	87/145 (60%)	96/148 (64.9%)	RR 0.93 (0.77 to 1.11)	45 fewer per 1000 (from 149 fewer to 71 more)	⊕⊕OO LOW	
Primary outcome: Number of people with 1 or more acute exacerbations (assuming all patients lost to follow-up had exacerbations; these include people who were hospitalised) (follow-up 1 years; blinded assessor)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	none	96/145 (66.2%)	107/148 (72.3%)	RR 0.92 (0.79 to 1.07)	58 fewer per 1000 (from 152 fewer to 51 more)	⊕⊕OO LOW	
Primary outcome: Number of people with 1 or more acute exacerbations (assuming all patients lost to follow-up had exacerbations at the same rate as those who remained in the study; these include people who were hospitalised) (follow-up 1 years; blinded assessor)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	none	93/145 (64.1%)	104/148 (70.3%)	RR 0.91 (0.78 to 1.07)	63 fewer per 1000 (from 155 fewer to 49 more)	⊕⊕OO LOW	

mean difference in breathlessness score (follow-up 1 years; measured with: Transitional Dyspnoea Index; range of scores: -9-+9; Better indicated by less)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	none	145	156	-	MD 0.44 (-0.46 to 1.34)	⊕⊕OO LOW	
All-cause mortality (follow-up 1 years)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	very serious[4]	none	6/145 (4.1%)	6/148 (4.1%)	RR 1.02 (0.34 to 3.09)	1 more per 1000 (from 27 fewer to 86 more)	⊕OOO VERY LOW	
Adverse event: Pneumonia leading to mechanical ventilation or death (follow-up 1 years)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	very serious[4]	none	1/145 (0.7%)	1/148 (0.7%)	RR 1.02 (0.06 to 16.16)	0 more per 1000 (from 7 fewer to 106 more)	⊕OOO VERY LOW	
Adverse event: MI or acute arrhythmia (follow-up 1 years)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness[2]	very serious[4]	none	2/145 (1.4%)	2/148 (1.4%)	RR 1.02 (0.15 to 7.15)	0 more per 1000 (from 12 fewer to 86 more)	⊕OOO VERY LOW	

[1] possible attrition bias: dropout rates were 43% (tiotropium + salmeterol) versus 25% (tiotropium + salmeterol/fluticasone); study was not designed or powered to compare tiotropium + salmeterol versus tiotropium + salmeterol/fluticasone.

[2] inclusion criteria: people with post bronchodilator FEV1 < 65%; FEV1/FVC < 0.70 and who had ≥ 1 exacerbation of COPD requiring antibiotic or systemic steroids within previous 12 months.

[3] wide 95% CI that crosses MID

[4] wide 95% CI that cross MID twice; study not powered for this outcome

Evidence statements DRUG 6C: LAMA + LABA + ICS vs. LAMA + LABA

At one year, there was no significant difference between triple therapy (tiotropium + fluticasone/salmeterol) and tiotropium + salmeterol for:

- Proportion of people with 1 or more acute exacerbations (primary outcome; includes people who were hospitalised) [low quality]
- Mean difference in breathlessness score (measured with TDI) at 1 year [low quality]
- All cause mortality [very low quality]
- Pneumonia leading to mechanical ventilation or death [very low quality]
- MI or acute arrhythmia [very low quality]

Health economic methodological introduction

The literature was searched from 2003 onwards for economic evaluations comparing treatment with triple therapy versus long-acting muscarinic antagonists plus long-acting $beta_2$ agonists. This comparison was also subject to a call for unpublished evidence.

One study was identified in the update search that included this comparison[220]. This is summarised in the economic evidence profile below.

No studies were identified in the original guideline search.

Health economic evidence profile

Economic evidence: Triple vs LAMA+LABA (drug 6c)							
Study	***Limitations****	***Applicability*** **	***Other comments***	***Incremental[‡] cost (£)***	***Incremental[‡] effects***	***ICER[‡]***	***Uncertainty***
Najafzadeh et al (2008) – Canada	Potentially serious limitations[xx]	Partially applicable[yy]	1 year analysis of resource use and health outcomes (SGRQ – mapped to EQ-5D utility) in Optimal RCT[200] (FEV_1 <65% predicted).	£665[zz]	0.0108 QALYs	£61,574/QALY[aaa]	Not reported for this comparison[bbb]

*Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable; ICER = incremental cost-effectiveness ratio; [‡] Triple – LAMA+LABA

[xx] Key limitations: GDG concerns re clinical trial; LABA+ICS drug costs based on 250/50 microgram/puff inhaler, x2 puffs, twice daily – in UK this would cost £260 more than using the 500/50 microgram/puff inhaler x1puff, twice daily (not included in sensitivity analysis); one patient in triple arm had a 215 day hosp stay (included in base case although excluded in a sensitivity analysis). Minor limitations: Resource use may be influenced by trial setting. Time horizon is 1 year – investigations of impact of longer term extrapolation may be appropriate – authors consider this unlikely to impact results greatly.

[yy] Some uncertainty over the applicability of Canadian resource use and unit costs to UK.

[zz] Converted from 2006 Canadian dollars using 2006 Purchasing Power Parities[177]

[aaa] This analysis also included LAMA. Based on base case mean costs and QALYs, LAMA+LABA was dominated by LAMA alone (that is it was more expensive with less QALYs). This is therefore an inappropriate comparison in the analysis. ICER triple vs LAMA £130,308 – see triple vs LAMA.

[bbb] Analysis also included LAMA. As LAMA+LABA was dominated by LAMA in the base case the authors dropped LAMA+LABA from further analyses.

Health economic evidence statements

One study[220] found triple therapy not to be cost-effective compared to LAMA+LABA. The study was judged to be partially applicable due to its non-UK setting. This analysis was based on resource use and health outcomes collected within the OPTIMAL trial[200]. The study did not however collect utility data (required to calculate QALYs) – the analysis is based on mapping of SGRQ data to EQ-5D utility.

Sensitivity analysis was not carried out for this comparison as LAMA+LABA was dominated in the base case by LAMA which was also included in the analysis. Note that the base case however was based on costs for triple therapy that included a patient with a hospital stay of 215 days. Excluding this patient reduces the costs with triple therapy.

LABA+ICS costs in the analysis were based on costs for fluticasone/salmeterol 250/25 microgram/puff, two puffs twice daily, as this was the trial protocol dosing. However, the recommended UK dosing for LABA+ICS is fluticasone/salmeterol 500/50 microgram/puff, one puff twice daily and using this would result in lower drug cost of approximately £260 which would also improve cost-effectiveness[221,222]

7.3.6.3 Long-acting beta$_2$ agonists (LABA) and long-acting muscarinic antagonist (LAMA)

Methodological introduction

The literature was searched from 2003 onwards for RCTs and systematic reviews comparing combination therapy of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists with monotherapy consisting of either long-acting beta$_2$ agonists or long-acting muscarinic antagonists. RCTs of less than six months follow-up were excluded. Outcomes of interest were mortality, exacerbations, hospitalisations, health related quality of life measured with SGRQ, changes in FEV_1, dyspnoea (measured with TDI).

The GDG posed the following question:

Drug 5a) LAMA + LABA vs. LABA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists compared to long-acting beta$_2$ agonists in the management of people with stable COPD?

Two studies were identified. One published open labelled RCT compared treatment with formoterol (10 microgram b.i.d) plus tiotropium (18 microgram once daily) versus formoterol (10 microgram b.i.d) in adults with stable COPD (N=417; 6 month follow-up).[178].

An unpublished post hoc subgroup analysis of the UPLIFT trial was received in the Call for Evidence and it compared people with COPD randomised to placebo or tiotropium (18 microgram once daily) in which both arms had LABA at baseline (N=678).[201] It is important to note that only placebo and tiotropium were randomised; the background LABA was not randomised. It was also unclear if this subgroup analysis had sufficient statistical power to detect a difference between the two groups. The participants had predominantly moderate to severe COPD [GOLD stage II (43%) and GOLD stage III (46%)]. There was a higher percentage of males in the tiotropium plus LABA (at baseline) group compared with the placebo + LABA (at baseline) group (80% versus 73% males, respectively). The tiotropium + LABA (at baseline) group also had a longer smoking history than the placebo + LABA (at baseline) group (50.2 versus 47.0 pack years, respectively).

A GRADE profile is presented separately for this post-hoc subgroup analysis comparing tiotropium plus baseline LABA with placebo plus baseline LABA.

Evidence Profile Drug 5a : LAMA + LABA vs. LABA alone

Question: Should Tiotropium + formoterol vs. formoterol be used for COPD?

Bibliography: Vogelmeier C, Kardos P, Harari S et al. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study. Respiratory Medicine. 2008; 102(11):1511-1520.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Tiotropium + formoterol	formoterol	Relative (95% CI)	Absolute		
Primary outcome: FEV1 measured 2 h post-dose after 24 weeks of treatment (difference between groups at 24 weeks) (follow-up 6 months; range of scores: -; Better indicated by more)												
1[1]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness[2]	serious[3]	none	207	210	-	MD 0.07 (0 to 0.14)[4]	⊕⊕⊕O MODERATE	
Number of people with COPD exacerbations requiring additional therapy (includes people who were hospitalised) (follow-up 6 months)												
1[1]	randomised trial	serious[5]	no serious inconsistency	no serious indirectness[2]	very serious[6]	none	13/207 (6.3%)	17/210 (8.1%)	RR 0.78 (0.39 to 1.56)	18 fewer per 1000 (from 49 fewer to 45 more)	⊕OOO VERY LOW	
Number of people with COPD exacerbations requiring hospitalisation (follow-up 6 months)												
1[1]	randomised trial	serious[5]	no serious inconsistency	no serious indirectness[2]	very serious[6]	none	3/207 (1.4%)	1/210 (0.5%)	RR 3.04 (0.32 to 29.02)	10 more per 1000 (from 3 fewer to 140 more)	⊕OOO VERY LOW	

[1] Vogelmeier et al

[2] trial recruited people with COPD who had to be symptomatic on at least 4 of 7 days prior to randomisation; smoking history of ≥ 10 pack years; FEV1 < 70% predicted and FEV1-FVC ratio < 70%.

[3] wide 95% CI that crosses MID

[4] p=0.044

[5] unclear allocation concealment; open label; ITT performed; dropouts 12.1% dual therapy versus 11.9% formoterol
[6] wide 95% CI that crosses MID twice

Evidence Profile Call for Evidence Drug 5a : tiotropium + baseline LABA vs. Placebo + baseline LABA

Question: Should tiotropium + LABA (baseline medication) vs. placebo + LABA (baseline medication) be used in people with COPD?
Bibliography: Unpublished Data from UPLIFT RCT (Boehringer)

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	tiotropium + LABA (baseline medication)	placebo + LABA (baseline medication)	Relative (95% CI)	Absolute		
Mean post bronchodilator FEV1 at 1 year (follow-up 1 years; range of scores: -; Better indicated by more)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	276	278	-	MD 0.033 (0 to 0.066)[2]	⊕⊕OO LOW	
Mean post bronchodilator FEV1 at 4 years (follow-up 4 years; range of scores: -; Better indicated by more)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	212	180	-	MD 0.020 (-0.025 to 0.066)[3]	⊕⊕OO LOW	
Quality of Life at 1 year (follow-up 1 years; measured with: mean total SGRQ score; range of scores: 0-100; Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	268	264	-	MD -1.899 (-4.046 to 0.247)[5]	⊕OOO VERY LOW	

Quality of Life at 4 years (follow-up 4 years; measured with: mean total SGRQ score; range of scores: 0-100; Better indicated by less)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	206	172	-	MD -0.326 (-3.255 to 2.604)[6]	⊕⊕OO LOW	
Number of patients with COPD exacerbations (follow-up 4 years)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	223/332 (67.2%)	236/346 (68.2%)	HR 0.82 (0.69 to 0.99)[7]	73 fewer per 1000 (from 4 fewer to 136 fewer)	⊕⊕OO LOW	
Number of patients hospitalised for COPD exacerbations (follow-up 4 years)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	86/332 (25.9%)	87/346 (25.1%)	HR 0.95 (0.7 to 1.28)[8]	11 fewer per 1000 (from 68 fewer to 58 more)	⊕OOO VERY LOW	
Mean COPD exacerbations per patient year (expressed as rate ratio) (follow-up 4 years)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	332 (0.63 [SE 0.05] mean exacerbations/patient year)	346 (0.79 [SE 0.05] mean exacerbations/patient year)	rate ratio 0.80 (0.66 to 0.97)[9]	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	

Mean hospitalisations for COPD exacerbations per patient per year (expressed as rate ratio) (follow-up 4 years)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	332 (0.14 [SE 0.02] mean hospitalisations/patient year)	346 (0.16 [SE 0.02] mean hospitalisations/patient year)	rate ratio 0.89 (0.6 to 1.33)[10]	0 fewer per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	
Mortality (adjudicated on treatment and vital status censoring at 1470 days) (follow-up 1470 days)												
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	very serious[11]	none	53/332 (16%)	59/346 (17.1%)	HR 0.93 (0.64 to 1.35)[12]	11 fewer per 1000 (from 58 fewer to 53 more)	⊕OOO VERY LOW	

[1] UPLIFT trial: people randomisation to placebo or tiotropium. This is a post hoc subgroup analysis of people taking LABA at baseline; unclear allocation concealment; not true ITT; dropouts in this subgroup not reported; double blind. LABA was not randomised between the two groups.

[2] p = 0.0484; the mean, standard error, 95% CI, and p value are based on least squares mean estimate using repeated measures ANOVA model, adjusted for baseline values

[3] p = 0.3828; the mean, standard error, 95% CI, and p value are based on least squares mean estimate using repeated measures ANOVA model, adjusted for baseline values

[4] wide 95% CI that crosses MID

[5] p = 0.0835; mean, standard error, 95% CI, and p value are based on least squares mean estimate using repeated measures ANOVA model, adjusted for baseline values

[6] p = 0.8276; mean, standard error, 95% CI, and p value are based on least squares mean estimate using repeated measures ANOVA model, adjusted for baseline values

[7] p = 0.0380; HR and p value are based on Cox regression with treatment, baseline LABA use, and baseline LABA use by treatment interaction as covariates

[8] HR based on Cox regression with treatment, baseline LABA use, and baseline LABA use by treatment interaction as covariates

[9] p = 0.024. The Poisson with Pearson overdispersion model adjusting for time at risk was used to estimate the number of exacerbations per patient year and the ratio between tiotropium and placebo.

[10] The Poisson with Pearson overdispersion model adjusting for time at risk was used to estimate the number of hospitalisations per patient year and the ratio between tiotropium and placebo.

[11] wide 95% CI that crosses MID twice

[12] p = 0.7073; The p value and HR are based on Cox regression with treatment, baseline LABA use as covariates. Observations are censored at 1470 days for patients still in the risk set at that time

Evidence Statement DRUG 5a: LAMA + LABA vs. LABA alone

After six months, formoterol + tiotropium was significantly better than formoterol alone for:

- Mean post-bronchodilator FEV_1 (primary outcome) [moderate quality evidence]

After six months, there was no significant difference between people receiving tiotropium plus formoterol compared with formoterol alone for:

- Number of people having exacerbations requiring hospitalisation [very low quality evidence]
- Number of people having exacerbations requiring additional therapy (includes people who had been hospitalised) [very low quality evidence]

Evidence statements Call for Evidence Drug 5A : tiotropium + baseline LABA versus placebo + baseline LABA

Compared with people in the placebo plus baseline LABA group, people in the tiotropium plus baseline LABA group experienced a significantly

- Increased mean post bronchodilator FEV_1 at one year (primary outcome) [low quality evidence]
- Decreased risk of COPD exacerbations (includes hospitalisations) [low quality evidence]
- Fewer mean COPD exacerbations per patient year (includes hospitalisations; expressed as a rate ratio) [low quality evidence]

There was no significant difference between people on LABA at baseline randomised to placebo or tiotropium for:

- Mean post bronchodilator FEV_1 at four years (primary outcome) [low quality evidence]
- Health related quality of life (measured with SGRQ) at one year [very low quality evidence]
- Health related quality of life (measured with SGRQ) at four years [low quality evidence]
- Hospitalisations for COPD exacerbations [very low quality evidence]
- Mean hospitalisations for COPD exacerbations (expressed as a rate ratio) [very low quality evidence]
- Mortality [very low quality evidence]

Health economic methodological introduction

The literature was searched from 2003 onwards for economic evaluations comparing treatment with combined long-acting muscarinic antagonists plus long-acting $beta_2$ agonists versus long-acting $beta_2$ agonists alone. This comparison was also subject to a call for unpublished evidence.

No studies were identified in the update search or in the original guideline search.

DRUG 5b) LAMA + LABA vs. LAMA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists compared to long-acting muscarinic antagonists in the management of people with stable COPD?

Two double blind RCTs [178,200] compared dual therapy (LAMA + LABA) with tiotropium plus placebo. The Vogelmeier et al RCT compared tiotropium (18 microgram once daily) via HandiHaler plus formoterol (10 microgram b.i.d.) via MDDPI versus tiotropium (18 microgram once daily) via HandiHaler + placebo (b.i.d. via MDDPI) in adults with stable COPD (N=428; 6 months follow-up).[178]. In the OPTIMAL RCT [200] people with moderate to severe COPD (N=449; follow-up 1 year) were randomised to one of three arms: tiotropium (18 microgram once daily) plus placebo inhaler (two puffs twice daily) or tiotropium (18 microgram once daily) plus salmeterol (25 microgram/puff; 2 puffs; twice daily) or tiotropium (18 microgram once daily) plus fluticasone-salmeterol (250/50 microgram/puff, 2 puffs twice daily). The evidence profile below summarises the quality of evidence and outcome data for the two RCTs.

Evidence Profile: Drug 5b LABA + LAMA versus LAMA

Question: Should Tiotropium + LABA vs. tiotropium + placebo be used for COPD?
Bibliography: Vogelmeier et al; Aaron et al

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Tiotropium + LABA	tiotropium + placebo	Relative (95% CI)	Absolute		
number of people having exacerbation requiring further treatment												
2[1]	randomised trial	serious[2]	serious[3]	no serious indirectness	no serious imprecision	None	109/355 (30.7%)	121/377 (32.1%)	RR 0.95 (0.8 to 1.13)	16 fewer per 1000 (from 64 fewer to 42 more)	⊕⊕OO LOW	
Mean exacerbations per patient year (expressed as rate ratio) (follow-up 1 years)												
1[4]	randomised trial	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	None	148 (1.75 mean exacerbation/patient year	156 (1.61 mean exacerbation/patient)	rate ratio 1.09 (0.84 to 1.4)[6]	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	
Number of people Hospitalised for COPD exacerbations (follow-up 6 months)												
1[7]	randomised trial	serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	None	3/207 (1.4%)	5/221 (2.3%)	RR 0.64 (0.16 to 2.65)	8 fewer per 1000 (from 19 fewer to 38 more)	⊕OOO VERY LOW	

Mean hospitalisations for acute exacerbations of COPD per patient year (expressed as rate ratio) (follow-up 1 years)												
1[4]	randomised trial	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	None	148 (0.294 mean hospitalisations/patient year)	156 (0.355 mean hospitalisations/patient year)	rate ratio 0.83 (0.54 to 1.27)[10]	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	
Change from baseline in health related quality of life at 1 year (follow-up 1 years; measured with: total SGRQ score; range of scores: -; Better indicated by less)												
1[4]	randomised trial	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	None	148	156	-	MD -1.8 (0 to 0)[11]	⊕⊕OO LOW	
Mean difference in TDI score at 1 year (follow-up 1 years; measured with: TDI; range of scores: -; Better indicated by less)												
1[4]	randomised trial	very serious[5]	no serious inconsistency	no serious indirectness	serious[12]	None	148	156	-	MD -0.38 (-1.28 to 0.52)	⊕OOO VERY LOW	
difference in FEV1 after 24 weeks treatment (measured 2h post bronchodilator) (follow-up 6 months; range of scores: -; Better indicated by more)												
1[7]	randomised trial	serious[8]	no serious inconsistency	no serious indirectness	serious[12]	None	207	221	-	MD 0.06 (0 to 0.13)[13]	⊕⊕OO LOW	
all-cause mortality (follow-up 1 years)												
1[4]	randomised trial	very serious[5]	no serious inconsistency	no serious indirectness	very serious[9]	None	6/148 (4.1%)	4/156 (2.6%)	RR 1.58 (0.46 to 5.49)	15 more per 1000 (from 14 fewer to 117 more)	⊕OOO VERY LOW	
Number of people with pneumonia leading to mechanical ventilation or death (follow-up 1 years)												
1[4]	randomised trial	very serious[5]	no serious inconsistency	no serious indirectness	very serious[12]	None	1/148 (0.7%)	0/156 (0%)	RR 3.16 (0.13 to	0 more per 1000 (from 0 fewer to 0	⊕OOO VERY	

									76.99)	more)	LOW	
Number of people with MI or acute arrhythmia (follow-up 1 years)												
1[4]	randomised trial	very serious[5]	no serious inconsistency	no serious indirectness	very serious[9]	None	2/148 (1.4%)	2/156 (1.3%)	RR 1.05 (0.15 to 7.39)	1 more per 1000 (from 11 fewer to 83 more)	⊕OOO VERY LOW	

[1] Aaron et al; Vogelmeier et al

[2] high loss to follow-up over 1 year in 1 RCT(47% [tiotropium + placebo] and 43% [tiotropium + salmeterol] groups); unclear allocation concealment in other RCT

[3] significant heterogeneity I2 = 68%

[4] Aaron et al

[5] study was not designed or powered to compare tiotropium + placebo with tiotropium + salmeterol; high loss to follow-up over 1 year (47% [tiotropium + placebo] and 43% [tiotropium + salmeterol] groups)

[6] mean exacerbation/patient year were 1.75 (LABA + tiotropium) versus 1.61 (tiotropium + placebo)

[7] Vogelmeier et al

[8] unclear allocation concealment; low dropout rates 12.1% (tiotropium + formoterol) and 13.1% (tiotropium + placebo); ITT performed; double blind

[9] wide 95% CI that crosses MID twice

[10] mean hospitalisations for exacerbations per patient year were 0.294 (tiotropium + LABA) versus 0.355 (tiotropium + placebo)

[11] change from baseline in SGRQ score was -6.3 points (tiotropium + LABA) versus -4.5 points (tiotropium + placebo); p = 0.02

[12] wide 95% CI that crosses MID

[13] p = 0.066; mean FEV_1 and SD not reported in each group

Evidence statements DRUG 5b: LAMA + LABA vs. LAMA alone

There was no significant difference between treatment with tiotropium plus LABA versus tiotropium plus placebo for:

- The proportion of people having one or more exacerbations requiring additional therapy (this includes people who were hospitalised) [low quality evidence]
- Mean exacerbations per patient year (expressed as a rate ratio) [low quality evidence]
- Proportion of people hospitalised for COPD exacerbations [very low quality evidence]
- Mean hospitalisations per patient year (expressed as a rate ratio) [low quality evidence]
- Mean difference in post bronchodilator FEV_1 at six months [low quality evidence]
- Mean difference in breathlessness (measured with TDI) at one year [very low quality evidence]
- All -cause mortality at one year [very low quality evidence]
- MI or acute arrhythmia at one year [very low quality evidence]
- Pneumonia leading to mechanical ventilation or death at one year [very low quality evidence]

Dual therapy was significantly better than tiotropium + placebo for:

Change from baseline in health related quality of life at one year (measured with total SGRQ score) [low quality evidence]

Health economic methodological introduction

The literature was searched from 2003 onwards for economic evaluations comparing treatment with triple therapy versus long-acting muscarinic antagonists plus long-acting $beta_2$ agonists. This comparison was also subject to a call for unpublished evidence.

One study was identified in the update search that included this comparison[220]. This is summarised in the economic evidence profile below.

No studies were identified in the original guideline search.

Health economic evidence profile

Economic evidence: LAMA+LABA vs LAMA (drug 5b)							
Study	***Limitations****	***Applicability***	***Other comments***	***Incremental‡ cost (£)***	***Incremental‡ effects***	***ICER‡***	***Uncertainty***
Najafzadeh et al (2008) – Canada	Potentially serious limitations[ccc]	Partially applicable[ddd]	1 year analysis of resource use and health outcomes (SGRQ – mapped to EQ-5D utility) in Optimal RCT[200] (FEV_1 <65% predicted)	£66[eee]	-0.0052 QALYs[fff]	LAMA+LABA dominated by LAMA	One-way sensitivity analysis ICER range dominant to dominated[ggg]

*Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; ‡ LAMA+LABA – LAMA alone; Dominant = LAMA+LABA is cost saving with improved outcomes; Dominated = LAMA+LABA has higher costs with worse outcomes.

[ccc] Key limitation: GDG concerns re clinical trial. Minor limitations: Resource use may be influenced by trial setting. Time horizon is 1 year – investigations of impact of longer term extrapolation may be appropriate – authors consider this unlikely to impact results greatly.
[ddd] Some uncertainty over the applicability of Canadian resource use and unit costs to UK.
[eee] Converted from 2006 Canadian dollars using 2006 Purchasing Power Parities[177]
[fff] Lower QALYs and increased exacerbations reported
[ggg] LAMA+LABA was cost-effective at a threshold of £20,000 per QALY gained in the sensitivity analyses where only complete cases were used for the analysis, when non-COPD hospitalisations were included and in patients with severe COPD.

DRUG 5c) LAMA + LABA vs. LABA +ICS

The GDG posed the following question:

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists compared to long-acting beta$_2$ agonists plus inhaled corticosteroids in the management of people with stable COPD?

There were no RCTs identified for this question.

Health economic methodological introduction

The literature was searched from 2003 onwards for economic evaluations comparing treatment with combined long-acting muscarinic antagonists plus long-acting beta$_2$ agonists versus long-acting muscarinic antagonists alone. This comparison was also subject to a call for unpublished evidence.

No studies were identified in the update search or in the original guideline search.

Health economic evidence statements

One study found LAMA+LABA to be dominated (higher costs and worse health outcomes) by LAMA alone. The study was judged to be partially applicable due to its non-UK setting. This analysis was based on resource use and health outcomes collected within the OPTIMAL trial[200]. The study did not however collect utility data (required to calculate QALYs) – the analysis is based on mapping of SGRQ data to EQ-5D utility.

Results in sensitivity analyses ranged from LAMA+LABA being less costly than LAMA with better outcomes (more QALYs), to more costly with worse outcomes indicating high uncertainty in the results.

7.3.6.4 Long-acting muscarinic antagonists (LAMA) + Inhaled Corticosteroids (ICS)

The GDG posed the following two questions:

DRUG 4a) LAMA + ICS vs. LABA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus inhaled corticosteroids compared to long-acting beta$_2$ agonists in the management of people with stable COPD?

DRUG 4b) LAMA + ICS vs. LAMA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists in the management of people with stable COPD?

Methodological introduction

The literature was searched for RCTs or systematic reviews from 2003 onwards comparing long-acting muscarinic antagonists plus inhaled corticosteroids with either long-acting muscarinic antagonists or long-acting beta$_2$ agonists in the management of people with stable COPD. In order to be included, an RCT had to have a minimum follow-up of six months and report on any of the following outcomes: all-cause mortality, exacerbations, hospitalisations, decline in FEV_1, change in SGRQ, and adverse events (pneumonia, bone fractures, MI, arrhythmia, congestive heart failure).

As with the original guideline, there was no evidence for these drug comparisons.

Health economic evidence

The literature was searched from 2003 onwards for economic evaluations comparing treatment with LAMA plus ICS versus long-acting muscarinic antagonists or long-acting beta$_2$ agonists. This comparison was also subject to a call for unpublished evidence.

No studies were identified in the update search or in the original guideline search.

7.3.6.5 Health economic modelling for inhaled combination therapy

A cost-effectiveness model comparing LAMA, LABA+ICS and triple therapy (LAMA+LAMA+ICS) in people with COPD with FEV_1 < 50% predicted

Areas in the update were prioritised for new analysis by the GDG. The GDG was interested in assessing the cost-effectiveness of alternative regular maintenance therapies (or combinations of such therapies) for stable COPD. Following review of the clinical evidence and published cost-effectiveness literature it was considered that examining the following question was the highest priority: is LAMA, LABA+ICS or triple therapy more cost-effective as initial therapy in people with COPD with an FEV_1 < 50% predicted (severe to very severe COPD)?

These treatment options were selected as those that represent the most appropriate possible clinical options for people with COPD and an FEV_1 < 50% predicted. The GDG felt that the clinical and cost-effectiveness literature suggested that LAMA or LABA+ICS were probably the appropriate options for initial maintenance therapy for patients with an FEV_1 < 50% predicted. However, it was felt that if triple therapy could be justified on cost-effectiveness terms that it might be considered as an initial therapy. Therefore these options were incorporated into the model. It was felt unnecessary to include LABA as there was good existing evidence that use of LABA+ICS over LABA alone was more effective and cost-effective in this patient group. No data was available for LAMA+ICS as a treatment option and so it was considered inappropriate to include in the model. Clinical effectiveness data for LAMA+LABA was considered insufficient for it to be considered a primary treatment option and it was felt that it would only be appropriate to consider in patients in whom ICS was declined or not tolerated. On this basis, it was felt that inclusion of LAMA+LABA was also not a priority for inclusion in the model.

It was felt that in less severe patients (FEV_1 ≥ 50% predicted) the key issue was whether to use LAMA or LABA as initial therapy but that issues with the available clinical data would mean that new health economic modelling would be unlikely to reduce uncertainty around this decision and so it was considered less of a priority for modelling.

A summary of the analysis is provided below. The full report is included in appendix M.

Model overview

A cost-utility analysis was undertaken where costs and quality-adjusted life-years (QALYs) were considered from a UK NHS perspective. A time horizon of four years was used in the base case analysis.

Model inputs were selected following a review of the literature and validated with the GDG. Differences between treatments were based on data from the RCTs that compared these treatment options identified in the systematic clinical review detailed above:

- INSPIRE: LABA+ICS vs. LAMA
- OPTIMAL: Triple vs. LAMA
- UPLIFT subgroup of people on LABA+ICS at baseline: Triple vs. LABA+ICS

The model synthesised different clinical trial data and explored inconsistencies by examining the impact of using different clinical data sources to inform the treatment effect parameters of the model (see full report for more details).

Summary of results

The aim of this analysis was to evaluate which was the most cost-effective option from LABA+ICS, LAMA and triple therapy for initial management of people with COPD and an FEV_1 < 50%.

The base case analysis, which is driven by differences in exacerbations between treatments, found that LABA+ICS or LAMA was the most cost-effective option depending on which clinical data was used to inform the differences between treatments. Triple therapy was the most effective option (highest QALYs) but was not cost-effective. The GDG considered this analysis to be the most robust in terms of the available data. However, it was also considered likely to be conservative in terms of the benefits of treatment and may underestimate the value of triple therapy. The fact that either LABA+ICS or LAMA was the favoured option depending on the clinical data used in the analysis highlights an inconsistency in the clinical data but one that could not be resolved and so therefore was considered to represent an uncertainty over the preferred option.

In the sensitivity analysis which also incorporates a difference between treatments in terms of stable utility (quality of life), triple therapy was found to be the most effective (highest QALYs) and the most cost-effective option, irrespective of which clinical data was used to inform the differences between treatments. The GDG considered that a scenario where treatment impacted utility due to stable symptom improvement as well as exacerbations to be a realistic one but given the limitations of the estimate of treatment effect on stable utility they interpreted the results with caution.

A sensitivity analysis that looked at the impact of exacerbation rates found that as the baseline exacerbation rate increased so did the probability that triple therapy was cost-effective.

In the sensitivity analysis where a treatment effect in terms of mortality was incorporated, results varied greatly depending on the clinical data used and were sensitive to the time horizon taken. This reflected considerable inconsistency in the clinical data for this outcome. The GDG concluded that this result was difficult to interpret and it was not used to inform decision making.

Limitations

The availability of utility data to inform the estimation of QALYs was somewhat limited. EQ-5D utility data was identified for the initial impact of hospitalised and non-hospitalised exacerbations. Mapping of SGRQ data to EQ-5D utility was used to supplement this where necessary. GDG members indicated that they were aware of problems with mapping SGRQ to EQ-5D and were generally not in favour of an approach that primarily based QALY impact on this. For this reason, in the base case analysis we attributed a QALY loss to hospitalised and non-hospitalised exacerbations, which minimised the reliance on mapped data. This lack of direct utility data impacts most analyses in the area of COPD. A notable exception being a cost-utility analysis using patient level TORCH data where EQ5D utility data was collected at various time points throughout the trial and so could be used as a basis for QALY calculations.

In the model we assumed that an exacerbation impacted a patient (to a diminishing extent) for 3 months but then stable utility will return to the same level as prior to the exacerbation. The GDG noted that there is evidence that exacerbations may permanently impact quality of life and this assumption is likely to be somewhat conservative. It was however accepted as a reasonable simplification for modelling purposes.

As described in the model input section, there was discussion regarding whether the cost of a non-hospitalisation identified in the literature was too low. Sensitivity analysis showed however that the model was not especially sensitive to the cost of a non-hospitalised exacerbation and this uncertainty was therefore not considered a major limitation.

Note that other more minor data limitations were discussed throughout the model inputs section.

Conclusions

Based on the limitations of the clinical evidence for triple therapy and the results of the cost-effective model, the GDG concluded that patients with an FEV_1 < 50% should be offered LAMA or LABA+ICS as initial maintenance therapy. The GDG considered that while triple therapy was potentially effective and cost-effective, the evidence was not strong enough to warrant a recommendation that all patients with an FEV_1 < 50% be routinely started on triple therapy. Triple therapy was instead recommended if symptoms or exacerbations persisted. They noted that triple therapy was most likely to be cost-effective in patients who will obtain a benefit in terms of exacerbation reduction and symptom relief.

7.3.6.6 Evidence discussion for inhaled combination therapy

Evidence to recommendation for inhaled combination therapy

The GDG considered available evidence comparing use of long-acting bronchodilators from different classes used alone (discussed in section 7.3.4), in combination and in combination with inhaled steroid. The GDG discussed the presented evidence and drafted recommendations afresh, without reference to those from the previous guideline. The GDG based recommendations on increasing therapy in people who are symptomatic, exacerbating or experiencing a reduced quality of life.

Analysis of outcomes by length of follow-up was discussed. In order to assess the longevity of a particular outcome the GDG agreed that all evidence should be sub-grouped into outcome time-bands of 6 months, > 6 and ≤ 12 months and > 12 months. 1 year rather than 6 months follow up was desirable for exacerbation as an outcome. A period of 6 months might be subject to regression to mean and Hawthorne effects.

The GDG also deemed it useful to stratify studies by run-in periods (i.e. a period of time at the start of the trial before the randomised medication in which participants are either given no treatment or a LABA and ICS together) as a possible explanation for heterogeneity of results.

In the context of long term studies in COPD the GDG noted that patient drop out was inevitable. The GRADE methodology results in such studies being down-graded. The GDG did not accept that this was an appropriate assessment of the studies and it was further noted that differential dropout rates during study interventions might represent a true treatment effect, and not necessarily a reason to downgrade quality of evidence. Differential drop out may affect the interpretation of the outcome of the study.

This evidence links to recommendation U5.

Comparison of LABA+ICS with LABA alone or LAMA alone

There were a considerable number of clinical studies comparing LABA+ICS with LABA. The GDG would have liked to have been able to assess the evidence stratified by previous exacerbation frequency, but recognised that this information was not available.

The clinical evidence suggests that the LABA+ICS combination is superior to LABA alone. This includes studies for which the entry criteria stipulate patients with an FEV_1 below 60%. There is a greater body of evidence for patients with FEV_1 < 50%, and a suggestion from the post-hoc analysis of the Torch study[207] that benefit is most marked in participants with a lower FEV_1 (although differences between severity groups were not significant in this analysis). One combination of LABA+ICS is licensed in people with an FEV_1 of 60% or less.

The cost-effectiveness evidence supported the clinical conclusion, with a number of analyses

based on different clinical studies demonstrating that LABA+ICS was cost effective compared with LABA alone. This again included some data on those with FEV_1 < 60% predicted. One modelling study[210] specifically examined the cost effectiveness in different patient groups, stratified by FEV_1 level, and found that use of LABA+ICS in all people with COPD was not cost-effective compared to giving only to people with an FEV_1 < 50% predicted (those not receiving LABA+ICS received LABA alone).

In summary the GDG felt that the weight of evidence, both clinical and health-economic, clearly supported the LABA+ICS combination as being superior to LABA, particularly in those with FEV_1 < 50% predicted.

One study was available that compared LABA+ICS and LAMA, the INSPIRE study[219]. The GDG noted that from the INSPIRE RCT, a small improvement in quality of life in people in the LABA + ICS arm, but this was not regarded as clinically significant. Exacerbation rates were similar overall and non-significant.

The seemingly high dropout rates of 35 and 42% seen in this trial were not unexpected in COPD trials, and the quality should not necessarily be marked down on these grounds. In the absence of further analysis of the differential drop-out rates, the GDG agreed that this study did not provide strong clinical evidence in favour of either LAMA or the LABA+ICS combination.

No economic evaluations were identified comparing LABA+ICS to LAMA. LABA+ICS is moderately more expensive than LAMA in terms of drug costs alone. Both these agents were incorporated in a cost-effectiveness model undertaken for the guideline, which also included triple therapy. This analysis aimed to examine what is the most cost-effective option for initial maintenance therapy in patients with an FEV_1 < 50% predicted (that is, more severely affected patients). The base case results indicate that triple therapy is not cost-effective and that there is uncertainty over whether LAMA or LABA+ICS is the most cost-effective option.

The method of delivery of LABA and ICS was not specifically addressed, although all the evidence was based on single (for LABA alone) and combination (for LABA+ICS) inhalers with the drugs formulated as dry powders. The GDG agreed that any recommendation for ICS+LABA would have to relate to a combination inhaler (because all of the evidence was in combination inhalers). However the GDG took note of patient preference particularly relating to ability to use different devices and therefore felt that it was inappropriate to

specify a particular inhalation device. The GDG noted that high dose ICS is effective in COPD but that lower doses are sometimes prescribed inappropriately. Full effective doses for COPD should be prescribed.

The GDG discussed adverse events in general, and the trade off between benefit and harm, noting that the incidence of osteoporosis and cataracts was a significant fear for people with COPD. However they were reassured by the evidence from the long term studies that these were no longer serious concerns. They did however consider the more recent evidence that pneumonia appears more common in people receiving inhaled steroids in adverse event reports from studies, and debated this at some length.

Pneumonia had not been noted in COPD studies prior to TORCH[197], Kardos et al [223] and INSPIRE[219] as it had not been anticipated or grouped as a specific adverse event. These and previous trials had been too small, too short and not powered to examine this adverse event as an outcome. Heterogeneity in the recording of pneumonia was also noted. However, meta-analysis showed a statistically-significantly greater incidence of pneumonia in the LABA+ICS arm compared with the LABA arm (where the studies were of greater than six months' duration). The GDG noted that, although there was a difference, the absolute risk of pneumonia was low. The GDG also considered whether this was a class effect or related to a specific steroid molecule, but the published evidence available at the time of guideline development did not allow them to reach a conclusion on this point.

The GDG concluded that clinicians should be aware of the risk of pneumonia associated with ICS and be prepared to inform patients about this but not with wording that overstated it. Importantly, they were convinced that the small risk of pneumonia did not preclude a recommendation to use inhalers containing corticosteroid.

Taking into account the inconclusive clinical evidence and the results of the cost-effectiveness analysis the GDG concluded that it should recommend either LAMA or LABA+ICS for initial maintenance therapy in patients with FEV_1 < 50% predicted, but that it was not possible to recommend one over the other.

This evidence links to recommendations U5 and U6.

Comparison of triple therapy (LAMA + LABA + ICS) with LABA + ICS or LAMA alone

Evidence for comparison of triple therapy (LAMA+LABA+ICS) with combination long-acting $beta_2$ agonists and corticosteroid was available only from currently unpublished subgroup data[201] from the published UPLIFT RCT[224] made available following a call for evidence. Only the tiotropium/placebo was randomised. Participants had previously been taking background medication with LABA+ICS.

The GDG considered the study to provide evidence of clinical benefit when adding a LAMA to LABA+ICS medication, whilst noting reservations including the absence of sub-grouping by FEV_1, imperfect randomisation, and that this is based on a post hoc subgroup analysis of a clinical comparison that the trial was not designed to examine. Notwithstanding these limitations the data were felt to support a move to triple therapy in patients remaining symptomatic on LABA+ICS. However, more robust evidence would be needed before concluding that patients should move straight to the combination of three drugs, whatever their FEV_1, particularly given the higher cost of triple therapy. No economic evaluations were identified in the literature to inform this comparison.

Evidence for the comparison of triple therapy (LAMA+LABA+ICS) with long-acting muscarinic antagonists was available from the OPTIMAL RCT[200]. This trial used a time-to-first-event analysis for exacerbations (the primary outcome) rather than an event rate, which may have reduced statistical significance because of differential withdrawal. The GDG also noted clinical inconsistency in the results. There was no improvement in lung function but a reduction in hospitalisations and a big difference in health status in the triple combination, but without an overall difference in exacerbations. It is noted however that the magnitude of the rate ratio for exacerbations is the same as that seen in the UPLIFT trial subgroup comparison of triple therapy with LABA+ICS, despite being non-significant.

A cost-effectiveness analysis based on resource use and health outcomes collected within the OPTIMAL[220] study found triple therapy not to be cost-effective compared to LAMA alone with a high cost per QALY gained. However, it is considered likely that costs are overestimated for triple therapy in the analysis as they include a patient who had a 215 day hospital stay and high drug costs for LABA+ICS. Addressing these issues would improve cost-effectiveness; although it is still unknown if this would result in triple therapy becoming cost-effective.

A cost-effectiveness analysis undertaken as part of the guideline update compared all three options i.e. addressed the question of whether LAMA, LABA+ICS or triple therapy was the most cost-effective treatment option for initial maintenance therapy in patients with an FEV_1 < 50% predicted. It was considered that if cost-effectiveness evidence strongly supported triple therapy, this might impact the decision about whether it could be recommended as initial treatment. The base case results, driven by differences in exacerbations and hospitalisations, did not find triple therapy to be a cost-effective option. There was however uncertainty regarding this conclusion, as in a sensitivity analysis which also incorporates a difference between treatments in terms of stable utility (quality of life), triple therapy was found to be the most cost-effective option. The GDG considered that a scenario where treatment impacted utility due to stable symptom improvement as well as exacerbations to be a realistic one but given the limitations of the estimate of treatment effect on stable utility used in the model they interpreted the results with caution.

On balance the evidence suggested that triple therapy should be an acceptable treatment option, but that more evidence would be needed to recommend it as initial therapy, even in those with lower FEV_1. The GDG also considered whether they should make a recommendation for triple therapy but adding a stopping rule such that the combination would be cut or withdrawn if response is poor. However, given their evaluation of benefits and harms, and the enormous difficulty of implementing a stopping rule when one reason for prescribing these agents is reduction in exacerbations, they felt that this was not appropriate.

In conclusion, taking into account both the clinical evidence for triple therapy and the results of the cost-effective model, the GDG decided to recommend triple therapy as step-up treatment if symptoms or exacerbations persisted on current therapy. They noted that triple therapy was most likely to be cost-effective in patients who will obtain a benefit in terms of exacerbation reduction and symptom relief. They also concluded that there was not strong enough evidence for patients with an FEV_1 < 50% to be routinely offered triple therapy as initial maintenance therapy.

This evidence links to recommendations U7 and U8.

Comparison of LAMA + LABA + ICS with LABA + LAMA

The GDG considered evidence from the OPTIMAL RCT [200] which was underpowered for these outcomes and did not inform its discussions. The GDG therefore decided to make no recommendation.

Comparison of LAMA+LABA with LABA, LAMA or LABA+ICS

For LAMA + LABA compared with LABA alone, data was available from one six- month RCT[178]. The GDG noted the limitations of the six month study duration. This could explain the lack of difference in exacerbations. The GDG concluded that there was no evidence favouring LAMA + LABA from the published data, but that there might be a benefit in adding LAMA to LABA where patients remained symptomatic on LABA monotherapy. The GDG noted that the preferred increase in therapy from LABA monotherapy was LABA+ICS (in preference to LABA+LAMA) in people with COPD who remain symptomatic, since there is a greater body of evidence supporting this. However, the GDG were able to make a recommendation, in conjunction with its consideration of treatment with LABA +ICS discussed elsewhere, to offer treatment with LAMA + LABA in people with COPD who remain symptomatic on treatment with a LABA, and for whom treatment with LABA + ICS is not appropriate or possible.

For LAMA + LABA vs. LAMA alone, the GDG noted that in the six month Vogelmeier et al RCT[178] duration of follow-up was unlikely to highlight any difference in exacerbations. It also noted that although the OPTIMAL RCT[200] was powered to measure its primary outcome (the proportion of patients experiencing one or more acute exacerbations), it was underpowered to measure any of the other outcomes. After some debate the GDG decided they could not recommend moving to the LABA + LAMA combination in those already taking a LAMA as sole maintenance therapy.

For LAMA + LABA vs. LABA + ICS, the GDG decided, in the absence of clinical data, not to make any recommendation.

This evidence links to recommendations U5 and U6.

Comparison of LAMA+ICS with LABA or LAMA

The GDG felt that it was necessary to examine whether any studies were available since the NICE COPD 2004 guideline to assess the combination of long-acting muscarinic antagonist (LAMA) plus inhaled corticosteroid (ICS) in comparison with monotherapy with a long-acting beta agonist (LABA) or long-acting muscarinic antagonist (LAMA). Such evidence might help in guidance on sequencing of drug therapies. The GDG agreed that the guideline should note that there was a complete absence of published data on this comparison and that no recommendation could be made.

The GDG, when writing recommendation, used the phrasing “offer” to indicate a strong body of supportive evidence and “consider” indicating a lesser degree of supportive evidence.

Recommendations

R29	The effectiveness of bronchodilator therapy should not be assessed by lung function alone but should include a variety of other measures such as improvement in symptoms, activities of daily living, exercise capacity, and rapidity of symptom relief.	**Grade D**
R30	Deleted.	
R31	Deleted.	
R32	Deleted.	

NEW 2010 UPDATE RECOMMENDATION 4 (U4)

U4 Offer once-daily long-acting muscarinic antagonist (LAMA) in preference to four-times-daily short-acting muscarinic antagonist (SAMA) to people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, and in whom a decision has been made to commence regular maintenance bronchodilator therapy with a muscarinic antagonist[hhh].

NEW 2010 UPDATE RECOMMENDATION 5 (U5)

U5 In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, offer the following as maintenance therapy:

- if $FEV_1 \geq 50\%$ predicted: either long-acting $beta_2$ agonist (LABA) or LAMA
- if $FEV_1 < 50\%$ predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or LAMA.

[hhh] The British National Formulary states that a SAMA should be discontinued when a LAMA is started.

U6	**NEW 2010 UPDATE RECOMMENDATION 6 (U6)** In people with stable COPD and an $FEV_1 \geq 50\%$ who remain breathless or have exacerbations despite maintenance therapy with a LABA: • consider LABA+ICS in a combination inhaler • consider LAMA in addition to LABA where ICS is declined or not tolerated.	
U7	**New 2010 Update recommendation 7 (U7)** Offer LAMA in addition to LABA+ICS to people with COPD who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV_1.	
U8	**New 2010 Update recommendation 8 (U8)** Consider LABA+ICS in a combination inhaler in addition to LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with LAMA irrespective of their FEV_1.	
R33	The choice of drug(s) should take into account the person's symptomatic response and preference, and the drug's potential to reduce exacerbations, its side effects and cost.	**Grade D**

7.3.7 Delivery systems used to treat patients with stable COPD

The devices used to deliver drugs to the lungs are, in many respects, as important as the drugs themselves. If the device is inefficient at delivering the drugs to the lungs or is difficult for patients to learn, or remember how to use then the effectiveness of the therapy will be reduced. This is a difficult area to conduct blinded studies in because the identity of the device cannot be concealed from patients and there are no standardised validated tools that can be used to assess ease of use or patient preference.

One Health Technology Assessment was found[225], one systematic review [226] two additional RCTs [227,228] and one prospective study [229] that compared nebulisers, patient administered metered dose inhalers (pMDI) and or dry powered inhaler (DPI). Devices were all used to administer bronchodilators or saline placebo. The study by O'Driscoll et al. [229] was excluded due to methodological limitations.

Factors for consideration within this topic included small sample sizes (range of N=7 to N=47)[229], studies vary across settings (domiciliary, laboratory or clinic) raising the question of generalisability, duration of studies is extremely variable from 2 hours to 2 weeks, variable training in the use of devices (some devices require more manipulation and dexterity than others and hence may not be as user friendly in an elderly population), variable dropout rates, and differing drug doses in application to assessing clinical efficacy. Many of the studies were of a cross over design with variable washout periods (2 to 7 days) and variable age ranges (44 to 72 years) [226].

The recent BTS/SIGN guidelines for asthma[73] have also examined the evidence concerning the comparative effectiveness of different inhaler devices. They make several important observations about methodological difficulties with the evidence in this area:

- Studies comparing different inhaler devices recruit participants who are competent using the devices involved. This is very unlike clinical practice where a patient's abilities may vary markedly between devices.
- Some studies of inhaler devices are of parallel design and some crossover. The data in these two types of studies are often not easy to combine in a meta-analysis. (This statement refers to evidence derived from the HTA[225] in which parallel and crossover studies were not combined). In addition, crossover studies may not allow a suitable washout period for drugs with a longer duration of action.
- Many studies use doses of medication at the upper end of the prescribing range. This may bias towards an underestimate of difference between inhalers, if one exists.
- Clinical trials tend to recruit patients with more stable and less severe disease. Whilst this may reflect the bulk of clinical practice it does make observation of a significant difference, especially with less frequently occurring outcomes, less likely, particularly in smaller studies, so a real difference may be missed.
- Studies of novel new inhaler devices are highly likely to be prone to bias when preference is expressed. Many inhaler device studies are designed with a null hypothesis of bio-equivalence to show the new is as good as the older, established comparator. These studies may be underpowered to detect differences, if they exist.

- Although most medications are available in the pressurised Metered Dose Inhaler (pMDI) the choice of Dry Powder Inhaler (DPI) will be determined by the choice of medication, as not all devices are available to deliver all drugs.
- The recommendations are often based on a comparison of pMDI with other devices as most of the available evidence comes from trials making the comparison between newer devices and the longer established pMDI.

It is perhaps surprising that assessment of inhaler technique is so often neglected, both in individual patient terms and in terms of Phase 3 trials that include newly designed inhaler devices. Most patients whatever their age are able to acquire and maintain adequate inhaler technique given adequate instruction. The exception to this is that those with significant cognitive impairment (as a guideline, those with a Hodkinson Abbreviated Mental Test Score of 4 or less) are unable to use any form of inhaler device [230,231]. In most patients however, a pragmatic approach guided by individual patient assessment is needed in choosing a device. It is also important to recognise that retention of inhaler technique is as important as its acquisition and many elderly patients who successfully acquire adequate technique with a particular device will demonstrate inadequate technique when assessed a month later [232]. Regular reassessment and reinstruction is therefore essential, and this may explain why patients first prescribed inhalers in hospital have better technique than those first prescribed inhalers in primary care [233].

The standard metered dose inhaler (MDI), when used in isolation (i.e. without a large-volume spacer device) is rarely appropriate for elderly patients. Elderly patients are slower to learn adequate technique, many never acquire adequate technique, and those that do frequently fail to retain their knowledge when reassessed a month later [230,232-234]. The MDI is particularly difficult for those with impaired handgrip strength (common in those with arthritic conditions)[234]. The addition of a large-volume spacer improves both acquisition and retention of technique [232] and allows carers to assist with technique for those patients with cognitive impairment or physical disabilities affecting hand function. Large volume spacers have also been shown to reduce systemic absorption of inhaled corticosteroids [235].

The problems elderly patients have with MDIs have been recognised by the pharmaceutical industry with a resulting plethora of newer ‘patient friendly’ devices (including breath-activated devices) developed over recent years. Unfortunately very few of these devices have been formally assessed in elderly patients. It is generally the case that breath actuated devices, such as the Turbohaler and Autohaler, are easier for an elderly person to use [236,237], but more data is needed on the retention of technique. There will however, always be a few patients who seem unable to acquire inhaler technique with any device. This may be due to praxis problems (dyspraxia) or to previously unrecognised cognitive impairment. They have

further suggested that inability to acquire adequate technique in an elderly person should prompt screening for cognitive dysfunction [237,238].

Nebulised therapy involves the generation of respirable aqueous particles in a nebuliser chamber. The generation of the particles usually depends on compressed gas delivered from a cylinder or more commonly a compressor. The performance of both nebuliser chambers and compressors varies considerably and this can effect drug deposition and the efficacy of the therapy. European standards for nebuliser performance have been drawn up by the European Committee for Standardization (CEN) (EN 13544-1:2001) (www.cenorm.be) and manufacturers will be required to indicate if their products comply with these.

Nebulisers should not be seen as a panacea for those few patients unable to acquire and/or retain adequate inhaler technique. Nebuliser loading and operation requires manipulative and cognitive skill, and if lack of such skill is responsible for inadequate technique with inhaler devices it is likely that this may also be the case with a nebuliser. Nebulisers, like large volume spacers, do however have the advantage that carers can be trained in their use and provide useful support [239].

Recommendations on the use of nebulisers have been produced by the BTS [240] and the ERS [241] and these have informed some of the recommendations.

Evidence statements

The systematic review[226] compared pMDI with any other handheld inhaler device. The Turbohaler vs. pMD[242] (N=15) and Rotohaler vs. pMDI[243] (N=10) showed no significant differences in **any outcome**. However, the study[244] contained within the systematic review referred to above, using the Respimat vs. pMDI, (N=36, open label) showed significant increases in **FEV_1** (difference in change from baseline 70ml, 95% CI; 10 to 130 ml). Respimat is unlicensed in the UK. The effect on change in **FVC** was of similar size. There were no differences observed between these two devices for any other reported outcomes.	Ia

Using **FEV_1** as a primary outcome, there is no clinical benefit of using nebulised medication in addition to or as an alternative to a pMDI, with or without a spacer, or a DPI in stable COPD[149].	Ia
Cuvelier et al. [227] (DPI and MDI) and Eiser et al. [228] (MDI with a spacer vs. larger nebulised doses) found no significant differences between the two groups.	Ib
Handling of DPI was considered easier than the MDI (p=0.014) and the DPI was preferred to the MDI (p<0.001)[227].	Ib
Patient **ease-of-use** scores and **preference** scores were significantly better for the DPI (p=0.014 and p <0.001) respectively and 56% of patients considered the DPI easier to use than the MDI [227].	Ib
There were no significant differences in **quality of life** scores from the St George's questionnaires and the HAD scores[228].	Ib

GDG consensus statements

There is no evidence to dictate an order in which devices should be tested for those patients who cannot use pMDI. In the absence of evidence, the most important points to consider are patient preference and local cost.	IV
Cognitive function and praxis are more important than age in determining the ability of an older patient to use hand held inhalers or nebulisers.	IV

Older patients often soon forget correct inhaler technique.	IV
Patients experiencing difficulties using hand held inhalers may also have difficulty using nebulisers.	IV
Not all drugs are available in a formulation that can be used in a nebuliser.	IV
Regular use of nebulised therapy involves considerable time and may impair patient's ability to undertake other activities and inhibit their ability to leave their home.	IV
Regular use of high doses of bronchodilators via a nebuliser may produce significant side effects (e.g. tachycardia and tremor).	IV
Nebulised bronchodilator therapy may lead to significant improvements in symptoms, exercise capacity or quality of life which are not reflected in changes in FEV_1.	IV
Acute changes in lung function are not the most appropriate means of assessing the benefits of nebulised therapy.	IV

Recommendations about Inhalers

R45	In most cases bronchodilator therapy is best administered using a hand-held inhaler device (including a spacer device if appropriate).	**Grade D**
R46	If the patient is unable to use a particular device satisfactorily, it is not suitable for him or her, and an alternative should be found.	**Grade D**
R47	Inhalers should be prescribed only after patients have received training in the use of the device and have demonstrated satisfactory technique.	**Grade D**
R48	Patients should have their ability to use an inhaler device regularly assessed by a competent healthcare professional and, if necessary, should be re-taught the correct technique.	**Grade D**
R49	Deleted.	

Recommendations about spacers

R50	The spacer should be compatible with the patient's metered-dose inhaler.	**Grade D**
R51	It is recommended that spacers are used in the following way: • the drug is administered by repeated single actuations of the metered-dose inhaler into the spacer, with each followed by inhalation	**Grade D**

	• there should be minimal delay between inhaler actuation and inhalation • tidal breathing can be used as it is as effective as single breaths.	
R52	Spacers should be cleaned no more than monthly as more frequent cleaning affects their performance (because of a build up of static). They should be cleaned with water and washing-up liquid and allowed to air dry. The mouthpiece should be wiped clean of detergent before use.	**Grade D**

Recommendations about nebulisers

R53	Patients with distressing or disabling breathlessness despite maximal therapy using inhalers should be considered for nebuliser therapy.	**Grade D**
R54	Nebulised therapy should not continue to be prescribed without assessing and confirming that one or more of the following occurs: • a reduction in symptoms • an increase in the ability to undertake activities of daily living • an increase in exercise capacity • an improvement in lung function.	**Grade D**
R55	Nebulised therapy should not be prescribed without an assessment of the patient's and/or carer's ability to use it.	**Grade D**

R56	A nebuliser system that is known to be efficient should be used. Once available, Comité European de Normalisation (European Committee for Standardisation, CEN) data should be used to assess efficiency.	**Grade D**
R57	Patients should be offered a choice between a facemask and a mouthpiece to administer their nebulised therapy, unless the drug specifically requires a mouthpiece (for example, anticholinergic drugs).	**Grade D**
R58	If nebuliser therapy is prescribed, the patient should be provided with equipment, servicing, advice and support.	**Grade D**

7.4 Oral therapy

7.4.1 Oral corticosteroids

There is little evidence that inhaled steroids have any effects on the inflammatory cells present in COPD: neutrophils, unlike eosinophils are relatively insensitive to the effects of steroids. Even high doses of inhaled steroids do not reduce the number of inflammatory cells or the levels of cytokines [179,180]. Currently up to 70% of patients with COPD are prescribed an inhaled steroid and approximately 5% are prescribed oral steroids [33 181]. The rationale for this is unclear and at least some of this prescribing may have been based on an extrapolation from the effects of these drugs in asthma and their effects at the time of an exacerbation.

One meta-analysis that included ten trials was found that compared oral steroids to placebo [245]. The primary outcome measure was FEV_1.

In addition to the trials included in the meta-analysis, two RCTs were identified both of which are of a crossover design and compare oral steroids to placebo [246,247]. A further two RCTs [248,249] were excluded due to methodological limitations.

Factors for consideration within this topic include:

- sample size between trials varies (ranging from N=18 to N=168).
- trial follow-up periods vary (ranging from 2 weeks to 6 weeks) and hence data is available for acute, short-term studies only.
- the trials vary as to whether or not they use washout periods.
- a variety of different steroid drugs and dosages are used.
- geographical locations vary.

It is important to note that all of the studies of suitable methodological quality are focused upon the short-term effects relating to FEV_1. No long-term studies were identified. Hence the effects of sustained oral steroid therapy on FEV_1 and the potential long-term side effects of sustained therapy have not been established.

GDG consensus statements

There are no published studies that establish which, if any, patients benefit from long term oral steroid therapy.	IV
The GDG is aware that there are a small group of patients who experience frequent exacerbations and/or severe breathlessness for whom long term oral steroid therapy is the only pragmatic way of managing them.	IV
The RCP guidelines[250] on steroid-induced osteoporosis advise commencing prophylactic treatment without further monitoring or assessment in patients over the age of 65 who are starting long-term corticosteroid treatment.	IV

Recommendations

R41	Maintenance use of oral corticosteroid therapy in COPD is not normally recommended. Some patients with advanced COPD may require maintenance oral corticosteroids when these cannot be withdrawn following an exacerbation. In these cases, the dose of oral corticosteroids should be kept as low as possible.	**Grade D**
R42	Patients treated with long-term oral corticosteroid therapy should be monitored for the development of osteoporosis and given appropriate prophylaxis. Patients over the age of 65 should be started on prophylactic treatment, without monitoring.	**Grade D**

7.4.2 Oral theophylline

Theophylline and its derivatives have been used for many years to treat patients with COPD. The mechanism of action of these drugs remains uncertain[251] but it is generally assumed that they relax airway smooth muscle. Theophylline may also increase diaphragmatic strength in patients with COPD[252] and have effects on mucociliary clearance[253]. It also has extra pulmonary effects, particularly improvement in cardiac output[254] that may also be beneficial in patients with COPD. Because of potential toxicity and significant interactions with other drugs [255] [256] theophylline is no longer considered initial empirical treatment. When reference is made to theophylline it is to the long-acting/slow release formulations, unless otherwise stated.

One systematic review was found[257], which looked at oral theophylline compared to placebo in patients with stable COPD. Twenty worldwide RCTs of a cross over design were included in the systematic review with a total sample size of N=480. Study durations ranged from 7 to 90 days. All but two of the studies were double blind and none were open label studies (see comments pertaining to Rossi et al 2002 below). Eleven studies did not describe the washout periods and as such this means that there may be possible contamination. This

may have resulted in a possible over estimation of the carry over effects of theophylline within the placebo group. Concomitant therapy varied from none to any other bronchodilator plus corticosteroid. Ages ranged from 59 to 69 years.

One additional study by Rossi et al (2002)[163] was identified, which compared formoterol, theophylline and placebo arms within the same study (N=854, of which N=122 placebo and N=209 theophylline group) over a 12-month duration. However the study was limited by the fact that the slow release theophylline arm was open label and hence both the physicians and participants were aware of the drug intervention. The authors state their rationale as "*the required dose titration of oral slow release theophylline made blinding impossible and it was therefore administered at individualised doses on the basis of plasma concentrations in an open-label fashion*". This may have been underpinned by an ethics committee requirement however this is not stated. As this is a recently published study this may be a significant difference in the way in which study designs for this particular drug are now conducted compared to the date spans contained within the systematic review[257] when the dates range from 1979 to 1995. Rossi et al. [163] acknowledge this limitation and highlight that importantly "the unblinded nature of the theophylline arm might have contributed to the very high dropout rate associated with the treatment". Total discontinuation rates were quoted as formoterol (12μg) 25%, formoterol (24μg) 19%, placebo 27% and theophylline 39% [163].

This study illustrates the difficulty of undertaking a placebo-controlled double blind trial of the efficacy of theophylline. The need to balance achieving adequate, but not toxic therapeutic levels conflicts with the blinding of the investigators and patients. Early studies did not address this.

The trials cited above did not look at the therapeutic range for theophyllines.

Evidence statements

There was a statistically significant improvement in **FEV_1** and **FVC** in favour of the theophylline group compared to placebo. FEV_1 WMD 100ml; 95% CI; 40 to 160 ml. FVC WMD 210ml; 95% CI; 100 to 320 ml [257].	Ia
Theophylline was also significantly more effective at increasing **FEV_1** than placebo at every time point and for each visit (all $p < 0.005$) in the study by Rossi et al. [163] and the difference was clinically relevant at 5,7,8,10,11 and 12 hours.	Ib
There was a statistically significant improvement in oxygen uptake (**VO_2 max**) in favour of the treatment group. WMD 195 ml/min; 95% CI; 113 to 278 ml/min. Two studies (Fink 1994 and Newman 1994 with a sample size of N=32)[258,259] contributed to the data [257].	Ia
There was a statistically significant improvement in **PaO_2** with treatment. WMD 3.18 mmHg; 95% CI; 1.23 to 5.13 mmHg [257].	Ia
There was a statistically significant decrease in **$PaCO_2$** with theophylline compared to placebo. WMD –2.36 mmHg; 95% CI –3.52 to –1.21 mmHg [257].	Ia
Participants **preferred** theophylline to placebo. RR 2.27; 95% CI 1.26 to 4.11. Authors acknowledge an error in the text describing the data for this outcome but confirm that the results and meta view are correct as they stand. Two studies (Alexander [260] N=40 and Mulloy [261] N=10) contribute to this data [257].	Ia
Nausea was experienced more often in the theophylline	Ia

group compared to the placebo (RR 7.67; 95%CI; 1.5 to 39.9) [257].

There were no statistically significant differences for **distance walked**, VAS for **breathlessness**, symptoms of **wheeze** and **dyspnoea**, **exacerbations** or dropouts [257].	Ia
There were no statistically significant differences between the treatment groups for total **diary symptom scores or use of rescue medication** [163].	Ib
No data was available for **health status** or **mortality** [257].	Ia
There were fewer "moderate" and "severe" **exacerbations** over 12 months in patients treated with theophylline compared to placebo (5% v 8% (p =0.019) and 6 v 20) in an open label designed study [163].	Ib
Statistically significant improvements in the total **SGRQ** score over 12 months (compared to baseline) were seen for theophylline compared to placebo in an open label designed study (p=0.013)[163].	Ib

GDG consensus statements

The plasma levels of theophylline must be monitored to ensure that they are adequate but do not reach the toxic range[256].	IV
Although these drugs are effective, their usefulness is limited by the need to monitor plasma levels and their potential for	IV

interaction with other medication.

The need to monitor plasma levels and the potential for interaction with other medication restricts the therapeutic use of theophylline and its derivatives to patients who have already tried long-acting bronchodilators or who are unable to use inhaled therapy.	IV

Recommendations

R34	Theophylline should only be used after a trial of short-acting bronchodilators and long-acting bronchodilators, or in patients who are unable to use inhaled therapy, as there is a need to monitor plasma levels and interactions.	**Grade D**
R35	Particular caution needs to be taken with the use of theophylline in older people because of differences in pharmacokinetics, the increased likelihood of comorbidities and the use of other medications.	**Grade D**
R36	The effectiveness of the treatment with theophylline should be assessed by improvements in symptoms, activities of daily living, exercise capacity and lung function.	**Grade D**
R37	The dose of theophylline prescribed should be reduced at the time of an exacerbation if macrolide or fluoroquinolone antibiotics (or other drugs known to interact) are prescribed.	**Grade D**

7.4.3 Oral phosphodiesterase type 4 inhibitors

Only one RCT published to date was found pertaining to a phosphodiesterase-4 inhibitor (Cilomilast) compared to placebo for the treatment of COPD over a 6-week duration [262]. Ages ranged from 40 to 80 years and with the exception of short-acting beta$_2$ agonists and anticholinergic agents, all other COPD medications were discontinued. The GDG felt that there was insufficient long-term data on which to base any evidence statements or recommendations.

7.4.4 Oral mucolytics

Many patients with COPD cough up sputum [3]. Mucolytics are agents which are believed to increase the expectoration of sputum by reducing its viscosity. Some of these drugs, particularly N-acetylcysteine, may also have antioxidant effects which may contribute to their clinical effects.

In some European countries mucolytics are widely prescribed in the belief that they reduce the frequency of exacerbations and / or reduce symptoms in patients with chronic bronchitis. In contrast, in the U.K. mucolytics have not been recommended in previous guidelines and until recently were black listed and could not be prescribed on the NHS.

Clinical introduction

A recent upsurge in mucolytic use has followed the publication of the above studies and NICE guidelines 2004. Nevertheless practitioners are often unsure when mucolytics should be used. The current recommendations state that “mucolytics should be considered if there is chronic cough productive of sputum, and should be continued if there is symptomatic improvement”. There is no recommendation for their use in preventing exacerbations. Two new studies and an updated systematic review have been conducted since the NICE 2004 guidance[263-265].

The GDG agreed to revisit this question principally to investigate whether to add a recommendation on the use of mucolytics in the prevention of exacerbations and hospitalisations; some practitioners have advocated their use for this indication.

The question posed by the GDG was:

MUCO: What is the clinical and cost effectiveness of mucolytic agents vs. placebo in people with stable COPD?

Methodological introduction

The literature was searched from 2003 onwards for systematic reviews or RCTs comparing oral mucolytic therapy (Carbosysteine, Erdosteine, or N-acetylcysteine) with placebo in people with COPD. RCTs with less than six months follow-up were excluded. Outcomes of interest included all-cause mortality, exacerbations, hospitalisations, decline in FEV1, change in health related quality of life (measured with total SGRQ score), change in breathlessness (measured with TDI), and adverse events. The clinically important relative risk reduction (RRR) for mortality was 15%, exacerbations (20%), hospitalisation (20%), change in SGRQ (-4 points), FEV_1 (100 ml), and TDI (1 unit).

One systematic review [266] was updated with three additional RCTs [263 264 267] that compared mucolytic therapy with placebo in people with COPD. Studies with less than six months follow-up were removed from the meta-analysis in the Poole et al systematic review.

The double blind RCT of Schermer et al [267] randomised people with COPD or chronic bronchitis (N=192; 3 year follow-up) to either placebo or N-acetyl cysteine (600 mg/once daily).

In the double blind PEACE RCT [264] people with COPD (N=707; 1 year follow-up) were randomised to either placebo or carbocisteine (2x250 mg/3 times daily). In the PEACE study, there was low use of inhaled corticosteroids, $beta_2$ agonists, or anticholinergics in each arm.

The single blind RCT of Bachh et al randomised people with COPD (N=100; follow-up 1 year) to either placebo or N-acetyl cysteine (600 mg/once daily) for 4 months. [263] The Bacch et al RCT was considered to be low quality as it had unclear allocation concealment, and no detail for loss to follow-up or whether intention to treat analysis was performed.

The evidence profile below summarises the quality of the evidence and outcome data for mucolytics compared with placebo. For further forest plots, please see appendix O.

Evidence Profile: Mucolytics versus placebo

Question: Should mucolytics vs. placebo be used in people with stable COPD?

Bibliography: Bachh AA, Shah NN, Bhargava R et al. Effect of oral N-acetylcysteine in COPD - A randomised controlled trial. JK Practitioner. 2007; 14(1):12-16; Schermer T, Chavannes N, Dekhuijzen R et al. Fluticasone and N-acetylcysteine in primary care patients with COPD or chronic bronchitis. Respiratory Medicine. 2009; 103(4):542-551; Zheng JP, Kang J, Huang SG et al. Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study. Lancet. 2008; 371(9629):2013-2018.; Poole P, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2006 ;(Black Peter N. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews: Reviews 2006 Issue 3 John Wiley & Sons)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	mucolytics	placebo	Relative (95% CI)	Absolute		
Frequency of exacerbation (number of exacerbations per patient per month) (follow-up 0.5 to 3 years; range of scores: -; Better indicated by less)												
15	randomised trial	very serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	2049	2016	-	-0.03 (-0.04 to -0.03)	⊕OOO VERY LOW	
People with no exacerbations in study period (follow-up 0.5 to 3 years)												
11	randomised trial	very serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	593/1049 (56.5%)	409/1052 (38.9%)	RR 1.46 (1.34 to 1.6)	179 more per 1000 (from 132 more to 233 more)	⊕OOO VERY LOW	
								21%		96 more per 1,000		
								68%		312 more per 1,000		

Number of people hospitalised in the study period (follow-up .66 to 3 years)												
2	randomised trial	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	65/335 (19.4%)	88/343 (25.7%)	RR 0.76 (0.57 to 1.01)	62 fewer per 1000 (from 111 fewer to 3 more)	⊕⊕OO LOW	
Change from baseline in health related quality of life (follow-up 1 to 3 years; measured with: SGRQ; range of scores: 0-100; Better indicated by less)												
2	randomised trial	serious[7]	serious[8]	no serious indirectness	no serious imprecision	none	571	581	-	-0.57 (-2.1 to 0.95)	⊕⊕OO LOW	
FEV1 or % predicted FEV1 or PEFR at end of study (follow-up 0.5 to 3 years; range of scores: -; Better indicated by more)												
9	randomised trial	very serious[9]	no serious inconsistency[10]	no serious indirectness	no serious imprecision[11]	none	875	889	-	SMD 0.18 (0.06 to 0.3)	⊕⊕OO LOW	
Adverse events (follow-up 0.5 to 1 years)												
9	randomised trial	very serious[12]	no serious inconsistency	no serious indirectness	no serious imprecision	none	241/1525 (15.8%)	281/1522 (18.5%)	RR 0.86 (0.74 to 1)	26 fewer per 1000 (from 48 fewer to 0 more)	⊕⊕OO LOW	
								4%		5 fewer per 1,000		
								51%		71 fewer per 1,000		
death (follow-up 0.5 to 3 years)												
4	randomised trial	very serious[13]	no serious inconsistency	no serious indirectness	very serious[14]	none	11/490 (2.2%)	14/503 (2.8%)	RR 0.82 (0.38 to 1.75)	5 fewer per 1000 (from 17 fewer to 21 more)	⊕OOO VERY LOW	
								1%		1 fewer per 1,000		
								3%		5 fewer per 1,000		

[1] 2/15 studies did not conceal allocation and 10 /15 studies had unclear allocation concealment. 1/15 studies was open label. 8/15 studies had dropout rates above 20%. 9/15 studies did not perform an intention to treat analysis and 1/15 studies was unclear if intention to treat analysis was conducted.

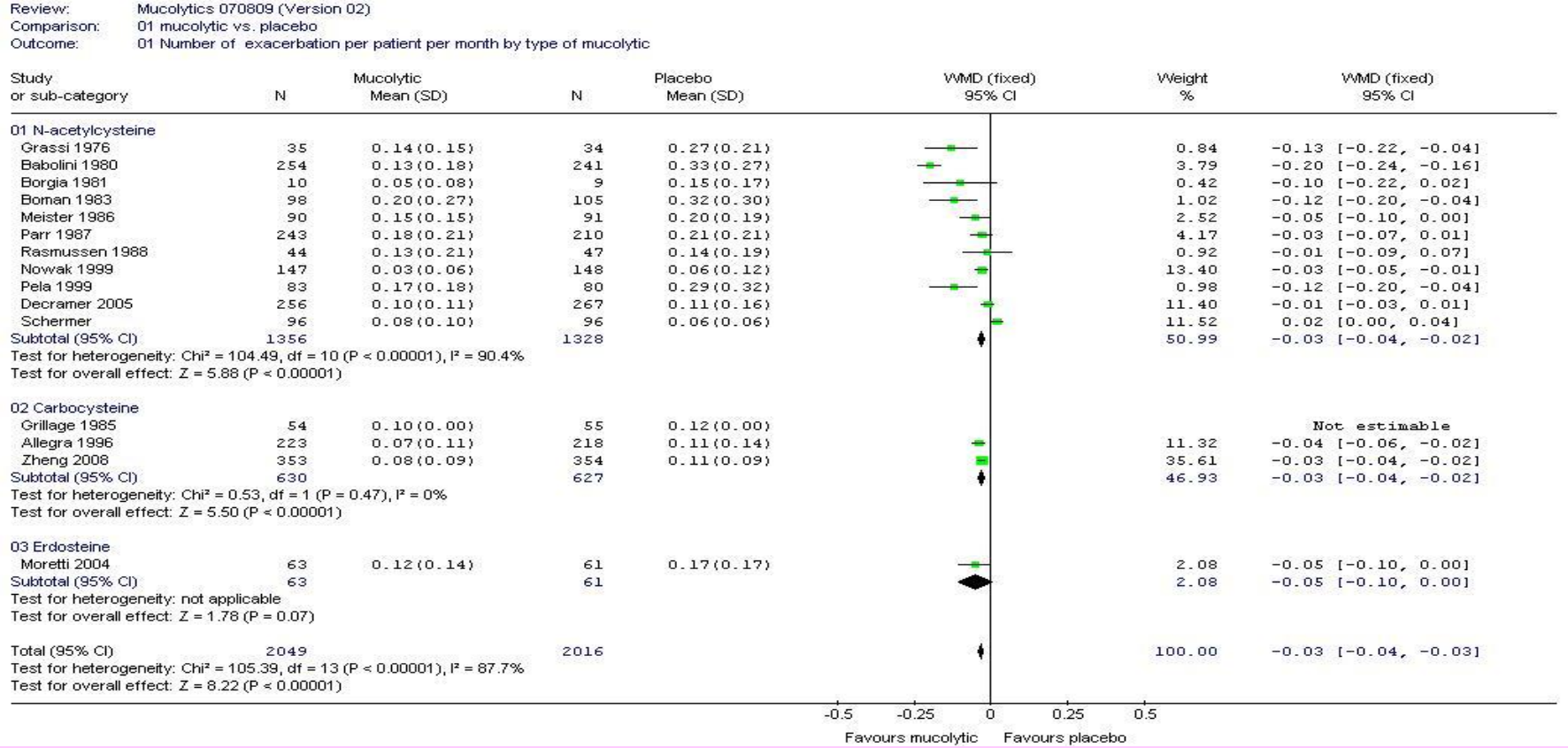
[2] High heterogeneity (I2 = 87.7% p <0.00001) that could not be explained

[3] 2/11 RCTs did not conceal allocation and 9/11 had unclear allocation concealment. 1/11 RCTs was open label. 5/11 RCTs had dropout rate 20% or more. 8/11 did not perform an intention to treat analysis and 1/11 was unclear if an intention to treat analysis had been conducted.
[4] High heterogeneity (I2= 68.3% p=0.0005)
[5] 2/2 RCTs had dropout rates > 20% and the smaller study (Moretti) had unclear allocation concealment, and did not perform an intention to treat analysis.
[6] wide 95% CI that crosses MID
[7] the larger RCT (Decramer) had dropout rates > 20% and unequal between arms
[8] High heterogeneity (I2 = 90%; p=0.002)
[9] 2/9 RCTs did not conceal allocation and 6/9 RCTs have unclear allocation concealment.1/9 studies was open label. 4/9 studies had a dropout rate of 20% or more and 1/9 studies had an unclear dropout rate. 5/9 did not perform intention to treat analyses and 2/9 were unclear as to whether or not an intention to treat analysis had been conducted.
[10] high levels of heterogeneity (I2= 81.5% p<0.0001) overall, however, this is explained by stratifying by drug type
[11] difficult to assess precision as the outcome is a combination of many different measures of lung function
[12] 2/9 RCTs did not conceal allocation and 6/9 studies have unclear allocation concealment. 1/9 studies is open label. 4/9 studies have a dropout rate of 20% or more. 4/9 RCTs did not perform an intention to treat analysis and one study was unclear if an intention to treat analysis had been conducted.
[13] 1/4 RCT had unclear allocation concealment and 1/4 did not have allocation concealment; 1/4 RCT open label; 2/4 RCT had dropout rates > 20%; 2/4 RCT did not perform ITT
[14] wide 95% CI that crosses MID twice.

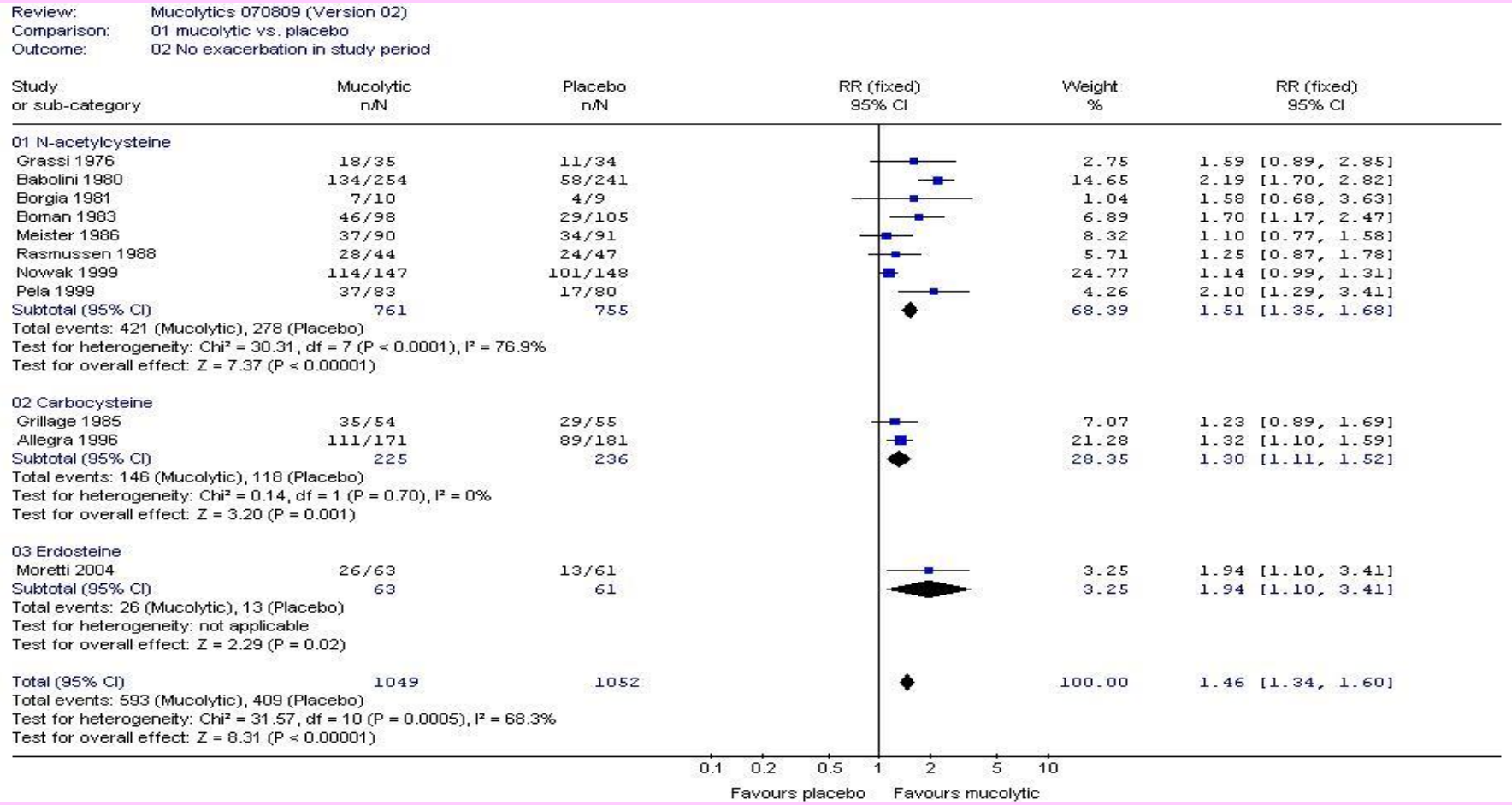
Forest Plots:

Mucolytics versus Placebo

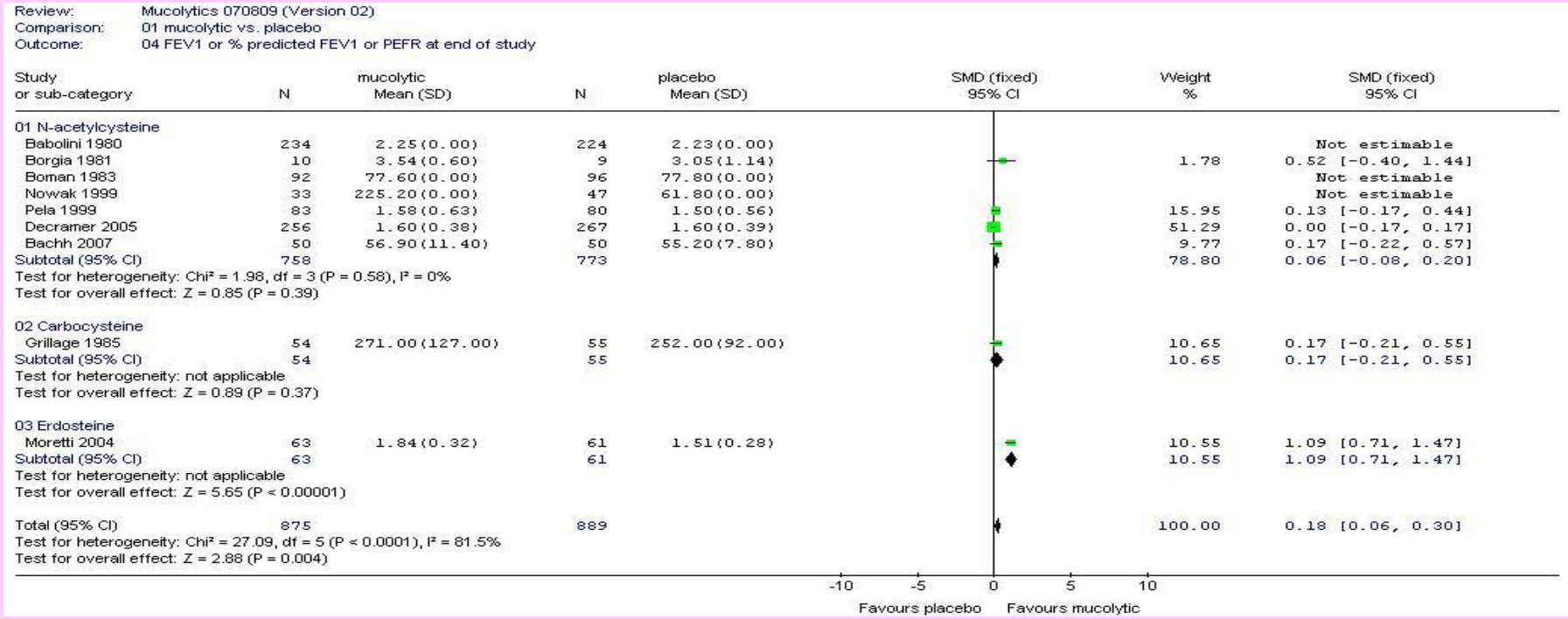
Frequency of exacerbations



Number of people with no exacerbations



FEV_1 or % predicted FEV_1 or PEFR at study end



Evidence statements

Compared with placebo, mucolytics significantly:

- Reduce the frequency of exacerbation (expressed as number of exacerbations per patient per month) (very low quality evidence)
- Increase the number of people who remain exacerbation free (very low quality evidence)
- Increase FEV_1, % predicted FEV_1 or PEFR (low quality evidence).

There was no significant difference between mucolytics and placebo for:

- Hospitalisation (low quality evidence)
- Change from baseline in health related quality of life (measured with total SGRQ score) (low quality evidence)
- Adverse effects (low quality evidence)
- Death (very low quality evidence)

Health economic evidence statements

One paper by Grandjean et al. [268] was found on the cost effectiveness of oral NAC.

The results of the cost effectiveness analysis model show that mucolytic therapy is a cost effective treatment compared to placebo as it reduces the rate of exacerbations, leading to a reduction in hospitalisation and resource use. It is also associated with a reduction in days off sick, leading to a decrease in indirect costs.

The cost effectiveness of mucolytic therapy is mainly dependent on reducing the number of exacerbations in patients with mild disease. Five of the nine studies used to calculate the effectiveness were also included in the clinical review detailed above; these were Grassi 1976, Boman 1983, Meister 1986, Parr 1987 and Rasmussen 1988[269-273].

2010 update: New economic evidence was sought but none was identified.

Evidence to recommendation

The purpose of updating this section of the original 2004 guideline was to establish whether or not a recommendation could be made on the use of mucolytics in preventing exacerbations. Although the evidence did show that, compared with placebo, overall there was indeed a positive effect, the GDG noted that the grading of the quality of the evidence meant that the estimate of the effect was very uncertain; there was a high degree of heterogeneity, and also short lengths of follow-up. The GDG considered possible reasons for the heterogeneity and concluded that a greater positive effect seemed to be linked to having less treatment with other COPD maintenance therapy. It was further noted that the absence of any beneficial effect on quality of life called into question the clinical validity of the exacerbation data from a patient perspective.

No new health economic evidence was available, but the GDG noted that previously documented benefit from mucolytics related to people with predominant chronic bronchitis (i.e. regular cough with sputum production) rather than the general COPD population[268].

It was felt that, whilst it was possible to interpret some of the evidence to imply that a beneficial effect might be more likely in patients not receiving inhaled corticosteroids, the GDG did not feel there was a sufficiently strong evidence base to make a recommendation for this selected group of patients. In addition, there was concern that a positive recommendation for the use of mucolytics purely to prevent exacerbations in this group might preclude the use of other therapies which have a strong evidence base, and incorrectly imply that mucolytics should be the first-line treatment for exacerbation prevention.

Coupled with the facts that many of the studies used N-acetylcysteine (a drug currently without a UK marketing authorisation for use as a mucolytic) and that comparisons were with placebo (and not other known effective therapies), the GDG felt that the routine use of mucolytics primarily for the purpose of preventing exacerbations should not be recommended at the present time, and that future research would be appropriate.

Recommendations

R94	Mucolytic drug therapy should be considered in patients with a chronic cough productive of sputum. (NB The recommendation has been downgraded from A to B due to extrapolation. The studies were designed to look at a population of people with chronic bronchitis rather than COPD specifically).	**Grade B**
R95	Mucolytic therapy should be continued if there is symptomatic improvement (for example, reduction in frequency of cough and sputum production).	**Grade D**
U10	**NEW 2010 UPDATE RECOMMENDATION 10 (U10)** Do not routinely use mucolytic drugs to prevent exacerbations in people with stable COPD.	

7.4.5 Oral anti-oxidant therapy

There is now very good evidence for the presence of oxidative stress in people with COPD. This is critical to the inflammatory response and leads to proinflammatory gene expression [274]. Various attempts have been made to enhance the lung antioxidant activity, including administering antioxidants such as vitamin C and vitamin E. Attempts have also been made to supplement lung glutathione using glutathione itself or its precursors, particularly N-acetylcysteine (NAC) [275]. NAC also acts as a mucolytic and is considered in section 7.4.4 but at least some of its effects in reducing exacerbation rates may be due to the antioxidant properties of this drug.

There was a large cross over in studies found from the literature search for mucolytics and antioxidant therapy in patients with stable COPD. Papers found upon literature searching in this area were primarily focused upon epidemiology, pathophysiology or populations non specific to COPD (acute bronchitis and bronchopneumonia). Two papers were identified that were ultimately critically appraised.

Rautalahti *et al* [276] undertook a long term (5 to 8 years) double blind placebo controlled RCT in Finland to look at the effect of alpha-tocopherol and $beta_2$-carotene supplementation (ATBC) on COPD symptoms. N=10,284 for symptom follow-up.

The ATBC Cancer Prevention Study Group 1994 published a separate paper highlighting the design, methods, participant characteristics and concordance to the alpha tocopherol and $beta_2$ carotene lung cancer prevention study[277]. This paper provided quality appraisal information.

Epidemiological studies have looked at the relationship between dietary antioxidant intake, lung function impairment and the effects of smoking. These studies do not allow conclusions to be drawn about causality but may indicate areas for future research.

Evidence statements

During the follow up the supplementations did not affect the recurrence or incidence of **chronic cough, phlegm** or **dyspnoea**. The authors conclude that the results indicate **no** benefit from supplementation with alpha tocopherol or beta-carotene on the symptoms of COPD but support the beneficial effect of dietary intake of fruit and vegetables [276].	Ib
Neither of the antioxidant supplements had a statistically significant effect on the risk of being **admitted to hospital** due to a COPD diagnosis [276].	Ib

Recommendations

R96	Treatment with alpha-tocopherol and beta-carotene supplements, alone or in combination, is not recommended.	**Grade A**

7.4.6 Anti-tussive therapy

Cough is the most common symptom of COPD but anti-tussive therapy is not used in the UK. This may be because of a lack of data to support their efficacy. When considering studies in this area it is important to note the difficulty in demonstrating effectiveness with objective criteria.

No systematic reviews of anti-tussive therapy were found. Four RCTs were identified [278-281] and 1 Polish observational study [282].

All 5 studies had methodological limitations which included a range of issues such as under-powering, small sample sizes, potential systematic biases and confounders, short duration of studies, variability in measuring compliancy and variability in reporting outcomes as either intention to treat or per protocol analysis. In some cases a heterogeneous group of respiratory disorders was reported.

Drugs included Helicidine vs. placebo [281], Moguisteine vs. codeine [279], Moguisteine vs. Dextromethorphan [280] and Moguisteine vs. placebo [278].

Due to the methodological limitations apparent in these trials all results should be treated with caution and hence the GDG felt it inappropriate to present evidence statements based on these data.

Recommendation

R97	Anti-tussive therapy should not be used in the management of stable COPD.	**Grade D**

7.4.7 Oral prophylactic antibiotic therapy

Prophylactic antibiotic therapy was used some years ago in an attempt to prevent exacerbations and there has been renewed interest in this area recently.

One systematic review[283] was identified which was relevant to the use of prophylactic antibiotic therapy in chronic bronchitis. Although the methodology of the systematic review was of good quality the nine studies[284-292] (N=1055) contained within the review suffered from the methodological issues referred to below.

6 RCTs were found with situation specific populations relevant to COPD[287,291,293-296]. With all of these papers methodological limitations were evident that precluded the relevance of the results. Many of the papers pre dated the Consort Statement [297] and hence lacked detail. The GDG were also mindful of the change in COPD definition and the prevalence of other causes of chronic cough at this time and hence the relevance or otherwise of papers identified from the 1950s and 60s.

Methodological limitations included under-powering, small sample sizes, lack of operational definitions, systematic bias, potential confounders, lack of standardisation or technical details and heterogeneity of results.

A further 9 papers of varying research design were excluded due to heterogeneity of the study population [284,298-305].

The results of all of these trials should be treated with caution due to the inherent methodological limitations and in light of these the GDG felt it inappropriate to present evidence statements based on these data.

Recommendation

R98	There is insufficient evidence to recommend prophylactic antibiotic therapy in the management of stable COPD.	**Grade D**

7.5 Combined oral and inhaled therapy

7.5.1 Beta$_2$ agonists and theophylline

One randomised, double-blind, placebo-controlled parallel trial; Zu Wallack 2001[306] (n = 943).

Evidence statements on combinations of beta$_2$ agonists and theophylline

Mean pre-dose **FEV$_1$** and **FVC** values significantly improved compared with baseline in both the salmeterol/theophylline group and the salmeterol group at week 4, week 8 and week 12 ($p<0.001$). Mean pre-dose **FVC** values significantly also improved compared with baseline in the theophylline group ($p<0.021$), with the exception of the pre-dose FVC assessment at week 12. The salmeterol/theophylline combination group experienced significantly greater improvement in FEV$_1$ & FVC than either the salmeterol alone group or the theophylline alone group ($p<0.02$) [306].	Ib

Patients in the salmeterol/theophylline combination group experienced significantly more **symptom-free days** (p = 0.023) compared with the theophylline group[306]. Ib

Over 12 weeks patients in the salmeterol/theophylline combination group experienced significantly greater improvements in **PEFR** compared with either the salmeterol alone group or theophylline alone group[306]. Ib

Salmeterol/theophylline combination group required significantly fewer **supplemental albuterol** treatments during the 12 weeks of the study compared with either the salmeterol alone group or theophylline alone group[306] . Ib

Salmeterol/theophylline combination group experienced significantly greater improvements in **dyspnoea** (TDI) scores) compared with either the salmeterol alone group or theophylline alone group[306]. Ib

During the study by Zu Wallack et al.[306], each treatment group experienced significant improvements compared with baseline in overall **CRDQ** scores. Ib

The mean overall change from baseline in the salmeterol/theophylline group (+11.2 points) was clinically meaningful (>10 points) and was significantly greater (p<0.019) at week 4 compared with the salmeterol group and the theophylline alone group.

At week 12, mean improvements in overall **CRDQ** scores were +12.7 points in the salmeterol/theophylline group, +7.6 points in the salmeterol group, and +8.6 points in the theophylline group. A significantly higher percentage of patients in the salmeterol/theophylline group (52 to 54%) experienced a clinically important improvement overall compared with the salmeterol group (36 to 45%) or the theophylline group (31 to 42%) at week 4 and week 12 (p<0.014).

Salmeterol/theophylline combination treatment was rated as providing

significantly greater overall **satisfaction with treatment** compared with the theophylline group at all time points (p<0.012) and compared with the salmeterol group at week 8 and week 12 (p<0.041). Salmeterol treatment provided significantly greater **satisfaction with treatment** with respect to side effects than either treatment involving theophylline (p<0.028).

Over 12 weeks **exacerbations** were experienced by significantly fewer patients in the salmeterol/theophylline group (40 patients, 48 exacerbations) compared with the theophylline group (62 patients, 96 exacerbations; p = 0.023), but not the salmeterol group (56 patients, 71 exacerbations; p = 0.076)[306]. Ib

The proportion of patients reporting **adverse events** was not significantly different among treatment groups; however, the proportion of patients reporting adverse events that were judged to be related to study drug was significantly higher in both of the groups that received theophylline compared with the salmeterol group, most notably for gastro intestinal (GI) events (p<0.042)[306]. Ib

7.5.2 Anticholinergics and theophylline

One randomised, double-blind, placebo-controlled parallel trial; Bellia 2002[307] (n = 236) and 1 randomised, double-blind crossover trial; Nishimura 1995[308] (n = 24).

Evidence statements on combinations of anticholinergics and theophylline

Although **FEV_1** and **FVC** values increased in patients treated with the oxitropium/theophylline combination, oxitropium alone and theophylline alone groups at weeks 4-8, no statistically significant differences between groups was observed[307]. Ib

Without inhalation of bronchodilators, **FEV_1** was significantly lower Ib

during ipratropium/salbutamol combination compared with ipratropium/salbutamol/theophylline combination ($p<0.01$) [308].

At 15 and 60 minutes after inhalation of salbutamol, 400ug the FEV_1 was significantly lower during ipratropium/salbutamol combination compared with ipratropium/salbutamol/theophylline combination ($p<0.01$) [308]. Ib

At 15 and 60 minutes after inhalation of ipratropium 80ug, the FEV_1 was significantly lower during ipratropium/salbutamol combination compared with ipratropium/salbutamol/theophylline combination ($p<0.01$). The **FVC** was not significantly different between the ipratropium/salbutamol combination compared with ipratropium/salbutamol/theophylline combination before and 15 and 60 minutes after the inhalation of the bronchodilating agents[308]. Ib

Decreased symptom intensity for **cough frequency, cough intensity** and **dyspnoea** were observed in the majority of patients in all three groups over 8 weeks; however, no significant differences were observed between groups[307]. Ib

No significant alteration of **cough, sputum, wheezing, and shortness of breath** was observed throughout the different phases of treatment [308]. Ib

Morning and evening baseline pre-dosing **PEFR** showed very little change at week 8 in oxitropium/theophylline combination, oxitropium alone and theophylline groups. In contrast, the morning post-dosing PEFR markedly increased in all three groups, particularly in the combination group.; however, no statistically significant difference was observed between treatment groups for either morning or evening post-dosing PEFR change [307]. Ib

Both pre-inhalation and post-inhalation values of daily **PEFR** were Ib

significantly higher during the ipratropium/salbutamol/theophylline combination period than during the ipratropium/salbutamol period ($p<0.01$)[308].

Total **SGRQ** score decreased in all groups; oxitropium/theophylline combination, oxitropium alone and theophylline alone and the change was statistically significant compared with baseline ($p<0.002$). The decrease in total score reached the level of "clinical significance" only in patients treated with oxitropium whether alone (4 ± 1.1 units) or in combination with theophylline (4.7 ± 1.1 units). The variance measure (standard error or standard deviation) is undefined in the primary paper. The decrease was mainly due to changes in activity and impact scores. No significant differences between treatments were observed[307]. Ib

The proportion of patients reporting treatment-related **adverse events** ($p<0.02$) and gastrointestinal treatment-related adverse events ($p<0.04$) in the theophylline group was significantly greater than that found in oxitropium/theophylline combination and oxitropium group[307]. Ib

Sixteen patients (67%) complained of gastrointestinal side effects while receiving ipratropium/salbutamol/theophylline and 10 patients (42%) reported similar effects during ipratropium/salbutamol administration[308]. Ib

GDG consensus statements

When considering increasing therapy, adding a drug to existing therapy rather than increasing the dose of an existing therapy may reduce the risk of adverse events. IV

When combining therapies there may be advantages in terms of convenience, concordance and cost, if equivalent doses of the same drugs are available in single inhaler devices. IV

Recommendations

R43	If patients remain symptomatic on monotherapy, their treatment should be intensified by combining therapies from different drug classes. Effective combinations include: • Deleted bullet point 1* • beta$_2$ agonist and theophylline • anticholinergic and theophylline • Deleted bullet point 4* *Bullet points 1 and 4 have been updated by the new recommendations on combined inhaled therapies.	**Grade A**
R44	Deleted.	

7.6 Oxygen

As the COPD progresses patients often become hypoxaemic. Many patients tolerate mild hypoxaemia well, but once the resting PaO_2 falls below 8 kPa patients begin to develop signs of cor pulmonale, principally peripheral oedema. Once this occurs the prognosis is poor and if untreated the 5 year survival is less than 50%.

Some patients with COPD also become transiently hypoxaemic on exercise and oxygen has been used to try to improve exercise capacity and reduce disability in these individuals. Oxygen is also used to provide symptomatic relief of breathlessness.

Oxygen should be used with caution in patients with COPD as some patient's respiratory drive depends on their degree of hypoxia rather than the usual dependence on hypercapnia. Thus uncontrolled oxygen therapy can result in suppression of respiratory drive, carbon dioxide narcosis and ultimately respiratory arrest.

Thus, in stable COPD oxygen can be administered for long periods during the day and night (long term oxygen therapy (LTOT)), as ambulatory oxygen (either as part of LTOT or on its own to facilitate exercise) or as short burst therapy to relieve symptoms.

When considering the effects of oxygen therapy it is necessary to consider each of these uses separately. It is also necessary to consider the most effective form of supply. Oxygen can be supplied from cylinders, from tanks of liquid oxygen and can be purified from room air by electrically driven oxygen concentrators.

A rigorous literature search was not performed in this area as much of the evidence has been reviewed in the Department of Health sponsored report on oxygen therapy produced by the Royal College of Physicians [309]. The statements and recommendations contained in this report were reviewed and inform some of the guideline recommendations.

As well as looking at the report, two systematic reviews were found looking at oxygen therapy [170;171].

The GDG is aware that the Department of Health and Welsh Assembly Government are reviewing the processes for assessing patients for oxygen therapy and its provision. These guidelines reflect the current position but they may need revision in the light of this review.

The total cost of oxygen therapy in England and Wales in 2002-3 was £34.8 million. This is made up of £19.8 million for oxygen cylinders and £15.0 million for oxygen concentrators.

Since publishing the original COPD guideline the provision of oxygen services has been changed by the Department of Health and some statements about availability are no longer valid.

7.6.1 Long-term oxygen therapy (LTOT)

Long term oxygen therapy aims to improve survival in patients with COPD who have severe hypoxaemia (PaO_2 < 8kPa) as well as reducing the incidence of polycythaemia, reducing the progression of pulmonary hypertension and improving neuropsychological health.

There is more evidence about which patients require LTOT, its efficacy and its supply, than about the other forms of oxygen therapy.

The following evidence statements are derived from the RCP Report [309] and are therefore graded IV this does not necessarily reflect the strength of the underlying evidence.

Evidence statements

"Although two randomised controlled trials showed survival benefit of LTOT in patients with COPD, when used for at least 15 h daily [310,311] the precise mechanism of the improvement in survival with oxygen therapy is unknown."	IV
"Generally, the effects of LTOT on pulmonary artery pressure (PAP) have been small, and PAP may be of prognostic significance as a reflection of the severity of the disease. In the NOTT trial, survival after 8 years was related to the decrease in mean PAP during the first 6 months of treatment [312]. In the MRC trial, LTOT prevented a rise in PAP of 3 mmHg, seen in the control group, though a fall in PAP was not found."	IV
"In patients with COPD, airflow obstruction continues to deteriorate despite LTOT, and the level of the FEV_1 is the strongest predictor of survival in these patients [313,314]. A recent European study found that the majority of patients on LTOT died eventually as a result of respiratory failure [315]."	IV

"The UK MRC trial of LTOT showed benefits of oxygen therapy only in patients who were hypercapnic and who had had a previous documented episode of oedema indicating cor pulmonale [310]. Data from the NOTT trial also showed that the benefits of LTOT were present in relatively normocapnic patients [311]. It is thus a reasonable assumption that improvements in survival are likely in the presence of chronic hypoxaemia, irrespective of chronic hypercapnia or previous episodes of oedema. This assumption is reflected in the advice of all current international guidelines on the prescription of LTOT." IV

"In COPD patients considered for LTOT, the FEV_1 should normally be less than 1.5 litres, or less than 40% of predicted normal values. The presence of arterial hypoxaemia with a higher FEV_1 suggests that there may be another cause for the hypoxaemia, e.g. sleep apnoea, and further investigations will be required. Patients should be prescribed LTOT for at least 15 h per day, although survival improves when LTOT is used for more than 20 h per day. Thus the hours of LTOT use should not be restricted, especially in severe COPD. There is no benefit in the use of LTOT in COPD patients with a PaO_2 above 8 kPa." IV

Evidence statements on provision of LTOT

Oxygen concentrators are currently the most convenient and economical method of providing domiciliary long term oxygen therapy[316]. IV

The major disadvantage of liquid oxygen is that the oxygen evaporates and thus the cylinders have to be refilled, even if not used. Liquid oxygen for the provision of LTOT may also be more expensive to provide than oxygen concentrators in view of the costs of the deliveries. No formal costings comparing liquid oxygen and other modes of oxygen therapy delivery are currently available. There may be difficulties in supply of liquid-oxygen systems in isolated areas of the country where the distances between deliveries are greater [309]. IV

Health economic evidence

One study was found which was a cost minimization analysis of providing oxygen by concentrator or cylinder in the home[317] . No difference in efficacy or other resource use was assumed. Their conclusion is that as long as more than three cylinders a month are being used, independent of flow rate or duration of prescription, it is always to cheaper to prescribe a concentrator. If the duration of prescription is likely to be 12 months or longer, it is always cheaper to prescribe a concentrator when two or more cylinders are being used per month whatever the flow rate. Although this was based on data from Northern Ireland, they state that the cost of contracts for provision of concentrators are similar throughout the UK and are equivalent to other European countries.

Recommendations

R59	Clinicians should be aware that inappropriate oxygen therapy in people with COPD may cause respiratory depression.	**Grade C**
R60	LTOT is indicated in patients with COPD who have a PaO_2 less than 7.3 kPa when stable or a PaO_2 greater than 7.3 and less than 8 kPa when stable and one of: secondary polycythaemia, nocturnal hypoxaemia (oxygen saturation of arterial blood [SaO_2] less than 90% for more than 30% of the time), peripheral oedema or pulmonary hypertension.	**Grade A**
R61	To get the benefits of LTOT patients should breathe supplemental oxygen for at least 15 hours per day. Greater benefits are seen in patients receiving oxygen for 20 hours per day.	**Grade A**

R62	The need for oxygen therapy should be assessed in: • all patients with very severe airflow obstruction (FEV_1 < 30% predicted) • patients with cyanosis • patients with polycythaemia • patients with peripheral oedema • patients with a raised jugular venous pressure • patients with oxygen saturations ≤ 92% breathing air. Assessment should also be considered in patients with severe airflow obstruction (FEV_1 30-49% predicted).	**Grade D**
R63	To ensure all patients eligible for LTOT are identified, pulse oximetry should be available in all healthcare settings.	**Grade D**
R64	The assessment of patients for LTOT should comprise the measurement of arterial blood gases on two occasions at least 3 weeks apart in patients who have a confident diagnosis of COPD, who are receiving optimum medical management and whose COPD is stable.	**Grade D**
R65	Patients receiving LTOT should be reviewed at least once per year by practitioners familiar with LTOT and this review should include pulse oximetry.	**Grade D**
R66	Oxygen concentrators should be used to provide the fixed supply at home for long-term oxygen therapy.	**Grade D**
R67	Patients should be warned about the risks of fire and explosion if they continue to smoke when prescribed oxygen.	**Grade D**

7.6.2 Ambulatory oxygen therapy

Ambulatory oxygen is defined as oxygen delivered by equipment that can be carried by most patients. It provides portable oxygen during exercise and activities of daily living. It may be used as part of continuous oxygen therapy in which case its benefits are those of long term oxygen therapy. But it is also used in isolation in the hope of improving exercise tolerance and quality of life.

The efficacy of ambulatory oxygen therapy is currently limited by the duration of oxygen supply from portable size cylinders even at low flow rates (this is a local provider issue).

Table 7.3 Deleted

Evidence statements

Oxygen conserving devices that provide oxygen with each breath are now available with very lightweight cylinders. These can last for a similar period of time to liquid-oxygen cylinders[309].	IV

GDG consensus statements

Ambulatory oxygen therapy can be used as a way of ensuring that patients who require long term oxygen therapy and who leave the home on a regular basis receive oxygen for sufficient hours to gain the benefits of LTOT.	IV

In patients who do not meet the criteria for LTOT ambulatory oxygen therapy has been proposed as a means of improving exercise capacity and or health status:

- A recent cross over trial[318] (N=41) suggested benefits in health status. Ib

- In a small number of appropriately assessed patients who show desaturation on exercise, ambulatory oxygen therapy improves exercise capacity in patients with COPD. IV

- Overall, in patients who have not undergone such an assessment, evidence available to date[171 319] does not allow any firm conclusions to be drawn concerning the effectiveness of ambulatory oxygen therapy in patients with COPD. Ia

Most of the devices for the provision of ambulatory oxygen therapy are not currently available on prescription. IV

Liquid oxygen is considerably more costly to provide for the patient. Liquid-oxygen portable systems can on average supply 8 hours of oxygen at 2 l/min, though they may be used in conjunction with oxygen-conserving devices. These liquid units must be filled from a large reservoir that is delivered to the patient's home. As liquid oxygen systems evaporate with time, the large home reservoir unit requires frequent filling or replacement. IV

The technology for the provision of ambulatory oxygen is developing rapidly. IV

Health economic evidence

A cost utility analysis was found which compared oxygen supplied by a concentrator with cylinders for ambulation with liquid oxygen both at home and for ambulation. The total costs of using liquid oxygen were higher but liquid oxygen led to better quality of life assessed using the sickness impact profile. No significant difference was found by the EQ-5D however [320].

Recommendations

R68	People who are already on LTOT who wish to continue with oxygen therapy outside the home, and who are prepared to use it, should have ambulatory oxygen prescribed.	**Grade D**
R69	Ambulatory oxygen therapy should be considered in patients who have exercise desaturation, are shown to have an improvement in exercise capacity and/or dyspnoea with oxygen, and have the motivation to use oxygen.	**Grade D**
R70	Ambulatory oxygen therapy is not recommended in COPD if PaO_2 is greater than 7.3 kPa and there is no exercise desaturation.	**Grade D**
R71	Ambulatory oxygen therapy should only be prescribed after an appropriate assessment has been performed by a specialist. The purpose of the assessment is to assess the extent of desaturation, and the improvement in exercise capacity with supplemental oxygen, and the oxygen flow rate required to correct desaturation. Phrase deleted pertaining to oxygen saturation.	**Grade D**
R72	Small light-weight cylinders, oxygen-conserving devices and portable liquid oxygen systems should be available for the treatment of patients with COPD.	**Grade D**
R73	A choice about the nature of equipment prescribed should take account of the hours of ambulatory oxygen use required by the patient and the oxygen flow rate required. Table 7.4 Deleted	**Grade D**

7.6.3 Short-burst oxygen therapy

Short-burst oxygen therapy is widely prescribed [321] and is one of the most expensive therapies used in the NHS. It has been claimed that it may simply be an expensive placebo and that some of its apparent benefits are due to a cooling effect of the oxygen on the face rather that a correction of hypoxia.

Short burst oxygen is commonly prescribed for use by patients who do not meet the criteria for LTOT but who remain breathless after minimal exertion despite other therapy. It is usually provided from cylinders.

Evidence statements

Previous studies have shown variable results on the issue of short-burst oxygen therapy. Some improvement has been found in exercise capacity and dyspnoea, when using short-burst oxygen before exercise, though oxygen saturation was not measured [322].	IIb
Patients report considerable symptomatic benefit and earlier recovery after exercise with short-burst oxygen, though there is little evidence to support this finding and effects may not be reproducible with time [323].	IIb
One study showed that patients with chronic hypoxaemia due to COPD or interstitial lung disease show reduction in dyspnoea after 10 minutes of supplemental oxygen therapy, though normoxaemic patients were not studied [324].	IIb
Some patients reporting improvements with short-burst oxygen may show exercise desaturation, though this has not been specifically studied in relation to short-burst intermittent oxygen use.	IV

Health economic evidence

No evidence was found on the cost effectiveness of short burst oxygen use in the home. However, it should be noted that this is an area with a high cost and relatively unknown benefit. Although current recommendations are for conservative prescription by the specialist when all other treatments have shown no effect, it is recommended that research be carried out into the cost effectiveness.

Recommendations

R74	Short-burst oxygen therapy should only be considered for episodes of severe breathlessness in patients with COPD not relieved by other treatments.	**Grade C**
R75	Short-burst oxygen therapy should only continue to be prescribed if an improvement in breathlessness following therapy has been documented.	**Grade D**
R76	When indicated, short-burst oxygen should be provided from cylinders.	**Grade D**

7.7 Non-invasive ventilation

Non-invasive ventilation (NIV) is a method of providing ventilatory support that does not require the placement of an endotracheal tube. It is usually delivered via a mask that covers the nose, but occasionally a full face mask covering the nose and the mouth is required. The ventilators themselves are compact and portable and some can be run off car batteries as well as mains electricity.

NIV is most commonly used to treat acute respiratory failure during exacerbations of COPD (see section 8.13); however, interest has grown in using it as a treatment for chronic hypercapnic respiratory failure in selected patients. In these patients it may be combined with LTOT.

There are a number of mechanisms by which NIV might benefit patients with stable COPD. NIV might rest the chronically fatigued respiratory muscles and allow recovery of the inspiratory muscle function [325]. NIV may also improve sleep time and efficiency [326] by reducing episodes of hypoventilation associated with desaturation. Thirdly, by reducing nocturnal hypoventilation NIV may allow the respiratory centre to be reset thereby leading to improvements in daytime hypercapnia [327].

One systematic review was found[190] that compared NIV plus standard therapy with standard therapy alone. The review consisted of four RCTs. These studies all used different inclusion criteria and different ventilator settings with the result that it was felt that analysis of their pooled results was invalid.

One additional RCT was also identified[328] (N=122), which compared NIV plus long-term oxygen therapy (LTOT) with LTOT alone. However, this study used lower inflation pressures than are normally used, relied on some historical control data and was not powered to detect differences in exacerbation rates. These issues make it difficult to draw firm conclusions from this study and further large scale, long-term studies are required in this important area.

Evidence statements

The addition of NIV to LTOT in stable COPD patients with chronic ventilatory failure improved **daytime $PaCO_2$** during oxygen breathing[328].	Ib
Resting dyspnoea significantly improved over time in the NIV + LTOT group and at month 24 was significantly better than in the LTOT alone group. Month 12 treatment effect 0.4, 95% CI 0.02 to 0.78 (p = 0.048). Month 24 treatment effect 0.6, 95% CI 0.15 to 1.05 (p = 0.013)[328].	Ib

After 2 years **quality of life** (measured by the MRF-28) significantly improved in the NIV + LTOT group compared to the LTOT group, treatment effect 7.1, 95% CI; 0.13 to 4.07; (p=0.041). The SGRQ also showed a trend to improvement in both groups[328].	Ib
Hospital admissions were not significantly different between groups during follow-up[328].	Ib
The addition of non invasive ventilation (NIV) to long-term oxygen therapy (LTOT) in stable COPD patients with chronic ventilatory failure does not improve **lung function**[328].	Ib

GDG consensus statements

There is additional inconsistent data from a small number of studies on small numbers of patients that NIV produces improvements in blood gases, dyspnoea, quality of life and exacerbation rates.	IV
Patients with chronic hypercapnic respiratory failure who have been ventilated during an exacerbation or who are intolerant of LTOT may get improvements in blood gases, dyspnoea, quality of life and exacerbation rates when treated with NIV.	IV

Recommendations

R77	Adequately treated patients with chronic hypercapnic respiratory failure who have required assisted ventilation (whether invasive or non-invasive) during an exacerbation or who are hypercapnic or acidotic on LTOT should be referred to a specialist centre for consideration of long-term NIV.	**Grade D**

7.8 Management of pulmonary hypertension and cor pulmonale

Hypoxic patients with COPD develop pulmonary hypertension (i.e. pulmonary artery pressure > 20mmHg). Initially this is as a result of hypoxic vasoconstriction but structural changes also develop and these may be due to inflammatory processes. Pulmonary hypertension may be present for years without causing symptoms but in some patients it leads to the development of the clinical syndrome of cor pulmonale. For the purposes of this guideline, a clinical definition of cor pulmonale based on the pathological definition proposed by Behnke et al. [329] has been adopted: *"Alteration in the structure and function of the right ventricle resulting from diseases affecting the lungs except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart."*

In the context of this guideline, the term “cor pulmonale” has been adopted to define a clinical condition that is identified and managed on the basis of clinical features. This clinical syndrome of cor pulmonale includes patients who have right heart failure secondary to lung disease and those in whom the primary pathology is retention of salt and water, leading to the development of peripheral oedema.

Cor pulmonale is defined as a clinical syndrome characterised by fluid retention, peripheral oedema and a raised venous pressure in patients with COPD who have no other cause of ventricular dysfunction.

Although the development of cor pulmonale and the diagnosis of pulmonary hypertension are significant events in the natural history of COPD and have implications for prognosis, a full literature search and critical appraisal process was not undertaken in this area, due to the time limitations within the guideline development process. However, a MEDLINE and Cochrane Database search, and a selective review of frequently cited papers and key review articles was undertaken as part of the development of a background paper for discussion by the guideline development group (as per section 2).

7.8.1 Diagnosis of pulmonary hypertension and cor pulmonale

Evidence statements

Pulmonary arterial hypertension is associated with widening of the descending pulmonary artery on a plain chest radiograph. A high hilar cardiothoracic ratio (>35) in patients with COPD was reported to be 95% sensitive and 100% specific for the presence of pulmonary hypertension [330], but could not predict the degree of hypertension and considerable inter observer variation in its measurement has been reported [331].	III
Detection of right ventricular hypertrophy on ECG is specific but not sensitive[332].	III

Echocardiography can be used to assess Ppa non-invasively[333].	IV
Examinations are technically inadequate because of hyperinflation in up to 35% of patients[334,335] and there is not always a good correlation between Ppa measured using echocardiography and the Ppa measured invasively in COPD.	III
Two dimensional echocardiography can measure right ventricular dimensions and wall thickness but this is technically difficult and there is no gold standard for comparison[334,336].	III
Doppler echocardiography measuring the tricuspid regurgitant jet is the best method of assessing Ppa non-invasively it cannot be used to accurately predict Ppa in individual patients.	IV
MRI appears to be the most accurate method for measuring right ventricular dimensions non-invasively[337].	III
Radionuclide ventriculography is an accurate and reproducible non-invasive way of measuring **left** ventricular function but it is less good for right ventricular function because of overlap of RA and RV and presence of tricuspid regurgitation[333,338].	III

GDG consensus statements

Pulmonary hypertension in COPD can be non-invasively assessed by echocardiography but examinations may be limited by hyperinflation and may not accurately assess the pulmonary artery pressure.	IV
Pulmonary hypertension in COPD can only be quantified accurately by right heart catheterisation but this is rarely indicated.	IV

The diagnosis of cor pulmonale is essentially clinical but depends on excluding other causes of peripheral oedema (including left ventricular failure and chronic thromboembolic disease).	IV
The diagnosis of right heart failure can be supported by ECG changes or echocardiography and, in addition, these tests can exclude other causes of oedema and heart failure.	IV
MRI scanning and radionuclide ventriculography are the most accurate ways of measuring right ventricular function in patients with COPD.	IV
Chest radiography cannot be relied upon to identify pulmonary hypertension in COPD.	IV

Recommendations

R78	A diagnosis of cor pulmonale should be considered if patients have: • peripheral oedema • a raised venous pressure • a systolic parasternal heave • a loud pulmonary second heart sound.	**Grade D**
R79	It is recommended that the diagnosis of cor pulmonale is made clinically and that this process should involve excluding other causes of peripheral oedema.	**Grade D**

7.8.2 Treatment of cor pulmonale

Treatment of cor pulmonale aims to correct hypoxia and overcome salt and water retention.

Uncontrolled studies of ACE inhibitors have shown variable results and cannot be relied upon. ACE inhibitors may have benefits in reducing salt and water retention but these have not been shown to be clinically relevant in long term studies.

Diuretics are widely used but there are no trials in COPD to support their use. There are theoretical concerns that they may reduce cardiac output by reducing ventricular filling pressures. They may also cause a metabolic alkalosis thereby reducing ventilatory drive.

Evidence statements

Oxygen

LTOT reduces the progressive rise in Ppa seen in hypoxic patients[310].	Ib
Oxygen reduces the abnormal rise in Ppa seen during exercise[312] and prevents the fall in right ventricular ejection fraction[339].	IIa

ACE Inhibitors

One study was found on the use of an ACE inhibitor[340] and one study on the use of an angiotensin receptor antagonist[341] in pulmonary hypertension but there were methodological limitations with these studies such that it was not possible to formulate any evidence statements.	N/A

Calcium channel blockers

Two studies, one of 18 months duration[342] and one of 3 months duration[343] failed to show benefits of nifedipine.	Ib

Alpha-blockers

Alpha-blockers reduce pa in patients with COPD but their use is limited by their side-effects[344-346].	IIb

Digoxin

Studies of the effects of digoxin have failed to show any benefit in cor pulmonale unless there was co-existent left ventricular failure[347-349].	IIa

GDG consensus statements

Diuretics

There is insufficient evidence to recommend changing the current clinical practice of using diuretics to control peripheral oedema in patients with cor pulmonale.	IV

Recommendations

R80	Patients presenting with cor pulmonale should be assessed for the need for long-term oxygen therapy.	**Grade A**
R81	Oedema associated with cor pulmonale can usually be controlled symptomatically with diuretic therapy.	**Grade D**
R82	The following are not recommended for the treatment of cor pulmonale: • angiotensin-converting enzyme inhibitors • calcium channel blockers • alpha-blockers • digoxin (unless there is atrial fibrillation).	**Grade C**

7.9 Pulmonary rehabilitation

Pulmonary rehabilitation can be defined as a multidisciplinary programme of care for patients with chronic respiratory impairment that is individually tailored and designed to optimise each patient's physical and social performance and autonomy. It is widely used for patients with COPD [350].

Pulmonary rehabilitation is an increasingly popular and effective option for patients with moderate to severe COPD. Rehabilitation aims to prevent deconditioning and allow the patient to cope with their disease. Most programmes are hospital based and comprise individualised exercise programmes and educational talks.

Pulmonary rehabilitation has been available in North America and Europe for some years, but availability is still limited in the UK. Individual programmes differ in the precise exercises used, are of different duration, involve variable amounts of home exercise and have

different referral criteria. There is growing interest in running rehabilitation in community settings which may make it easier for patients to attend.

When reviewing the evidence for pulmonary rehabilitation many papers were rejected due to small sample size, lack of methodological detail, no comparison group or because the paper had been included in a systematic review or meta-analysis already reviewed. Pulmonary rehabilitation was compared to either usual care or education. The Cochrane Systematic Review by Lacasse [214], ACCP Evidence-Based Guidelines [351], BTS Statement [350] and a meta-analysis[352] were reviewed.

Clinical introduction

Since publication of the COPD guideline in 2004, a number of studies have examined the timing of pulmonary rehabilitation.

Some studies have examined pulmonary rehabilitation initiated during an acute exacerbation, and continued beyond the exacerbation into the stable phase. The GDG agreed that "early" pulmonary rehabilitation was that which took place within one month of hospitalisation following an exacerbation, and therefore felt it was important to look at the comparison of early rehabilitation versus control (best conventional care).

The GDG felt it appropriate to compare the relative outcomes of pulmonary rehabilitation programmes commenced early in the recovery phase after exacerbation, with those delayed until later in the stable phase. The GDG decided that only RCTs should be reviewed and that the minimum follow-up should be six months. Outcomes agreed for assessment included, hospitalisations, exacerbations, mortality, A+E attendance, SGRQ, exercise performance (incremental shuttle walk and six minute walk), but not FEV_1 or breathlessness (TDI).

7.9.1 Benefits of pulmonary rehabilitation

There is good evidence about the benefits that pulmonary rehabilitation can produce. There has been no direct comparison of the effects of a pulmonary rehabilitation course and the effects of pharmacotherapy, but most programmes require optimisation of medical therapy prior to, or as part of, enrolment.

Evidence statements

Pulmonary rehabilitation leads to statistically significant and clinically meaningful improvements in **health related quality of life** (CRQ), **functional exercise capacity** (WMD 49 meters 95% CI 26 to 72) and **maximum exercise capacity** (WMD 5.4 watts 95% CI 0.5 to 10.2)[351].	Ia
Pulmonary rehabilitation reduces **dyspnoea**[350,351].	IV & Ia
A single study (n=119) using the Centres for Epidemiologic Studies Depression Scale (CES-D) showed that there was no effect on **depression**[353].	Ib
The ACCP evidence-based guideline [351] highlight that there is currently little information available from RCTs that evaluate the utilisation of health care resources for patients completing a comprehensive pulmonary rehabilitation programme. It has been shown in several non randomised and observational studies that there is a trend towards a decrease in the total number of **hospitalisation days** as well as the **total number of hospitalisations** required for a patient with COPD in the years following the completion of a comprehensive pulmonary rehabilitation programme compare to the year preceding rehabilitation.	Ia
The GDG was aware of one RCT[354] (n=200) contained within the Lacasse systematic review[355], which found no difference between the rehabilitation and control groups in the number of **hospitalisations.**	Ib
There was conflicting evidence regarding the **number of days spent in hospital**.	
Griffiths et al. [354] found that the number of days rehabilitation patients compared to control patients spent in hospital differed significantly (mean 10.4 days versus 21.0 days, p=0.022) in favour of the rehabilitation patients.	Ib

However Ries et al. [356] in a smaller RCT (n=119) found that duration of hospital stay was non significant. Ib

In relation to the outcome of **primary care consultations**, Griffiths et al. [354] found that the rehabilitation group had more primary care consultations at the GP's premises than did the control group (p=0.033) but fewer home visits (p=0.037). Ib

A single centre RCT has shown that patients with more severe COPD undergoing a 8 week programme of pulmonary rehabilitation maintain improvements in exercise capacity and health status for up to 6 months however these were not sustained at one year[357]. Ib

Health economic evidence

Fourteen papers of potential relevance were found. Some studies were not full economic evaluations and estimated the cost of providing a pulmonary rehabilitation service. Two studies estimated the cost effectiveness in the UK. The cost per QALY was estimated at between £2,000 and £8,000 based on a minimum of four weeks rehabilitations[358]. Griffiths et al[359] undertook an economic evaluation alongside a clinical trial and estimated that pulmonary rehabilitation was cost saving and increased quality of life. The probability of the cost per QALY generated being below £0 was 0.64 [359].

There is good evidence that pulmonary rehabilitation is **cost effective** in the outpatient setting compared to usual care [359]. 1b

GDG consensus statements

The magnitude of the effects of pulmonary rehabilitation on **exercise capacity, dyspnoea** and **health related quality of life** are significantly greater than the effects of bronchodilator drugs.	IV

7.9.2 Course content, setting and duration

Traditionally pulmonary rehabilitation courses have been run in secondary care settings, usually on an out-patient basis but also on an in-patient basis in countries outside the UK. Recently community based programmes have also been developed. There is good evidence on the content of the programme, but less information on the optimum duration or comparative efficacy in different settings.

Evidence statements

The GDG found comprehensive evidence-based guidelines on pulmonary rehabilitation [351]. These guidelines focus upon **course content** and included lower and upper extremity training, ventilatory muscle training and psychosocial, behavioural & educational components. The authors conclude that in patients with COPD, lower extremity training improves exercise tolerance whilst upper extremity training improves arm function. The evidence for ventilatory muscle training (VMT) currently does not support the routine use of VMT.	Ia
The evidence to date does not support the benefits of short-term psychosocial single interventions however longer-term interventions may be beneficial. Scientific evidence in this area is lacking.	N/A
Two meta analyses were found of **respiratory muscle training** [360,361], which demonstrate conflicting findings.	Ia

The Smith[360] meta-analysis of 17 RCTs demonstrated no significant findings for FEV_1 (8 trials), maximum inspiratory pressure respiratory muscle strength (11 trials), respiratory muscle endurance (9 trials), laboratory exercise capacity (9 trials), functional exercise capacity (9 trials) and functional status (QoL). The only significant effect was for respiratory muscle strength as measured by maximum voluntary ventilation. This equates to an 8.8L difference (p=0.02) (7 trials). Overall there is little evidence in support of respiratory muscle training. A disparity was noted by the GDG in the results published within the abstract and those of the body of the text for this meta-analysis. Overall the results remain the same. Ia

Lotters[361] updated the work in this area and includes five of the studies that had previously been included in the Smith [360] meta-analysis. Ia

Lotters [361] demonstrated significant findings for inspiratory muscle strength (effect size 0.56, 95% CI 0.35 to 0.77) (15 studies), endurance (0.41, 95% CI 0.14 to 0.68) (7 studies) and dyspnoea (TDI) (2.3, 95% CI 1.44 to 3.15) (2 studies). From this recent meta-analysis, it can be concluded that inspiratory muscle training significantly improves inspiratory muscle strength and endurance whilst the sensation of dyspnoea significantly decreases. Ia

A single centre study[362] with small numbers of patients (N=47 between three arms) examined the effects of **strength, endurance or combined strength training**. At the end of the training period and at 12 weeks after training, all patients in the three groups showed significant increases in the duration of endurance testing as compared with pre training values. All training modalities showed significant improvements of the breathlessness score and the dyspnoea dimension of the chronic respiratory questionnaire. III

The BTS statement on pulmonary rehabilitation [350] provides an evidence update to the ACCP guidelines [351] and concludes that pulmonary rehabilitation is effective in all **settings** including hospital inpatient, hospital outpatient, the community, and possibly the home. IV

Puente-Maestu [363] undertook a small (n=41) RCT comparing the effects of **supervised versus self-monitored training programmes** in patients with COPD. Both types of training improved exercise tolerance, but the magnitude and the extent of physiological improvements were larger ($p<0.05$) in patients training under supervision. Ib

A single centre study[364] compared **duration** of three compared with eighteen months of exercise training. There were small but statistically significant differences in favour of the eighteen-month programme for self reported physical disability using the Fitness Arthritis and Seniors Trial Functional Performance Inventory. There were statistically but not clinically significant improvements in six minute walk distance (6MWD). Ib

GDG consensus statements

The majority of studies have been performed in a hospital outpatient setting. There is limited data on effectiveness in community or home studies and there have been no comparative studies. IV

The GDG concluded that the evidence regarding prolonged supervised outpatient programmes showed very modest benefits and that such programmes were unrealistic. IV

The COPD GDG augmented the BTS statement with the following italicised consensus addition: IV

In relation to **duration of the initial programme**, and taking in to account current evidence (cited in[350]) the GDG believe that outpatient programmes should contain a minimum of 6 weeks *and a maximum of 12 weeks* of physical exercise, disease education, psychological and social interventions.

7.9.3 Referral criteria

No randomised trials were found looking at whether pre-determined factors influence a patient's response to pulmonary rehabilitation. Some data was found from retrospective analyses on which factors predicted concordance and response. The position statements of the BTS, ERS and ATS were considered in formulating the statements and recommendations.

Evidence statements

One cross sectional study was found[365] (n=91) that looked at whether people who declined or failed to complete COPD rehabilitation programmes differed in terms of demographics, physiological or psychological factors from those people who completed.	III
The non-adherent group compared to the adherent group were more likely to be widowed or divorced and less likely to be currently married ($p<0.001$), more likely to live alone (39% vs. 14%, $p<0.02$), and more likely to live in rented accommodation (31 vs. 6%, $p<0.002$). They were also more likely to be current smokers (28 vs. 8%, $p<0.02$). Inadequate social support for COPD related problems (51 vs. 2%, $p=0.001$) was more common in the non-adherent group.	
The introduction of rehabilitation becomes appropriate when patients become aware of their disability [350].	IV
There is currently no justification for selection on the basis of **age, impairment, disability, smoking status** or **use of oxygen**. Some patients with serious co-morbidity such as cardiac or locomotor disability may not benefit as much [350].	IV
The only issues material to selection are poor motivation and the logistical factors of **geography, transport, equipment usage**, and the **group composition** [350].	IV

GDG consensus statements

The COPD GDG augmented the BTS statement [350] with the following italicised consensus addition: Rehabilitation should be considered at all stages of disease progression when symptoms *and disability* are present and not at a predetermined level of impairment. The threshold for referral would usually be breathlessness equivalent to MRC dyspnoea grade 3 (see table 6.1).	IV

7.9.4 Repeat programmes

The benefits of pulmonary rehabilitation appear to wane with time. There is limited evidence concerning the benefits of attendance at further pulmonary rehabilitation programmes.

Evidence statements

There was evidence that repeated pulmonary rehabilitation led to further temporary improvements in breathlessness and exercise capacity and reduced exacerbations [366]. The GDG was aware of methodological limitations of this study. The sample size was small, n=61, of which only 36 patients of the groups combined were available for evaluation.	Ib

7.9.5 Timing of rehabilitation programmes

The GDG posed the following question:

> **REHAB: Does early pulmonary rehabilitation (within one month of hospital discharge) in people who had an acute exacerbation improve outcomes compared with usual care (or no rehabilitation), in people with COPD?**

Methodological introduction

The literature was searched for RCTs or systematic reviews comparing pulmonary rehabilitation after acute exacerbation of COPD with conventional community care (or control).

The clinically important relative risk reduction (RRR) for mortality was 15%, exacerbations (20%), hospitalisation (20%), change in SGRQ (-4 points), shuttle walk distance (48 meters), FEV_1 (100 ml), TDI (1 unit), and six minute walk distance (50 m).

One systematic review [367] and one additional RCT [368] were identified. The Eaton et al RCT [368], which was added to the Puhan et al systematic review, randomised patients who had an exacerbation (N=97; follow-up 3 months) to an inpatient pulmonary rehabilitation program consisting of exercise; followed by an 8 week outpatient pulmonary rehabilitation programme upon hospital discharge, or to usual care. [368] One RCT [369] was excluded from the Puhan et al systematic review as it excluded patients who had an exacerbation within one month prior to patient enrolment.

It should be noted that the six RCTs included in the updated Puhan et al SR were all open trials (patient and investigator blinding is not possible) and consisted of mostly older people with COPD (mean age range 64-70 years; range FEV1% predicted 32%-40%). Table 7.5 summarises the characteristics of the six included RCTs, specifically outlining the type of rehabilitation programme.

For further forest plots, please see appendix O.

Table 7.5 Summary of pulmonary rehabilitation programmes offered to people with COPD following an exacerbation

Included trials	Follow up	N	Rehabilitation details
Behnke 2000 [370,371]	18 months	26	Inpatient rehab consisting of endurance exercise (5 walking sessions/day for 10 days); followed by outpatient rehab of 6 months of supervised home-based endurance training 3 walking sessions/day
Kirsten 1998[372]	11 days	29	Inpatient rehab started after 6-8 days when patients were stable enough to participate. Inpatient rehab consisted of exercise training (5 walking sessions/day + 6MWD test) daily for 10 days
Nava 1998[373]	6 weeks	80	Inpatient rehab in RICU started 2-5 days after admission once patients were considered clinically stable. Inpatient rehab consisted of two daily sessions of progressive ambulation training + exercise training. Total length of RICU stay was 33.2 days control versus 38.1 days rehab NS
Eaton 2009[368]	3 months	97	Inpatient rehab consisting of exercise and patients encouraged to exercise 30 min/day; followed by Outpatient rehab consisting of supervised exercise training plus education twice/weekly for 8 weeks in a hospital based outpatient programme

Mann 2004[374]	3 months	42	Outpatient rehab started within 10 days of hospital discharge. Rehab consisted of 8 week rehab program of 2 classes/week of exercise and education +home based exercise encouraging 20 min/day
Murphy 2005[375]	6 months	26	Outpatient rehab initiated immediately after discharge from hospital consisting of twice weekly supervised exercise sessions in their homes for 6 weeks

Evidence Profile: Early pulmonary rehabilitation post exacerbation compared with usual care/control

Author(s): Milo Puhan, Madlaina Scharplatz, Thierry Troosters, E. Haydn Walters, Johann Steurer
Date: 2009-08-24
Question: Should Early Rehabilitation versus control/usual care be used for people with COPD who have had an acute exacerbation?
Settings:
Bibliography: Puhan M, Scharplatz M, Troosters T, Walters EH, Steurer J. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease [Data only. When citing this record quote "Cochrane Database of Systematic Reviews 2009, Issue 1".]. Cochrane Database of Systematic Reviews [Year], Issue [Issue].; Eaton T, Young P, Fergusson W et al. Does early pulmonary rehabilitation reduce acute health-care utilization in COPD patients admitted with an exacerbation? A randomized controlled study. Respirology. 2009; 14(2):230-238.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Early Rehabilitation versus control/usual care	control	Relative (95% CI)	Absolute		
Hospital admission (to end of follow-up) (follow-up 3-18 months)												
4	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/94 (19.1%)	42/96 (47.8%)	RR 0.43 (0.27 to 0.7)	272 fewer per 1,000	⊕⊕OO LOW	
Mortality (follow-up 6 weeks -18 months)												
3	randomised trial	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	14/94 (14.9%)	7/53 (9.5%)	RR 0.88 (0.37 to 2.11)	11 fewer per 1,000	⊕OOO VERY LOW	

Exacerbations (follow-up 6-18 months)												
2	randomised trial	very serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/36 (8.3%)	8/36 (25.8%)	RR 0.38 (0.11 to 1.26)	159 fewer per 1,000	⊕OOO VERY LOW	
Health-related quality of life (follow-up 3-6 months; measured with: SGRQ; range of scores: -; Better indicated by less)												
2	randomised trial	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0	0	-	MD -11.14 (-17.11 to -5.17)	⊕⊕OO LOW	
Change from baseline in 6 minute walking test (follow-up 11 days-18 months; measured with: Six minute walking distance; range of scores: -; Better indicated by more)												
3	randomised trial	very serious[6]	serious[7]	no serious indirectness	no serious imprecision	none	0	0	-	MD 124.81 (97.94 to 151.68)	⊕OOO VERY LOW	
6MWD difference between groups at end of follow-up (follow-up 11 days-18 months; measured with: Six minute walking distance; range of scores: -; Better indicated by more)												
4	randomised trial	very serious[8]	serious[9]	no serious indirectness	no serious imprecision	none	136	95	-	MD 173.36 (157.45 to 189.28)	⊕OOO VERY LOW	
Change from baseline in shuttle walk test (follow-up 3-6 months; range of scores: -; Better indicated by more)												
2	randomised trial	very serious[5]	no serious inconsistency	no serious indirectness	serious[10]	none	0	0	-	MD 81.23 (47.52 to 114.95)	⊕OOO VERY LOW	

[1] 3/4 RCTs had unclear allocation concealment; 4/4 RCTs open label; high loss to follow-up in Behnke RCT (38% rehab; 39% usual care); 3/4 RCTs did not perform ITT analysis

[2] 3/3 RCTs had unclear allocation concealment; 3/3 open label; high loss to follow-up in Behnke RCT (38% rehab; 39% usual care); 3/3 RCTs did not perform ITT analysis

[3] wide 95% CI that crosses MID twice

[4] 1/2 RCTs had unclear allocation concealment; 2/2 RCTS were open; high loss to follow-up in Behnke RCT (38% rehab; 39% usual care); 2/2 RCTs did not perform ITT analysis

[5] 1/2 RCTs had unclear allocation concealment; 2/2 RCTs open label; 2/2 RCTs did not perform ITT analysis

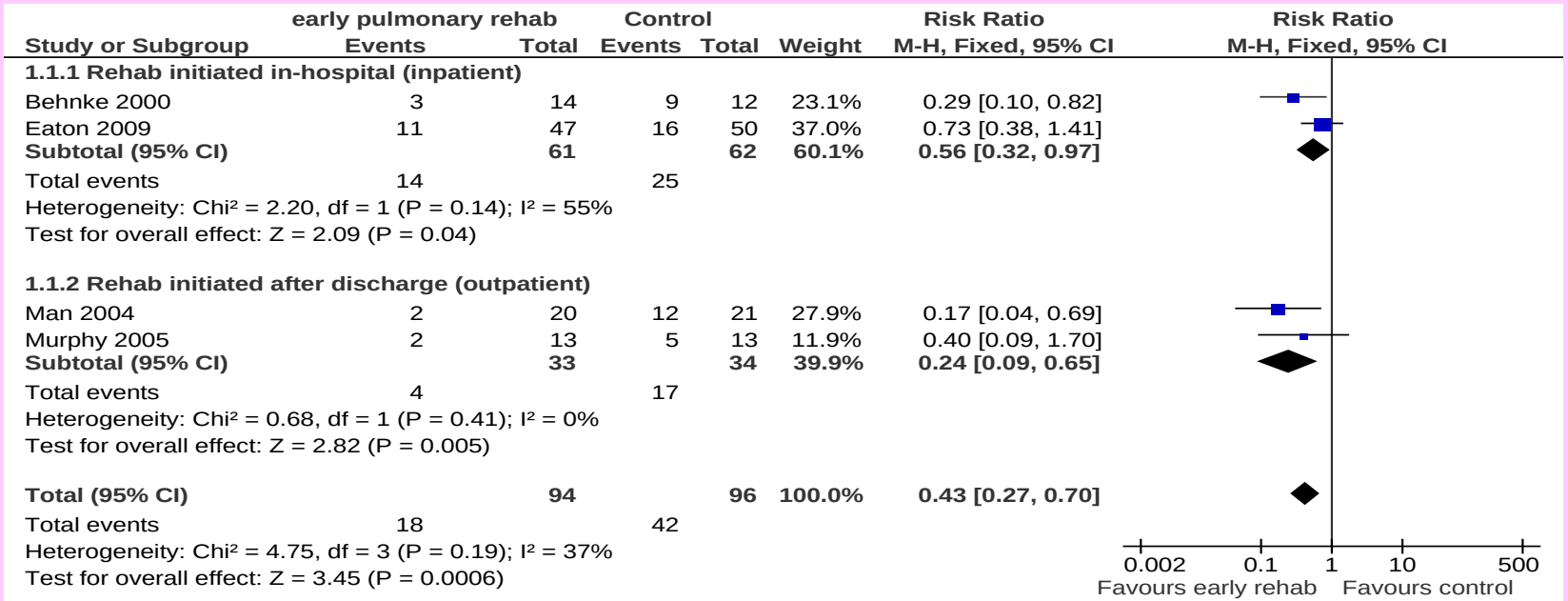
[6] 3/3 RCTs had unclear allocation concealment; 3/3RCTs open label; high loss to follow-up in Behnke RCT (38% rehab; 39% usual care); loss to follow-up not clearly reported in Nava and Kirsten; 3/3 RCTs did

not perform ITT analysis
[7] high heterogeneity (I2 = 90%) that could not be explained by sub-grouping according to whether rehab occurred in the index hospitalisation or whether rehab occurred post discharge from hospital

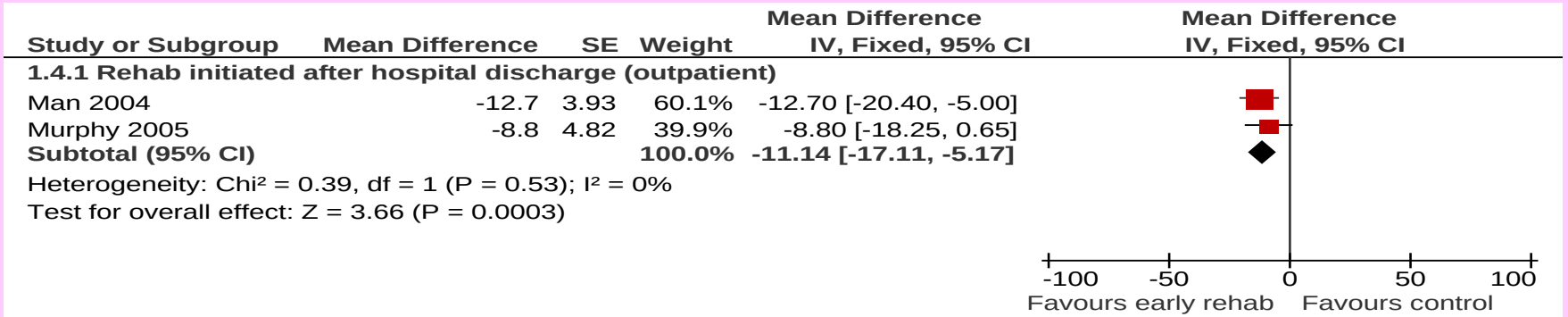
[8] 4/4 RCTs had unclear allocation concealment; 4/4 RCTs open label; high loss to follow-up in Behnke RCT (38% rehab; 39% usual care); loss to follow-up not reported clearly in Nava and Kirsten; 3/4 RCTs did not perform ITT analysis
[9] high heterogeneity (I2 = 97%) that cannot be explained
[10] wide 95% CI that crosses MID

Forest Plots

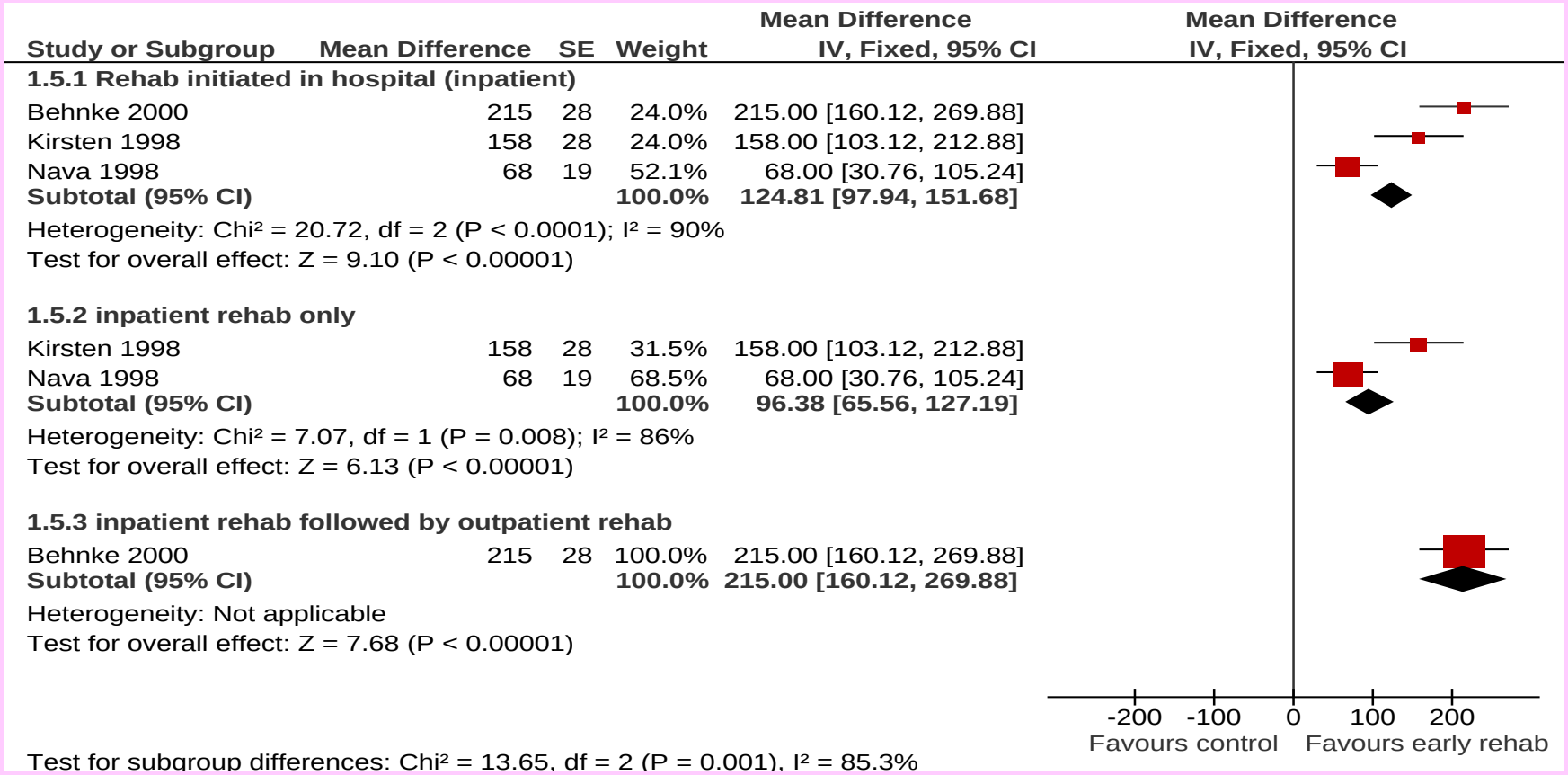
Readmission



Change in SGRQ

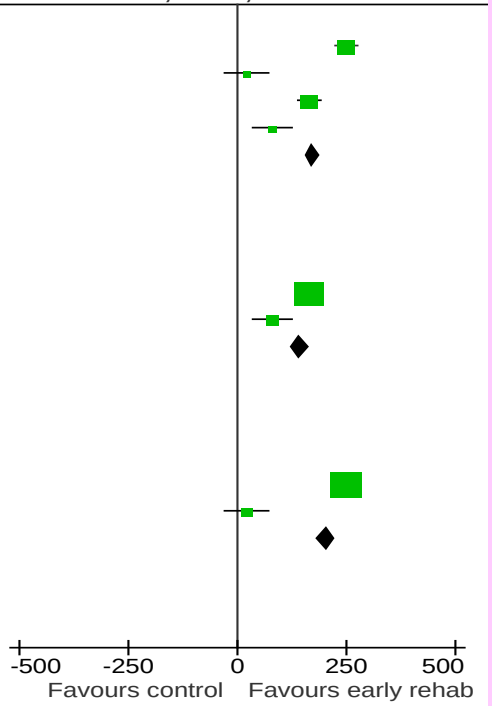


Change from baseline in 6 minute walk test

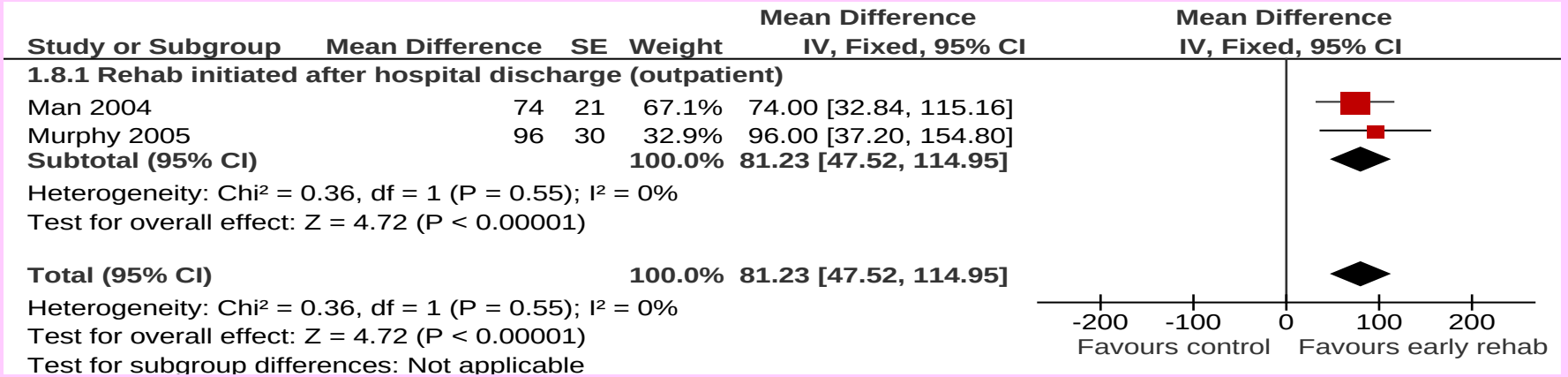


Mean difference between groups in six minute walk test at end of follow-up

Study or Subgroup	early pulmonary rehab Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 Rehab initiated in hospital (inpatient)								
Behnke 2000	480	40	15	230	30	15	39.5%	250.00 [224.70, 275.30]
Eaton 2009	334	119	47	313	126	45	10.1%	21.00 [-29.13, 71.13]
Kirsten 1998	420	42	14	255	27	15	37.7%	165.00 [139.10, 190.90]
Nava 1998	220	110	60	140	80	20	12.6%	80.00 [35.23, 124.77]
Subtotal (95% CI)			**136**			**95**	**100.0%**	**173.36 [157.45, 189.28]**
Heterogeneity: Chi² = 87.84, df = 3 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 21.35 (P < 0.00001)								
1.6.2 inpatient rehab only								
Kirsten 1998	420	42	14	255	27	15	74.9%	165.00 [139.10, 190.90]
Nava 1998	220	110	60	140	80	20	25.1%	80.00 [35.23, 124.77]
Subtotal (95% CI)			**74**			**35**	**100.0%**	**143.68 [121.27, 166.10]**
Heterogeneity: Chi² = 10.38, df = 1 (P = 0.001); I² = 90%								
Test for overall effect: Z = 12.56 (P < 0.00001)								
1.6.3 inpatient rehab followed by outpatient rehab								
Behnke 2000	480	40	15	230	30	15	79.7%	250.00 [224.70, 275.30]
Eaton 2009	334	119	47	313	126	45	20.3%	21.00 [-29.13, 71.13]
Subtotal (95% CI)			**62**			**60**	**100.0%**	**203.50 [180.91, 226.09]**
Heterogeneity: Chi² = 63.89, df = 1 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 17.66 (P < 0.00001)								



Change from baseline in shuttle walk test



Evidence statement: Early rehabilitation versus usual care/control

Compared with usual care, people with an exacerbation of COPD who received early pulmonary rehabilitation had a significantly decreased:

- Risk of readmission to hospital [low quality evidence]

Compared with usual care, people with an exacerbation of COPD who received early pulmonary rehabilitation had a significantly improved:

- Six minute walk distance (expressed as change from baseline) [very low quality evidence]
- Six minute walk distance (expressed as mean difference between groups at end of follow-up) [very low quality evidence]
- Shuttle walk distance (expressed as change from baseline) [very low quality evidence]
- Health related quality of life (expressed as SGRQ total score) [low quality evidence]

There was no significant difference between people receiving early pulmonary rehabilitation compared with usual care for:

- Mortality [very low quality evidence]
- Exacerbations [very low quality evidence]

Health economic evidence

The literature was searched for economic evaluations evaluating early pulmonary rehabilitation (within one month of hospital discharge) in people who had an acute exacerbation improve outcomes compared with usual care (or no rehabilitation), in people with COPD.

No relevant studies were identified.

Evidence to recommendation

This question addressed whether it is better to provide what is normally considered to be a programme of pulmonary rehabilitation (e.g. a 6-8 week course for 2 days per week in an outpatient community setting) earlier or later in the stable phase of COPD. Early pulmonary rehabilitation was considered to be that which took place within one month of hospitalisation following an exacerbation.

The focus of the question was to examine the impact of the timing of pulmonary rehabilitation upon patient outcomes, and not to consider whether rehabilitation should be conducted in an in-patient or outpatient setting. Review of in-patient rehabilitation studies did however inform the discussion.

The question did not consider identification of new candidates for pulmonary rehabilitation, but only those eligible under current recommendations such that any recommendations would remain cost-neutral.

One systematic review [367] compared pulmonary rehabilitation after acute exacerbation of COPD with conventional community care (or control) in people who had an acute exacerbation of COPD. Six RCTs included in this review were open trials (as patient and investigator blinding is not possible) and included mostly older people with COPD (mean age range 64-70 years; range FEV_1% predicted 32%-40%). In one RCT included in this review [373] study participants were in-patients for more than 30 days, and included ICU admission, and for the majority of patients, intubation and ventilation. It was noted that ICU rehabilitation demands are very different from those on general hospital wards, and that this may skew results as in-patient physiotherapy is not necessarily considered a rehabilitation programme.

Three of the RCTs included 6-8 week pulmonary rehabilitation programmes [374] [375] [368] In the Eaton et al RCT [368], rehabilitation commenced as an inpatient and continued after discharge. Only 50% eligible patients were enrolled, and of these approximately 50% completed the programme. The other included RCTs [370-372] included in-patient rehabilitation and were excluded from consideration.

Two studies were identified for consideration which examined pulmonary rehabilitation in the early stable phase of COPD, and followed the 'UK model' of a 6- 8 week course for 2 days per week in an outpatient community setting.

For hospital readmission, there were overall concerns about the comparisons made in the studies considered. The systematic review [367] was considered problematic due to pooled data with a heterogeneous group of study designs. The GDG also noted that with care in the community, many COPD patients 'exacerbate' at home and there are no data available on community exacerbations.

It was noted that no time frame for readmission was identified in the studies. The results of the meta-analysis should be treated with caution, but the GDG felt that the outcome was probably correct.

The GDG also acknowledged that for secondary outcomes of mortality, exacerbations, quality of life (SGRQ) and exercise capacity, a number of limitations were noted in the studies considered. Most outcomes had wide confidence intervals, treatment allocation was poorly described, and few used intention to treat (ITT) analysis, such that studies were considered to have 'serious limitations' by GRADE analysis. **For mortality** as an outcome, there were serious concerns regarding pooling of the data in a meta-analysis. Mortality detection was limited in studies with a relatively short follow-period. One study in an ICU setting led to study bias. **For exacerbations and readmissions**, numbers were considered too small with few events, and few studies reported exacerbation outcome. Exacerbations were also included within the admissions data. **For quality of life (SGRQ)** the GDG noted that both studies identified reported SGRQ and both showed a benefit from pulmonary rehabilitation. **For exercise capacity,** the studies showed significant unexplained heterogeneity for 6 minute walking test (6MWD). Two studies included an incremental shuttle walk test and demonstrated benefit in favour of early pulmonary rehabilitation.

It therefore was apparent to the GDG that all of the secondary outcomes had limitations. However, overall the studies suggest that there are some advantages to early rehabilitation. The GDG also noted the strong evidence supporting the benefits of rehabilitation programmes generally, and could see no reason why patients who had recently suffered from an exacerbation should not be considered for a course of pulmonary rehabilitation. A modification to the existing recommendation was therefore made to this effect.

Recommendations

R83	Deleted.	
U11	**NEW 2010 UPDATE RECOMMENDATION 11 (U11)** Pulmonary rehabilitation should be made available to all appropriate people with COPD (see R84) including those who have had a recent hospitalisation for an acute exacerbation.	
R84	Pulmonary rehabilitation should be offered to all patients who consider themselves functionally disabled by COPD (usually MRC grade 3 and above). Pulmonary rehabilitation is not suitable for patients who are unable to walk, have unstable angina or who have had a recent myocardial infarction.	**Grade D**
R85	For pulmonary rehabilitation programmes to be effective, and to improve concordance, they should be held at times that suit patients, and in buildings that are easy for patients to get to and have good access for people with disabilities. Places should be available within a reasonable time of referral.	**Grade D**
R86	Pulmonary rehabilitation programmes should include multicomponent, multidisciplinary interventions, which are tailored to the individual patient's needs. The rehabilitation process should incorporate a programme of physical training, disease education, nutritional, psychological and behavioural intervention.	**Grade A**
R87	Patients should be made aware of the benefits of pulmonary rehabilitation and the commitment required to gain these.	**Grade D**

7.10 Vaccination and anti-viral therapy

Pneumococcal vaccination and annual influenza vaccination and are recommended for patients with chronic respiratory disease by the Chief Medical Officer. The role of newer anti viral agents in preventing or treating influenza has been looked at separately by NICE[376] but clinical experience with these drugs is limited.

Since publication of the 2004 COPD guideline NICE have replaced:

TA67 Flu prevention – amantadine andoseltamivir with TA158

TA58 Flu treatment – zanamivir (review) amantadine and oseltamivir with TA168

Influenza

One systematic review was identified[377] relating to influenza vaccine for patients with COPD. This review included studies that compared live or inactivated virus vaccines (intramuscular or intranasal routes) with placebo either alone or with another vaccine. Nine trials were included but only four (N=215) were specific to a stable COPD population. These were all carried out some years ago and used vaccines that differ from those used now.

One additional retrospective cohort study was identified relating to influenza vaccine [378]. Although this study included a heterogeneous population with chronic lung disease (N=1898) it was worthy of consideration as it included an elderly population.

Treatment of influenza

One NICE Technology Appraisal Guidance (TAG), No 58 (2003) 'Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza' [376] was identified which replaces the NICE Technology Appraisal Guidance, No 15 (2000) 'Guidance on the use of zanamivir (Relenza) in the treatment of influenza'[379].

A systematic review and economic decision modelling for the prevention and treatment of influenza A and B [380] underpins the NICE TAG, No 58 [376].

The TAG and systematic review referred to above relate to Zanamivir, Oseltamivir and Amantadine. Zanamivir is a neuraminidase inhibitor and is taken using an inhaler (Diskhaler). It is licensed for the treatment of influenza A and B. Oseltamivir is also a neuraminidase inhibitor. It can be taken orally and is licensed for the treatment of influenza A and B. Amantadine is not currently recommended for the treatment of influenza[376].

Pneumococcal vaccination

Two retrospective cohort studies were found[381,382], which appear to use the same population. These studies were included despite having a heterogeneous chronic lung disease population. The first study looks at the health benefits associated with pneumococcal vaccination of elderly patients with chronic lung disease. The second paper by Nichols et al. [382] looks at the additive benefits of influenza and pneumococcal vaccination during influenza seasons among elderly people.

It is important to note that due to the relevance of the three retrospective cohort studies by Nichols the GDG felt that the studies were worthy of inclusion. However, the study design, retrospective cohort, falls lower down the hierarchy of evidence and in addition to this, extrapolation meant that the study recommendations were downgraded as per the current NICE grading system.

One Canadian RCT was found, N=189, that looked at the efficacy of Pneumococcal vaccine compared to placebo in severe COPD patients [383]. This was subsequently excluded by the GDG due to a heterogeneous population and the date of the study.

One RCT was identified[384] relating to Haemophilus influenzae vaccine for prevention of exacerbation for chronic bronchitis. This was excluded as the population included bronchiectasis and chronic bronchial asthma.

Evidence statements

Influenza vaccination

Nichols et al. [378] compared vaccinated to unvaccinated people in a cohort of N=1898 elderly persons with chronic lung disease (CLD) over three influenza seasons and demonstrated a 52% reduction in **hospitalisations** for both pneumonia and influenza (Adjusted risk ratio 0.48 p=0.008).	IIa
There was no difference in the number of hospitalisations for all respiratory conditions between the two groups[378].	
There was a 70% reduction in risk for **death** (Adjusted odds ratio, 0.30; p<0.001) in the vaccinated patients[378].	
During the influenza season, for **outpatient visits**, influenza vaccination was *not* associated with a lower risk for having at least one visit for either pneumonia or all respiratory conditions[378].	

Treatment of influenza

Italics represent direct quotes from the Technology Appraisal Guidance No. 58 [376]:	NICE

Amantadine

"Amantadine is not recommended for the treatment of influenza".

Zanamivir

"The Assessment Report identifies five RCTs (un referenced in the TAG) *of zanamivir in elderly people and otherwise at-risk people (% of COPD patients not defined). A meta-analysis of these trials, N=371 people were treated with zanamivir and N=392 received placebo. On an ITT basis, the median time to alleviation of symptoms was 0.93 days sooner with zanamivir (95% CI –0.05 to 1.90 days). For people who had confirmed influenza within these groups (N=236 treated with zanamivir and N=248 placebo), the median time to symptom alleviation was 1.99 days sooner with zanamivir compared with placebo (95% CI; 0.90 to 3.08 days). The median ties to return to normal activities were 0.09 days sooner for the treatment group (95% CI; -0.78 to 0.95 days) on an ITT basis and 0.20 day (95% CI; -0.79 to 1.19 days) for the influenza positive subgroup."*

"There is some evidence that treatment with zanamivir for influenza reduces complications. An analysis of a set of trials including both otherwise healthy and at risk individuals (proportion of COPD not defined) found that in a pooled subgroup of 230 high risk adults and children with laboratory confirmed influenza, antibiotics were required by 24% in the placebo group and 13% in the zanamivir group; odds ratio 0.49, 95% CI; 0.23 to 1.04."

"In clinical trials, Zanamivir has not been extensively tested in people with chronic respiratory disease. In post licensing experience, there have been very rare reports of allergic reactions such as facial and oropharyngeal oedema, rash and urticaria".

Oseltamivir

"The Assessment Report identifies five RCTs of oseltamivir in elderly people and otherwise at-risk adults (proportion of COPD not defined) *that have been used in a meta-analysis. The analysis involved 557 people treated with oseltamivir and 577 with placebo. On an ITT basis, the median time to alleviation of symptoms was 0.35 days sooner with oseltamivir (95% CI; -0.71 to 1.40 days). For people who had confirmed influenza within these groups (341 treated with oseltamivir and 387 who received placebo), the median time to symptom alleviation was 0.45 days sooner with oseltamivir compared with placebo (95% CI; -97 to 1.88 days). With oseltamivir, the median times to return to normal activities were 2.45 days sooner for the treatment group (95% CI; 0.05 to 4.86) on an ITT basis and 3.00 days (95% CI; 0.13 to 5.88 days) for the influenza positive*

subgroup."

"There is some evidence that treatment with oseltamivir treatment for influenza reduces complications. In an overlapping set of trails involving both otherwise health and at risk people (proportion of COPD not defined) who were diagnosed as influenza positive, 19 out of 1063 receiving placebo developed pneumonia, compared with 9 out of 1350 receiving oseltamivir (odds ratio 0.37, CI 0.15 to 0.86)."

"Oseltamivir, in clinical trials, is generally well tolerated, but has been associated with a higher rate of nausea (3 to 7% higher) and vomiting (2% higher) compared with placebo."

Pneumococcal vaccination

Nichol et al. [381] over two influenza seasons looked at the health and economic benefits associated with pneumococcal vaccination of a cohort (N=1989) of elderly persons with chronic lung disease. Findings demonstrated that pneumococcal vaccination was associated with:

IIa

- a 43% reduction in the number of **hospitalisations** for pneumonia and influenza (Adjusted RR, 0.57; p=0.005).

- a 29% reduction in the risk for **death** from all causes (Adjusted RR, 0.71; p=0.008)[381].

Influenza and pneumococcal vaccinations

Nichols et al. [382] looked at the additive benefits of influenza and pneumococcal vaccinations among a cohort of N=1898 elderly persons with chronic lung disease over three influenza seasons. Results of the study indicate that for both influenza and pneumococcal vaccination there was: IIb

- a 63% (95% CI; 29 to 80) reduction in the risk for hospitalisation for pneumonia.

- a 81% (95% CI; 68 to 88) reduction in the risk of death (versus when neither vaccination had been received).

There was no evidence of an interaction between the vaccinations.

Health economics evidence statements

Hak et al[385] found that in the Netherlands, immunization of elderly patients with chronic lung disease against influenza is effective and cost saving.

Guidance from the NICE technology appraisal no. 58 [376] recommends routine immunisation of people of any age with chronic respiratory disease, where it is known that either influenza A or influenza B is circulating in the community.

“Vaccination offers a very cost effective initial empirical treatment of defence against influenza.”

"The Committee concluded that the evidence indicated that, when influenza is circulating, it would be both clinically effective and cost effective for at-risk people with influenza-like illness to be treated with zanamivir or oseltamivir if they can begin their course of medication within 48 hours of the appearance of symptoms."

People who have chronic respiratory disease (including COPD) are considered to be at risk.

Recommendations

R88	Pneumococcal vaccination and an annual influenza vaccination should be offered to all patients with COPD as recommended by the Chief Medical Officer[iii].	**HSC**
R89	Deleted.	

[iii] See also 'Oseltamivir, amantadine (review) and zanamivir for the prophylaxis of influenza' (NICE technology appraisal guidance 158) and 'Amantadine, oseltamivir and zanamivir for the treatment of influenza' (NICE technology appraisal guidance 168).

7.11 Lung surgery

Bullectomy, lung volume reduction surgery (LVRS) and lung transplantation have all been used to treat patients with COPD. Bullectomy usually involves the removal of a single large bulla that leads to collapse of surrounding lung tissue. LVRS aims to improve breathlessness by removing areas of poorly functioning lung, thereby decreasing the intra-thoracic volume and reducing the mechanical disadvantage faced by the respiratory muscles.

LVRS and transplantation are usually only considered in advanced disease that is unresponsive to medical therapy and appropriate selection of patients is vital. This is a decision for individual surgeons and referral processes, including the extent of investigations required prior to referral vary. Some investigations required to assess the appropriateness of surgery may only be available in specialist centres. The recommendations have been limited, regarding referral for surgery, to investigations that are generally available, but clinicians should be aware of local policies on investigation and referral.

Although lung surgery is an important option for some patients with COPD, a systematic literature search and formal critical appraisal process was not undertaken in this area, due to the time limitations within the guideline development process. However, a MEDLINE and Cochrane Database search and a selective review of frequently cited papers and key review articles was undertaken as part of the development of an expert opinion background paper (see section 2). This was then discussed by the guideline development group.

Bullectomy

Most studies of the effectiveness of bullectomy were carried out some years ago and are not RCTs. The GDG conclusions were based on a recent review of the results of previous case series [386]. This was not a systematic review but it was based on an extensive search of *Index Medicus* and it included all studies published since 1950. Long-term follow-up of clinical and physiologic data were given in relatively few articles and these data were difficult to interpret because of the variable way in which they were presented.

Lung volume reduction surgery

One systematic review of LVRS in emphysema was found[387].

This identified 2 RCTs and two additional RCTs were found[388,389]. In addition interim results from the same 4 year RCT were published to highlight the high mortality rate in a subgroup of patients [247].

There have been no RCTs comparing LVRS with lung transplantation but there have been reports of case series of the effectiveness of LVRS in patients on a transplant waiting list [390]. There are other case series comparing LVRS with transplantation [391,392].

Lung transplantation

There have been no RCTs of lung transplantation for COPD. COPD accounts for 47% of all 7204 single lung transplants reported to the International Society for Heart & Lung Transplant (ISHLT) Registry and 20.1% of all 5420 bilateral lung transplants [393]. Outcomes from individual transplant centres have been reported as case series [394].

Latest figures show that there were only 117 lung transplants for all indications across all age groups, including children, in 2002-2003 (data from www.uktransplant.org). This compares with 1385 kidney transplants in the same period. This means that, in practice, lung transplantation is not a widely available therapeutic option for most patients with COPD.

International guidelines for selection of lung transplantation candidates have been published and these have been adopted by the GDG [395]. Patients under consideration for lung transplantation should be assessed in accordance with the International guidelines. The guidelines deal with general criteria e.g. renal function, nutritional status, presence of osteoporosis, and criteria specific to COPD. They also discuss the fact that older patients, even those with no co morbidities, have a significantly worse survival rate than younger patients and make recommendations about upper age limits for the procedure. All of these factors limit the usefulness of transplantation as a therapeutic option in many patients with COPD.

Evidence statements

Bullectomy

Bullectomy is indicated for the relief of dyspnoea or for the management of complications of the bulla: • recurrent or persistent pneumothorax • infection with failure of medical treatment and evidence of abscess formation in bulla • suspicion of carcinoma • massive haemoptysis.	IV
Study of serial CXR is helpful in judging whether the collapse of normal lung surrounding bullae is responsible for the patient's functional state.	IV
The size of bullae, the presence of emphysema in the non-bullous lung and the amount of collapse are best assessed by CT.	III
Pulmonary function (FEV_1, VC, RV, and TLC and Dco) was better at 5 years than preoperatively in patients whose bullae occupied more than one third of a hemithorax.	III
Other predictors of a successful outcome are a large volume of sequestered gas, a reasonably preserved T_LCO and a normal $PaCO_2$.	III
Postoperative mortality was not always given in published reports and varied greatly, from 0 to 22.5% with a weighted mean in 262 patients of 8.0%.	III

One third to one half of the patients appeared to maintain improvement in pulmonary function for about 5 years.	III
Nine of 12 patients reviewed 5 to 10 years after surgery all reported a gradual return of **dyspnoea** with a mean fall of **FEV_1** of 82 ml/yr; 5 of the 9 still maintained some of their postoperative improvement.	III
Among 11 patients operated on for bullous disease 4 to 20 years earlier, **FEV_1** (prebronchodilator) and **T_LCO** declined more rapidly in 6 smokers than in 5 ex-smokers ($p<0.05$), suggesting the great importance of smoking cessation after surgery.	III
In general, resection of giant bullae does not seem to affect the size of other bullae.	III

Lung volume reduction surgery (LVRS)

LVRS improves **FEV_1**[389,396].	Ib
The effect seems to be maximal at 6 months and thereafter there is a variable but significant decline towards pre-surgical values[389,396].	
LVRS improves **walking distance** [389,396].	Ib
LVRS improves **quality of life** [389,396].	Ib

Overall, LVRS does not appear to have any effect on long term **survival** (but see subgroup results below)[389,396].	Ib
LVRS results in an unacceptably high mortality in patients who have[389,397] : • a low forced expiratory volume in 1 second (<20% predicted) • and either non-upper lobe predominant emphysema or a very low transfer factor (<20% predicted).	Ib
With the exclusion of patients at high risk for death from surgery according to the interim analysis, overall **mortality** in the surgery group was 0.09 death per person-year, as compared with 0.10 death per person-year in the medical-therapy group (risk ratio, 0.89; P=0.31); **exercise capacity** after 24 months had improved by more than 10 W in 16 percent of patients in the surgery group, as compared with 3 percent of patients in the medical-therapy group (p<0.001)[389].	Ib
Among patients with predominantly upper-lobe emphysema and low exercise capacity (40W in men and < 25W in women), mortality was lower in the surgery group than in the medical-therapy group (risk ratio for death, 0.47; P=0.005). Among patients with non–upper-lobe emphysema and high exercise capacity, mortality was higher in the surgery group than in the medical-therapy group (risk ratio, 2.06; p=0.02)[389].	Ib
Clinically and statistically significant benefits of LVRS on **mortality, exercise capacity** and **SGRQ** were seen in patients with upper lobe emphysema and low exercise capacity (<40W in men and < 25W in women). LVRS led to increased mortality and deterioration in exercise capacity in patients with non-upper lobe emphysema and high exercise capacity. Some benefits were seen in patients with upper lobe emphysema and high exercise capacity and in patients with non- upper lobe emphysema and low exercise capacity but these were less marked[389].	Ib

	Low exercise capacity	High exercise capacity
Upper lobe emphysema	↓ Mortality (RR 0.47) ↑ Exercise (OR ∞) ↑ SGRQ (OR 8.38)	→ Mortality (RR 0.98) ↑ Exercise (OR 5.81) ↑ SGRQ (OR 5.67)
Non-upper lobe emphysema	→ Mortality (RR 0.81) → Exercise (OR 1.77) ↑ SGRQ (OR 7.35)	↑ Mortality (RR 2.06) ↓ Exercise (OR 0.90) → SGRQ (OR 1.35)

Transplantation

COPD patients are considered potentially to be in the transplant window if they meet the following criteria [395]: IV

- FEV_1 < 25% of predicted (without reversibility)
- and/or $PaCO_2 \geq$ 55mmHg (7.3kPa) and/or elevated pulmonary artery pressures with progressive deterioration, e.g. cor pulmonale
- preference should be given to those patients with elevated $PaCO_2$ with progressive deterioration who require long-term oxygen therapy, as they have the poorest prognosis.

Older patients have significantly worse survival rates following transplantation and the following age limits are suggested [395]: IV

- single lung transplants ~ 65 years
- bilateral lung transplants ~ 60 years.

In a case series of 306 consecutive lung transplants for emphysema **hospital mortality** was 3.9%, overall **five year survival** was 58.6%±4.4%, and there was no difference in α-1 AT deficient patients. Better 5 yr survival rates were achieved by bilateral compared to single lung transplants 66.7%±4.0% v 44.9%±6.0%)[394].	III
Lung transplantation leads to improvements in **FEV_1**, **exercise capacity** and **quality of life** [398].	III
Bilateral lung transplantation results in a greater improvement in FEV_1, but improvements in exercise capacity are not always significantly greater [398].	III

LVRS vs. Transplantation

GDG consensus statements

LVRS is an alternative to lung transplantation in selected patients.	IV
LVRS offers an earlier treatment option as a bridge to lung transplantation.	IV
LVRS provides treatment for patients with COPD who are not otherwise candidates for lung transplantation.	IV

Health economics evidence statements

One paper was identified, however it was deemed irrelevant as it was a comparison of techniques and did not look at the cost effectiveness of lung surgery per se. This is outside the scope of the guideline.

Recommendations

R90	Patients who are breathless, and have a single large bulla on a CT scan and an FEV_1 less than 50% predicted should be referred for consideration of bullectomy.	**Grade C**
R91	Patients with severe COPD who remain breathless with marked restrictions of their activities of daily living, despite maximal medical therapy (including rehabilitation), should be referred for consideration of lung volume reduction surgery if they meet all of the following criteria: • FEV_1 more than 20% predicted • $PaCO_2$ less than 7.3 kPa • upper lobe predominant emphysema • T_LCO more than 20% predicted.	**Grade A**
R92	Patients with severe COPD who remain breathless with marked restrictions of their activities of daily living despite maximal medical therapy should be considered for referral for assessment for lung transplantation bearing in mind comorbidities and local surgical protocols. Considerations include: • age • FEV_1 • $PaCO_2$ • homogeneously distributed emphysema on CT scan • elevated pulmonary artery pressures with progressive deterioration.	**Grade C**

7.12 Alpha-1 antitrypsin replacement therapy

Alpha-1 antitrypsin deficiency is an uncommon cause of COPD, accounting for around 2% of cases of COPD. There is considerable variability in the clinical manifestations it produces: some patients having minimal or no symptoms and others developing severe emphysema at an early age. Smoking is the major factor influencing the development of emphysema but some non-smokers develop airflow limitation in later life and this appears to be associated with a history of asthma or pneumonia [399]. Recombinant alpha-1 antitrypsin is now available and replacement therapy has been proposed as a way of treating patients with alpha-1 antitrypsin deficiency.

No systematic reviews were identified on the role of alpha-1 antitrypsin replacement therapy. Dirksen [400] was the only RCT. This was powered to detect a 50% difference in decline in FEV_1 over 3 years but there is no information about completeness of follow-up and it was underpowered to detect changes in the secondary outcome measure of changes in lung density on CT. Considerations was also given to data from the alpha-1 antitrypsin deficiency register study group [401](n=1129, 36 clinical centres in USA and 1 in Canada). The authors state that the results cannot be generalised as the cohort was not a representative sample. Decisions about treatment were made by the referring physician and may be subject to bias.

An uncontrolled cohort study was identified [402] comparing a treated German population with an untreated Danish population but this was excluded due to methodological limitations.

The GDG was aware of the difficulties in attempting an RCT in this area (large sample size required, timing of intervention, long term-follow up difficult to achieve and expensive augmentation treatment required).

Evidence statements

Both Dirksen [400] and the Registry study [401] found no significant effect of alpha-1 antitrypsin replacement therapy on the rate of decline in **FEV_1**.	Ib & III

The Registry study was the only study to examine mortality. It found that patients receiving alpha-1 antitrypsin replacement therapy had a lower **mortality** (RR 0.64 95% CI 0.43 to 0.94, p-=0.02) but this may have been affected by the biases referred to above [401]. III

Dirksen highlighted a trend towards a reduced rate of **loss of lung tissue** assessed by CT scanning in patients receiving alpha-1 antitrypsin replacement therapy[400]. Ib

Health economics evidence statements

Only one economic study was found [403]. This model is 12 years old and was very uncertain around efficacy, had many assumptions, is US based and the costs of therapy and treatment may now be outdated.

The guideline developers were unable to derive any evidence statements based on this health economic evidence and felt that none of this economic evidence was useful for contributing to the formulation of the recommendations.

Recommendations

R93	Alpha-1 antitrypsin replacement therapy is not recommended for patients with alpha-1 antitrypsin deficiency (see also recommendation 11).	**Grade D**

7.13 Multidisciplinary management

Doctors, nurses, physiotherapists, occupational therapists and pharmacists are essential members of the multi-disciplinary team managing patients with COPD. In more severe COPD the multidisciplinary team will also include: dietician, social worker, mental health trained worker, behaviour nurse therapist, clinical psychologist or liaison psychiatrist. These individuals may fulfil a variety of roles including those listed below.

Many of these activities may be undertaken in the clinic or in the practice as part of routine care by the practitioner seeing the patient but in certain circumstances the patient may need to be referred to a specialist department e.g. physiotherapy. Multidisciplinary working means breaking down historic demarcation of roles because many of the activities in managing COPD can be undertaken by individuals from different professional backgrounds. Competencies are more important than professional boundaries.

R99	COPD care should be delivered by a multidisciplinary team.	**Grade D**
R100	The following functions should be considered when defining the activity of the multidisciplinary team: • assessing patients (including performing spirometry, assessing the need for oxygen, the need for aids for daily living and the appropriateness of delivery systems for inhaled therapy) • care and treatment of patients (including non-invasive ventilation, pulmonary rehabilitation, hospital-at-home/early discharge schemes, providing palliative care, identifying and managing anxiety and depression, advising patients on relaxation techniques, dietary issues, exercise, social security benefits and travel) • advising patients on self-management strategies • identifying and monitoring patients at high risk of exacerbations and undertaking activities which aim to	**Grade D**

avoid emergency admissions

- advising patients on exercise
- education of patients and other health professionals.

7.13.1 Respiratory nurse specialists

Research on the role of the clinical nurse specialist (CNS) in COPD is scarce. Unlike the role of the CNS in asthma, where the role is established in the BTS / SIGN guidelines for asthma[73], and where structured review of the patient by nurses has a clearer evidence base.

COPD specialist nurses are found both in the primary and secondary care settings.

Their role varies from place to place depending on local circumstances. But there are some common themes.

Education of patients and their carers is a key component of their work. Nurses often have more time to spend with patients and their carers than doctors and patients may feel less inhibited about asking questions or showing their lack of understanding. In their work with patients, nurses will cover many of the topics discussed in appendix C.

Support and education for other professionals caring for COPD patients, through formal and informal education sessions. Sessions on use of spirometry and early detection of COPD and on the topics covered above.

Co-ordination of care: The nurse is usually the main point of contact for the patients and their families and as such provides them with a link to the multidisciplinary team.

Through this they may pre-empt or prevent hospital admission by early intervention.

Through needs assessment they can refer patients to other professionals e.g. dietician, social services.

Assessing and monitoring stable COPD over time: through use of spirometry, oxygen saturation and symptom measurements e.g. the BORG breathlessness scale.

They provide **psychological and emotional support** for the patient and their family. Through advice on anxiety management, helping them deal with issues of loss of role in the family.

Nurse prescribing, an increasing number of nurses can now prescribe, allowing them to adjust treatments according to patient's needs.

Home care provision. Nurses play a pivotal role in home care provision both in the stable COPD and during exacerbation.

Oxygen Assessment, Nurses are often involved in oxygen assessments. They monitor patients on LTOT through home assessment of oxygen saturation levels, spirometry and symptom measurement, and for evidence of heart failure.

Monitoring of patients on **home ventilation.**

Hospital-at-home: Other nurses are involved in "hospital-at-home" for COPD patients. They assess and monitor patients at home who would otherwise have required hospitalisation due to their exacerbation.

Role of the Respiratory Nurse Consultant: can be seen as evolving COPD nursing further, not just in drug management but also in other therapeutic and supportive interventions.

Due to the time limitations within the guideline development process a systematic literature search and formal critical appraisal process was not undertaken in this area, see section 2. However, a MEDLINE and Cochrane Database search, and a selective review of frequently cited papers and key review articles was undertaken. The authors of a systematic review on the role of respiratory nurse specialists which is under development[404] were also contacted and they provided a database of relevant papers which included the grey literature. These studies were reviewed as part of the development of an expert opinion background paper which was then discussed by the guideline development group.

There is little robust evidence relating to the role of respiratory nurses in COPD. One systematic review was identified[302] of home care by outreach nursing. Some of the studies related to specific aspects of COPD care (e.g. hospital-at-home schemes) which are covered elsewhere in the guideline.

GDG consensus statements

Respiratory nurse specialists form an important part of the multidisciplinary team managing patients with COPD.	IV
Their role within the multi-disciplinary team will vary depending on local circumstances and individual competencies.	IV

Recommendations

R101	It is recommended that respiratory nurse specialists form part of the multidisciplinary COPD team.	**Grade D**

7.13.2 Physiotherapy

Respiratory physiotherapy is a specialised area of care which has three main aims:

- to help reduce the work of breathing associated with respiratory disease
- to help restore patients' maximal function
- to help improve peripheral and respiratory muscle weakness

Core treatments delivered by physiotherapists include:

Techniques to reduce the work of breathing using for example relaxed breathing control in combination with positioning to maximise the function of the respiratory muscles and enhance diaphragmatic displacement. In chronic asthma, the use of diaphragmatic breathing where an element of dysfunctional breathing was identified, has shown a significant benefit on health related quality of life [405]. Pursed lip breathing techniques may also be effective in helping patients manage breathlessness although data is limited.

Physiotherapeutic management of dyspnoea may include sputum clearance techniques where copious secretions cause distress. Therapists commonly use the active cycle of breathing technique (ACBT) with forced expirations to enhance expectoration. The use of the forced expiration technique (FET) appears to enhance peripheral mucus transport in patients with normal or high elastic recoil. Where secretions are basal and particularly tenacious gravity assisted drainage with manual chest percussion may aid clearance.

An extensive literature search was undertaken in this area and yielded a hit rate of 314 studies. 286 of these were excluded, as they did not focus upon the area for address, papers tended to focus on rehabilitation and / or exacerbations (addressed elsewhere in the guideline) and inspiratory muscle training.

No systematic reviews were found and overall there was generally limited research in this area. Most of the studies identified were of small sample sizes (range 7 to 44 participants). None of the identified trials were UK based. Six of the eight identified randomised controlled studies were excluded due to methodological limitations and also because short-term interventions only were considered [406-411]. A cohort study by Kolaczkowski et al. [412] was also excluded due to limited methodological details being available.

One randomised controlled trial was identified[413] and one quasi-experimental study [414] that met quality appraisal criteria.

Christensen et al. [413]1990 in a Danish RCT looked at the long term treatment of chronic bronchitis (N=44) with positive expiratory pressure mask and chest physiotherapy. Diaphragmatic breathing performed through a PEP mask followed by forced expirations and cough was compared to self-administered diaphragmatic breathing followed by forced expirations and cough.

Casciari et al. [414] undertook a quasi-experimental study (controlled study without randomisation) in an American population, with a sample size of N=22. Effects of breathing retraining in patients with COPD were compared. The intervention group received exercise and breathing training and a comparison group received exercise reconditioning alone.

Evidence statements

IIa

Casciari et al. [414]found that the respiratory rate in the group receiving breathing retraining at rest decreased from 17.4 breaths per minute (bpm) to 15 bpm after the exercise component (not significant) to 9.7 bpm after the breathing retraining ($p<0.01$). During maximal exercise, the respiratory rate decreased from 32.6 bpm (baseline) to 30.3 bpm after exercise (non significant) to 23.8 bpm after breathing retraining ($p<0.05$).

Tidal volume during exercise increased from 800ml at baseline to 910ml after exercise (not significant) to 1,320ml after breathing retraining ($p<0.05$)[414].

During exercise, PaO_2 increased between exercising and breathing retraining ($p<0.01$)[414].

After 9 weeks, **PaO_2** and base excess differed significantly between the two groups in favour of the breathing retraining group; PaO_2 breathing retraining 77.5 compared to the control group 60.0 (mmHg)[414].

There were no significant differences in exercising respiratory rates or the tidal volume and arterial blood gases during rest and exercise for the group receiving exercise reconditioning only[414].

“The increment in work performance during the final three weeks of the program was significantly higher in the group that received breathing retraining ($p<0.002$). Data indicate that compared with controls, exercise performance increased significantly in the group of

COPD participants who received breathing retraining compared to those who received exercise only" [414].

Christensen et al. [413] compared diaphragmatic breathing performed through a PEP mask followed by forced expirations to self-administered diaphragmatic breathing followed by forced expirations. The PEP group reported significantly less **cough** (p=0.025), less **mucus production** (p=0.013) fewer **exacerbations** compared to the control group (6 vs. 28). Ib

There was a significantly lower rate of **antibiotic** use in the PEP group compared to the control (p<0.05). The use of **mucolytics** was also significantly lower in the PEP group compared to the control group (p<0.05)[413].

There was a statistically significant difference in the **FEV_1** at one year in favour of the PEP group (p=0.039)[413].

Recommendations

R102	If patients have excessive sputum, they should be taught:	
	• the use of positive expiratory pressure masks	**Grade B**
	• active cycle of breathing techniques.	**Grade D**

7.13.3 Identifying and managing anxiety and depression

COPD leads to disabling and distressing symptoms. Patents often become socially isolated and have to give up activities that they enjoy. These factors may lead to the development of anxiety and or depression. The symptoms and signs of these may be similar to those of COPD itself and may be overlooked. Depression is also relatively common and the two conditions may simply co-exist; however, the presence of depression or anxiety may significantly worsen patients' quality of life. A concurrent depressive disorder may bring the patient into a vicious circle: the depressed mood reduces the patient's ability to cope with the physical symptoms, which become less tolerable. The psychosocial effects of the disease may be enforced by the depressed mood.

Two systematic reviews were identified[415,416]. One [415] examined the prevalence of depression in COPD, the other [416] examined psychologically-based interventions to reduce anxiety and panic in patients with COPD. 2 additional RCTs were critically appraised one with n = 36[417] and the other with n = 56 [418] but this was rejected because of methodological limitations. One randomised self-controlled crossover trial was critically appraised [419] and 3 case-controlled studies [420-422], 2 uncontrolled cross-sectional cohort studies [423,424] and 4 uncontrolled longitudinal cohort studies [87,425-427] were critically appraised. One of the case controlled studies [420] and two of the cohort studies [426,427] were rejected because of methodological limitations.

Factors for consideration within this topic include:

- considerable pre-screening of patients
- the majority of studies are cohort studies with poor methodology
- small patient populations in some studies
- studies are in a number of different settings; outpatient, inpatient, community
- a number of different rating scales with different thresholds for depression are used in studies (see identification of depression section below)
- the majority of studies are uncontrolled
- participants baseline FEV_1 varies considerably i.e. patients have different severity of COPD.

Evidence statements

Overall prevalence of anxiety and depression

In the systematic review of 10 case-control and uncontrolled trials [415] the methodologically best-rated studies did not find a statistically significant difference in the **prevalence** of depression between patients with COPD and controls.	III
A striking difference in prevalence of depression was seen between studies (between 6% and 42%).	
Van Manen et al.[421] (case-control (n=521)) found, 21.6% of COPD patients had a score of 16 or more on the CES-D scale compared with 25% of patients with severe COPD (FEV <50%), 19.6% of those with mild to moderate COPD (FEV 50-80%), and 17.5% of the controls.	IIb
Results were adjusted to account for demographic variables and co morbidity. In the multivariate analysis there appeared to be no risk for depression in the total group of COPD patients (OR 1.5, 95% CI 0.8 to 2.6) or in the subgroup of patients with mild to moderate COPD (OR 1.1, 95% CI 0.5 to 2.1).	
Patients with severe COPD had a 2.5 times greater risk for depression than controls (OR 2.5, 95% CI 1.2 to 5.4).	
Lacasse [424] in a cross-sectional cohort (n = 109)) found that 62 (57%; 95% CI: 47 to 66) patients with COPD presented significant **depressive symptoms** (GDS score: 11-19).	III
In addition, 20 patients (18%; 95% CI: 12 to 27) were severely depressed (GDS > 20/30).	

Yohannes [423](cross-sectional cohort (n = 137)) found that 25 (18%) of patients were **clinically anxious** and 57 (42%) were **clinically depressed**. Twenty-one of the 57 depressed COPD participants (37%) had a clinical anxiety score > 3 whereas four of the 80 non-depressed COPD participants (5%) had a clinical anxiety score > 3. (p<0.001). III

In the depressed elderly COPD population, 17 (30%) were mildly depressed (MADRS score 7-19); 39 (68%) were moderately depressed (MADRS score 20-34) and one (2%) was severely depressed (MADRS score 35-60)[423].

The most powerful predictor of severity of anxiety was MADRS (the more depressed patients being more likely to suffer anxiety)[423].

Relationship of depression to severity of COPD

Van Manen [421] (case-control (n = 521)) found that 21.6 compared with 25% of patients with **severe** COPD (FEV <50%)% had a score of 16 or more on the CES-D scale, compared with 19.6% of those with **mild to moderate** COPD (FEV 50-80%), and 17.5% of the controls. IIb

Results were adjusted to account for demographic variables and co morbidity. In the multivariate analysis there appeared to be no risk for depression in the total group of COPD patients (OR 1.5, 95% CI 0.8 to 2.6) or in the subgroup of patients with mild to moderate COPD (OR 1.1, 95% CI 0.5 to 2.1)[421].

Patients with severe COPD had a 2.5 times greater risk for depression than controls (OR 2.5, 95% CI 1.2 to 5.4)[421].

The risk of depression was significantly increased in patients with a reversibility FEV_1 of < 1.1% predicted (OR 3.7, 95% CI 1.3 to 11)[421].

Lacasse [424] (cross-sectional cohort (n = 109)) found that depression scores correlated with 7 of the 8 domains of the **SF-36**. Depression was associated with a substantial impairment in psychological and physical functioning. III

Yohannes [423] cross sectional cohort (n = 137) found that the most powerful predictor of severity of depression was the MRADL score which accounted for 22% of the variance in MADRS (the more disabled patients being more likely to suffer depression). III

Depressed COPD patients (identified by GMS) had poorer **quality of life** scores compared with non-depressed patients (54 $\pm$ 1.8 vs. 36 $\pm$ 1.2, p = 0.04)[423].

Depressed COPD patients (identified by GMS) had lower mean **MRADL** scores compared with non-depressed patients (9.9 $\pm$ 0.7 vs. 14.4 $\pm$ 0.5, p = 0.05)[423].

Van Manen [421] (case-control (n = 521)) found that the risk of depression was significantly increased in patients with COPD with severe impaired physical functioning (OR 5.6, 95% CI 1.6 to 19.9). IIb

Yohannes [423] cross sectional cohort (n = 137) found that depressed COPD patients (identified by GMS) had higher prevalence of hospital admission episodes within the previous 12 months compared with non-depressed patients (34/57 (60%) vs. 28/80 (35%), p = 0.007). III

Mean inpatient days of hospitalisation for depressed was 9.8 ± 1.7 and non-depressed was 2.3 ± 0.6 days (p<0.0001)[423].

Yohannes [87] (uncontrolled longitudinal cohort study (n = 137)) found that depression scores and QOL scores do not predict **mortality**. IIb

Identification of depression and anxiety in COPD patients

The Brief Assessment Schedule Depression Cards (BASDEC) has been validated in patients with COPD including those over 60 years of age [87,422,423]. IIa

Other scales that have been used are: III

- Hospital Anxiety and Depression Scale (HADS)[428]
- Geriatric Depression Scale [424]
- Geriatric Mental State Schedule [423]
- Montgomery Asberg Depression Rating Scale [423]
- Centre for Epidemiological Studies Depression Scale (CES-D)[421]
- Clinical Global Improvement Scale [417]
- Hamilton Depression Rating Scale (HAM-D) [417]
- Patient Related Anxiety Scale [417]

Management (pharmacological/non-pharmacological) of anxiety and depression in COPD patients

There is a lack of evidence that **psychologically based interventions** reduce anxiety in COPD [416]. Ia

Borson et al. [417] (RCT (n = 36)) found that **Nortriptyline** treatment was superior to placebo for treatment of depression. Ib

CGI rating showed that 10/13 (77%) patients receiving active drug experienced a sustained improvement in mood disorder compared with 2 out of 17 (12%) patients taking placebo [417].

Scores on the HAM-D improved by 60% in the nortriptyline group (29.6 $\pm$ 7.6 to 12.6 $\pm$ 6.9) compared with 17% (29.5 $\pm$ 6.4 to 22.8 $\pm$ 11.3) in the placebo group (p = 0.01)[417].

Nortriptyline treatment was accompanied by marked improvements in anxiety. Anxiolytic effects of nortriptyline were reflected by a 45% reduction in mean score on the pRAS (54.3 $\pm$ 17 to 29.9 $\pm$ 11.4) compared with only 4% improvement (47.4 $\pm$ 21.5 to 45.3 $\pm$ 28.6) in patients receiving placebo (p<0.005)[417].

Oxygen therapy improved anxiety but not depression in a small subgroup of patients who were hypoxic [429]. IIa

Yohannes [430] found that patient uptake of fluoxetine was poor (14 out of 57 patients aged 60-89 years). The reasons for refusing treatment varied but were largely due to misapprehension by the patient. III

GDG consensus statements

The presence of depression or anxiety may be overlooked in patients with COPD because of the overlap of many of the symptoms of these conditions and COPD.	IV
A number of assessment tools have been used to identify anxiety and depression in patients with COPD. Many of these were not designed to be used in, and have not been validated for use in patients with chronic disease.	IV
Depression and anxiety are more common in patients with severe COPD and particularly in those who are hypoxic or severely dyspnoeic than in normal individuals.	IV
The patient's acceptance of treatment may be influenced by the way in which the diagnosis is presented to the patient and by a discussion about the reasons for their concern about starting treatment.	IV

Recommendations

R103	Health care professionals should be alert to the presence of depression in patients with COPD. The presence of anxiety and depression should be considered in patients: • who are hypoxic (SaO_2 reference value deleted) • who have severe dyspnoea • who have been seen at or admitted to a hospital with an exacerbation of COPD.	**Grade D**
R104	Deleted and replaced by CG91. 'Depression in adults with a chronic physical health problem' (NICE Clinical Guideline 91)[431].	
R105	Deleted and replaced by CG91. 'Depression in adults with a chronic physical health problem' (NICE clinical guideline 91)[431].	
R106	Deleted and replaced by CG91. 'Depression in adults with a chronic physical health problem' (NICE clinical guideline 91)[431].	

NICE guidance CG91 on the treatment and management of depression in adults with a chronic physical health problem (October 2009) updates the recommendations on the treatment of depression in patients with COPD. This guidance notes the importance of offering psychological and psycho-social interventions before considering anti-depressant drugs.

7.13.4 Nutritional factors

Many patients with COPD lose weight as a consequence of decreased food intake as a result of breathlessness, altered absorption as a result of hypoxia and increased resting energy expenditure as a result of the increased work of breathing [432]. The mechanisms of this remain unclear but probably relate to systemic effects of cytokines, particularly TNF-α [433].

There has been some interest in the consequences of this weight loss, particularly whether it is an independent predictor of outcome, and whether interventions are effective both at increasing weight and influencing outcome.

One systematic review was identified[434] that compared oral, enteral or parenteral nutritional support (nutritional support was defined as any caloric supplementation given for more than two weeks) with placebo or usual diet or other treatment regimens such as anabolic substances.

Two additional randomised controlled trials were critically appraised[435,436] and 14 cohort studies were critically appraised[437-450], all but two of these [449,450] had methodological limitations and hence were subsequently excluded.

Factors for consideration within this topic include:

- considerable pre-screening of patients
- the majority of studies are cohort studies with poor methodology
- small patient populations in some studies
- studies are in a number of different settings; outpatient, inpatient, community
- not yet established which outcome best predicts nutritional status (weight, BMI, fat free mass etc)
- the majority of studies are uncontrolled
- some studies rely on patient recall of diet and weight.

Evidence statements

Landbo [440] (uncontrolled cohort study n = 2132) found that there was an independent effect of Body Mass Index (BMI) on **survival**, with significantly higher mortality seen in underweight participants than in those of normal weight. IIa

The effect of BMI on **all-cause mortality** is dependent on the stage of COPD. A significant effect of BMI on all-cause mortality was present only in participants with severe COPD (FEV_1 %pred <50) in whom mortality was lowest in the obese and increased with decreasing BMI (p<0.001)[440].

COPD mortality was highest in underweight participants and decreased for increasing BMI in both men and women (p<0.001). The impact of BMI on COPD mortality was stronger than that on all-cause mortality, with RRs between the lowest and highest BMI of 5.56 (range 2.47 to 12.54) and 7.17 (range 2.45 to 21) in men and women respectively[440].

Schols [448] (survival analysis – retrospective n = 400) found that **survival** was significantly decreased in both underweight and normal weight patients as compared with overweight and obese patients (p<0.0001). IIb

Marquis [441] (uncontrolled cohort n = 142) found that a midthigh muscle cross-sectional area obtained by CT scan (MTCSAct) <70 cm2 was associated with a fourfold increase (95% CI, 1.52 to 8.09) in **mortality** rate, independently of any other variables (p = 0.004). IIb

Compared with patients with an FEV >50% predicted and a MTCSAct > 70 cm^2, those with an FEV < 50% predicted and a MTCSAct > 70cm^2 had a **mortality** odds ratio of 3.37 (95% CI 0.41 to 28), whereas patients with an FEV <50% predicted and a MTCSAct < 70cm2 had a mortality odds ratio of 13.16 (95% CI, 1.74 to 99.20)[441].

In all three stages of COPD the highest mortality was found in underweight participants. In participants with severe COPD mortality continued to decrease with increasing BMI, with an RR of 7.11 (range 2.97 to 17.05) in underweight compared with obese participants. A similar but weaker association was found in participants with mild and moderate COPD as defined in the study [441].

Schol [448] (post hoc analysis of prospective study) found that a history of weight loss was significantly related to decreased **survival** ($p<0.005$). IIb

Weight gain (>2kg/8wk) in depleted and non-depleted patients with COPD was significantly associated with decreased mortality risk[448].

Prescott [442] (uncontrolled cohort study n = 1612) found that among participants with COPD, all-cause mortality was increased in participants who lost > 1 BMI unit. An excess mortality was seen in participants who lost >3 units BMI (~10 kg). Mortality in participants who gained weight did not differ significantly from those with a stable weight. IIb

Effect of weight change on mortality did not differ with severity of COPD. The effect of baseline BMI was U shaped with excess mortality associated with both under and overweight. In participants with mild (FEV_1 % predicted ≥ 70) or moderate (FEV_1 % predicted 50–69), COPD and in participants without COPD, no modification of the effect of baseline BMI was found; however, among patients with severe COPD (FEV_1 % predicted < 50), effect of weight change differed with baseline weight[442].

In all groups, weight loss was associated with increased mortality; however, normal and underweight participants (BMI <25) with severe COPD differed from the remaining in experiencing increased survival after weight gain. The reverse was found in the overweight

and obese (BMI > 25), among whom the best survival was seen in participants who had stable weight or who had decreased their weight[442].

The highest risks were found in participants who lost weight between examinations, whereas weight increase did not seem to increase risk of COPD-related death. Unlike all-cause mortality, the risk function for baseline BMI was linear with the lowest risk seen in patients who increased their weight[442].

Sahebjami [443] (uncontrolled cohort study n = 126) found that: IIb

BMI is significantly correlated with diffusing capacity for carbon monoxide (DLCO), FEV_1 and the FEV_1/FVC ratio (p<0.001).

Underweight patients (BMI < 20) are significantly more likely to have abnormally low levels of DLCO compared with normal weight (BMI = 20-27) and overweight patients (BMI>27) (p<0.001).

Underweight patients (BMI < 20) are significantly more likely to have lower FEV_1 and FEV_1/FVC compared with normal weight (BMI = 20-27) and overweight patients (BMI>27) (p<0.001).

Underweight (BMI < 21 kg/m2) patients with COPD are more dyspnoeic than normal weight (BMI 21-28 kg/m2) (p = 0.03) - Dyspnoea scale normal weight 2.5 $\pm$ 1.2 vs. underweight 3.1 $\pm$ 0.9.

Carbon monoxide diffusing capacity (DLCO) was significantly lower in underweight compared with normal weight patients – DLCO % predicted normal weight 57 $\pm$ 17 vs. underweight 36 $\pm$ 11 (p<0.001).

Maximum inspiratory pressure (Pimax) was significantly lower in underweight patients compared with normal weight patients. Pimax cmH2O normal weight 66 $\pm$ 19 vs. underweight 55 $\pm$ 18 (p = 0.02). Pimax % predicted normal weight 62 $\pm$ 17 vs. underweight 52 $\pm$ 17 (p = 0.03).

Gray-Donald [445] (uncontrolled cohort study n = 135) found that in underweight COPD participants **peak exercise performance** and **ventilatory muscle strength** are decreased. IIb

Submaximal exercise performance, dyspnoea and **overall quality of life** are not affected[445].

Schols [446] (uncontrolled cohort study n = 255) after stepwise analysis on total group of patients (normal weight and underweight) established that the functional measures Pimax, maximal expiratory pressure (Pemax) and 12 minute walking distance were better predicted by FFMPIBW (fat-free mass as a percentage of ideal body weight) than PIBW (percent ideal body weight). IIb

Baarends [438] (uncontrolled cohort study n = 62) found that peak VO2 correlated significantly with the FFM index (kg/m2; r = 0.57, p<0.001) BMI (kg/m2; r= 0.56, p<0.001) and intracellular water (kg/m2; r = 0.54, p<0.001). IIb

Depletion of FFM contributes to a blunted VT (tidal volume) and decreased peak oxygen pulse in response to peak exercise (multiple regression analysis)[438].

Stepwise analysis demonstrated that the fat free mass index and transfer factor for carbon monoxide (T_LCO) explained 53% of the variation in peak VO_2[438].

Marquis [441] (uncontrolled cohort n = 142) also found that a midthigh muscle cross-sectional area obtained by CT scan (MTCSAct) <70 cm2 was associated with a fourfold increase (95% CI, 1.52 to 8.09) in mortality rate, independently of any other variables (p = 0.004). IIb

Engelen [439] (uncontrolled cohort n = 72) found that depleted patients are more likely to exhibit lower values for respiratory and peripheral skeletal muscle strength than nondepleted patients. IIb

Measures of muscle strength were lower in the depleted group, but only the difference in handgrip strength reached statistical significance ($p<0.01$)[439].

Sahebjami [443] (uncontrolled cohort study n = 126) found that 46.8% of COPD patients (n =126) had nutritional abnormalities (i.e. underweight BMI <20kg/m2 = 23% and overweight BMI >27 kg/m2 = 23.8%). IIb

Schols [446] (uncontrolled cohort study n = 255) found that depletion of body weight, fat-free mass and muscle mass is most pronounced in patients suffering from chronic hypoxemia and in normoxic patients with severe airflow obstruction (FEV<35%) but also occurred in ± 25% of patients with moderate airflow obstruction. IIb

Prescott [442] (uncontrolled cohort study n = 1612) found that in females, baseline BMI was lower in people with impaired lung function ($p = 0.009$) whereas no difference was found in males. IIb

In both females and males, weight changes differed with lung function with mean weight loss seen in participants with poorest lung function and mean weight gain seen in participants without airways obstruction ($p<0.001$)[442].

The proportion of participants that lost > 1 unit BMI (~3.8kg) increased with decreasing lung function reaching 35.3% and 27.4%, respectively in females and males with severe COPD. ($p<0.001$)[442].

Gray-Donald [445](uncontrolled cohort study n = 135) found that 24.4% of COPD participants had % IBW of <90%. IIb

86% of those with a weight of <80% IBW and 60% of those with weight < 90% had an abnormally low triceps skin fold thickness (TSF) (< 60% standard)[445].

Among underweight participants (IBW <90% predicted), 32% reported weight loss of > 5% in the last year[445].

When compared with their usual weight, 81% of underweight participants had lost > 10% body weight, with self-reported weight losses of as much as 43%[445].

The mean weight loss from usual weight in the underweight group was 17% (± 13%)[445].

IIb

The systematic review / meta-analysis[434] (n = 277 participants) found that there was no evidence from this analysis that simple nutritional support had any significant effect on anthropometric measures, lung function or exercise capacity in patients with stable COPD.

Ia

Otte [435] (RCT (n = 28)) found that nutritional supplementation produced weight gain (fed mean 1.5kg vs. 0.16kg control p<0.01) in malnourished patients with pulmonary emphysema, but it did not change other indices of well-being.

Ib

Schols [448] (survival analysis (n = 603)) found that nutritional intervention resulted in a significant increase in weight, fat-free mass and fat-mass whereas no significant changes in any of these parameters were seen in the placebo group.

IIb

Relative to a similar body weight gain as the group receiving nutritional support only, the anabolic steroids group showed a larger increase in fat-free mass and maximal inspiratory mouth pressure without causing adverse side effects[448].

On the basis of weight change > 2kg/8wk, 50% of the treated patients were characterised as responders, including 24% of placebo group[448].

In 62% of the patients an improvement in Pimax was shown[448].

Weight gain in depleted and non-depleted patients with COPD was significantly associated with decreased mortality risk[448].

GDG consensus statements

BMI may be less reliable as an index of nutritional status in older patients because of age-related changes in height, posture and ratio of fat to muscle. In these patients changes in weight, particularly if greater than 3kg should be noted and acted upon.	IV
Exercise may augment the effects of nutritional supplementation on weight gain.	IV

Recommendations

R107	BMI should be calculated in patients with COPD: • the normal range for BMI is 20 to less than 25[451] * • if the BMI is abnormal (high or low), or changing over time, the patient should be referred for dietetic advice • if the BMI is low patients should also be given nutritional supplements to increase their total calorific intake and be encouraged to take exercise to augment the effects of nutritional supplementation. Refer to 'Nutrition support in adults' (NICE clinical guideline 32). * This recommendation was not reviewed as part of the 2010 guideline update. 'Obesity' (NICE clincial guideline 43), published in 2006, states a healthy range is 18.5 to 24.9 kg/m^2, but this range may not be appropriate for people with COPD.	**Grade D**
R108	In older patients attention should also be paid to changes in weight, particularly if the change is more than 3 kg.	**Grade D**

7.13.5 Palliative care

Palliative care is the active total care of patients and their families by a multiprofessional team when the patient's disease is no longer responsive to curative treatment. It is similar, but distinct from terminal care. Although traditionally linked to cancer, it is increasingly recognized that palliative care has a role for patients dying from non-cancer conditions including COPD.

The management of severe COPD has a large palliative element and focuses on symptom control and optimising quality of life.

Among its principles, palliative care promotes open communication between doctor and patient, which includes access to information about diagnosis and prognosis where appropriate. The prognosis for some patients with COPD can be very poor: a recent audit of

1400 patients admitted to hospital with an exacerbation of COPD showed that 14% had died within 3 months [449,452]. However, for most patients with COPD, the interval from diagnosis to death may be many years, so that choosing the right moment to discuss the prognosis of the disease and the patient's views on issues such as ventilatory support or advance directives can be difficult.

There was limited evidence about palliative care approaches in COPD. One Cochrane systematic review was identified[351] and four qualitative studies [449,453-456].

The systematic review [351] looked at opioids for the palliation of breathlessness in terminal illness. Although 14 RCTs were specifically related to a COPD population, there were limitations with these studies: including small sample sizes varying from 6 to 18 patients and variable time durations to drug interventions ranging from one off dose of drug through to 2 week periods. All of the COPD studies utilised a cross over design but were subject to variable washout periods.

The GDG acknowledge that palliative care is a difficult area in which to conduct research.

Evidence statements

A statistically significant effect of opioids was demonstrated for **breathlessness** using non-nebulised opioids, SMD –0.40 (-0.63 to –0.17), p=0.0006. However this was a heterogeneous population that was inclusive of both COPD and cancer patients[457].	Ia
There was no statistically significant effect for breathlessness in the studies using nebulised opioids.	
In a subgroup analysis of nine COPD studies there was no statistically significant difference for breathlessness between the treatment and control group, SMD -0.26 (-0.44 to 0.08) p=0.0042[457].	Ia

The four other identified studies were of a qualitative nature in their design.

Heffner [456] used a cross sectional descriptive questionnaire in the USA to assess the attitudes of N=105 patients in a pulmonary rehabilitation program with chronic lung conditions about end-of-life decision-making. 87% of the sample constituted people with COPD.

Sullivan [454] interviewed fifteen respirologists in a Canadian study to elicit what physicians told end-stage patients with COPD about intubation and mechanical ventilation.

Rhodes [455]in a UK study interviewed nine relatives of end-stage COPD deceased patients and although this represents a small sample size it does provide useful insights derived from narrative thematic experiences. The potential limitation of this study is that due to the limited sample size it may be unrealistic to generalise the experiences outside of the one UK Health Authority area from which it was derived.

Elkington [453] conducted a questionnaire survey of General Practitioners of one inner London Health Authority (N=389) to establish the role that discussions of prognosis play in GP's management of patients with severe COPD.

It was not possible to derive the same type of evidence statements from these qualitative studies as from RCTs but several important themes were identified.

Emergent Themes

Areas identified by Heffner [456] in a USA population included; patient interest in Advance Directives (AD), patient-doctor discussion about end-of-life issues and patient's interest in decision-making.	III

Patient interest in Advanced Directives (ADs)

89% of patients stated that they would be interested in learning more about Advanced Directives whilst 69% wanted to learn more explicit details about intubation and mechanical ventilation.

Patient doctor discussions about end-of-life issues

99% of patients stated that they would find discussions with physicians about ADs, intubation and mechanical ventilation acceptable. Despite their stated interests, only 19% had already discussed AD with physicians and only 15% had had discussion about life support interventions.

There was a 50:50 split regarding whether patients thought physicians should initiate discussions or wait until patients initiated these discussion about ADs. However the data showed that waiting for the physician to initiate the discussion was an ineffective strategy; of the 20 patients who already had discussions about ADs, 19 of these had initiated these discussions themselves.

Patient interest in decision making

Most patients wished to actively participate in decision about life support. In the circumstances of being hospitalised with a serious illness 72% stated that they would want to decide themselves about life support.

Sullivan [454] highlighted emergent themes from a population of Canadian physicians which included; timing of the discussion, importance of "knowing" the patient, content of the discussion, framing the information, decision difficulty, style and delivery of discussion. III

Timing of the discussion

There was agreement that an intubation and mechanical ventilation (MV) discussion should be initiated when a patient is in a stable condition.

Importance of "knowing" the patient

Knowing the patient allowed physicians to determine the patient's perceptions of their quality of life, satisfaction with current functioning and expectations in life. All of the 15 physicians interviewed used a combination of these factors in their decisions making.

Content of the discussion

Discussions included a tube being placed down the patient throat with emphasis on discomfort and inability to eat or speak. Regardless of whether the patient chose to be intubated the availability of analgesia was discussed. Content of discussion also included that following intubation and mechanical ventilation the best a patient may hope for was return to their pre exacerbation state of health. "Death" was not stressed by name in initial discussions.

Framing the information

Information was usually framed according to the physician's clinical judgement. The physician would take into account how successful the mechanical ventilation outcome was likely to be including eventual quality of life. A negatively framed physician discussion included palliative care.

Decision difficulty

80% of physicians highlighted the importance of family in facilitating the decision making process.

Style and delivery of discussion

Content of the narrative was similar although the style and delivery of the information varied between physicians.

Rhodes [455] identified the following themes; quality of life, services in the community, adaptations and equipment, informal care, after death support and meeting needs. III

Relatives reported that **quality of life** in the year before death was often very low.

Regarding **services in the community, t**here was little contact with the community nursing service or social workers, none had been offered or used day care.

Those transferring home from hospital were assessed for **home adaptations**, aids and equipment, similar assessments for those who had not had a hospital admission were patchy. The central role of the GP in gaining access to services was reiterated. Often services were provided too late to be of benefit.

Many of the **informal caregivers** were elderly persons themselves and had their own health problems. None of those interviewed seemed to realise that their relative's illness had been terminal.

After death support was identified as a theme. Bereaved people within the sample as a whole valued being able to talk to their GP, ask questions and talk through the illness and death. Those who received a post-death visit or letter appreciated it. A follow-up form a district nurse was also appreciated.

In relation to **meeting needs** much of the care for this group was described as being through crisis intervention and hospital admission.

Elkington [458] highlighted descriptive percentages from 214 UK GPs relating to discussions of prognosis in severe COPD. III

82% of respondents agreed that GPs have an important role in discussions of prognosis. 37% of GPs agreed that they found it hard to start the discussions about prognosis with patients (and 30% of GPs stated that they left it for patients or their relative to raise the subject of prognosis).

67% stated that they found it difficult to predict prognosis for individual cases (45% of GPs stated that there was insufficient information about COPD patients in the GP records to discuss prognosis with them).

GDG Consensus statement

Opioids, benzodiazepines, tricyclic anti-depressants and major tranquilizers are useful in palliating symptoms in patients in the end stages of COPD. IV

Oxygen may also be used to palliate breathlessness not relieved by other therapies (see section 7.6).	IV
Patients dying with COPD can benefit from the services of multidisciplinary palliative care teams, including admission to hospices.	IV

Recommendations

R109	Opioids should be used when appropriate to palliate breathlessness in patients with end-stage COPD which is unresponsive to other medical therapy.	**Grade D**
R110	Benzodiazepines, tricyclic antidepressants, major tranquillisers and oxygen should also be used when appropriate for breathlessness in patients with end-stage COPD unresponsive to other medical therapy.	**Grade D**
R111	Patients with end-stage COPD and their family and carers should have access to the full range of services offered by multidisciplinary palliative care teams, including admission to hospices.	**Grade D**

7.13.6 Assessment for occupational therapy

The prevalence of respiratory disability in moderate and severe COPD is high. Respiratory disease has been recognised for many years as the second commonest cause of major disability in elderly people [459], and the vast majority of respiratory disability is due to COPD. Despite this the level of community support provided to patients disabled by COPD is low. It compares unfavourably with that provided to patients with similar or even lower levels of disability caused by musculoskeletal or neurological problems [459,460]. This may be in part the result of a lack of recognition of disability by healthcare professionals. Patients with respiratory disability do not carry an obvious `badge' of disability such as a walking frame or a hemiparesis that marks them out (at rest) as someone in potential need of support. Until recently there has been a lack of appropriate assessment tools validated for the measurement of activities of daily living (ADL) (as opposed to quality of life) in patients with respiratory disease. Two such tools have recently been devised and validated independently [461-464] and can be used for the global assessment of patients. An assessment tool has been developed to assess patients needs for occupational therapy [465] but this has not been validated specifically in patients with COPD.

ADL assessment, whether by questionnaire or formal occupational therapy review may take place in the outpatient setting, but commonly occurs towards the end of an inpatient stay during an exacerbation. Even when assessment has previously been performed in the stable outpatient situation it should be repeated in inpatients, particularly if patients have previously demonstrated borderline coping abilities when clinically stable. Such patients may need temporary or even permanent domiciliary support on discharge. It is well recognised that disability level is a predictor of recurrent hospital admission for COPD, though it remains unclear whether alleviation of disability or provision of appropriate support reduces admission frequency.

Occupational therapy may be relevant across the spectrum of COPD, including:

- recently diagnosed patients
- during exacerbations
- during pulmonary rehabilitation
- as part of palliative care.

GDG consensus statements

Assessment tools such as the Manchester Respiratory Activities of Daily Living (MRADL) questionnaire[461], the London Chest Activity of Daily Living scale (LCADL)[464] or the Canadian Occupational Performance Measure (COPM)[465,466], can be used to formally assess patients need for occupational therapy.	IV
Occupational therapy assessment of patients needs may take place as part of a programme of respiratory rehabilitation, and should certainly form part of a multidisciplinary assessment and planning package prior to discharge from hospital.	IV

Recommendations

R112	Patients should be regularly asked about their ability to undertake activities of daily living and how breathless they become when doing these.	**Grade D**
R113	Clinicians involved in the care of people with COPD should assess their need for occupational therapy using validated tools.	**Grade D**

7.13.7 Social services

Patients and their carers may be entitled to claim benefits including benefits for people who cannot work and benefits for the extra costs of disability. It may be possible to receive more than one benefit at a time. As well as benefits, patients may be entitled to disabled person's tax credit (DPTC), which is not a benefit: it is a payment from the Inland Revenue for disabled people who work. DPTC is payable in addition to benefits, for example, disability living allowance, but it depends on a person's income.

Information on benefits can be obtained from The Benefits Agency telephone help line which provides information on benefits for sick and disabled people and carers. The help line can also arrange for a person to ring a claimant adviser to help them with forms completion for disability living allowance and attendance allowance.

Benefits Enquiry Line: 0800 882200

Minicom: 0800 243355

Website: www.dwp.gov.uk

Patients and their carer can also obtain advice from the Citizens Advice Bureau and The British Lung Foundation also produces a leaflet describing the benefits that may be available for patients with COPD.

GDG consensus statements

There is a greater access to financial benefits for patients aged under 65 years.	IV
The processing time for many applications for financial and social assistance reduces the potential benefits for many patients.	IV

Recommendations

R114	Patients disabled by COPD should be considered for referral for assessment by a social services department.	**Grade D**

7.13.8 Advice on travel

Recommendations for patients planning air travel are contained in BTS guidelines [467]. Information about other modes of transport and details about specific airlines policies are available from the British Lung Foundation and are summarised in their leaflet "Going on Holiday with a lung condition". The four general points contained in this leaflet are included below and the BTS recommendations on assessment of fitness to fly have been adopted.

Modern aircraft are pressurised to cabin altitudes up to 2438 m (8000 ft) and at this altitude the partial pressure of oxygen will have dropped to the equivalent of breathing 15.1 % oxygen at sea level. Arterial oxygen tensions fall in healthy passengers and altitude exposure will exacerbate hypoxaemia in patients with COPD, particularly those who are hypoxaemic at sea level. The physiological compensations for acute hypoxaemia at rest are mild to moderate hyperventilation (lowering of arterial carbon dioxide tension (Paco,) moderates the hyperventilation) and a moderate tachycardia but the clinical significance of temporary altitude induced hypoxaemia in patients with COPD is unclear. The BTS Working Party concluded, "The available controlled studies involve relatively small numbers of patients with stable disease and no co-existing medical problems. Simulated altitude exposure did not generally exceed 1 hour. These studies also largely excluded additional stressors such as exercise, dehydration, sleep, and active smoking. The only report to study exercise suggested that FEV, <50% predicted is a risk factor for desaturation."

The BTS Working Party also noted "COPD patients with large bullae are theoretically at increased risk of pneumothorax as a result of volume expansion at reduced cabin pressures. The volume of gas in a non-communicating bulla will increase by 30% on ascent from sea

level to 2438 m (8000 ft). There is one case report of fatal air embolism in a patient with a giant intrapulmonary bronchogenic cyst [468]. However, there are no data to state with any confidence what the maximum volume of a bulla should be before it reaches an unacceptable level of risk of rupture leading to tension pneumothorax, pneumomediastinum, or air embolism."

GDG consensus statements

The following points are important for patients with COPD who are considering travel: IV

- plan in advance
- be realistic
- shop around because of variability in the cost and availability of support (especially oxygen) and the regulations of different airlines, train, coach and ferry companies.
- ask questions
- travel with all necessary medication
- ensure necessary medication is accessible during journeys.

Fitness to fly can be assessed by an initial measurement of arterial oxygen saturation using a pulse oximeter, combined with history and examination (with particular reference to cardiorespiratory disease, dyspnoea, and previous flying experience) and the results of spirometry. IV

Depending on the results of the initial assessment a hypoxic challenge test may be necessary (see Table 7.6). IV

Table 7.6 Results of initial assessment

Screening result	Recommendation
Sea level SaO_2 >95%	Oxygen not required [B]
Sea level SaO_2 92-95% and no risk factor*	Oxygen not required [C]
Sea level SaO_2 92-95% and additional risk factor*	Perform hypoxic challenge test with arterial or capillary measurements [B]
Sea level SaO_2 <92%	In-flight oxygen [B]
Receiving supplemental oxygen at sea level	Increase the flow while at cruising altitude [B]

*Additional risk factors: hypercapnia; FEV <50% predicted; lung cancer; restrictive lung disease involving the parenchyma (fibrosis), chest wall (kyphoscoliosis) or respiratory muscles; ventilator support; cerebrovascular or cardiac disease; within 6 weeks of discharge for an exacerbation of chronic lung or cardiac disease.

Recommendations

R115	All patients on LTOT planning air travel should be assessed in line with the BTS recommendations[467].	**Grade D**
R116	All patients with an FEV_1 < 50% predicted who are planning air travel should be assessed in line with the BTS recommendations.	**Grade D**
R117	All patients known to have bullous disease should be warned that they are at a theoretically increased risk of developing a pneumothorax during air travel.	**Grade D**
R118	Scuba diving is not generally recommended for patients with COPD. Advise people with queries to seek specialist advice.	**Grade D**

7.13.9 Education

When reviewing the evidence in this area it was apparent that education is usually offered as part of a comprehensive pulmonary rehabilitation programme. Few studies have evaluated the effects of education alone on patient outcomes.

There is little robust evidence relating to COPD patient education. Many of the papers identified were excluded due to poor sample size and quality appraisal issues. Abstracts were also excluded due to lack of information upon which to quality appraise the study.

Four studies were identified that met the quality criteria [469-472]. In addition the Guideline Development Group was aware that both the ACCP Pulmonary Rehabilitation Guidelines [351] and the BTS Pulmonary Rehabilitation Statement [350] contribute information to the area of education although their primary focus is towards pulmonary rehabilitation.

One meta-analysis was found of psycho education [473], which was rejected because of quality appraisal issues.

Evidence statements

Sassi-Dambron [469] compared dyspnoea management strategies to general health education (not directly related to lung disease) in patients with COPD. At the end of the six-week treatment, there were no significant differences between the treatment and control groups on any outcome measure. Outcomes included eight dyspnoea measures, exercise tolerance, quality of life, anxiety, depression, FEV_1 and FVC.	Ib
Gallefoss [471,472] examined whether patient education affected medication concordance and quality of life in a combined population of asthmatics and COPD patients. The results for both of these trials were analysed as separate populations (the groups were also educated separately). The intervention group received a short education program whilst the comparison group were “followed by their GPs” only.	Ib

There were significant differences in the response to education between patients with COPD and asthma.

The educated patients with COPD received less than half the amount of rescue medication compared with the control group (p=0.03). More of the educated patients with COPD reported oral steroid courses but this was not statistically significant (69% vs. 44%) (p=0.07).

For **HRQL**, there were no statistically significant HRQL scores or FEV_1 results in the educated patient with COPD compared with the control group. (Patient education did increase the HRQL and FEV_1 among asthmatics but not among patients with COPD).

Howland [470] compared education to a control group in a quasi-experimental design. In patients with mild to severe COPD (defined respectively as FEV,/FVC 70 to 60 per cent and FEV1/FVC <45 percent) the only significant finding in favour of the education group was for health locus control (p=0.003), one of five measures used to assess general health perception. There were no other significant differences on any measure of **health or symptom status, physical function, mental health or social function.** IIa

Health economic evidence

Education varies in its content and there is extremely limited economic data about this area. What there is does suggest that patient education is reasonably cost effective, due to the change in behaviour and consequent reduction in resource use. There is not enough evidence to be confident in this however.

Recommendations

R119	There are significant differences in the response of patients with COPD and asthma to education programmes. Programmes designed for asthma should not be used in COPD.	**Grade A**
R120	Specific educational packages should be developed for patients with COPD. • Suggested topics for inclusion are listed in appendix C. • The packages should take account of the different needs of patients at different stages of their disease.	**Grade D**
R121	Patients with moderate and severe COPD should be made aware of the technique of NIV. Its benefits and limitations should be explained so that if it is ever necessary in the future they will be aware of these issues. (See section 8.13).	**Grade D**

7.13.10 Self-management

Self-management plans have been used successfully for many years for patients with asthma, although very few patients have actually been given a written self-management plan. These plans are concerned with guiding responses to subtle day-to-day variations in symptoms and lung function. Self-management plans in COPD on the other hand are designed to enable patients to respond appropriately to the first signs of an exacerbation and are not concerned with minor day-to-day variations in symptoms. If used correctly they will often lead to patients starting courses of antibiotics or oral steroids that they have been given to keep at home and may lead to reduced hospital admissions. Self-management plans need to be structured in a way that takes into account the age and mental state of patients with COPD.

One systematic review was identified[474] and one additional RCT (N=191)[475].

The main aim of self-management is to prevent exacerbations by life style adaption and to allow patients to acquire the skills to treat their exacerbation at an early stage [474]. This can be achieved either by self-management education and/or self-management plans. A self-management plan was defined as a plan (either written or verbal) designed with the primary purpose of patient self-management of COPD exacerbations. The plan advised patients in the event of a COPD exacerbation about starting or adjusting medication.

It was noted that a variety of interventions and comparisons were evident when looking at the research in this area. In summary, Monninkhof [474] cites seven studies with self-management education components [470,476-481]. Two additional studies have a self-management education component augmented with a self-management action plan [471,482], however of the management plans, only one was aimed specifically at self-treatment of exacerbations. The systematic review excludes studies that are primarily focused on pulmonary rehabilitation. Interventions were compared to usual care.

The Bourbeau [475] study combined a COPD specific self-management program consisting of teaching and exercise with a customised action plan for exacerbations compared to usual care. The exercise component comprised of a training program with supervised home sessions (including an exercise bicycle) of at least 3 times per week for 30 to 45 minutes per session. In light of this exercise component and in order to be congruent with the exclusion cited by the systematic review[474] the Bourbeau study was excluded.

There were varying degrees of detail when operationally defining COPD and importantly Monninkhof et al. [474] highlights that the time span over which the trials were conducted (1986 to 2003) means that changes in both the educational content and method of delivery together with background changes to treatment will have an impact on the trial outcomes. Follow up periods ranged from 2 months to one year.

Evidence statements

Monninkhof [474] in a meta-analysis of Gallefoss and Littlejohns [472,478], showed a statistically significant increase in the use of **oral steroid** courses in the educated patients compared to the control group, relative risk 1.30 (95% CI 1.02 to 1.91).	Ia

Within the Monninkhof systematic review[474], two studies, Watson and Littlejohns [478,482] assessed the use of **antibiotics** for respiratory problems. Littlejohns reported that 79% in the intervention group compared to 52% in the control group were prescribed antibiotics. Watson examined days on antibiotics via symptom diaries and found that 10% vs. 4% in the intervention and control group respectively were prescribed antibiotic therapy[474]. Ia

Use of **rescue medication** (short-acting beta$_2$ agonist) was assessed by Gallefoss[472] as cited in the systematic review[474]. The original paper by Gallefoss[472] highlights that the educated patients received less than half the amount of rescue medication (median 125 defined daily dosage (DDD)) compared with the control group (median 290 DDD) p=0.03. Ib

Monninkhof[474] reported four studies [478-480,483] (overall sample size n=417) that looked at COPD related **hospitalisations** and found no statistically significant overall differences. Ia

Monninkhof [474] highlights that meta-analysis of two studies [478,483] which report data about the number of patients with **one of more admissions**, demonstrated a non-significant reduction of hospitalisations in favour of the treatment group. Relative risk 0.80, (95% CI 0.43 to 1.50). Ia

There were no statistically significant differences between the groups for **emergency room visits, use of other health care facilities, days lost from work**[474]. Ia

Gallefoss and Watson [471,482](total sample size N=131) measured SGRQ outcomes. SGRQ total scores and domain scores were all lower (indicating a better HRQoL) in the self-management education groups but these differences did not reach clinical significance. Although the Ia

SGRQ demonstrated a statistically significant result for the **activity component** only in favour of the intervention group, WMD –10.2 (95% CI; -18.5 to –2.0) there was significant **heterogeneity** between the results p<0.05[474].

There were no statistically significant differences between the groups for **lung function**[474]. Ia

There were no statistically significant differences between the groups for **symptom scores**[474]. Ia

GDG consensus statements

The GDG believed that the effects of self management look promising but further studies are required to refine the content of self management plans. IV

There is no evidence that self management plans similar to those used in asthma are of value in COPD. IV

Self management plans need to be refined and the key components identified. IV

Recommendations

R122	Patients at risk of having an exacerbation of COPD should be given self-management advice that encourages them to respond promptly to the symptoms of an exacerbation.	**Grade A**
R123	Patients should be encouraged to respond promptly to the symptoms of an exacerbation by: • starting oral corticosteroid therapy if their increased breathlessness interferes with activities of daily living (unless contraindicated) • starting antibiotic therapy if their sputum is purulent • adjusting their bronchodilator therapy to control their symptoms.	**Grade D**
R124	Patients at risk of having an exacerbation of COPD should be given a course of antibiotic and corticosteroid tablets to keep at home for use as part of a self-management strategy (see recommendation 150).	**Grade D**
R125	The appropriate use of these tablets should be monitored.	**Grade D**
R126	Patients given self-management plans should be advised to contact a health care professional if they do not improve.	**Grade D**

7.14 Fitness for general surgery

Due to the time limitations within the guideline development process and the fact that these questions address a topic at the periphery of the guideline a full literature search and critical appraisal process was not undertaken in this area. However, a MEDLINE search, a selective review of frequently cited papers and key review articles were undertaken as part of the development of a background paper for discussion by the guideline development group. See section 2 for the methodology.

Patients with COPD appear to have an increased risk of post-operative pulmonary complications (3.0 fold for unselected surgery and 4.7 fold for thoracic or abdominal surgery[484]). The risk may increase with increasing "severity" of COPD, but it also depends on duration of anaesthesia and nature of surgery. The GDG was aware of the conclusions of the National Confidential Enquiry into Perioperative Deaths (NCEPOD), particularly their report and recommendations relating to deaths in elderly patients [485].

GDG consensus statements

Pulmonary risk factors alone do not predict the risk of post-operative pulmonary complications.	IV
FEV_1 on its own has little clinical usefulness in predicting post-operative pulmonary complications [486-488].	III
Composite assessment tools such as the widely used ASA scoring system [489] can be used to assess operative risk and plan patients' management.	IV

Recommendations

R127	The ultimate clinical decision about whether or not to proceed with surgery should rest with a consultant anaesthetist and consultant surgeon taking account of the presence of comorbidities, the functional status of the patient and the necessity of the surgery.	**Grade D**
R128	It is recommended that lung function should not be the only criterion used to assess patients with COPD before surgery. Composite assessment tools such as the ASA scoring system are the best predictors of risk.	**Grade D**
R129	If time permits, the medical management of the patient should be optimised prior to surgery and this might include undertaking a course of pulmonary rehabilitation.	**Grade D**

7.15 Follow-up of patients with COPD

Throughout the course of the disease, the management of COPD is likely to be shared between health care professionals in both primary and secondary care. Most patients with mild and moderate symptoms and those who are not experiencing frequent exacerbations will be managed predominately in primary care. Follow-up of patients with more severe disease will also be predominantly in primary care but there will also be a need for access to secondary care services. Patients with severe COPD are likely to have frequent exacerbations leading to hospital admissions. They often have complex problems with co-morbidities, may be on high levels of treatment, and need monitoring for LTOT.

Clinicians in primary care have the skills to assess patients' symptoms and the adequacy of their control, monitor the progression of their disease, identify the development of complications and the need for referral to secondary care or other specialists (see section 6.11 on referral for specialist advice). There are no data to guide decisions on how frequently patients should be reviewed but clearly this will vary according to individual

circumstances and the severity of the patient's disease. Some patients with COPD deteriorate faster than others and it is important to identify these individuals as they need specialist input. Reasons for referral to hospital services are dealt with in Section 6.11.

Many of the recommendations in this section of the guideline are based on expert opinion rather than on the result of research studies, due to the paucity of evidence and difficulty of conducting studies in this area. See section 2 for the methodology underpinning this section. This does not undermine the value or importance of these recommendations, which may have a large impact on the quality of care and outcome for the person with COPD and their carers. The GDG's consensus statements are broadly based on statements contained in the BTS COPD Guidelines [71].

GDG consensus statements

Follow up of patients with mild or moderate COPD (FEV_1 > 50%) will usually take place in primary care.	IV
For patients with severe disease, shared care between the hospital and primary care team is the usual pattern although there are no data to show how care should be provided to achieve the best combination of clinical and cost effectiveness.	IV
Patients with severe disease requiring interventions such as non-invasive ventilation should be reviewed regularly by specialists.	IV

Recommendations

R130	Follow-up of all patients with COPD should include: • highlighting the diagnosis of COPD in the case record and recording this using Read codes on a computer database • recording the values of spirometric tests performed at diagnosis (both absolute and percent predicted) • offering smoking cessation advice • recording the opportunistic measurement of spirometric parameters (a loss of 500 ml or more over 5 years will select out those patients with rapidly progressing disease who may need specialist referral and investigation).	**Grade D**
R131	Patients with COPD should be reviewed at least once per year, or more frequently if indicated, and the review should cover the issues listed in table 7.7.	**Grade D**
R132	For most patients with stable severe disease regular hospital review is not necessary, but there should be locally agreed mechanisms to allow rapid access to hospital assessment when necessary.	**Grade D**
R133	When patients with very severe COPD are reviewed in primary care, they should be seen at least twice a year, and specific attention should be paid to the issues listed in table 7.7.	**Grade D**
R134	Patients with severe disease requiring interventions such as long-term non-invasive ventilation should be reviewed regularly by specialists.	**Grade D**

Table 7.7 Summary of follow-up of patients with COPD in primary care

	Mild/moderate/severe (stages 1 to 3)	**Very severe (stage 4)**
Frequency	**At least annual**	**At least twice per year**
Clinical assessment	• smoking status and desire to quit • adequacy of symptom control: - breathlessness - exercise tolerance - estimated exacerbation frequency • presence of complications • effects of each drug treatment • inhaler technique • need for referral to specialist and therapy services • need for pulmonary rehabilitation	• smoking status and desire to quit • adequacy of symptom control: - breathlessness - exercise tolerance - estimated exacerbation frequency • presence of cor pulmonale • need for long-term oxygen therapy • patient's nutritional state • presence of depression • effects of each drug treatment • inhaler technique • need for social services and occupational therapy input • need for referral to specialist and therapy services • need for pulmonary rehabilitation
Measurements to make	• FEV_1 and FVC • calculate BMI • MRC dyspnoea score	• FEV_1 and FVC • calculate BMI • MRC dyspnoea score • SaO_2

8 Management of exacerbations of COPD

8.1 Introduction

Exacerbations, particularly those that result in admission to hospital, are significant events in the natural history of COPD. They are distressing and disruptive for patients, and account for a significant proportion of the total costs of caring for patients with COPD.

Much of the research into the epidemiology, pathology and management of exacerbations has been hampered by the lack of an agreed uniform definition. This is in part due to the inherent difficulties in defining exacerbations[490]. The GDG propose the definition that follows.

8.2 Definition of an exacerbation

An exacerbation is a sustained worsening of the patient's symptoms from his or her usual stable state that is beyond normal day-to-day variations, and is acute in onset. Commonly reported symptoms are worsening breathlessness, cough, increased sputum production and change in sputum colour. The change in these symptoms often necessitates a change in medication.

8.3 Consequences of having an exacerbation

In the UK, hospitalisation or management in a hospital-at-home scheme is a major event in the natural history of COPD, heralding a significant worsening of prognosis. See section 2 for the methodology underpinning this section.

Evidence statements

In patients admitted to hospital in the UK with an exacerbation of COPD a retrospective audit of 1400 admissions has shown that 34% were **re-admitted** and 14% had **died** within 3 months[452].	III

In a Spanish study of patients admitted to hospital with an exacerbation of COPD 63% were **readmitted** within 1 year[491]. III

The factors associated with an increased risk of readmission were:

- ≥ 3 admissions in the previous year (Hazard Ratio 1.66, 95%CI 1.16 to 2.39)
- FEV_1 % predicted (Hazard Ratio 0.97, 95%CI 0.96 to 0.99)
- PaO_2 (Hazard Ratio 0.88, 95%CI 0.79 to 0.98)
- lower levels of physical activity (Hazard Ratio 1.85, 95%CI 1.16 to 2.94)
- need for an anticholinergic bronchodilator (Hazard Ratio 1.81, 95%CI 1.11 to 2.94) [491].

A study in the USA of patients admitted to an ITU with an exacerbation of COPD (Median FEV_1 = 0.8 l, Mean age = 70, 78% had ≥ 2 co-morbid illnesses) has shown that the 2, 6, 12 and 24 month **mortality rates** were 20%, 33%, 43% and 49% respectively [492]. III

Studies of a cohort of patients observed in the community have shown that **symptoms** and **peak expiratory flow rates** recover slowly after an exacerbation. III

The median (and inter quartile range) for recovery of symptoms was 7 days (IQR 4-14 days) and for recovery of peak expiratory flow was 6 days (IQR 1-14 days).

Recovery of PEFR to baseline was not complete in 24.8% at 35 days and 7.1% at 91 days[493].

Studies in the same cohort have shown that patients experiencing frequent exacerbations (more than 2.92 per year) have more rapid III

lung function decline (40.1 ml/yr (95% CI 38 to 42 ml/yr) -v- 32.1 ml/yr (95%CI 31 to 33 ml/yr) p<0.05)[494].

Studies in the same cohort have also shown that **health related quality of life** measured using the SGRQ was significantly worse in patients experiencing frequent exacerbations (3 or more per year) (Total score –15.1 (95%CI –22.3 to –7.8, p < 0.0005; Symptoms score –21.9 (95%CI –29.7 to –14.0, p < 0.0005; Activities score –12.2 (95%CI –21.2 to –5.3, p < 0.001; Impacts score –14.1 (95%CI –22.9 to –5.6, p < 0.002) [495]. III

Health economics Evidence statements

The costs of an exacerbation of COPD to the health care system have been estimated by Andersson et al (2002)[496] and Price et al (1999)[497] and have been estimated according to the severity of the exacerbation (See also Section 14) and using the severity classification current at that time.

Andersson et al (2002)[496].

Costs given in SEK, converted to GB£ by using purchasing power parities for 2002 from the OECD (www.oecd.org).

Mild	£7.94
Mild/moderate	£23.43
Moderate	£139.74
Severe	£1,446.48

Price M J et al(1999)[497].

Mild	£14.81
Moderate	£95.20
Severe	£1,658.59

The cost of an exacerbation clearly depends on the severity of the exacerbation and there is a considerable difference in cost between a mild exacerbation and a severe exacerbation. This is mostly due to the requirement for hospitalisation for severe exacerbations.

GDG consensus statements

The **long term outcomes** of exacerbations of COPD managed in the community in the UK are not known.	IV

8.4 Causes of an exacerbation

A number of factors are known to cause exacerbations of COPD. Although bacteria can be cultured for the sputum of patients with stable COPD there is evidence that they are also responsible for exacerbations. Viruses are also important aetiological agents, particularly during winter months. Non-infectious agents are also responsible for some exacerbations. See section 2 for the methodology underpinning this section.

GDG consensus statements

The following factors are known causes of exacerbations of COPD[498]. IV

Infections	Rhinoviruses (common cold)
	Influenza
	Parainfluenza
	Coronavirus
	Adenovirus
	Respiratory Syncytial Virus
	C pneumoniae
	H influenzae
	S pneumoniae
	M catarrhalis
	Staph aureus
	P aeruginosa
Common pollutants	Nitrogen dioxide
	Particulates
	Sulphur dioxide
	Ozone

The cause of the exacerbation may be unidentifiable in up to 30% of exacerbations. IV

8.5 Symptoms of an exacerbation

Exacerbations may lead to different constellations of symptoms, of varying severity, in different patients. There is no single defining symptom of an exacerbation, but changes in breathlessness, cough and sputum production are common. See section 2 for the methodology underpinning this section.

GDG consensus statements

Exacerbations of COPD can be associated with the following symptoms: IV

- increased dyspnoea
- increased sputum purulence
- increased sputum volume
- increased cough
- upper airway symptoms (e.g. colds and sore throats)
- increased wheeze
- chest tightness
- reduced exercise tolerance
- fluid retention
- increased fatigue
- acute confusion

Chest pain and fever are uncommon features of COPD exacerbations and should prompt a search for other aetiologies. IV

8.6 Differential diagnosis of an exacerbation

Other conditions may present with similar symptoms in patients with COPD. These must be considered and excluded when making a diagnosis of an exacerbation. See section 2 for the methodology underpinning this section.

GDG consensus statements

Other causes of similar symptoms in patients with COPD are: IV

- pneumonia
- pneumothorax
- left ventricular failure/pulmonary oedema
- pulmonary embolus
- lung cancer
- upper airway obstruction
- pleural effusion
- recurrent aspiration

8.7 Assessment of the severity of an exacerbation

Some exacerbations are mild and self-limiting. These are frequently managed by patients at home without consulting healthcare professionals. Other exacerbations are severe, carry a risk of death and require hospitalisation. A number of factors can be used to assess the severity of an exacerbation. Not all will be present, but the occurrence of any of these should alert the clinician. See section 2 for the methodology underpinning this section.

GDG consensus statements

The following signs are features of a severe exacerbation: IV

- marked dyspnoea
- tachypnoea
- purse lip breathing
- use of accessory muscles (sternomastoid and abdominal) at rest
- acute confusion
- new onset cyanosis
- new onset peripheral oedema
- marked reduction in activities of daily living

8.8 Assessment of need for hospital treatment

Most patients with an exacerbation of COPD can be managed at home but a few need hospital treatment. This may be because of the severity of the exacerbation, the need for therapies that are not available to that patient at home (such as oxygen or nebulised bronchodilators), or the need for specialist interventions such as non-invasive ventilation. The decision about referral to hospital involves an assessment of the severity of symptoms (particularly the degree of breathlessness, the presence of cyanosis or peripheral oedema and the level of consciousness), the presence of co-morbidities, whether or not the patient is already receiving long term oxygen therapy, the level of physical functioning, and the patient's ability to cope at home. See section 2 for the methodology underpinning this section.

Recommendations

R135

Factors that should be used to assess the need to treat patients in hospital are listed in table 8.1:

Grade D

Table 8.1 Factors to consider when deciding where to treat the patient

Factor	Treat at home	Treat in hospital
Able to cope at home	Yes	No
Breathlessness	Mild	Severe
General condition	Good	Poor/deteriorating
Level of activity	Good	Poor/confined to bed
Cyanosis	No	Yes
Worsening peripheral oedema	No	Yes
Level of consciousness	Normal	Impaired
Already receiving LTOT	No	Yes
Social circumstances	Good	Living alone/not coping
Acute confusion	No	Yes
Rapid rate of onset	No	Yes
Significant comorbidity (particularly cardiac and insulin-dependent diabetes)	No	Yes
SaO_2 < 90%	No	Yes
Changes on chest radiograph	No	Present
Arterial pH level	≥ 7.35	< 7.35
Arterial PaO_2	≥ 7 kPa	< 7 kPa

8.9 Investigation of an exacerbation

The diagnosis of an exacerbation is made clinically and does not depend on the results of investigations; however, in certain situations, investigations may assist in ensuring appropriate treatment is given. Different investigation strategies are required for patients in hospital (who will tend to have more severe exacerbations) and those in the community. See section 2 for the methodology underpinning this section.

Changes in lung function at the time of an exacerbation are usually small and are not helpful in routine practice.

Patients may present for the first time with an exacerbation of COPD. In this situation, patients need assessing and their diagnosis confirmed as described in Section 6.

Sending sputum samples for culture in primary care is of very limited value because empirical therapy is effective and should be prescribed promptly if the sputum is purulent.

Recommendations for primary care

R136	In patients who have their exacerbation managed in primary care: • sending sputum samples for culture is not recommended in routine practice • pulse oximetry is of value if there are clinical features of a severe exacerbation.	**Grade D**

Recommendations for patients referred to hospital

R137	In all patients with an exacerbation referred to hospital: • a chest radiograph should be obtained • arterial blood gas tensions should be measured and the inspired oxygen concentration should be recorded • an ECG should be recorded (to exclude comorbidities) • a full blood count should be performed and urea and electrolyte concentrations should be measured • a theophylline level should be measured in patients on theophylline therapy at admission • if sputum is purulent, a sample should be sent for microscopy and culture • blood cultures should be taken if the patient is pyrexial.	**Grade D**

8.10 Hospital-at-home and assisted-discharge schemes

Over the last few years there has been considerable interest in hospital-based rapid assessment units and early discharge schemes for patients with exacerbations of COPD. Rapid assessment units aim to identify those patients that can safely be managed at home with additional nursing and medical input rather than being admitted[499]. Early discharge schemes aim to facilitate the early discharge of patients admitted with an exacerbation of COPD[500]. Rapid assessment units generally involve a full assessment of the patient at the hospital by a multidisciplinary team and discharge to the community with appropriate support. This may include additional equipment (e.g. a nebuliser and compressor or an oxygen concentrator), nursing supervision from visiting respiratory nurse specialists, and increased social service input. Patients remain under the care of the hospital consultant but GPs are made aware of the fact that they are receiving home care. Early discharge schemes aim to identify patients in hospital who could be discharged before they have fully recovered by providing increased support in their homes.

When reviewing the evidence in this area account was taken of the site of assessment together with the length of stay in hospital before transferring home. It was important to distinguish between those schemes that constitute hospital-at-home and those that were referred to as assisted or early discharge. Assisted or early discharge schemes by their very nature involved hospital admission and usually at least one over-night stay.

Four RCTs were found[501-504], one qualitative study [505], one survey[506] and one service evaluation[499] which were applicable to hospital-at-home care. One RCT[507] relates to early discharge. All but the qualitative research[505] and the survey[506] were situation specific to COPD exacerbations.

The GDG acknowledged that it was difficult to distinguish what constitutes hospital-at-home and early discharge from the papers reviewed and agreed not to make a distinction based on the minimum time spent in hospital. The GDG felt that the important distinction was whether services could be initiated at any time of day seven days per week, with the obvious implications on resources and impact on the primary care.

Evidence statements

There were no significant differences in FEV_1[501-503] or **readmission rates**[501-504] between hospital-at-home and home care for patients with COPD exacerbations. There were also no significant differences between the two groups for the **number of days in care**[503].	Ib
There were no significant differences in **mortality** rates between those patients cared for as part of a hospital-at-home scheme and in-patients[502-504].	Ib
Two studies showed no significant differences between the groups for **HRQL (SGRQ)** (subgroup analysis)[502], **chronic respiratory questionnaire (CRQ**)[501]. One Spanish study showed significant improvement in **SGRQ**[504].	Ib

There were no significant differences between the groups for **symptom scores**[503]. Ib

In relation to **additional support services** Skwarska et al[501], found that GPs and carers did not differ significantly between hospital-at-home and in-patient care during an 8 wk follow up period. Ib

There were no significant differences in the **satisfaction scores** with the care package for either patient or carers between the two groups[503]. Ib

Qualitative research, using a grounded theory approach (N=29) in a population of older patients (65 to 89 years) highlighted that the likelihood of surviving illness was the most important **determinant of preference** for home or hospital care in acute illness. For some, home care was seen as a low intensity service. Factors influencing perceptions included social support, self -reliance and past experience with illness[505]. This study is limited by the geographical location of the research (USA) where differences in payment of healthcare systems may affect the patient's preference for site of care. This study is also not specific to COPD patients. III

Cotton et al [507], N=81 found on an intention to treat basis that a policy of early discharge reduced **in-patient stay** from a mean of 6.1 days (range 1 to 13 days) with conventional management to 3.2 (range 1 to 16) days with an early discharge scheme. This study is limited by its relatively small sample size. Ib

There were no significant differences in the number of patients that were **readmitted** in each group, the number of **additional days readmitted patients spent in hospital** or the **mortality rate**[507]. Ib

Health economics evidence statements

Seven small studies were found. Some studies were specific to patients with severe COPD. Many of the studies had methodological limitations and were not full economic evaluations, they only gave limited details of cost. One study suggested that there was an increase in overall healthcare costs for hospital-at-home. This was mainly because of an increased use of GP services and other primary care resources, as well as the cost of the hospital-at-home care. This means that costs may be shifted to primary care when patients spend fewer days in the hospital and use the hospital-at-home scheme[508].

There is limited evidence that a hospital-at-home scheme is more expensive than inpatient care, as it shifts resource use to primary care[508]. In a Spanish study based around tertiary referral hospitals, hospital-at-home was cheaper in the short term than conventional care[504].

There is limited evidence that a supported discharge scheme may be cheaper than usual inpatient care[501].

Recommendations

R138	Hospital-at-home and assisted-discharge schemes are safe and effective and should be used as an alternative way of caring for patients with exacerbations of COPD who would otherwise need to be admitted or stay in hospital.	**Grade A**
R139	The multiprofessional team required to operate these schemes should include allied health professionals with experience in managing COPD, and may include nurses, physiotherapists, occupational therapists and generic health workers.	**Grade D**
R140	There are currently insufficient data to make firm recommendations about which patients with an exacerbation are most suitable for hospital-at-home or early discharge. Patient selection should depend on the resources available and absence of factors associated with a worse prognosis, for example, acidosis.	**Grade D**
R141	Patients' preferences about treatment at home or in hospital should be considered.	**Grade D**

8.11 Pharmacological management

8.11.1 Inhaled bronchodilators

Increased breathlessness is a common feature of an exacerbation of COPD. This is usually managed by taking increased doses of short-acting bronchodilators. The GDG has not reviewed the evidence for the effects of these drugs in this context but has considered their efficacy as bronchodilators in Section 7.

As well as taking increased doses of bronchodilators at the time of an exacerbation, these drugs may be given using different delivery systems. This is considered in the next section.

8.11.2 Delivery systems for inhaled therapy during exacerbations

Bronchodilators are used to treat the increased breathlessness that occurs during exacerbations. Some patients who normally inhale these drugs from hand held inhalers use nebulised therapy during exacerbations. In this section the evidence underpinning this practice is reviewed. See section 2 for the methodology underpinning this section.

Evidence statement

One meta-analysis was found[509] of bronchodilator delivery in acute airflow obstruction.	Ia
Subgroup analysis of 48 patients from 3 studies with COPD gave a small but non-significant treatment effect size (favouring wet nebulization) of 0.23 (95% CI –0.35 to 0.81)[509].	

GDG consensus statements

Hand-held inhalers (when used with spacer devices and a good inhaler technique) and nebulizers are equally effective in achieving bronchodilation in COPD exacerbations[241].	IV
For low dose bronchodilator therapy - for example, 100-400 mg salbutamol or terbutaline - treatment with a metered dose inhaler is more convenient whilst a nebuliser can deliver higher doses more easily[240].	IV
Breathless patients are less likely to be able to inspire slowly or breath hold for optimum lung deposition from a metered dose inhaler[240].	IV
Nebulizers are widely used in most hospitals because they are regarded as more convenient for healthcare staff to administer and because less patient education or cooperation is required. Based on ERS[241].	IV
This usage does not imply that nebulized therapy is superior and this should be made clear to patients and their relatives[241].	IV
A nebuliser has the advantage of being independent of effort or breathing pattern when a patient is distressed. This means that a patient can begin nebulised treatment using a mask or a mouthpiece while the medical attendant can continue with other tasks. The use of a metered dose inhaler in this situation would require the medical attendant (or respiratory therapist or nurse) to stand by the patient and supervise or administer multiple doses of treatment, possibly more than 20, at one minute intervals[240].	IV

Nebulised treatment might have a further beneficial effect due to its physical properties. Inhaled droplets may alter mucus viscosity in the airways and nebulised terbutaline or saline may help patients with bronchiectasis to expectorate. Whether this is also true in acute COPD is not known[240]. IV

Theoretically a mouthpiece may be better as it avoids nasal deposition of drugs, although no advantage has been found in two small clinical studies in stable asthma and COPD. IV

Patients may prefer a face mask, especially when acutely breathless, a situation where patients are likely to mouth breathe and thus diminish the theoretical disadvantages of the face mask. A mouthpiece may avoid the risk of ocular complication with anticholinergic agents[241].

Recommendations

R142	Both nebulisers and hand-held inhalers can be used to administer inhaled therapy during exacerbations of COPD.	**Grade A**
R143	The choice of delivery system should reflect the dose of drug required, the ability of the patient to use the device and the resources available to supervise the administration of the therapy.	**Grade D**
R144	Patients should be changed to hand-held inhalers as soon as their condition has stabilised because this may permit earlier discharge from hospital.	**Grade D**
R145	If a patient is hypercapnic or acidotic the nebuliser should be driven by compressed air, not oxygen (to avoid worsening hypercapnia). If oxygen therapy is needed it should be administered simultaneously by nasal cannulae.	**Grade D**
R146	The driving gas for nebulised therapy should always be specified in the prescription.	**Grade D**

8.11.3 Systemic corticosteroids

This section focuses on the area of oral or systemic steroids (excluding inhaled steroids) in relation to exacerbations of COPD. Three systematic reviews were identified[510-512] relating to the use of oral / systemic steroids in the treatment of COPD exacerbations.

The trials within each of the systematic reviews were mostly small to moderate in sample size with short to medium term follow up of a maximum of 6 months. Drug preparations, dosages and routes of administration also varied significantly.

The GDG was aware of methodological limitations in the Bullard et al paper[513] which was included in the above systematic reviews. After transfer from emergency care blinding was broken and 12 patients (10%) crossed protocol. In addition to this there appeared to be an error in reporting the data for lung function parameters. The results reported being outside of the boundaries of the 95% confidence interval. This error was evident in the PEFR and FEV_1 data for the non-steroid group. The FEV_1 0-6 hour data may have been incorporated into the Wood Baker systematic review[511] within the FEV_1 meta-analysis. Comments pertaining to this are noted on the Cochrane Internet site within the comments section (McCrory 1999). When reviewing the FEV_1 meta-analysis weighted % the Bullard[513] data only contributed 7.7%. The other two systematic reviews[510,512] did not undertake any meta-analysis. Hence the Bullard paper has been excluded from the evidence statements made below.

In addition to the three systematic reviews, one additional randomised controlled trial was found[514] (N=199, 10 days follow-up), using oral prednisolone and a placebo.

The GDG also observed that the dose of steroids used in the North American studies was considerably higher than the doses used in the UK. In addition to this, although there are data on the incidence of acute adverse events, there are no data on the long term consequences of frequent courses of oral steroids.

Evidence statements

Three systematic reviews[510-512] all reviewed virtually the same RCTs. The reviews demonstrated a significant effect in favour of steroids over placebo for **FEV_1 for at least 72 hours**. In the meta-analysis by Wood Baker et al [511] of 6 RCTs, the WMD was 120 ml (95% CI; 5ml to 190ml). Ia

One additional RCT was found[514]. This trial also demonstrated significant improvements in **FEV_1 up to 36 hours** with a mean difference of 160ml (95% CI; 9ml to 240ml) in favour of the intervention compared to placebo. Ib

Davies et al[515], Niewoehner et al[516] and Thompson et al[517] (all trials included in the systematic reviews) measured FEV_1 at multiple time points over differing time frames. These trials found statistically significant improvements occurred in the first 3 to 5 days of corticosteroid treatment compared to the control.[510]. Ia

Maltais et al[514] and Thompson[517] demonstrated a statistically significant improvement in arterial **PaO_2** in the first 72 hours in favour of the steroid group compared to placebo <0.05. Ib

Significantly shorter **duration of hospitalisation** was demonstrated by Niewoehner et al[516] (p=0.03) and Davies et al[515] (p=0.027) in favour of the steroids compared to placebo. Ib

In one further study with no objective assessment of fitness for discharge, Maltais[514] found no significant differences in the mean duration of hospitalisation between steroid and placebo groups. Ib

A meta-analysis of 5 RCTs found no statistically significant differences between the steroid and control groups for **mortality** [511]. Ia

The systematic review by McCrory et al[510] highlighted the current debate around **duration** of steroid treatment and **dose** during COPD exacerbations[515,516,518]. Ia

Niewoehner et al[516] included a randomised comparison between a 2 and 8-week course of systemic corticosteroids. Findings demonstrated that there were no important clinical differences in clinical outcomes between the two courses.

There is still debate about the optimal dose and duration of treatment of steroids. "Small studies suggest that even lower doses[515] and even shorter courses of treatment[518] may be effective".

Meta-analysis by Wood Baker et al[511] of 5 RCTs showed a significantly beneficial effect of steroids compared to placebo at reducing **treatment failure**, OR 0.50 (95% CI; 0.32 to 0.79). It should be noted however that there was significant heterogeneity between the trials p=0.0071. This was potentially due to differences in operational definitions between the trials. Ia

Three RCTs[515,516,518] were combined in a meta-analysis by Wood Baker et al[511] for **adverse events.** "Overall, patients receiving corticosteroid treatment were 2.7 times more likely to have an adverse drug reaction than those receiving placebo". Ia

Niewoehner et al[516] (N=271) found that a greater proportion of patients in the steroid compared to placebo group required treatment for hyperglycaemia (15% vs. 4%, p=0.002). 67% of the steroid treated patients with hyperglycaemia had diabetes. Maltais et al[514] also found an increased incidence of hyperglycaemia. The hyperglycaemia was asymptomatic in patients in both studies and there was no increase in the onset of diabetes. Ib

Recommendations

R147	In the absence of significant contraindications oral corticosteroids should be used, in conjunction with other therapies, in all patients admitted to hospital with an exacerbation of COPD.	**Grade A**
R148	In the absence of significant contraindications, oral corticosteroids should be considered in patients in the community who have an exacerbation with a significant increase in breathlessness which interferes with daily activities.	**Grade B**
R149	Patients requiring corticosteroid therapy should be encouraged to present early to get maximum benefits (see recommendations 122-126).	**Grade D**
R150	Prednisolone 30 mg orally should be prescribed for 7 to 14 days.	**Grade D**
R151	It is recommended that a course of corticosteroid treatment should not be longer than 14 days as there is no advantage in prolonged therapy.	**Grade A**
R152	For guidance on stopping oral corticosteroid therapy it is recommended that clinicians refer to the British National Formulary section 6.3.2.	**Grade D**
R153	Osteoporosis prophylaxis should be considered in patients requiring frequent courses of oral corticosteroids.	**Grade D**
R154	Patients should be made aware of the optimum duration of treatment and the adverse effects of prolonged therapy.	**Grade D**

R155	Patients, particularly those discharged from hospital, should be given clear instructions about why, when and how to stop their corticosteroid treatment.	**Grade D**

8.11.4 Antibiotics

Bacteria can be isolated from sputum samples during periods of stability in COPD but are also associated with exacerbations. Antibiotics are commonly prescribed for episodes of purulent sputum. The bacteria that have been isolated during exacerbations are generally sensitive to most broad-spectrum antibiotics. There has been controversy about whether antibiotics have a benefit in exacerbations and more specifically about whether their use should be restricted to patients with purulent sputum. Early studies included patients with clinically defined "chronic bronchitis" rather than COPD as defined by airflow obstruction. This makes extrapolation difficult[519].

There have been two recent publications[510,520] that have assimilated the evidence base (including the meta-analysis by Saint et al[521] relating to the use of antibiotics during COPD exacerbation. These publications were of rigorous methodological quality and hence the evidence statements cited below are mainly based upon their content.

In addition, three other studies were found[522-524] that following critical appraisal were also worthy of inclusion.

Because of the uncertainty over the role of antibiotics in the management of exacerbations of COPD and the methodological limitations of studies that aim to determine the relative efficacy of different antibiotic drugs without including a placebo comparison, the GDG have only considered studies that include a placebo comparison. The antibiotic drugs that were studied included tetracycline, doxycycline, chloramphenical, penicillin, streptomycin, ampicillin, amoxicillin and cotrimoxazole compared to placebo. The fact that there was no agreed definition of an exacerbation limits the interpretation of these studies.

A meta-analysis of nine trials[521] cited in[510] found a small but statistically significant effect favouring antibiotics over placebo in patients with **exacerbations of COPD**. Effect size 0.22 (95% CI, 0.1 to 0.34). Ia

Four studies[525-527] all cited by AHRQ[510]and Allegra et al[524] assessed whether there was a relationship between **severity of exacerbation** and the effectiveness of antibiotic use. Ia

Three of these studies suggest that the worse the COPD severity of exacerbation (lung function impairment (FEV_1, PEFR), purulence of sputum) then the greater the degree of benefit from antibiotics. Ib

Anthonisen et al[525] showed a relationship of better outcomes with antibiotic versus placebo treatment based upon the severity of exacerbations. **Type 1 exacerbations (increased amount and purulence of sputum and dyspnoea)** benefited the most with resolution of symptoms in 63% of the antibiotic treated exacerbations and 43% of the placebo group. Patients with type-3 exacerbation (who met none of the three criteria) did not show any benefit. Ib

Berry et al[527] assessed the severity of exacerbation at presentation on a 4-point scale (baseline, mild, moderate or severe). Mild exacerbations demonstrated no significant difference. For patients presenting with **moderate or severe exacerbations**, the antibiotic group had significantly less severe symptoms on days 2 and 7 (but were not significant at two weeks). Ib

Allegra 2001 (N=46) in a retrospective data analysis of a previously reported RCT, re-clustered patients on the basis of severity of baseline lung function. The original RCT compared amoxicllin-clavulanic acid to placebo in patients with exacerbations of chronic bronchitis. The improvement or success rate vs. the failure rate was significantly different in **severe exacerbation** patients compared to those with exacerbations of a less severity. IIb

In relation to the use of quinolones, the SIGN publication on Community Management of Lower Respiratory Tract Infection[520] cites Davies et al[528]. Although quinolones have performed equally well in clinical trials, no clinical superiority over other antibiotics has yet been shown[528]. Ib

Nouira et al[522] undertook a small RCT (N=90) assessing the efficacy of oral ofloxacin in patients with severe exacerbation of COPD requiring ventilation. In relation to **deaths,** 4% (N=2) of patients receiving ofloxacin and 22% (N=10) in the placebo group died in hospital ARR 17.5%, 95% CI 4.3 to 30.7, p=0.01. Treatment with ofloxacin significantly reduced the need for **additional courses of antibiotics** ARR 28.4%, 95% CI 12.9 to 43.9, p=0.0006. **Duration of mechanical ventilation** and **hospital stay** was significantly shorter in the antibiotic group than placebo group (Absolute difference 4.2 days, 95% CI, 2.5 to 5.9) and (Absolute difference 9.6 days, 95% CI, 3.4 to 12.8) respectively. Ib

Sin et al[523] undertook a large population based retrospective cohort study (N=26,301) to determine the association between outpatient use of oral antibiotics and 30-day all-cause mortality following hospitalisation in a group of elderly COPD patients. Patients who used antibiotics within 30-days of the index hospitalisation date experienced lower odds for all-cause 30-day **mortality** after hospitalisation than those who did not receive antibiotics. (OR 0.83, 95% CI, 0.75 to 0.92). In relation to antibiotic use, macrolides had the lowest relative odds for mortality (OR 0.58, 95% CI 0.47 to 0.73) and fluoroquinolones had the highest relative odds (OR 0.98, 95% CI 0.84 to 1.15). III

Health economics Evidence statements

A pharmacoeconomic review was found, looking at the cost effectiveness of antibiotic therapy[529]. This concluded that due to the small number of economic evaluations and the nature of the designs, it was not possible to make a definitive statement recommending which specific antibacterial should be preferred on cost effectiveness grounds for the management of acute bacterial exacerbations of chronic bronchitis and future research is suggested.

Key points from the review by Morris et al[529] are:

- accurate diagnosis is a key factor affecting the cost effectiveness of antibacterials, in order to avoid unnecessary prescribing.
- initial empirical treatment antibiotics which are more effective but usually more costly in terms of drug acquisition price are likely to be more cost effective. This is mainly due to reducing the high costs associated with treatment failure.

A decision analytic model which was included in the review, constructed by Backhouse et al[530], supported the use of amoxicillan clavulnic acid as first and second line therapy over amoxicillin. Even though this drug has a higher acquisition cost, its higher efficacy rate was found to reduce the cost of treatment failure. The model was based on a general practice setting in the UK from the perspective of the NHS. The model was constructed in 1995, did not include side effects and there are concerns over the quality of the clinical data used in the model. Many of the studies were uncontrolled, had small sample sizes, differed in operational definitions of treatment success and study endpoints and are now considered old. We cannot be confident that this model applies to current conditions and there is too much uncertainty over the effectiveness data used to recommend the results. Further research is suggested on this issue[530].

One study[531] undertook an economic evaluation alongside a trial to estimate the incremental cost per quality adjusted life year (QALY) of ciprofloxacin vs. usual antibacterial care. In a subgroup analysis of patients with severe chronic bronchitis, ciprofloxacin was more cost effective, dominating usual antibacterial care.

Recommendations

R156	Antibiotics should be used to treat exacerbations of COPD associated with a history of more purulent sputum.	**Grade A**
R157	Patients with exacerbations without more purulent sputum do not need antibiotic therapy unless there is consolidation on a chest radiograph or clinical signs of pneumonia.	**Grade B**
R158	Initial empirical treatment should be an aminopenicillin, a macrolide or a tetracycline. When initiating empirical antibiotic treatment prescribers should always take account of any guidance issued by their local microbiologists.	**Grade D**
R159	When sputum has been sent for culture, the appropriateness of antibiotic treatment should be checked against laboratory culture and sensitivities when they become available.	**Grade D**

8.11.5 Theophylline and other methylxanthines

As well as their apparent actions as bronchodilators, theophylline also appears to increase respiratory drive[532,533] and this appears capable of overcoming some of the respiratory depression present during exacerbations[534]. For these reasons they have been used to treat patients admitted to hospital with an exacerbation.

The GDG was aware of one systematic review[535] relating to the use of methyl-xanthines for exacerbations of COPD. All other abstracts identified by the literature search were either already included in the systematic review[535] or were excluded due to use in stable COPD patients[137,163,306,536,537] or small sample size[538].

Evidence statements

The systematic review[535] identified three RCTs and one abstract with a total sample size of N=169. Methyl-xanthines were compared to placebo in patients with exacerbations of COPD. However, the following limitations were noted: the mean age of participants was low (mean age 65 years), limited outcome measures e.g. changes in FEV_1 were used, and only three trials[539-541] plus one abstract[542] were available for review. These studies had relatively small sample sizes (N=50,52,39 respectively). There were no significant differences in **pulmonary function** or **symptom scores.**	Ia

GDG Consensus statement

The GDG concluded that there was inadequate evidence to recommend a change from the current clinical practice of using intravenous theophylline to treat exacerbations of COPD.	IV

Recommendations

R160	Intravenous theophylline should only be used as an adjunct to the management of exacerbations of COPD if there is an inadequate response to nebulised bronchodilators.	**Grade D**
R161	Care should be taken when using intravenous theophylline because of interactions with other drugs and potential toxicity if the patient has been on oral theophylline.	**Grade D**
R162	Theophylline levels should be monitored within 24 hours of starting treatment and subsequently as frequently as indicated by the clinical circumstances.	**Grade D**

8.11.6 Respiratory stimulants

During exacerbations some patients develop hypercapnic respiratory failure. This is now usually managed using non-invasive ventilation (see section 8.13), but centrally acting drugs have also been used to stimulate respiratory drive. These drugs have a short duration of action and must be given by intravenous infusion.

One systematic review[543] was found and one RCT[544] which looked at the role of respiratory stimulants in patients with exacerbations of COPD. Both papers had methodological limitations, which included lack of detail of power calculations, small sample size, and lack of operational definitions.

The Greenstone systematic review[441] identified 4 RCTs (n=176 in total). One study compared doxapram with placebo[545] but approximately 40% of patients had a pH > 7.35 at entry and patients had an age range of 21 to 78 years. Another unblinded RCT by Angus et al[546] compared doxapram with NIV (n=17). The third study[547] contained in the review[441] compared doxapram with other stimulants not currently used. The fourth study contains data from an

unpublished study[548] comparing doxapram with non-invasive ventilation. No numerical data is available for inclusion into the analyses.

An additional RCT[544] was found which compared oral almitrine to placebo (n=23) but there was no power analysis. There was a general lack of methodological detail (e.g. randomisation, concealment and blinding processes). Only 74% of patients completed the study. The data was analysed on an intention to treat basis.

The results of all of these trials should be treated with caution due to the inherent methodological limitations and in light of these it was felt to be inappropriate to present evidence statements based on these data.

GDG consensus statements

Whilst the GDG acknowledges that doxapram is effective the group believe that non-invasive ventilation is more effective and is the treatment of choice for patients with respiratory failure during exacerbations of COPD.	IV
There is insufficient evidence to recommend a change from current clinical practice of using doxapram to treat respiratory failure during exacerbations of COPD.	IV

Recommendations

R163	It is recommended that doxapram is used only when non-invasive ventilation is either unavailable or considered inappropriate.	**Grade D**

8.12 Oxygen therapy during exacerbations of COPD

The exacerbation section of this guideline was outside the scope of the 2010 update. However the GDG was aware that some recommendations in the 'Oxygen therapy during exacerbations of COPD' section (section 8.12) of the guideline were out of date. Readers should refer to local protocols. Out of date recommendations have been deleted to appendix K.

During exacerbations of COPD patients develop worsening breathlessness. This may be associated with hypoxia and oxygen is commonly used to relieve the symptoms and raise arterial oxygen saturations. Patients are often given oxygen during their transfer to hospital in an ambulance, whilst being assessed at hospital and during the treatment of their exacerbation. The main aim is to prevent life-threatening hypoxia; however, in patients with COPD, this must be done with caution as some patient's respiratory drive depends on their degree of hypoxia rather than the usual dependence on hypercapnia. Thus uncontrolled oxygen therapy can result in suppression of respiratory drive, carbon dioxide narcosis and ultimately respiratory arrest.

Much of the literature concerning the use of oxygen therapy for exacerbations of COPD is old and many studies did not have control groups. A group of respiratory emergency medicine and intensive care physicians in the North West of England have reviewed the literature in this area[549] and developed guidelines on the use of emergency oxygen therapy for breathless patients[550]. These guidelines are not exclusively for patients with COPD but do make specific recommendations regarding the administration of oxygen to patients with exacerbations of COPD. The GDG has considered these recommendations when formulating its consensus statements and recommendations. See section 2 for the methodology underpinning this section.

Evidence statements

During exacerbations patients with COPD may become significantly hypoxic. Three studies[551-553] have shown that the PaO_2 falls from 55-60mmHg to 25-50mmHg during an exacerbation.	III
There are marked variations in the response of individual patients to oxygen. King et al[554] gave 24% oxygen to patients with exacerbations of chronic respiratory failure. They recorded a mean PO_2 of 40.4 mm Hg in these patients on room air and a mean PO_2 of 57.3 mm Hg after 30 to 60 minutes of 24% oxygen but 15 out of 40 patients did not	IIb

increase their PO_2 beyond 50 mm Hg.

In a prospective randomised crossover study Agusti et al[553] gave oxygen to 18 patients with COPD, within 48 hours of an admission with acute respiratory failure. Oxygen was given via nasal prongs at 2-4 l/min and Venturi masks at 24-28%. These concentrations raised the oxygen saturation to greater than 90% immediately in all cases. Oxygen was administered for 24 hours via each device and the oxygen saturation monitored continuously. Patients subsequently had an oxygen saturation less than 90% for a mean of 3.7 hours using the Venturi mask and 5.4 hours using nasal prongs. In extreme cases patients were poorly oxygenated for as long as 15 hours. It was found that the oxygen saturation was between 70 and 80% for a mean of 80 minutes, between 60 and 70% for a mean of 38 minutes and between 50 and 60% for a mean of 4 minutes during these periods of poor oxygenation. Inter-subject variability was considerable. Ib

Oxygen therapy may lead to hypercapnia and acidosis.

Plant et al[555], in 2000, found a significant negative correlation between pH and PaO_2 in 972 patients after oxygen therapy. The more oxygenated patients became the greater the magnitude of the subsequent respiratory acidosis. 47% of patients were hypercapnic, 20% of patients were acidotic and 4.6% of patients had a pH less than 7.25. More than 50% of hypercapnic patients were acidotic if the PaO_2 was greater than 75 mm Hg[555]. III

Degaute et al[556] gave 35 patients with exacerbations of COPD 28% oxygen for one hour. The average $PaCO_2$ rose from 59 mm Hg to 63 mm Hg during that period. IIb

Smith et al[557] gave 27 patients with an exacerbation of COPD and respiratory failure 24% to 28% oxygen for four hours. Sixteen patients had increases in $PaCO_2$ and, in two of these, dangerous respiratory acidosis developed with the pH decreasing to below 7.25. IIb

Eldridge et al[558] gave oxygen at flow rates ranging from 2 to 12 litres per minute in random order for at least 20 minutes at each level to 19 patients with exacerbations of COPD. In 17 patients there were progressive rises in $PaCO_2$ with increasing PaO_2 and the $PaCO_2$ fell when the arterial PaO_2 changed from a higher to a lower value. Again, there was great variability in the increases in $PaCO_2$ for a given increase in PaO_2 between patients. IIb

Prime and Wenstlake[559] gave 100% oxygen to 35 patients with stable COPD for 30 to 40 minutes. Thirty-three had increases in $PaCO_2$ ranging from 1.2 to 25.4 mm Hg. IIb

Aubier *et al*[560] gave 100% oxygen for 15 minutes to 22 patients with an exacerbation of COPD and respiratory failure. There was an average increase in $PaCO_2$ of 23 +/- 5 mm Hg and there was an average drop in pH from 7.34 +/- 0.01 to 7.25 +/- 0.02. IIb

Radial stabs to obtain blood for arterial blood gas analysis are not more painful than arterialised ear lobe gases [561]. III

Arterialised ear lobe gases may not accurately reflect PaO_2 but are acceptable for $PaCO_2$[561-564]. III

GDG Consensus statements

Arterialised ear lobe samples are an alternative way of obtaining arterial blood gases if there is local expertise and may be less painful for patients. IV

Recommendations

The exacerbation section of this guideline was outside the scope of the 2010 update. However the GDG was aware that some recommendations in the 'Oxygen therapy during exacerbations of COPD' section (section 8.12) of the guideline were out of date. Readers should refer to local protocols. Out of date recommendations have been deleted to appendix K.

R164	The oxygen saturation should be measured in patients with an exacerbation of COPD, if there are no facilities to measure arterial blood gases.	**Grade D**
R165	If necessary, oxygen should be given to keep the SaO_2 within the individualised target range.[jjj]	**Grade C**
R166	Pulse oximeters should be available to all health care professionals involved in the care of patients with exacerbations of COPD and they should be trained in their use. Clinicians should be aware that pulse oximetry gives no information about the pCO_2 or pH.	**Grade D**
R167	Deleted.	
R168	Deleted.	
R169	When the patient arrives at hospital, arterial blood gases should be measured and the inspired oxygen concentration noted in all patients with an exacerbation of COPD. Arterial blood gas measurements should be repeated regularly, according to the response to treatment.	**Grade D**
R170	Deleted.	

[jjj] Readers should refer to local protocols

8.13 Non-invasive ventilation (NIV) and COPD exacerbations

Non-invasive ventilation (NIV) is a method of providing ventilatory support that does not require the placement of an endotracheal tube. It is usually delivered via a mask that covers the nose, but occasionally a full face mask covering the nose and the mouth is required. The ventilators themselves are compact and portable.

Non invasive ventilation is now widely used for the treatment of respiratory failure occurring during exacerbations of COPD. It has many advantages over intubation and ventilation and can be used outside ITUs.

Three systematic reviews were identified[565-567] and two additional RCTs[568,569] that compared NIV (nasal or mask) to usual medical care. Conti et al[569] compared NIV to conventional ventilation (endotracheal ventilation).

Factors for consideration within this topic include; 1) Operational definitions regarding what constitutes an Intensive Care Unit (ICU) differ between countries; 2) Due to the type of intervention applied (NIV) double blinding is not possible; 3) The comparator of 'standard treatment' is not always defined but include oxygen, antibiotics, bronchodilators, steroids, respiratory stimulants and methylxanthines; 4) Trials are generally of small sample size and 5) Lastly, as highlighted by Ram et al[567], there is potential systematic bias in the trials as patients who failed treatment before 1 hour are missing in the one hour measurements.

The RCT by Thys et al[568] had methodological limitations (sample size N=20) was stopped at the interim analysis stage as the ten patients in the placebo NIV and convention medical care group all required active ventilation (3 full endotracheal intubation). Conti et al[569], for the majority of the outcomes, only provides descriptive statistics in the form of percentages rather than inferential statistics.

Evidence statements

NIV compared to usual medical care decreases **mortality**. Relative risk 0.41 (95% CI; 0.26 to 0.64)[567]. Odds ratio (OR) 0.22; (95% CI; 0.09 to 0.54 for COPD only trials)[566]. Risk difference -0.13 (95%CI; -0.21 to -0.06 for COPD sub group)[565].	Ia
NIV compared to usual medical care decreased the need for **intubation**. Relative risk 0.42 (95%CI 0.31 to 0.59)[567]. OR 0.12 (95%CI; 0.05 to 0.29 for COPD only trials)[566]. Risk difference -0.18 (95% CI; -0.33 to -0.03 for COPD sub group)[565].	Ia
NIV compared to usual medical care resulted in improvement in **pH** in the first hour of treatment WMD 0.03 (95% CI; 0.02 to 0.04), **$PaCO_2$** WMD –0.40kPa, (95% CI; -0.78 to –0.03), and respiratory rate WMD –3.08 rpm, (95% CI; -4.26 to –1.89)[567].	Ia
NIV compared to usual medical care resulted in fewer **complications** (principally ventilator associated pneumonia) in the NIV group, relative risk (RR) 0.32, (95%CI 0.18 to 0.56)[567].	Ia
NIV compared to usual medical care resulted in a shorter **duration of hospital stay** WMD –3.24 days, (95%CI –4.42 to –2.06)[567]. Risk difference –5.66 (95% CI; -10.10 to –1.23 for COPD sub group)[565].	Ia
Although the Plant et al paper is included in two of the systematic reviews quoted above[565,567] this is the only study to be carried out in a general medical and respiratory ward **setting** in the UK. As such the GDG felt it worthy of presenting the outcomes of this study separately. The study compared NIV to standard treatment. Overall, NIV significantly reduced the need for intubation p=0.02 and mortality was reduced p=0.05. NIV compared to standard care also led to a rapid improvement in pH in the first hour p=0.02, a greater	Ib

fall in respiratory rate at 4 hours p=0.035 and the duration of breathlessness was also reduced p=0.025. N.B. This study was *not* designed to identify the best setting to deliver NIV though.

The GDG noted that the hospital stay mortality in the group receiving standard care was high at 20%. This compares to a hospital stay mortality quoted by Connors et al (1996)[492] of 11%.

GDG consensus statements

Although the mean age of patients in these studies was 60 years there is no reason to suppose that the benefits are not the same in older patients. IV

Heath economics

Five papers were found. There were some methodological limitations in the papers. Keenan et al[570] showed that NIV is cost effective in patients with a severe exacerbation of COPD as it is more effective and less expensive, compared to standard therapy alone.

Plant et al[571] found that the addition of ward based NIV to standard treatment is cost effective when compared to standard treatment alone, with an incremental cost effectiveness ratio of -£645 per death avoided. Whilst costs are increased on the respiratory wards, these are offset by savings in the cost of ICU.

Modelling of results showed that providing a NIV service will avoid 6 deaths and 3-9 admissions to ICU per annum.

There is evidence that NIV is cost effective in patients with a severe exacerbation of COPD, being more effective and less expensive, compared to standard therapy alone. Keenan et al[570], Plant et al 2003)[571].

Recommendations

R171	NIV should be used as the treatment of choice for persistent hypercapnic ventilatory failure during exacerbations despite optimal medical therapy.	**Grade A**
R172	It is recommended that NIV should be delivered in a dedicated setting with staff who have been trained in its application, who are experienced in its use and who are aware of its limitations.	**Grade D**
R173	When patients are started on NIV there should be a clear plan covering what to do in the event of deterioration and ceilings of therapy should be agreed.	**Grade D**

8.14 Invasive ventilation and intensive care

Although non-invasive ventilation is the initial treatment of choice for respiratory failure during exacerbations of COPD, some patients do not respond adequately to NIV and require intubation and ventilation. Other patients have multiple organ system impairment or reduced levels of consciousness and in these settings ITU care may be the appropriate first line management option. In the past there has often been a reluctance to intubate patients with COPD or admit them to ITUs because of concerns about weaning and long term outcomes. The GDG has reviewed the evidence about the outcomes of ventilation and ITU care.

The GDG identified four descriptive case series of relevance[572-575]. Esteban et al[573] looked at the characteristics and outcomes in adult patients receiving endotracheal ventilation in a 28 day international study N=15,757 involving 361 ICUs and 20 countries. The study is limited due

to a heterogeneous population of ventilated patients and only limited details regarding COPD patients.

Nevins et al[575] looked at predictors of outcome for patients with COPD requiring invasive ventilation. This was a retrospective analysis of patients with a history of COPD to identify the patient characteristics at the time of hospital admission that predicted a poor outcome.

Seneff et al[572] in a situation specific population of patients with exacerbations of COPD looked at hospital and one year survival of patients admitted to ICU.

Rieves et al[574] looked at a population of patients with severe COPD and acute respiratory failure and examined correlates for survival at the time of intubation.

Evidence statements

The mean **duration of mechanical ventilation** for COPD patients compared to acute respiratory distress syndrome (ARDS) patients was 5.1 vs. 8.8 respectively p<0.001[573]. However Nevins et al 2001[575] identified a mean duration of ventilation was 9 days (median 4 days).	III
Duration of weaning was non significant between the two groups[573].	III
Length of hospital stay in ICU was 1.2 days in the COPD patients compared to 24.5 days in the ARDS patients, p=0.07, whilst **length of stay in hospital** was 21.2 days in the COPD group versus 24.5 days in the ARDS group p=0.07[573]. Nevins et al[575] identified a mean duration of hospital stay of 22 days in COPD patients requiring ventilation.	III

The **mortality** rate in ICU for patients who received ventilation for an exacerbation of COPD was estimated at 22%. Patient receiving mechanical ventilation due to acute decompensation of COPD had a significantly lower mortality than patients receiving mechanical ventilation because of acute respiratory failure (ARF) of other aetiologies. COPD OR 0.70; (95% CI 0.59 to 0.83); p=<0.001 compared to coma OR 1.31; (95%CI; 1.19 to 1.45); p<0.001[573].	III
There was a high mortality rate for those patients who required >72 hrs mechanical ventilation compared to those with <72 (37% vs. 16%; p=<0.01), those without previous episodes of mechanical ventilation (33% vs. 11%; p<0.01) and those with a failed extubation attempt (36% vs. 7%; p=0.0001)[575].	III
NIV can be successfully used to shorten duration of mechanical ventilation (p=0.002)[576].	Ib

GDG consensus statements

The decision on which patients with exacerbations of COPD will benefit from intubation is difficult and involves balancing health status with an estimate of expectation of survival. Factors that are likely to influence this decision are prior functional status, BMI, requirement for oxygen when stable, co-morbidities and previous ITU admissions.	IV

Recommendations

R174	Patients with exacerbations of COPD should receive treatment on intensive care units, including invasive ventilation when this is thought to be necessary.	**Grade C**
R175	During exacerbations of COPD, functional status, BMI, requirement for oxygen when stable, comorbidities and previous admissions to intensive care units should be considered, in addition to age and FEV_1, when assessing suitability for intubation and ventilation. Neither age nor FEV_1 should be used in isolation when assessing suitability.	**Grade D**
R176	NIV should be considered for patients who are slow to wean from invasive ventilation.	**Grade A**

8.15 Respiratory physiotherapy and exacerbations

Physiotherapy has traditionally been used to assist sputum clearance during exacerbations of COPD. The GDG have looked at the evidence regarding the role of respiratory physiotherapy. Physiotherapists are also involved in the reablement of patients prior to discharge but the GDG have not looked at the evidence base for this aspect of management.

An extensive literature search of the role of respiratory physiotherapy was undertaken, which identified 62 potential papers. Of these 46 were excluded from the abstract. 16 papers were retrieved and a further 10 were excluded upon full paper review. 6 papers were critically appraised. Two systematic reviews were identified[510], two RCTs[577,578] and two quasi-experimental studies[579,580].

Interventions included postural drainage, chest percussion, vibration, chest shaking, directed coughing, forced exhalation, and expiration under positive pressure (PEP mask).

There was little research in this area and there were methodological limitations inherent in the studies identified. Limitations included heterogeneous populations, Jones et al 2002[475] (COPD stable and exacerbations, asthmatics, cystic fibrosis) and McCrory 2001[510] (stable, exacerbations and post exacerbation population), small sample sizes Bellone et al 2000[577] N=10, Wollmer et al 1985[580] N=10) and hence potentially significant under powering, short-term interventions, short term outcome assessments or did not report suitable outcome data[510]. Many of the trials precluded meta-analysis due to the diversity of patient groups and outcomes[475]. One RCT by Bellone 2000[577] on the effects of using a PEP mask included selected patients with mucus hyper secretion making it difficult to be sure that the results of this small study (sample size of N=27) can be generalised.

The results of most of these trials[510,577,578,580] should be treated with caution due to the inherent methodological limitations and in light of this the GDG felt it inappropriate to present evidence statements based on these studies.

Evidence statements

Bellone et al[579] (N=27) looked at the short term effects of using a PEP mask in patients with exacerbation of COPD and mild acidosis requiring NIV who were hypersecreting mucus.	Ib
Sputum production was significantly higher in the PEP mask plus assisted coughing group (10g) compared to the control group (5g) of assisted coughing alone ($p<0.01$)[579].	
Weaning time from NIV was found to be significantly lower in the intervention group (5 days v 7 days) $p<0.01$[579].	

Brown et al (N=24) looked at the effect of short term mechanical vibration on sputum production and found a significant increase at 60 minutes but not over 24 hours[581]. Ib

Recommendations

R177	Physiotherapy using positive expiratory pressure masks should be considered for selected patients with exacerbations of COPD, to help with clearing sputum.	**Grade B**

8.16 Monitoring recovery from an exacerbation

In patients admitted to hospital or managed in a hospital-at-home or assisted discharge scheme it is important to monitor the response to treatment. This allows appropriate reduction in additional support that patients are receiving and require and determination of the timing of discharge.

Recommendations

R178	Patients' recovery should be monitored by regular clinical assessment of their symptoms and observation of their functional capacity.	**Grade D**
R179	Pulse oximetry should be used to monitor the recovery of patients with non-hypercapnic, non-acidotic respiratory failure.	**Grade D**
R180	Intermittent arterial blood gas measurements should be used to monitor the recovery of patients with respiratory failure who are hypercapnic or acidotic, until they are stable.	**Grade D**
R181	Daily monitoring of PEF or FEV_1 should not be performed routinely to monitor recovery from an exacerbation because the magnitude of changes is small compared with the variability of the measurement.	**Grade D**

8.17 Discharge planning

Advanced discharge planning can help to reduce the risk of readmission and reduce unnecessary hospital bed occupancy. Discharge planning involves an assessment of the patients fitness for discharge and assessment of their needs once back in the community.

A hospital admission gives an opportunity for spirometry to be performed on patients who may not otherwise have had this measured. Measurements taken at the time of admission or soon after may give an unrepresentative assessment of the severity of airflow obstruction and thus it is of more value to perform spirometry close to the time of discharge when the patient will be closer to their normal functional state. See section 2 for the methodology underpinning this area.

Recommendations

R182	Spirometry should be measured in all patients before discharge.	**Grade D**
R183	Patients should be re-established on their optimal maintenance bronchodilator therapy before discharge.	**Grade D**
R184	Patients who have had an episode of respiratory failure should have satisfactory oximetry or arterial blood gas results before discharge.	**Grade D**
R185	All aspects of the routine care that patients receive (including appropriateness and risk of side effects) should be assessed before discharge.	**Grade D**
R186	Patients (or home carers) should be given appropriate information to enable them to fully understand the correct use of medications, including oxygen, before discharge.	**Grade D**
R187	Arrangements for follow-up and home care (such as visiting nurse, oxygen delivery, referral for other support) should be made before discharge.	**Grade D**
R188	Before the patient is discharged, the patient, family and physician should be confident that he or she can manage successfully. When there is remaining doubt a formal activities of daily living assessment may be helpful.	**Grade D**

9 Audit criteria

The National Clinical Guidelines for COPD makes many specific recommendations concerning the management of COPD. These deal with diagnosis and assessment, and management of stable COPD and management of exacerbations. There are far too many recommendations to monitor them all but the GDG and CRG identified seven key areas where it was felt that recommendations were likely to have the biggest impact on the management of COPD (see section 5.1). The audit criteria in the following table relate to these key areas on the management of COPD in primary and secondary care. Two additional audit criteria relating to a sentinel event audit, that links with data collected as part of the national audit of COPD exacerbations[582], and a patient-centred audit have also been included.

One of the criteria (non-invasive ventilation) relates specifically to secondary care and two relate to management in primary care (diagnosis and smoking cessation). The remainder should be applied in both primary and secondary care settings. It is anticipated that the standards will be detailed in local delivery plans in England and service and financial frameworks in Wales, but it is important that these targets reflect the development of a high quality service for people with COPD. Year-on-year improvements in the results of the audit criteria is important, an comparison with other local health care communities may be helpful in setting realistic milestones towards the target standard. There should be locally agreed plans to facilitate the achievement of the targets.

The “exception” boxes list the circumstances where applying the criterion would be inappropriate for an individual patient. It is recognised that there will be other situations where a clinical decision may be taken not to follow the guideline (for example taking into account the informed patient’s wishes), and interpretation of performance should take these factors into account. COPD disease registers are a necessary pre-requisite for performing these audits. They are needed to establish the denominator and to facilitate accurate data collection, and are also one of the quality markers in the contract for General Practitioners.

The criteria that relate to key recommendations are all process criteria. The sentinel event audit of patients readmitted within 28 days of discharge following an exacerbation of COPD is also to some extent an outcome audit, but it is important to note that it would be unrealistic to expect a routine audit to differentiate between an ‘avoidable’ and an ‘unavoidable’ admission. Nevertheless this sentinel audit reflects the fact that frequent exacerbations are associated with worse health status and more rapid decline in lung

function. Exacerbations are also a major factor in determining the cost of caring for people with COPD and result in significant hospital bed occupancy.

The patient-centred audit involves asking people with COPD to record their experience of services.

The advantages of this approach are:

- it ensures a comprehensive coverage of all services
- it reflects patient experience directly
- it can be used to stimulate a general interest in services locally

The disadvantages are:

- it is anecdotal, just giving specific instances and not a statistical result
- it generates huge amounts of data
- specific standards cannot be set or checked
- it may be difficult for patients to criticise the team that cares for them

A potential problem with the criteria proposed is that general practices that have low identification rates of COPD (perhaps because of poor coding, or under investigation) may apparently perform very well against these criteria. Therefore, it is proposed that an additional data item that should be reported in general practice is age-specific prevalence of COPD. This would allow the standards achieved to be interpreted against the practice specific prevalence.

Sentinel events audit

The recommendations above concern monitoring services as routinely delivered. A second approach to audit is to use adverse events to highlight particular areas of low quality service. This requires identification of agreed 'sentinel events'. In people with COPD readmission to hospital with one month of an admission with an exacerbation of COPD may represent such an event.

Criterion

Percentage of patients readmitted to hospital with an exacerbation of COPD within 28 days of discharge

Patient-centred audit

Finally it is recommended that health care commissioning organizations should consider using a patient-centred audit approach intermittently, to investigate the totality of services and identify particular areas that need further development.

• Key priority	• Criterion	• Exception
1. Diagnose COPD A diagnosis of COPD should be considered in patients over the age of 35 who have a risk factor (generally smoking) and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter 'bronchitis' or wheeze. The presence of airflow obstruction should be confirmed by performing spirometry. All health professionals managing patients with COPD should have access to spirometry and they must be competent in the interpretation of the results.	a) percentage of smokers over the age of 35 consulting with a chronic cough and/or breathlessness who have had spirometry performed b) percentage of patients with a diagnosis of COPD who have had spirometry performed	Inability to perform spirometry, for example because of facial paralysis
2. Stop smoking Encouraging patients with COPD to stop smoking is one of the most important components of their management. All COPD patients still smoking, regardless of age should be encouraged to stop, and offered help to do so, at every opportunity.	Percentage of patients with COPD who are current smokers recorded in the general practice records as having been offered smoking cessation advice and or therapy	
3. Effective inhaled therapy Long-acting inhaled bronchodilators should be used in people with COPD who remain symptomatic (e.g. breathlessness or exacerbations) despite the use of short-acting drugs. A long-acting $beta_2$ agonist or a long-acting muscarinic antagonist should be used in people with COPD and FEV_1 > 50% predicted who continue to experience problems despite the use of short-acting	Appropriateness of inhaled steroid therapy	Patient choice

drugs. Either a long-acting beta$_2$ agonist and inhaled corticosteroid in a combination inhaler, or a long-acting muscarinic antagonist should be used in patients with an FEV_1 < 50% predicted who continue to experience problems despite the use of short-acting drugs. Additional treatment with a long-acting muscarinic antagonist should be used in people with COPD who remain symptomatic despite taking a long-acting beta-agonist and inhaled steroid in a combination inhaler, irrespective of their FEV_1.		
4. Pulmonary rehabilitation for all who need it Pulmonary rehabilitation should be offered to all patients who consider themselves functionally disabled by COPD. Pulmonary rehabilitation programmes must meet clinical needs in terms of access, location and availability.	Percentage of patients with COPD who have undergone pulmonary rehabilitation	Patient choice
5. Use non-invasive ventilation Non-invasive ventilation (NIV) is the treatment of choice for persistent hypercapnic respiratory failure during exacerbations after optimal medical therapy. It should be delivered by staff trained in its application, experienced in its use and aware of its limitations. When patients are started on NIV there should be a clear plan covering what to do in the event of deterioration and ceilings of therapy should be agreed.	Percentage of patients presenting with acute hypercapnic respiratory failure who have received non-invasive ventilation	Patient choice

6. Manage exacerbations The frequency of exacerbations should be reduced by appropriate use of inhaled corticosteroids and bronchodilators, and vaccinations. The impact of exacerbations should be minimised by: • giving self-management advice on responding promptly to the symptoms of an exacerbation • starting appropriate treatment with oral steroids and or antibiotics • use of non-invasive ventilation when indicated • use of hospital-at-home or assisted-discharge schemes	Frequency and appropriateness of oral steroid and antibiotic therapy	Patient choice

10 Areas for Future Research

The GDG recognises that there is a large amount of ongoing research activity in many aspects of the management of COPD. The evidence tables also highlight that there is a large volume of research that is already relevant to the COPD guidelines. Nevertheless a large number of studies were rejected because of methodological limitations and as well as identifying specific areas for future research the GDG concluded that there was a need to make some general recommendations about the design of studies on the management of COPD.

10.1 General Points

Many of the papers that were reviewed as part of the guideline process lacked operational definitions for example:

- an adequate and explicit operational definition of stable COPD.
- explicit operational definitions of COPD disease severity.
- lack of a system for adequately defining COPD exacerbations
- operational definitions vary between countries e.g. differences in what constitutes an Intensive Care Unit (ICU) between countries.
- lack of definition regarding packages of care, e.g. differences between hospital-at-home schemes versus assisted or early discharge schemes.

These deficiencies must be overcome in future studies.

Trials that are adequately powered for primary outcomes were often potentially underpowered for the secondary outcomes. The GDG recommends that future trials on the management of COPD are adequately powered (i.e. have a large enough sample size) are of sufficient duration to determine long term efficacy of therapies and include patients with an appropriate range of ages. The study design and analysis should allow for the heterogeneity of the disease and patients should be appropriately characterized to allow sub group analysis of different phenotypes. Account also needs to be taken of the stability of the

patients included and in particular whether they have recently had an exacerbation. Patients included in studies should be representative of the spectrum of patients with COPD seen in practice but steps should be taken to avoid the inclusion of patients with asthma.

As well as placebo controlled studies to show efficacy there is a need for studies of the comparative efficacy of management strategies (both pharmacological and non-pharmacological) to try to identify which therapies should be used and when.

Studies should include a range of outcome measures and not concentrate simply on FEV_1. Ideally there should be agreed standardized outcome measures to allow comparison of results across studies and facilitate meta-analysis. In addition to this details regarding the primary and secondary outcomes should be clearly specified. Cost effectiveness analyses should be included in the study design. Results should be reported in a way that allows identification of subgroups which show particularly large or small effects.

The GDG also noted that there may be practical issues regarding the organization of randomized placebo controlled double blind clinical trials. These include ethical concerns about the withholding of therapies such as oxygen or non-invasive ventilation, and the difficulties in obtaining supplies of medication and matching placebo for studies not sponsored by the pharmaceutical industry. The GDG recommends that the costs of medication and placebo are met by research sponsors and that manufacturers should supply them to studies that have been peer reviewed and are supported by recognised funding agencies. The GDG also concluded that there was a need for studies supported by independent funding agencies as well as those supported by the pharmaceutical industry.

10.2 Specific points

The GDG concluded that there was a particular need for studies in three broad areas

10.2.1 Pharmacological Management

There is a need for long term studies on the absolute and comparative efficacy of

- long-acting bronchodilators
- theophylline
- mucolytics (including the development of outcome measures)

- combination therapies
- ambulatory oxygen
- alpha-1 antitrypsin replacement therapy

10.2.2 Adjunctive therapies

There is a need for further studies on the efficacy of:

- nebulised therapy
- non-invasive ventilation
- oxygen delivery systems
- physiotherapy
- pulmonary rehabilitation

10.1.3 Patient focused strategies

There is a need for further studies on:

- the content and efficacy of educational packages for patients with COPD
- the content and efficacy of self management strategies for exacerbations

10.3 NEW 2010 UPDATE Future research recommendations

NB see appendix L for criteria for selecting high-priority research recommendations

Future Research Recommendation 1 (FRR1)			
Question: In people with COPD, does pulmonary rehabilitation during hospital admission for exacerbation and/or in the early recovery period (within one month of an exacerbation) improve quality of life and reduce hospitalisations and exacerbations compared to a later (defined as after one month) pulmonary rehabilitation programme?			
Population	**Intervention**	**Comparison**	**Outcomes**
In people with COPD	Early pulmonary rehabilitation programme: • during hospital admission • during hospital admission and in the early recovery period (within one month of admission) • during the early recovery period (within one month of admission	Later pulmonary rehabilitation programme (after one month)	• Hospitalisations • Exacerbations • QoL • Cost effectiveness
Supporting text: The greatest reconditioning and potential benefit from rehabilitation may occur in the early post exacerbation phase. If inpatient pulmonary rehabilitation is demonstrated to be effective this may potentially impact upon service delivery e.g. early discharge schemes. The cost effectiveness of early versus later pulmonary rehabilitation programmes should also be evaluated. Studies should be cluster randomised, be of sufficiently long duration and be adequately powered.			

Future Research Recommendation 2 (FRR2)

Question: Could a simple multidimensional assessment be used to give a better indication of COPD outcomes than either FEV_1 or other components measured alone in a wide range of COPD patients, and applicable in a primary care setting?

Population	**Intervention**	**Comparison**	**Outcomes**
In people with COPD	Multi-dimensional assessments – BODE index or other combinations of assessments (e.g. MRC score, 6 MWT, Shuttle Walk, Clinical Assessment Test (CAT) and other assessments)	FEV_1 or other component measures alone	Prognosis and response to treatment: • Mortality • Hospitalisations • Exacerbations • QoL • Cost effectiveness

Supporting text: The BODE index assessment is time-consuming and impractical in a primary-care setting. The GDG considered that people entering COPD studies should be characterised by the BODE index to assess whether it has an effect on outcome. Multidimensional assessments should be validated in a general UK COPD population, and in a primary-care setting, in a wider range of outcomes than mortality. Any multidimensional assessment index would need to be subjected to health economic evaluation. All clinical studies of sufficiently long duration should routinely include health economic evaluation.

Future Research Recommendation 3 (FRR3)			
Question: In people with COPD does triple therapy improve outcomes when compared with single or double therapy?			
Population	**Intervention**	**Comparison**	**Outcomes**
In people with COPD	LAMA+LABA+ICS	LAMA or LABA or LABA+ICS	Prognosis and response to treatment: • Mortality • Hospitalisations • Exacerbations • QoL • Cost effectiveness
Supporting text: Currently available studies were not designed or powered to assess whether people with mild COPD on single therapy with LABA or LAMA or double therapy with LABA+ICS might benefit from triple therapy. All clinical studies of sufficiently long duration should routinely include health economic evaluation.			

Future Research Recommendation 4 (FRR4)			
Question: In people with COPD, does mucolytic drug therapy prevent exacerbations in comparison with placebo and other therapies?			
Population	**Intervention**	**Comparison**	**Outcomes**
In people with COPD	Mucolytic drugs	Placebo or other effective therapies (e.g. inhaled LABA, LAMA and LABA+ICS)	Prognosis and response to treatment: • Mortality • Hospitalisations • Exacerbations • QoL • Cost effectiveness
Supporting text: People with COPD should have a definitive diagnosis of COPD. Baseline severity and clinical phenotype should be well defined. Concomitant therapies should be stratified in the study design. Comparisons should be made with other effective therapies as well as placebo.			

11 Appendix A Details of questions and literature searches

Reference made to the Cochrane Library in the table below is inclusive of the following; Cochrane Systematic Reviews database, CENTRAL and DARE. The Cochrane Systematic Reviews database contains items that are constantly updated. CENTRAL contains items resulting from searches performed in the process of creating Cochrane Systematic Reviews and goes back as far as the Cochrane searches to date. The DARE database was set up by the NHS Centre for Reviews and Dissemination in 1994. It does, however, include records that have an earlier publication date. For example, it contains a set of records from a systematic reviews database maintained by the UK Cochrane Centre prior to 1995. This set of records is no longer updated and have not been assessed by the NHS CRD.

Question	Population	Study Type	Database and Years
Q1 What is a useful, robust definition of COPD? Q2 Must the definition of COPD include the presence of airflow obstruction? Q3 Must the definition of COPD include reversibility criteria?			Expert Review

Q4 Must the definition of COPD discuss causation and pathophysiology?			
Q5 What is the current and future burden of COPD in England & Wales?			Expert Review
Q6 Can COPD be detected before the onset of symptoms? Q7 What factors can be used to identify patients opportunistically as being at risk of having COPD? Q8 What methods can be used to confirm the diagnosis in patients identified opportunistically as being at risk of having COPD?			Expert Review
Q9 Question removed.			
Q10 Does early diagnosis of COPD affect the success of smoking cessation therapy?			Expert Review
Q11 What are the aims of COPD management?			Expert Review
Q12 What symptoms are suggestive of a diagnosis of COPD?			Expert Review

Q13 What other conditions may present with similar symptoms/signs/results?			
Q14 In patients with suspected COPD, what are the most effective diagnostic criteria?			Expert Review
Q15 What clinical signs are useful (confirm or refute the diagnosis) in stable COPD?			Expert Review
Q16 What are the most appropriate tests in a patient with suspected COPD to confirm the diagnosis?			Expert Review
Q17 What is the role of spirometry in the diagnosis of COPD? Q18 Where and by whom should spirometry be performed in order to maximise reliable and valid test result outcomes?	COPD	All study types	Cochrane Library Medline 1966-2003 Embase 1980-2003 CINAHL 1982-2003
Q19 What is the role of reversibility testing in the diagnosis of COPD? Q20 What is the role of reversibility testing in the prediction of response to COPD drugs?	COPD	All study types	Cochrane Library Medline 1966-2003 Embase 1980-2003 CINAHL 1982-2003
Q21 What is the role of other lung function tests in the diagnosis of COPD? (IRC, T_LCO,KCO, Lung Volumes)			Expert Review

Q22 How should the severity of stable COPD be assessed?			Expert Review
Q23 In patients with stable COPD, how should the (initial) management plan be determined?			Expert Review
Q24 Which patients with stable COPD should be referred for specialist advice?	Stable COPD Exclude asthma	Systematic Reviews RCT Cohort	Cochrane Library Medline 1966-2003 Embase 1980-2003 CINAHL 1982-2003 AMED 1985-2003
Q25 Which patients with stable COPD should be referred for an oxygen assessment?			Expert Review
Q26 What is the most appropriate smoking cessation strategy in patients with stable COPD?	COPD Exclude asthma	Systematic Reviews RCTs Cohorts	Cochrane Library Medline 1966-2003 Embase 1980-2003 CINAHL 1982-2003 PsycINFO 1887-2003 AMED 1985-2003

Q27 What drug therapy is effective (reduces morbidity or mortality in) for patients with stable COPD?	This is not a question in its own right but merely a heading for questions 28-57.		
Q28 Which patients with stable COPD should be treated with short-acting inhaled bronchodilators?	This is not a question in its own right but merely a heading for questions 29 and 30.		
Q29 Which patients with stable COPD should be treated with short-acting beta$_2$-agonists? Q31 How should the effects of this treatment be assessed?	COPD Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003
Q30 Which patients with stable COPD should be treated with short-acting anticholinergics? Q31 How should the effects of this treatment be assessed?	COPD Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003
Q32 Which patients with stable COPD should be treated with long-acting inhaled bronchodilators?	This is not a question in its own right but merely a heading for questions 33 and 34.		
Q33 Which patients with stable COPD should be treated with long-acting beta$_2$-agonists?	COPD	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003

Q35 How should the effects of this treatment be assessed?	Exclude asthma		Embase 1980-2003
Q34 Which patients with stable COPD should be treated with long-acting anticholinergics? Q35 How should the effects of this treatment be assessed?	COPD Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003
Q36 Which patients with stable COPD should be treated with methylxanthines / PDE4 inhibitors? Q37 How should the effects of this treatment be assessed?	Stable COPD Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003
Q38 & Q39 Questions removed.			
Q40 Which patients with stable COPD should be treated with inhaled steroids? Q41 How should the effects of this treatment be assessed?	COPD Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003
Q42 Which patients with stable COPD should be treated with oral steroids?	COPD Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003

Q43 How should the effects of this treatment be assessed?			Embase 1980-2003
Q44 What is the role of combination therapy in patients with stable COPD? Q45 How should the effects of this treatment be assessed?	Stable COPD Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003
Q46 What are the most appropriate delivery systems for giving inhaled therapy to patients with stable COPD? Q47 Which patients with stable COPD benefit from nebulised therapy compared to other delivery mechanisms?	Stable COPD Exclude asthma except in elderly patients	Systematic Reviews RCTs	Cochrane Library 1980-2003 Medline 1980-2003 Embase 1980-2003 CINAHL 1982-2003
Q48 What is the role of mucolytic therapy in patients with stable COPD? Q49 In patients with stable COPD, what is the comparative efficacy of mucolytic therapy? Q50 In patients with stable COPD, does mucolytic therapy reduce morbidity?	Stable COPD Exclude asthma	Systematic Reviews RCTs Cohorts	Cochrane Library Medline 1966-2003 Embase 1980-2003

Q51 What is the role of antioxidant therapy in patients with stable COPD? Q52 In patients with stable COPD, what is the comparative efficacy of antioxidant therapy? Q53 In patients with stable COPD, does antioxidant therapy reduce morbidity?	Stable COPD Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003 AMED 1985-2003
Q54 What is the role of antitussive therapy in patients with stable COPD? Q55 In patients with stable COPD, what is the comparative efficacy of antitussive therapy? Q56 In patients with stable COPD, does antitussive therapy reduce morbidity?	Stable COPD Exclude asthma	All	Cochrane Library Medline 1966-2003 Embase 1980-2003
Q57 What is the role of α1-antitrypsin replacement therapy in patients with stable COPD?	Stable COPD Exclude asthma	All	Cochrane Library Medline 1966-2003 Embase 1980-2003

Q58 What is the role of antibiotic therapy in patients with stable COPD?	Stable COPD Exclude asthma	Systematic Reviews RCTs Cohorts	Cochrane Library Medline 1966-2003 Embase 1980-2003
Q59 What are the benefits of pulmonary rehabilitation programmes for patients with stable COPD? Q60 In stable COPD patients referred for pulmonary rehabilitation programmes, what is the optimal course content, setting & duration? Q61 Which patients with stable COPD should be referred for pulmonary rehabilitation and when? Q62 In patients with stable COPD, are there benefits in repeated pulmonary rehabilitation attendances?	Stable COPD Include asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003 CINAHL 1982-2003 AMED 1985-2003

Q63 In patients with stable COPD how can right heart failure / chronic salt and water retention be identified? Q64 In patients with stable COPD what therapies can be used to manage right heart failure / chronic salt and water retention?			Expert Review
Q65 In patients with stable COPD how can pulmonary hypertension be identified? Q66 In patients with stable COPD what therapies can be used to manage pulmonary hypertension?			Expert Review
Q67 Main Stem Question How are patients with stable COPD affected by anxiety and / or depression? Q68 In patients with stable COPD, how can anxiety and depression be identified? Q69 How can anxiety and depression in stable COPD patients be managed? (Pharmacological & non-pharmacological)	COPD Include asthma	Systematic Reviews RCTs Cohorts	Cochrane Library 1980-2003 Medline 1966-2003 Embase 1980-2003 CINAHL 1982-2003 PsycINFO

Q70 What is the significance of nutritional problems in both stable and acute exacerbations of COPD? Q71 In patients with stable COPD, how can nutritional problems be identified? Q72 In patients with stable COPD, how can nutritional problems be managed?	COPD Exclude asthma	Systematic Reviews RCTs	Cochrane Library 1980-2003 Medline 1980-2003 Embase 1980-2003 CINAHL 1982-2003 PsychINFO 1980-2003
Q73 Do self-management plans & patient education affect concordance with treatment and improve outcomes in patients with stable COPD?	COPD Exclude asthma	All study types	Cochrane Library Medline 1966-2003 Embase 1980-2003 CINAHL 1982-2003 PsychINFO 1887-2003
Q74 What is the role of oxygen therapy in patients with stable COPD? Q75 In patients with stable COPD, what is the best method of oxygen supply?			Expert Review

Q76 In patients with stable COPD, what are the benefits of short burst oxygen? Q77 In patients with stable COPD, what are the benefits of portable oxygen? Q78 In patients with stable COPD, what are the criteria for continuous oxygen therapy?			
Q79 What is the role of immunisation in patients with stable COPD?	COPD Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003
Q80 What is the role of non-invasive ventilation in patients with stable COPD?	Stable COPD Exclude asthma	Systematic Reviews RCTs	Cochrane Library 1980-2003 Medline 1980-2003 Embase 1980-2003

Q81 What management strategies can be used to provide palliative care in the end stages of COPD?	COPD Exclude asthma	All study types	Cochrane Library Medline 1966-2003 Embase 1980-2003 CINAHL 1982-2003
Q82 How should the long term care of patients with stable COPD be organised in order to maximise patient outcomes? Q83 Where (Primary care versus secondary care) should the long term care of patients with stable COPD be organised in order to maximise patient outcomes? Q84 How often should the long term care of patients with stable COPD be reviewed in order to maximise patient outcomes?			Expert Review
Q85 In patients with stable COPD, what is the role of respiratory nurse specialists?			Expert Review

Q86 What is the role of respiratory physiotherapy in the management of patients with stable COPD?	Stable COPD Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003 CINAHL 1982-2003
Q87 What is the role of lung surgery in patients with stable COPD? Q88 In patients with stable COPD, what is the operation of choice (bullectomy, lung volume reduction, transplantation) in reducing morbidity or mortality? Q89 In patients with stable COPD, what are the referral criteria for lung surgery?			Expert Review
Q90 What is a robust and useful definition of an exacerbation of COPD?			Expert Review
Q91 What symptoms are suggestive of an exacerbation of COPD? Q92 What other conditions present with similar symptoms?			Expert Review

Q93 What are the factors known to cause exacerbations of COPD?			Expert Review
Q94 What is known about the consequences (short & long term outcome impact) of having an exacerbation (chest episodes, infective episodes) of COPD?			Expert Review
Q95 What clinical signs are useful (confirm or refute) in making a diagnosis and assessing the severity of an exacerbation of COPD?			Expert Review
Q96 What are the most appropriate tests in a patient with suspected exacerbation of COPD? Q97 What are the most appropriate tests to confirm the diagnosis of an exacerbation of COPD? Q98 What are the most appropriate tests to assist in the management of an exacerbation of COPD? Q99 In patients with an exacerbation of COPD, what are the most appropriate tests to assess severity?			Expert Review

Q100 In patients with an exacerbation of COPD, what are the most appropriate tests to monitor recovery?			
Q101 Which patients with an exacerbation of COPD benefit from admission to hospital?	COPD Exacerbations Exclude asthma	Systematic Reviews RCTs Cohorts	Cochrane Library Medline 1966-2003 Embase 1980-2003
Q102 What is the role (reduction of morbidity or mortality and comparative efficacy) of pharmacotherapy in patients with an exacerbation of COPD?	This is not a question in its own right but merely a heading for questions 103-110 & 112-113		
Q103 Are bronchodilators useful / effective in the treatment of patients with an exacerbation of COPD? Q104 Which patients with an exacerbation of COPD should be treated with bronchodilators?	COPD Exacerbations Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003
Q105 Are oral steroids useful / effective in the treatment of patients with an exacerbation of COPD?	COPD Exacerbations	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003

Q106 Which patients with an exacerbation of COPD should be treated with oral steroids?	Exclude asthma		
Q107 Question removed.			
Q108 Which delivery systems should be used for giving inhaled therapy to patients with an exacerbation of COPD?			Expert Review
Q109 Are antibiotics useful / effective in the treatment of patients with an exacerbation of COPD? Q110 Which patients with an exacerbation of COPD should be treated with antibiotics?	COPD Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003
Q111 Which patients with an exacerbation of COPD should be treated with oxygen (how much and how monitored, including use during transfer to hospital)?			Expert Review

Q112 What is the role of theophylline in patients with exacerbations of COPD?	COPD Exacerbations Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003
Q113 What is the role of respiratory stimulants in patients with exacerbations of COPD?	COPD Exacerbations Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003
Q114 What is the role of therapies for managing right heart failure / chronic salt and water retention in patients with exacerbations of COPD?			Expert Review
Q115 Question removed.			
Q116 Which patients with exacerbations of COPD require non-invasive ventilation? Q117 In patients with exacerbations of COPD who require non-invasive ventilation, where should this be performed (Ward/HDU/ITU) so that morbidity or mortality measures are minimised?	COPD Exacerbations Exclude asthma	Systematic Reviews RCTs	Cochrane Library 1980-2003 Medline 1980-2003 Embase 1980-2003

Q118 Which patients with exacerbations of COPD require IPPV / ITU care?			
Q119 In patients with exacerbations of COPD, what is the role of hospital-at-home / assisted discharge schemes compared to inpatient management taking into account morbidity or mortality outcomes. Q120 What multi professional team membership is effective in providing hospital-at-home / assisted discharge schemes for patients with exacerbations of COPD? Q121 In patients with an exacerbation of COPD, what criteria are useful in assessing the suitability of and planning for home treatment / early discharge? Q122 In patients with an exacerbation of COPD, what is the optimal duration of home care?	COPD Exacerbations Exclude asthma	Systematic Reviews RCTs	Cochrane Library Medline 1966-2003 Embase 1980-2003 CINAHL 1982-2003

Q123 What is the role of respiratory physiotherapy in the management of exacerbations of COPD?	COPD Exacerbations Exclude asthma	Systematic Reviews RCTs Cohorts	Cochrane Library Medline 1966-2003 Embase 1980-2003 CINAHL 1982-2003
Q124 Which patients with COPD benefit from referral to palliative care services? Q125 Which patients with COPD benefit from referral to occupational therapists? Q126 Which patients with COPD benefit from referral to social services?			Expert Review
Q127 What information / education / support is needed for stable COPD patients and their families to understand and cope with the diagnosis, treatment and outcome in COPD? Q128 In patients with stable COPD and their relatives / carer, what effect does education have on morbidity, quality of life, advanced directives or mortality measures?	Stable COPD Exclude asthma	All studies	Cochrane Library Medline 1966-2003 Embase 1980-2003 CINAHL 1982-2003 PsycINFO 1887-2003

Q129 Do cultural factors modify the uptake of COPD care? Question and section relating to cultural factors deleted by NICE as defined as “outside of Scope”	COPD Exclude asthma	All	Cochrane Library Medline 1966-2003 Embase 1980-2003 CINAHL 1982-2003 AMED 1985-2003
Q130 What advice should be given to patients with COPD who wish to travel?			Expert Review
Q131 How should the fitness for surgery of patients with COPD be assessed?			Expert Review

12 Appendix B Cost effectiveness of opportunistic case finding in primary care

Background

The GDG was interested in the issue of opportunistic case finding of COPD in primary care.

Since the BTS guidelines were published in 1997 [71], the use of spirometry has become more widespread in primary care. Spirometry can be used to detect the presence of airflow obstruction in a patient. At present, the mean age of detection of COPD in the UK is 55, as by this time the patient usually presents with symptoms. Use of spirometry can detect the presence of airflow obstruction earlier, even if no symptoms are present.

It is well known that the biggest factor that can have an impact on disease progression is smoking cessation [113,583]. Smoking cessation can alter length of life and quality of life and the earlier smoking cessation is achieved, the greater the effect[121]. Patients detected at age 55 are encouraged to quit smoking as it can alter their disease progression. If COPD were detected earlier, patients could be referred to smoking cessation programmes with an added incentive of extra benefit.

Smoking cessation has a greater effect if it is achieved earlier in life, therefore the advantages of detecting people with airflow obstruction earlier are three fold:

- Additional life years saved.
- Quality of life gain.
- A greater incentive to quit (as they have been diagnosed at an earlier stage of their disease, they can be told that they can make a difference if they quit smoking).

A recent study by van Schayk et al [107] found that in a population with the following characteristics; age over 35, smoker/ex smoker and a chronic cough, 27% of people had airflow obstruction when tested using spirometry.

If a policy of opportunistic case finding by spirometry in primary care was followed, the results of the van Schayk study suggest that there would be a reasonably high yield. These patients could then be targeted with an intensive smoking cessation programme.

This is associated with a substantial resource input from primary care, both in terms of the time and equipment used in spirometry and the subsequent cost of smoking intervention programmes.

The GDG was interested in the cost effectiveness of this strategy, based on the results of the van Schayk study. They were interested in whether the extra resources involved in testing for airflow obstruction and the subsequent intervention of smoking cessation was worth the additional expected benefits. A simple cost effectiveness model was therefore built to look at this issue.

Aim

The aim was to compare the costs and benefits of opportunistically testing patients who present at the GP with the following characteristics; age over 35, smoker/ex smoker, chronic cough, with the costs and benefits of current practice. The cost per life year gained and the cost per quality adjusted life year (QALY) gained were calculated.

Methods

A cost effectiveness model was built from the perspective of the NHS. A simple decision tree was constructed which outlined the pathways of the alternative options (see figure 1). A decision node is indicated by a square and a circle indicates a chance node. Each of the 8 pathways is labelled with a letter, from A to H, at the end of each pathway.

The primary outcome measure used was life years gained and the primary outcome of the model is the cost per life year gained. The use of life years gained as the primary outcome measure may not capture all the benefit, as there is likely to be a quality of life improvement if the disease progression is slowed down. A secondary outcome measure for the model is therefore quality adjusted life years (QALY) gained and the cost per QALY is calculated.

For each of the 8 pathways (A-H) of the model, the total costs, life years and quality adjusted life years were calculated. The data sources and assumptions used in calculating these are described in more detail below. The expected cost, life years and quality adjusted life years were then calculated for each arm of the decision node (opportunistically case find or don't opportunistically case find). Costs were discounted at 6% and benefits at 1.5% in line with current NICE recommendations. The incremental cost per life year saved and the incremental cost per QALY were then calculated as follows.

Incremental cost per life year gained = $(C_1 - C_2) / (Y_1 - Y_2)$

Incremental cost per QALY = $(C_1 - C_2) / (Q_1 - Q_2)$

Where C_1 = Expected cost of opportunistic case finding

C_2 = Expected cost of not opportunistic case finding

Y_1 = Expected life years if opportunistically case find

Y_2 = Expected life years if don't opportunistically case find

Q_1 = Expected quality adjusted life years if opportunistically case find

Q_2 = Expected quality adjusted life years if don't opportunistically case find

Data sources and assumptions

The table below lists the baseline values used in the model along with the data sources or assumption where appropriate. More details are provided on the methods of calculating each of these values below.

Life expectancy	Baseline value	Source
A	74.5	Fletcher C (1977)[583] and HTA (2002) [121]
B	71	Fletcher C (1977)[583] and HTA (2002) [121]
C	71	Fletcher C (1977)[583] and HTA (2002) [121]
D	79.73	Life tables (http://www.gad.gov.uk/Life_Tables/Interim_life_tables.htm)
E	73.1	Fletcher C (1977)[583] and HTA (2002) [121]
F	71	Fletcher C (1977)[583] and HTA (2002)
G	71	Fletcher C (1977) and HTA (2002) [121]
H	79.73	Life tables

Probabilities	Baseline value	Source
COPD	0.27	van Schayck (2002) [107]
no COPD	0.73	van Schayck (2002) [107]
success of smoking if early	0.1305	HTA (2002) [121]
Failure of smoking if early	0.8695	HTA (2002) [121]
success of smoking if late	0.1305	HTA (2002) [121]
Failure of smoking if late	0.8695	HTA (2002) [121]
Compliance if early	0.9	Assumption
Non concordance if early	0.1	Assumption
Compliance if late	0.5	Assumption
Non concordance if late	0.5	Assumption

Cost	Baseline value	Source
Incremental cost p.a. for mild COPD	£159.63	Britton et al 2003 [33]
Incremental cost p.a. for moderate COPD	£328.21	Britton et al 2003 [33]
Incremental cost p.a. for severe COPD	£1,394	Britton et al 2003 [33]

Cost	**Baseline value**	Source
Cost of spirometry test in GP practice	£9.91	From estimates provided by GDG
Cost of intensive smoking cessation programme	£171.49	HTA (2002) [121]
Other diagnosis costs	£50	Assumption

Utility	**Baseline value**	**Source**
Mild	0.6102	Data from Harper et al (1997)[584]
Moderate	0.5659	Data from Harper et al (1997)[584]
Severe	0.5428	Data from Harper et al (1997)[584]
Non COPD	1	Assumption

Explanation of assumptions and data used

Probability of airflow obstruction

The probability of having COPD was taken to be 27% (the same as the van Schayk study[107]). The mean age of this sub group of smokers who have a chronic cough was 46 (van Schayk, personal communication). This was used as the basis for calculating life expectancy as this is the average age of the population being tested.

The mean age of detection of COPD was provided by the GDG group as 55 years old.

Life expectancy and time spent in each stage of the disease

As well as estimating the life expectancy of each pathway, the years spent in each state of the disease (mild, moderate, severe) was estimated. This was to allow more accurate calculations of the cost of care and quality of life.

Data on the natural history of COPD is very limited. A paper by Fletcher and Peto[583] looked at the natural history of chronic airflow obstruction in a prospective study on London working men. They looked at the decline of % of predicted FEV_1 over a lifetime for a smoker, a non smoker/not susceptible to smoke, a smoker who stops at age 45 and a smoker who stops at age 65. These were the only data available and it should be noted that this was a highly selective population.

The definitions for severity of COPD recommended in this guideline are:

Mild: <80 % predicted FEV_1

Moderate 50-80 % predicted FEV_1

Severe <30% predicted FEV_1

Fetcher and Peto plot a graph of FEV_1 as a percentage of predicted value at age 25 against age in Figure 1 of their paper[583]. Using this and the above classification for disease state, the time spent in each disease state in years and total life expectancy was read off from the graph for a smoker who does not quit.

The graph also shows the FEV_1 curve for a smoker who stops at age 65. The cost effectiveness model requires data on a person who quits at age 55. An assumption was made that the FEV_1 curve for this would be midway between the 45 year old and the 65 year old at the same rate of decline.

The age of death for a smoker who does not quit was read to be 71 from the graph.

Data from an HTA report (2002 pp51) [121] gives the gain in life years for someone who quits smoking at age 45-54 as 3.5 years (undiscounted) and for age 55-64 as 2.1 years (undiscounted).

The life years gained for a 45 and 55 year old were assumed to be 3.5 and 2.1 respectively. This is potentially underestimating the benefit. The years spent in each state were then read off the Fletcher and Peto graph for each of these alternatives.

The life expectancy of a smoker who does not have COPD (or is not susceptible) was estimated using life tables for a 46 year old today.
(http://www.gad.gov.uk/Life_Tables/Interim_life_tables.htm)

Men and women's life expectancy was combined and divided by 2. (This may be an overestimate as even though they are not diagnosed with COPD, they are still at a greater risk for other diseases).

The life expectancy was estimated as 79.73. From the Fletcher and Peto graph, a person who has never smoked or is not susceptible to smoke has mild airflow obstruction at age 62. They therefore spend 79.73 –62 years = 17.73 years in the mild state. Although this is a very crude method, this was the best data available at the time.

Compliance

This was estimated to be 90% if detected at age 46 and 50% if detected at age 55. This was an assumption and different rates will be tested out in the sensitivity analysis.

Success of the intervention (smoking cessation)

This was taken as 0.1305 and was taken from the HTA report [121]. The quit rate was assumed to be the same for both a 46 year old and a 55 year old. A study by Risser and Belcher[109] looked at whether giving patients information about their pulmonary status provided enhanced motivation to quit. Although not statistically significant from the control group, 20% of patients had CO validated cessation at 12 months when assuming loss to follow up to be smokers. Although not a long term quit rate, this figure will be used in the sensitivity analysis.

Costs

All costs are for the year 2000/01

Cost of spirometry

The cost of spirometry was estimated using data provided by David Bellamy, a member of the GDG.

Equipment cost for a spirometer was given as £300-£1500 with a useful lifetime of 5 years. Maintenance and consumables cost £200 p.a. It takes a practice nurses 10 minutes to carry out the test and spirometry is carried out approximately 1-10 times per week. Assuming a practice nurse salary is £27 per hour[585] and a 6% discount rate and not paid in arrears for calculating the annual equivalent cost for the spirometer, the cost per test was estimated as £9.91. The minimum cost was estimated as £5.01 and the maximum cost as £14.81.

Diagnosis costs

When a patient is diagnosed, they are other procedures recommended in the guideline to be carried out. They are:

- Chest radiograph
- Assessment of breathlessness
- Full blood count
- BMI calculated.

The cost of these is assumed to be £50, as time constraints did not permit detailed costing of these. This figure was tested out in the sensitivity analysis.

Intervention

The cost of the intervention (smoking cessation programme) was taken from the HTA report [121]. It is the lifetime quit rate for a package of counselling, NRT and bupropion SR. The same intervention is given to patients whether they are 45 or 55 at the time of diagnosis.

Cost of care

As the model is taking a lifetime perspective, the costs of care for each year alive are included for each pathway.

For COPD, the cost of care each year is taken by using data by Britton [33] on the costs for mild, moderate and severe COPD and multiplying it by the time spent in each state. It is assumed that patients not diagnosed until the age of 55 still occur the costs of their underlying disease, however this will be tested in the sensitivity analysis.

For non COPD costs of care, no cost is applied apart from the years in mild disease, as the COPD cost from the Britton data [33] is taken to be the incremental cost of having COPD (i.e. the cost over and above the cost of a non COPD person to the NHS. For the years in mild, the cost of mild COPD is assumed. The paper by Britton asks patients about their resource use to do with their COPD, giving more weight to this assumption. Patients with severe COPD are approximately 8 times more expensive p.a. than patients with mild COPD. By slowing the progression of the disease, patients will be in the milder state for longer, therefore reducing the costs.

QALYs

There is extremely limited data available for generating QALYs for COPD health states. Data was obtained from a study comparing outcome measures in COPD[584]. One of the outcome measures used was the SF-6D which is a preference based measure of quality of life and can be used to estimate QALYs as each health state generated is associated with a utility value. In the study, SF-6D values were collected as well as % predicted of FEV_1. Using the classification of disease severity recommended in this guideline, a mean SF-6D score was calculated for mild, moderate and severe COPD. This data must be treated with caution, as it has not been adjusted for anything. The mean SF-6D utility was multiplied by the number of years spent in each state to give the total number of QALYs. Area under the curve was not used to calculate the QALY gain. Instead, the patient was assumed to stay at the utility level of the mild state for all the years they were in the mild state until they reached the moderate state. The utility value for a non COPD person was assumed to be 1.

Discounting

Benefits (life expectancy and QALYs) are discounted at 1.5% in line with current NICE recommendations and costs are discounted at 6%. Sensitivity analysis will examine the effects of using rates of 0% for both, 3% for both 6% for both and 10% for both.

General assumptions of the model

Those who present and have spirometry, with a result of no airflow obstruction, would usually be offered brief smoking cessation advice from the GP. As the lifetime cessation success rate is small (0.018)[121] and there is unlikely to be an incentive due to them receiving a 'clear' diagnosis, and the cost of this intervention (estimated at £3.53[121] is small, this has been excluded from the model, in order to keep the model simple.

The mean age of the van Schayk cohort was 46. The Fletcher and Peto graph shows the decline in lung function of a person who quits at age 45. This decline is assumed to be the same as for a 46 year old for the model, as there is only 1 year of difference.

Results

The results of the model using baseline values are shown below.

Opportunistically case finding	
Life expectancy	25.25
QALYS	19.36
Cost	£1,731.83

Not opportunistically case finding	
Life expectancy	25.20
QALYS	19.32
Cost	£1,696.33

Incremental life expectancy	0.050
Incremental QALYs	0.044
Incremental cost	£35.49

Incremental cost effectiveness ratio (ICER)	
Cost per life year gained	£713.16
Cost per QALY	£814.56

Under the base case analysis, the cost per life year gained is £713.16 and the cost per quality adjusted life year gained is £814.56. Under current decision making conditions, this is a very favourable cost effectiveness ratio.

Sensitivity Analysis

As the model is subject to much uncertainty due to the many different data sources and the uncertainty associated with these, one way sensitivity analysis was carried out on key parameters. One way sensitivity analysis varies one parameter at a time whilst keeping the other parameters at their baseline values.

The main parameters of the model were varied one at a time to examine the effect on the model results. Parameters varied were the discount rate, the prevalence of COPD, smoking cessation success rate, concordance with smoking cessation programme if diagnosed early, cost of diagnosis and the cost of the intervention.

The parameters were varied between the following ranges as these were thought to be plausible or were guided by the literature.

Parameter	Range			
Discount rate of costs and benefits	Both 0%	Both 3%	Both 6%	Both 10%
Prevalence of COPD	5%	10%	20%	35%
Smoking cessation success rate	3%	5%	10%	20%
Compliance for early diagnosis	50%	60%	70%	
Cost of diagnosis	Base+low spirometry	£150+high spirometry	£300+high spirometry	
Cost of the intervention	£300	£500	£1,000	

Appendix B.1 shows the results of the 1 way sensitivity analysis. The costs per life year gained/QALY are plotted against the different values of the parameter being varied.

The results are fairly sensitive to the discount rate, as increasing benefits to be in line with costs at 6% gives a cost per LYG of £2,261.59 and a cost per QALY of £2,219.26. Increasing both discount rates to 10% gives a cost per LYG of £10,770.89 and a cost per QALY of £8,935.03.

Decreasing the prevalence (or proportion who are found to have airflow obstruction when tested) reduces the cost effectiveness, however even at 5%, the cost per life year gained is £6,009.59 and the cost per QALY is £6,864.04 which would still be considered to be reasonably cost effective.

The results are fairly sensitive to the smoking cessation rate. Altering the early smoking cessation rate to 20%[109] and leaving the later quit rate at the baseline value of 0.1305 gives a cost per LYG of -£23.30 and a cost per QALY of -£27.76. These are both dominant cases, in that the intervention increases the benefit and decreases the cost (graph not shown).

Altering both smoking cessation rates to just 5% gives a cost per LYG of £3,246.21 and a cost per QALY of £3,707.76.

Reducing the concordance rate to 50% for patients diagnosed early gives a cost per LYG of £2,945.18 and a cost per QALY of £2,833.34.

The results are sensitive to the cost of the intervention (smoking cessation programme). When the cost of the intervention is increased to £1,100, the cost per LYG increases to £3,755.82 and the cost per QALY increases to £4,289.83.

Finally, the cost of diagnosis was varied. The cost of the other tests was increased to £300 and the highest value for the spirometry test was used. This gave a cost per LYG of £5,016.15 and a cost per QALY of £5,729.34.

In order to test out the assumptions of the model further, the prevalence rate was lowered to 10% and the percentage who quit smoking was varied from 3-10%.

The results of this are shown in appendix B.2.

At a smoking cessation rate of 3%, the cost per LYG is £14,885.41 and the cost per QALY is £17,001.82.

The life years gained by quitting smoking at age 46 and 55 was taken from the HTA report[121]. The life years gained for a person who quits at age 35-44 is 5.5, age 45-54 is 3.5 and age 55-64 is 2.1.

The benefit used for a 46 year old was taken to be 3.5 and for a 55 year old, 2.1. Altering this assumption and giving a benefit of 5.5 years to the 46 year old quitter and 3.5 years to the 55 year old quitter does not make a big difference to the model results. The results are shown in appendix B.3. The cost per life year gained decreases to £510.94 and the cost per QALY decreases to £661.31

The assumption that a patient undiagnosed until 55 incurs costs of care the same as those with a patient with mild COPD is perhaps unrealistic as they will not be receiving treatment. They may still incur some costs, for example more frequent visits to the GP, or be given treatment for mild symptoms. To test this assumptions, the model was recalculated assuming 0 costs of care until diagnosis. This gave a cost per LYG of £6,567.43 and a cost per QALY of £7,501.19 (graph not shown).

Discussion

Even when conservative assumptions are applied, opportunistic case finding is a relatively cost effective strategy compared to current practice, in the current climate of current decision making.

This model is a simplistic version of real life and is built using many data sources and assumptions. The results are fairly sensitive to changes in parameters. Key parameters are the prevalence and the smoking cessation rate.

This model also assumes that spirometry has 100% sensitivity and specificity and is carried out by staff who are trained and competent in its use and interpretation. This is not the

status quo at present and not every practice has a spirometer. Things are changing however, especially since the publication of the BTS guidelines in 1997.

In order to improve the model, better data on the natural history of the disease, especially in relation to smoking cessation and quality of life would be desirable.

The Fletcher and Peto diagram gives the % predicted values for a 25 year old. This would be different for a 46 year old. This means that the benefit has been underestimated in this model, which would decrease the cost effectiveness ratios.

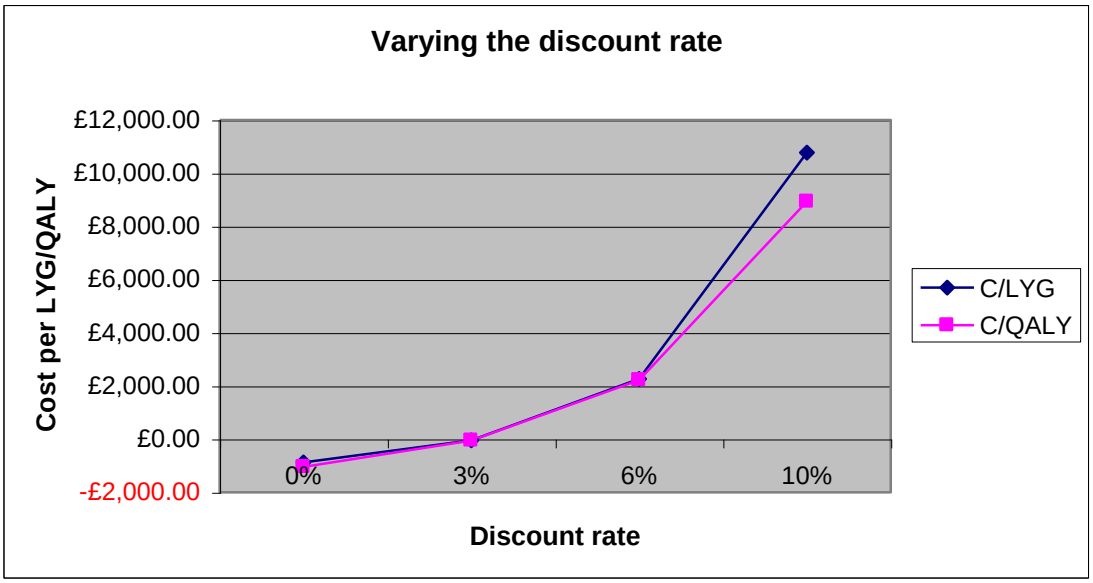
The utility weights used were also from a small sample of patients in a different study. There is a lack of utility data for COPD as most studies tend to use disease specific based measures rather than preference based measures. This is a simple deterministic model and better data would help to build a more sophisticated model.

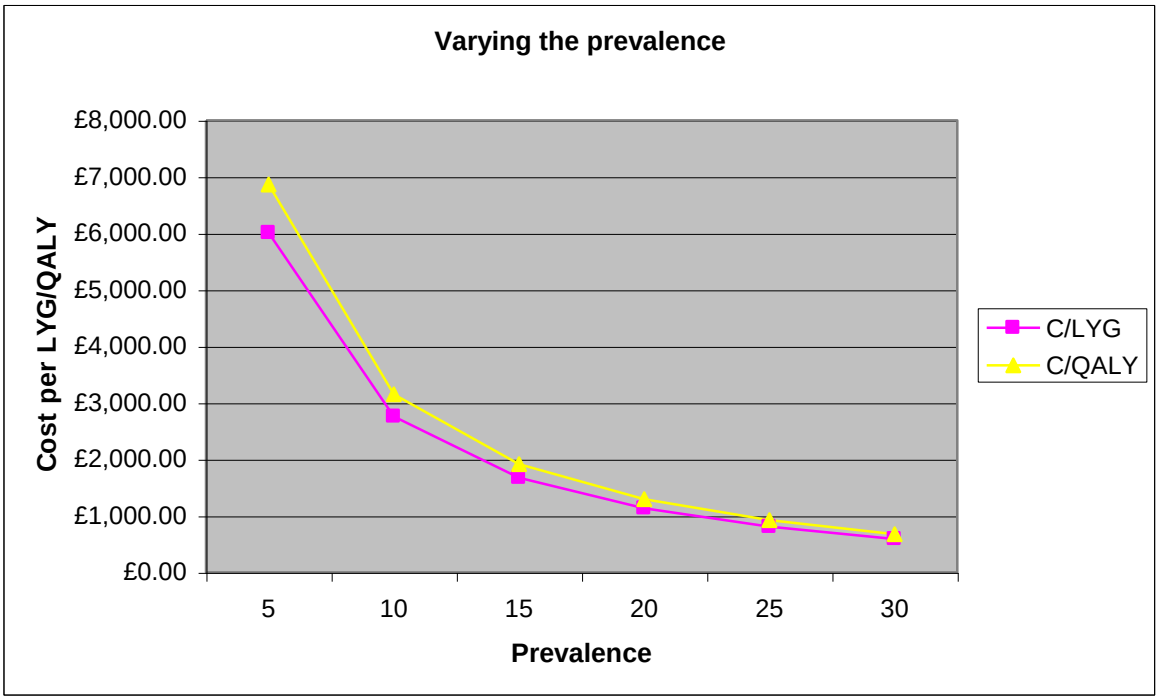
Conclusion

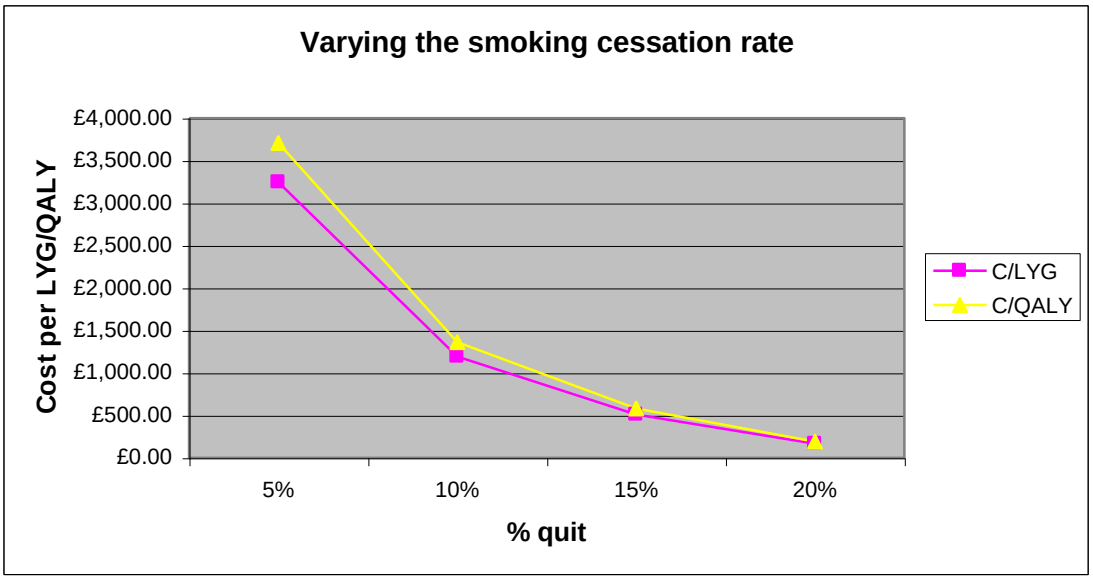
In summary, opportunistic case finding in primary care is a relatively cost effective strategy, subject to the assumptions outlined above. Key parameters are the prevalence of COPD that is undetected and the smoking cessation success rate. It should be noted that the model is quite sensitive to some of the parameters and there are many assumptions. Therefore, the results must be interpreted with this in mind.

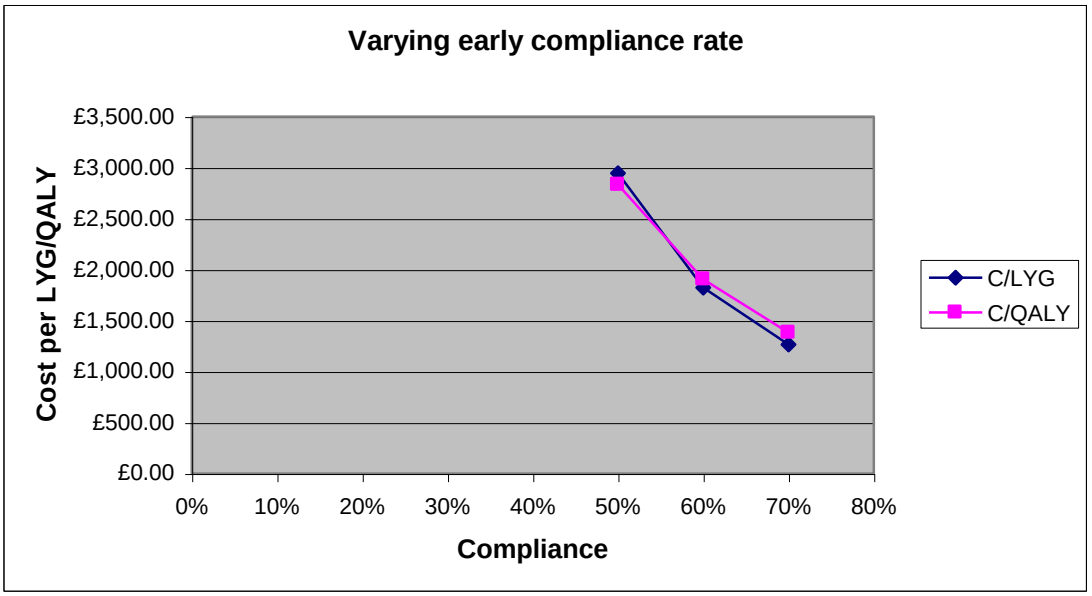
Appendix B.1

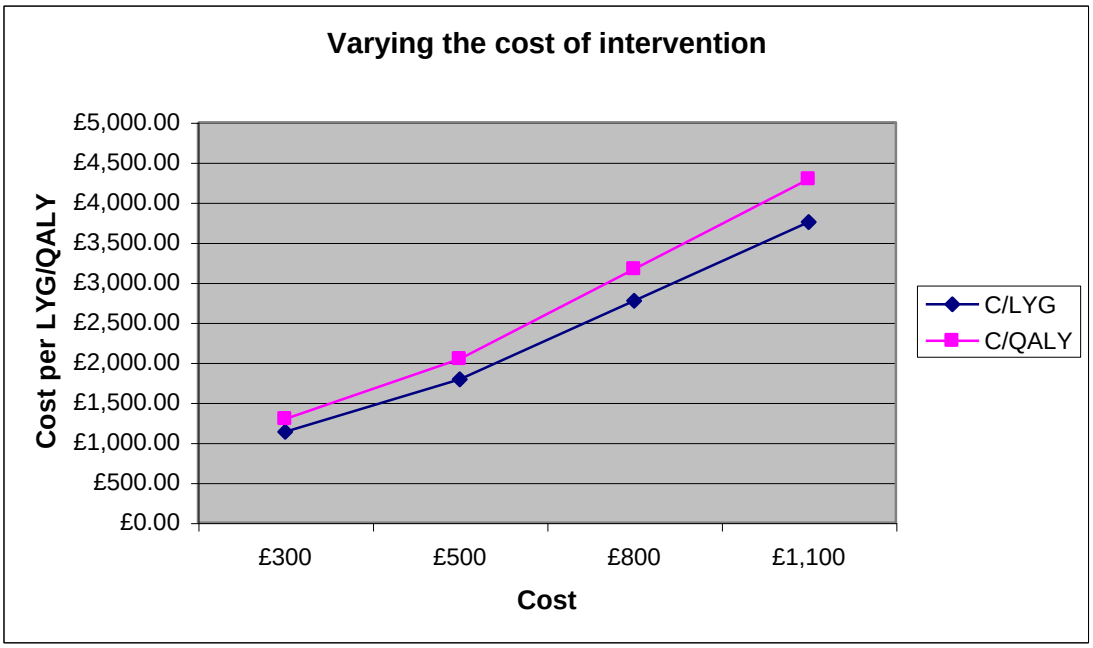
One-way sensitivity analysis

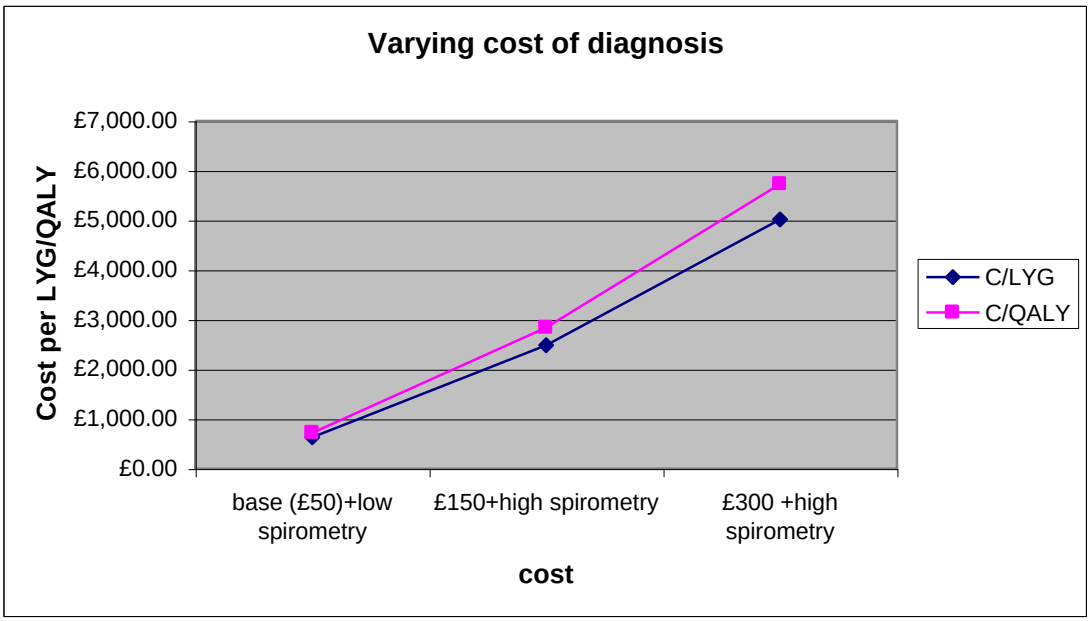





Varying the smoking cessation rate
Cost per LYG/QALY
£4,000.00
£3,500.00
£3,000.00
£2,500.00
£2,000.00
£1,500.00
£1,000.00
£500.00
£0.00
5%
10%
15%
20%
% quit
C/LYG
C/QALY

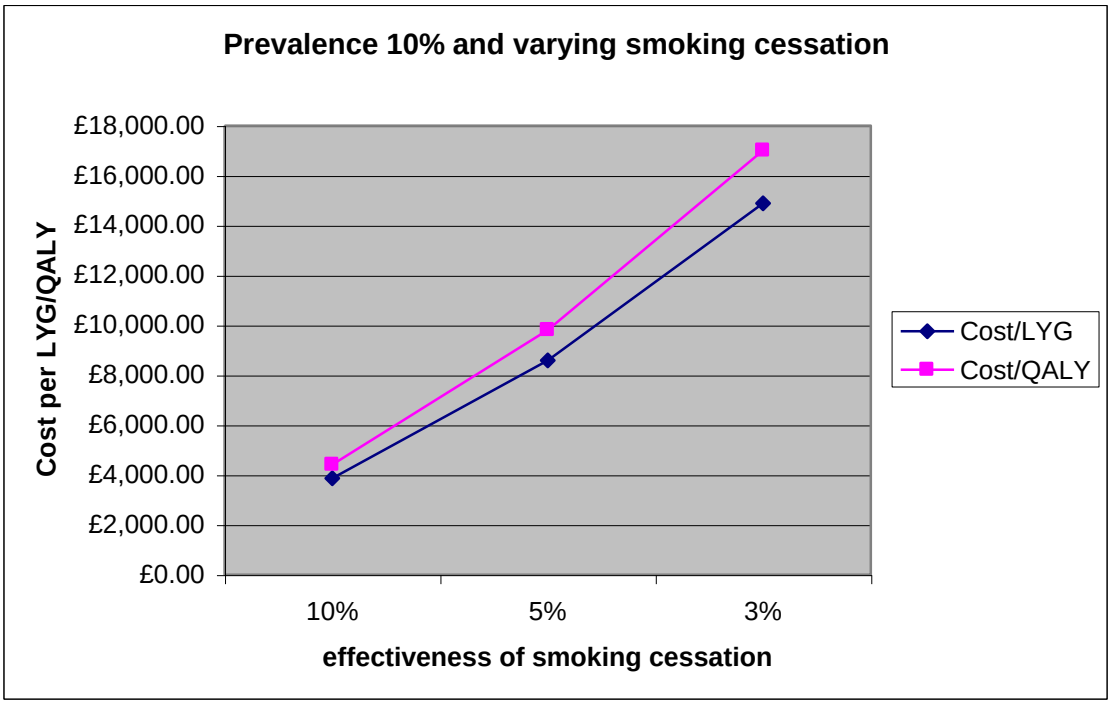

Varying early compliance rate
Cost per LYG/QALY
£3,500.00
£3,000.00
£2,500.00
£2,000.00
£1,500.00
£1,000.00
£500.00
£0.00
0%
10%
20%
30%
40%
50%
60%
70%
80%
Compliance
C/LYG
C/QALY


Varying the cost of intervention
£5,000.00
£4,500.00
£4,000.00
£3,500.00
£3,000.00
£2,500.00
£2,000.00
£1,500.00
£1,000.00
£500.00
£0.00
Cost per LYG/QALY
£300
£500
£800
£1,100
Cost
C/LYG
C/QALY


Varying cost of diagnosis
£7,000.00
£6,000.00
£5,000.00
£4,000.00
£3,000.00
£2,000.00
£1,000.00
£0.00
Cost per LYG/QALY
base (£50)+low spirometry
£150+high spirometry
£300 +high spirometry
cost
C/LYG
C/QALY

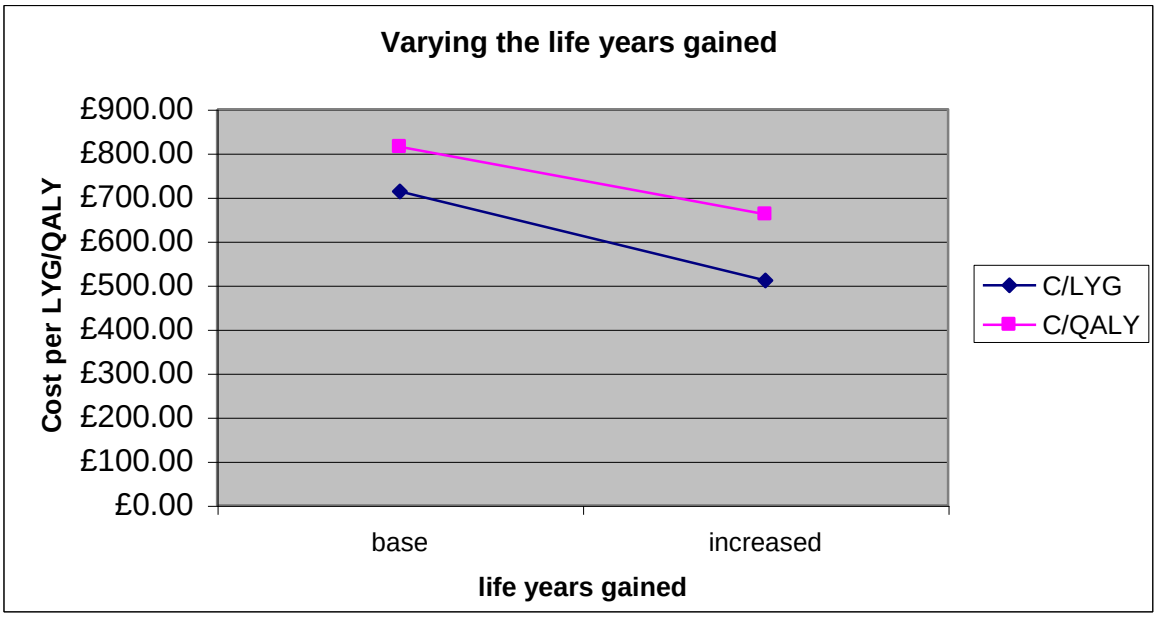
Appendix B.2

Varying the smoking cessation rate when the prevalence is 10%



Appendix B.3

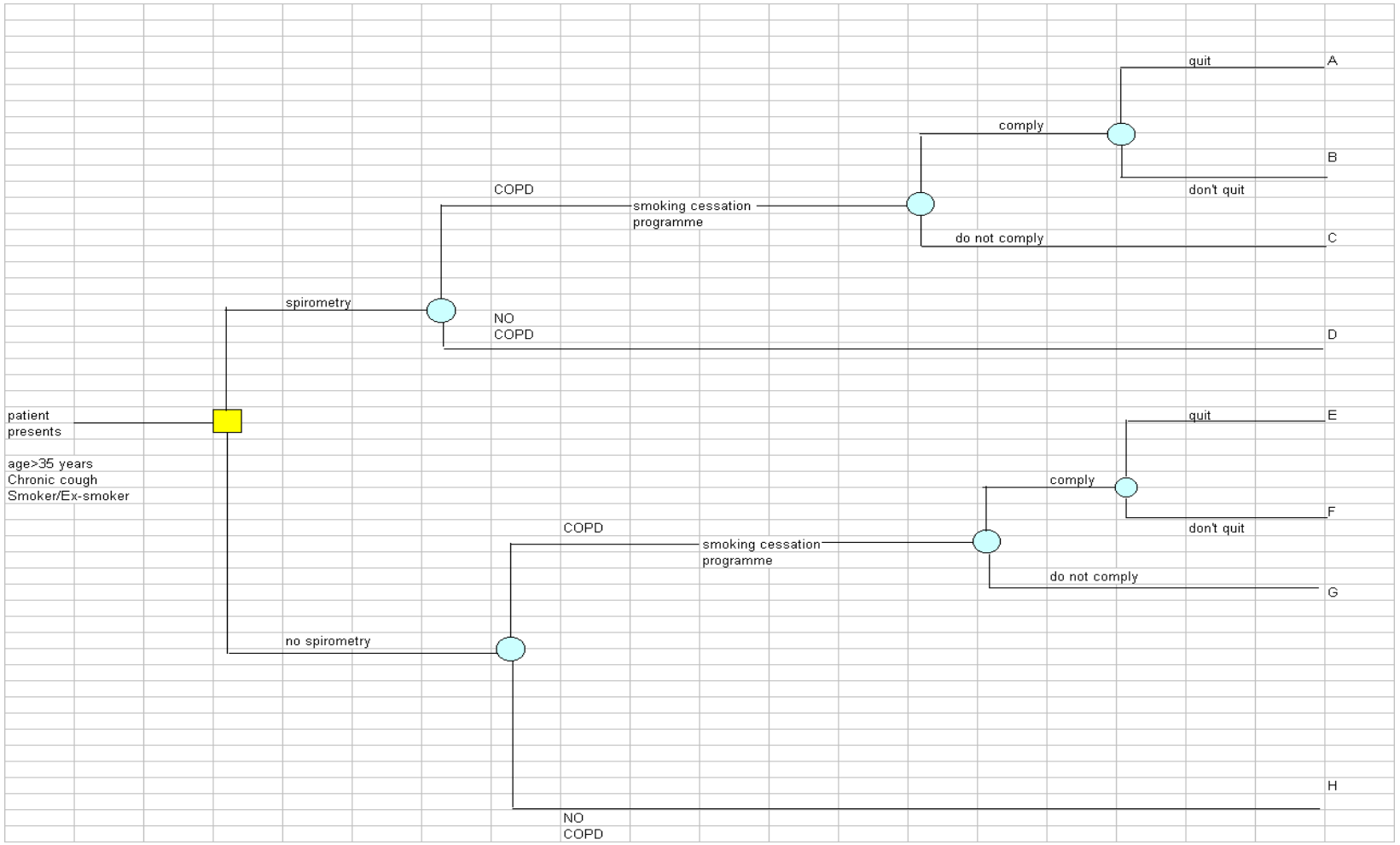
Varying the life years gained



Where 'base' is baseline parameter values of 3.5 years gained if quit smoking at age 46 and 2.1 years gained if quit smoking at age 55.

'Increased' is altering the life years gained to 5.5 years gained if quit smoking at age 46 and 3.5 years gained if quit smoking at age 55.

1 **Figure 1 Tree structure**



13 Appendix C Educational packages

Specific educational packages should be developed for patients with COPD. The packages should take account of the different needs of patients at different stages of their disease. Suggested topics for inclusion are:

- Disease education (Anatomy, physiology, pathology and pharmacology, including oxygen therapy & vaccination)
- Dyspnoea/symptom management, including chest clearance techniques
- Smoking cessation
- Energy conservation/ pacing
- Nutritional advice
- Managing travel
- Benefits system and disable parking badges
- Advance directives (living wills)
- Making a change plan
- Anxiety management
- Goal setting and rewards
- Relaxation
- Identifying and changing beliefs about exercise and health related behaviours
- Loving relationships/sexuality
- Exacerbation management (including when to seek help, self-management and decision making, coping with setbacks and relapses)
- Home care support
- Managing surgery (non thoracic)
- The benefits of physical exercise
- Support groups – such as the British Lung Foundation Breathe Easy groups, which operate throughout the UK

14 Appendix D Economic costs of COPD to the NHS

Titles were reviewed for references relating to the financial cost/economic burden of COPD in England and Wales. Studies relating to the cost in other countries were excluded.

Four relevant sources of information were identified. Two papers[586,587], an abstract[588] and a discussion document[589] were identified. In addition, one paper [33] was identified at a later date by referral from a GDG member as it had just been published. The paper by Sullivan et al was based on the NHS discussion document, another identified source. Only the Sullivan paper has been included.

References from these sources were checked for further references. No further references were identified. The details of each source are reported in the table below.

Author / Category	Calverley[588]	Guest 1999[586]	Sullivan 2000[587]	Britton 2003 [33]
Year for cost data	1995/6	1996/7	1996	2000/01
Sources	Used data from the 4th GP National Morbidity Study, Hospital Episode Statistics, Scottish NHS, Welsh Office, Mortality Statistics and DSS.	Based on a sub group analysis of a previously published prevalence-based burden of illness analysis	NHS Burdens of disease: a discussion document 1996	Telephone interviews. Part of the confronting COPD in North America and Europe survey. Collected data on resource use on a sample of the UK population with COPD. Used UK unit costs for resources to estimate an average per patient cost. Also estimated by severity of COPD

Method	Top down	Top down	Top down	Micro costing
GP costs £	21,000,000	236,500,000	88,000,000 (primary care and community based services)	105.54 per patient
Medications £	85,000,000		402,000,000	130.54 per patient
GP		116,900,000		
Hospital		8,900,000		
Oxygen	156,000,000		207,000,000 (ambulatory)	Home oxygen 22.30 per patient
Hospital £	224,000,000		151,000,000	
Inpatient		243,400,000		444.60 per patient
Outpatient		35,000,000		
Day Case				
Emergency Admission	174,000,000			116.47 per patient
Other £		164,300,000		
Total £	486,000,000	817,500,000	848,000,000	491,652,000 direct 982,000,000 direct and indirect combined
Per patient **Direct costs £**	**781**		**1,154**	**819.42**
Per patient **Indirect costs £**				**819.66**

The papers all differ in terms of their methodology and their data sources, as well as the costs that they include. The cost per patient for those using a top down approach also depends on the total number of patients they divide the total cost by. This may also explain some of the wide variation seen in the costs.

The paper by Britton et al also estimates the cost by disease severity.

Estimated cost by disease severity p.a. (2000/01) [33]

- Mild €232 £149.68
- Moderate €477 £307.74
- Severe €2026 £1,307.10

These cost estimates could be viewed as the incremental cost of a COPD patient compared to the general population, as the study asked patients about resource use related to their COPD.

Cost of an exacerbation

Four papers of potential relevance were found.

Andersson et al (2002)[496]

Costs given in SEK, converted to GB£ by using purchasing power parities for 2002 from the OECD http://www.oecd.org/

Mild	£7.94
Mild/moderate	£23.43
Moderate	£139.74
Severe	£1,446.48

Price et al (1999)[497]

Mild	£14.81
Moderate	£95.20
Severe	£1,658.59

Gibson et al (1998)[590] This identifies resource by COPD patients with an exacerbation but does not cost it.

McGuire et al (2001)[591]

This gives a total excess cost of exacerbations, but does not give a per patient cost.

1994/5 excess costs: £35.7 million.

Note that the cost-effectiveness analysis undertaken for the update of the guideline includes additional information about the cost of COPD exacerbations – see appendix M.

15 Appendix E Searching for health economics evidence

A separate search was carried out for health economics evidence as the clinical searches were not designed to capture this type of evidence. The searching was carried out by an information scientist at the School of Health and Related Research (ScHARR) with guidance on the search terms from the health economist.

Selection of papers and reviewing was carried out by the health economist.

Search Strategy

The search strategy used was as follows

Methodological search filters used

Economic evaluations

- economics/
- exp “costs and cost analysis”/
- economic value of life/
- exp economics, hospital/
- exp economics, medical/
- economics, nursing/
- economics, pharmaceutical/
- exp models, economic/
- exp “fees and charges”/
- exp budgets/
- ec.fs

- (cost or costs or costed or costly or costing$).tw
- (economic$ or pharmacoeconomic$ or price$ or pricing).tw
- or/1-13

Searches were restricted to1995 to the present (August 2002) and to the English language. The following databases were searched with the number of hits shown in brackets:

- Medline (430)
- Embase (207)
- NHS EED (41)
- OHE HEED (161)

Databases were searched on 01/08/02

In addition, reference lists from appraised papers were checked for further useful references. A list of health economic terms was given to the systematic reviewer and information scientist at the NCC to help them identify any papers of potential relevance. Any found were then passed on to the health economist. The GDG also highlighted references they thought might be useful.

Inclusion criteria

The titles, and where available the abstracts, were screened to assess whether the study met the following inclusion criteria:

Patients: at least some of the patients had COPD.

Economic evidence: the study was an economic evaluation or included information on resources, costs or specific quality of life measures.

Study design: no criteria for study design were imposed a priori.

Summary Results

After reviewing titles, abstracts and CRD/OHE HEED commentaries (where available), 115 potentially useful papers were included.

Full papers were obtained and led to a further exclusion of 47 papers. 68 papers were appraised and presented to the GDG. Very few of these were good quality formal economic evaluations. The table below shows the number of papers that were reviewed in each area.

Area	**Number of papers reviewed**
Financial cost of COPD to the NHS	5
Cost of an exacerbation	4
Bronchodilators	10
Pulmonary rehabilitation	15
Smoking cessation	4
Education	3
Oxygen-stable COPD: Long term oxygen therapy	1
Oxygen – stable COPD: Ambulatory oxygen therapy	1
Antibiotics	3
Hospital-at-home	7
Antitrypsin	1
Non invasive ventilation	5

Mucolytics	1
Immunisation	3
Lung volume reduction surgery	1
Corticosteroids for stable COPD	4

Areas not listed above did not have any useful economic evidence.

16 Appendix F Evidence tables

Evidence tables from the COPD update guideline (GC101) are available at http://guidance.nice.org.uk/CG101/EvidenceTables/pdf/English

The evidence tables for the original COPD guideline (CG12) are available at http://thorax.bmj.com/content/59/suppl_1

The evidence tables provide full details for the studies identified and critically appraised as part of the formal systematic review. They are organised according to the guideline sections.

17 Appendices for NEW 2010 update

- Update COPD Scope
- Update questions
- Update literature searches
- Update research protocols
- Deleted sections
- Criteria for selecting future research recommendations
- Cost effectiveness model
- Forest plots
- Declarations of Interest Register

18 Appendix G NEW 2010 update Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

Guideline title

Chronic obstructive pulmonary disease: the management of adults with chronic obstructive pulmonary disease in primary and secondary care (partial update)

Short title

COPD (partial update)

Background

a) The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Chronic Conditions to review recent evidence on chronic obstructive pulmonary disease and to update some sections of the existing guideline 'Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care' (NICE clinical guideline 12, 2004) for use in the NHS in England and Wales. The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) NICE clinical guidelines support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by NICE after an NSF has been issued have the effect of updating the Framework.

c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, if appropriate) can make informed decisions about their care and treatment.

Clinical need for the guideline

a) Since the publication of NICE clinical guideline 12 (2004), there has been progress in the management of chronic obstructive pulmonary disease (COPD) and the importance of systemic aspects of the disease also has been recognised. New initiatives such as the introduction of the Quality and Outcomes Framework for General Practice have helped the delivery of evidence-based care. But COPD is still a common cause of morbidity and mortality in England and Wales.

b) People with COPD experience progressive breathlessness and reduction in exercise capacity. Exacerbations frequently result in hospital admission. COPD remains the fifth most common cause of death in England and Wales, accounting for more than 28,000

deaths in 2005. It is also one of the ten most common causes of hospital admission. Many patients, including those with severe airflow obstruction, remain undiagnosed even though diagnostic testing using spirometry is increasingly available.

c) The development of a NSF for COPD was announced in 2006 and it is expected that this will be published in late 2008 or early 2009. This partial update will provide evidence-based recommendations that will support the implementation of the Clinical Strategy for COPD (formerly known as the NSF).

d) The guideline development process is described in detail in two publications that are available from the NICE website (see 'Further information'). 'The guideline development process: an overview for stakeholders, the public and the NHS' describes how organisations can become involved in the development of a guideline. 'The guidelines manual' provides advice on the technical aspects of guideline development.

e) This scope defines what this guideline will (and will not) examine, and what the guideline developers will consider. This scope should be read along with the original scope for 'Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care' (NICE clinical guideline 12, 2004), which is reproduced in the appendix.

f) The areas that will be addressed by the guideline are described in the following sections.

Population

Groups that will be covered

a) Adults with stable COPD (including chronic bronchitis, emphysema and chronic airflow limitation/obstruction).

Groups that will not be covered

a) People with asthma, bronchopulmonary dysplasia or bronchiectasis.

b) Children younger than 16 years.

c) People with an acute exacerbation of COPD.

Healthcare setting

a) Care given by primary and secondary healthcare professionals who have responsibility for patients with COPD and who make decisions concerning their care.

b) The guideline will also be relevant to the work, but will not cover the practice, of social services or patient support groups.

Clinical management

3.3.1 Topics that will be covered

a) Diagnosis and severity classification:

- spirometry and post bronchodilator values
- multidimensional severity assessment indices, for example the BODE Index which comprises body mass index, airflow obstruction, dyspnoea and exercise tolerance

b) Management of stable COPD and prevention of disease progression (updates section 7 of NICE clinical guideline 12):

- long-acting bronchodilators: beta$_2$-agonists and anticholinergics (tiotropium, formoterol fumarate, salmeterol) as monotherapy and in combination, both with and without inhaled corticosteroids
- mucolytic therapy (carbocisteine and mecysteine hydrochloride)

c) Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform their decisions for individual patients.

d) The Guideline Development Group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, or changing the approach to care to make more efficient use of resources can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

e) Where there is evidence, the guideline will consider any sub-groups (for example, ethnicity) in whom the recognition and diagnosis of COPD may differ from the general population.

3.3.2 Topics that will not be updated:

a) Short-acting bronchodilator therapy (except as a comparator with long-acting bronchodilator therapy)

b) Theophylline

c) Phosphodiesterase type 4 inhibitors

d) Delivery systems

e) Oxygen therapy

f) Management of pulmonary hypertension and cor pulmonale

g) Pulmonary rehabilitation interventions

h) Vaccination and anti-viral therapy

i) Lung surgery

j) Alpha-1 antitrypsin replacement therapy

k) Anti-oxidant therapy

l) Anti-tussive therapy

m) Prophylactic antibiotic therapy

n) Multi-disciplinary management (respiratory nurse specialist, physiotherapy, identifying and managing anxiety and depression, nutritional factors, palliative care, assessment for occupational therapy, social services, education, self-management, advice on travel),

o) Fitness for general surgery

p) Follow-up of patients with COPD

q) Management of exacerbations

r) Audit criteria

Status

Scope

This is the final version of the scope.

The guideline will partially update the following NICE guidance.

- Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. NICE clinical guideline 12 (2004).

The guideline will incorporate the following NICE guidance.

- Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007).

Guideline

The development of the guideline recommendations will begin in September 2008.

Further information

The guideline development process is described in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'
- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

Appendix: Scope for NICE clinical guideline 12

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

SCOPE

Guideline title

Chronic obstructive pulmonary disease: the management of adults with chronic obstructive pulmonary disease in primary and secondary care

Short title

COPD

Background

a) The National Institute for Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Chronic Conditions to develop a clinical guideline on the management of chronic obstructive pulmonary disease for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and National Assembly for Wales (see appendix). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.

Clinical need for the guideline

a) COPD is the fifth commonest cause of death in England and Wales, accounting for nearly 28,000 deaths each year and Britain has one of the highest death rates from COPD in the European Union. It is estimated that there are about 600,000 patients in the UK with diagnosed COPD and there may be as many again who remain undiagnosed. COPD patients are frequent users of primary and secondary care services with an estimate of one in eight hospital admissions being due to COPD. Consultation rates in general practice rise with age from 417 in those aged 45–64 per 10,000 population per year to 1032 in those aged 75–84 per year per 10,000 population (BTS, 1997). COPD results in an estimated 27 million lost working days per year.

b) Recent national guidelines in the area include the guideline developed by the British Thoracic Society (Thorax 1997; 52 [suppl 5]; S1), the GOLD International guidelines (2001), Use of Nebulisers (Thorax 1997; 52 [suppl 2]) and the NIV guidelines (in press: Thorax).

c) Technology appraisals on the Institute's programme that will inform this guideline include guidance on zanamivir (Relenza) for influenza, smoking cessation treatments and nicotine replacement therapy (expected March 2002) and comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature (Health Technology Assessment 2001; Vol. 5: No. 26).

The guideline

a) The guideline development process is described in detail in three booklets that are available from the NICE website (see 'Further information'). The Guideline Development Process – Information for Stakeholders describes how organisations can become involved in the development of a guideline.

b) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health and National Assembly for Wales (see Box).

c) The areas that will be addressed by the guideline are described in the following sections.

Population

Groups that will be covered

a) The guideline will offer best practice advice on the care of adults who have a clinical working diagnosis of COPD including chronic bronchitis, emphysema, and chronic airflow limitation/obstruction.

Groups that will not be covered

a) The guideline will not cover the management of people with asthma, bronchopulmonary dysplasia or bronchiectasis.

b) The guideline will not cover children (aged < 16 years).

Healthcare setting

a) The guideline will cover the care received from primary and secondary healthcare professionals who have direct contact with and make decisions concerning the care of patients with COPD.

b) The guideline will also be relevant to the work, but will not cover the practice, of social services, patient support groups or palliative care services.

Clinical management

The guideline will include recommendations in the following areas.

a) Diagnostic criteria, including the role of spirometry in primary and secondary care.

b) Identification of early disease to facilitate preventative approaches. The guideline will not cover general population screening, but will include opportunistic case find.

c) Management of stable patients, management of acute exacerbations and prevention of progression of the disease, to include:

- smoking cessation, including pharmacological and non-pharmacological approaches as they relate specifically to COPD
- bronchodilator management including methods of delivery and methods of assessing efficacy
- inhaled and oral corticosteroid therapy
- non-pharmacological interventions, including pulmonary rehabilitation and respiratory physiotherapy, lifestyle advice including nutritional/metabolic assessment and management and self-management techniques
- the management of right heart failure as it pertains to COPD
- oxygen therapy including when It should be used and what type is appropriate in different circumstances
- non-invasive ventilation
- indications for surgery

d) Criteria for admission and/or management at home of exacerbations.

e) Management of depression and/or anxiety as it pertains directly to patients with COPD and is outside the scope of the 'Management of Depression' guideline which is under development.

f) Advice on treatment options will be based on the best evidence available to the development group. When referring to pharmacological treatments, the guideline will normally recommend use within licensed indications. Exceptionally, and only where the evidence clearly supports it, recommendations for the guideline may recommend use outside the licence indications. The guideline assumes that prescribers will use the Summary of Product Characteristics to inform their prescribing decisions for individual patients.

Audit support within guideline

The guideline will include review criteria for audit.

Status

Scope

This is the final version of the scope.

Guideline

The development of the guideline recommendations will begin in the second quarter of 2002.

Further information

Information on the guideline development process is provided in:

- The Guideline Development Process – Information for the Public and the NHS
- The Guideline Development Process – Information for Stakeholders
- The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups.

These booklets are available as PDF files from the NICE website (www.nice.org.uk). Information of the progress of the guideline will also be available from the website.

References

BTS guidelines for the management of chronic obstructive pulmonary disease. The COPD Guidelines Group of the Standards of Care Committee of the BTS. Thorax 1997; 52 Suppl 5:S1-28.

Current best practice for nebuliser treatment. British Thoracic Society Nebulizer Project Group [published erratum appears in Thorax 1997 Sep; 52(9): 838] Thorax 1997; 52 (Suppl 2): S1-S3.

Pocket Guide to COPD Diagnosis, Management, and Prevention. Global Initiative for Chronic Obstructive Lung Disease; U.S. Department of Health and Human Services; Public Health Service; National Institutes of Health; National Heart, Lung, and Blood Institute; NIH Publication No. 2701B

Referral from the Department of Health and National Assembly for Wales

"To prepare clinical guidelines for the NHS in England and Wales for the prevention, diagnosis, management and treatment of COPD."

19 Appendix H NEW 2010 update PICO questions

DRUG 1: LABA vs. LAMA

What is the clinical and cost effectiveness of long-acting beta$_2$ agonists compared with long-acting muscarinic antagonists in the management of people with stable COPD?

DRUG 3a) LABA + ICS vs. LABA alone

What is the clinical and cost effectiveness of long-acting beta$_2$ agonists plus inhaled corticosteroids compared to long-acting beta$_2$ agonists in the management of people with stable COPD?

DRUG 3b) LABA + ICS vs. LAMA alone

What is the clinical and cost effectiveness of long-acting beta$_2$ agonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists in the management of people with stable COPD?

DRUG 4a) LAMA + ICS vs. LABA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus inhaled corticosteroids compared to long-acting beta$_2$ agonists in the management of people with stable COPD?

DRUG 4b) LAMA + ICS vs. LAMA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists in the management of people with stable COPD?

DRUG 5a) LAMA + LABA vs. LABA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists compared to long-acting beta$_2$ agonists in the management of people with stable COPD?

DRUG 5b) LAMA + LABA vs. LAMA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists compared to long-acting muscarinic antagonists in the management of people with stable COPD?

DRUG 5 c) LAMA + LABA vs. LABA +ICS

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting $beta_2$ agonists compared to long-acting $beta_2$ agonists plus inhaled corticosteroids in the management of people with stable COPD?

DRUG 6a) LAMA + LABA + ICS vs. LABA + ICS

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting $beta_2$ agonists plus inhaled corticosteroids compared to long-acting $beta_2$ agonists plus inhaled corticosteroids in the management of people with stable COPD

DRUG 6b) LAMA + LABA + ICS vs. LAMA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting $beta_2$ agonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists alone in the management of people with stable COPD?

DRUG 6c) LAMA + LABA + ICS vs. LABA + LAMA

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting $beta_2$ agonists plus inhaled corticosteroids compared to long-acting $beta_2$ agonists plus long-acting muscarinic antagonists in the management of people with stable COPD ?

DRUG 8: LAMA vs. SAMA

What is the clinical and cost effectiveness of long-acting muscarinic antagonists compared to short-acting muscarinic antagonists in the management of people with stable COPD?

DIAG 1: How does post bronchodilator FEV_1 (forced expiratory volume in one second) compare with pre bronchodilator FEV_1 in terms of: a) sensitivity / specificity of FEV_1 for diagnosis; b) classification of severity of disease?

DIAG2: In individuals where the diagnosis of COPD is considered and spirometry is conducted, what is the sensitivity and specificity of a fixed ratio FEV_1 / FVC compared with lower limit of normal FEV_1 / FVC ratio to diagnose COPD?

MUCO: What is the clinical and cost effectiveness of mucolytic agents vs. placebo in people with stable COPD?

REHAB: Does early pulmonary rehabilitation (within one month of hospital discharge) in people who had an acute exacerbation improve outcomes compared with usual care (or no rehabilitation), in people with COPD?

MULTI: Is routine assessment using multidimensional severity assessment indices (e.g. BODE) more predictive of outcomes compared to FEV_1 alone?

20 Appendix I NEW 2010 update research protocols

	Research protocol DIAG 1
Question	How does post bronchodilator FEV_1 (forced expiratory volume in one second) compare with pre bronchodilator FEV_1 in terms of: a) sensitivity / specificity of FEV_1 for diagnosis; b) classification of severity of disease?
Objective	To determine if spirometry should be performed pre or post bronchodilator in order to accurately diagnose COPD
Criteria	Observational studies that compare pre and post bronchodilator (BD) FEV_1 values to a clinical diagnosis of COPD (based on symptoms). Exclude studies if pre and post BD FEV_1 values were compared to identify COPD defined according to GOLD criteria (post bronchodilator $FEV_1/FVC < 0.70$). By definition, post bronchodilator FEV_1 would correlate better with a definition of COPD that is based on post bronchodilator FEV_1. Outcomes: sensitivity, specificity; % people identified with COPD; correlation coefficient
Search Strategy	Literature Search Strategy: Stable COPD **AND** FEV_1 **AND** Bronchodilators. Sources: MED,EMB,CIN,COCH.
Review Strategy	No RCTs; no GRADE performed; summary of study quality provided

	Research protocol DIAG 2
Question	**I**n individuals where the diagnosis of COPD is considered and spirometry is conducted, what is the sensitivity and specificity of a fixed ratio FEV_1 / FVC compared with the lower limit of normal FEV_1 / FVC ratio to diagnose COPD?
Objective	To determine if fixed FEV_1 / FVC ratio or lower limit of normal [LLN] FEV_1 / FVC is a more accurate way to diagnose COPD (especially in younger and older people).
Criteria	Observational/diagnostic studies comparing fixed FEV_1 / FVC ratio or lower limit of normal [LLN] FEV_1 / FVC ratio with a physician's diagnosis of COPD. Comparison is with a physician's diagnosis. Outcomes: sensitivity; specificity; % identified with COPD
Search Strategy	Literature Search Strategy: Fixed Ratio FEV_1 **AND** Lower Limit FEV_1. Sources: MED,EMB,CIN,COCH. Limits: Study Types: RCTs, SRs
Review Strategy	No RCTs; no GRADE performed; summary of study quality provided

Research protocol Mucolytics	
Question	What is the clinical and cost effectiveness of mucolytic agents vs. placebo in people with stable COPD?
Objective	to determine if mucolytic agents improve outcomes (specifically decrease exacerbations) in people with COPD
Criteria	SRs or RCTs with at least 6 months follow-up comparing oral mucolytic therapy (Carbosysteine, Erdosteine, or N-acetylcysteine) with placebo (or each other) in people with stable COPD. Outcomes of interest included all-cause mortality, exacerbations, hospitalisations, decline in FEV_1, change in health related quality of life (measured with total SGRQ score), change in breathlessness (measured with TDI), and adverse events. The clinically important relative risk reduction (RRR) for mortality was 15%, exacerbations (20%), hospitalisation (20%), change in SGRQ (-4 points), FEV_1 (100 ml), and TDI (1 unit).
Search Strategy	Literature Search Strategy: Stable COPD **AND** Mucolytics. Sources: MED,EMB,CIN,COCH. Limits: Study Types: RCTs, SRs, Years: 2003-20/8/09
Review Strategy	Meta-analysis where appropriate; important subgroups are type of mucolytic agent and study duration

Research protocol DRUG 1: LABA vs. LAMA	
Question	**DRUG 1: LABA vs. LAMA:** What is the clinical and cost effectiveness of long-acting beta2 agonists compared with long-acting antimuscarinic agents in the management of people with stable COPD?
Objective	To compare the 2 classes of long-acting bronchodilators
Criteria	SRs and RCTs with minimum 6 month follow-up comparing LABA with LAMA in adults with stable COPD (without asthma) characterised by no recent infections, exacerbations or hospitalisations in the previous month. Minimum of 10 smoking pack years. Outcomes: All cause mortality (at ≥1year), • Mean rate of exacerbation (at ≥1year), • Hospitalisation (at ≥1year), • Rate of decline of FEV_1 (at ≥1year) • SRGQ QoL (6-12 months), • TDI score (≥ 6 month follow up) • Adverse events (specifically MI, arrhythmia, CHF) The clinically important relative risk reduction (RRR) for mortality was 15%, exacerbations (20%), hospitalisation (20%), change in SGRQ (-4 points), FEV_1 (100 ml), and TDI (1 unit). adverse events (15%)
Search Strategy	Literature Search Strategy: **DRUG1,3,4,5,6 were run as one search**: Stable COPD AND (LABA OR LAMA OR ICS). Sources: MED,EMB,CIN,COCH. Limits: Study Types: RCTs, SRs, Years: 2003-20/8/09
Review Strategy	Original MA may be required or updating published MA

	Research protocol DRUG 3a: LABA + ICS vs. LABA / DRUG 3b) LABA + ICS vs. LAMA alone
Question	**DRUG 3a: LABA + ICS vs. LABA** What is the clinical and cost effectiveness of long-acting beta2 agonists plus inhaled corticosteroids compared to long-acting beta2 agonists in the management of people with stable COPD? **DRUG 3b) LABA + ICS vs. LAMA alone** What is the clinical and cost effectiveness of long-acting beta2 agonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists in the management of people with stable COPD?
Objective	To determine if addition of ICS to long-acting bronchodilators is clinically and economically beneficial compared with monotherapy with long-acting bronchodilators
Criteria	SRs and RCTs with minimum 6 month follow-up comparing LABA + ICS with either LABA alone or LAMA alone in adults with stable COPD (without asthma) characterised by no recent infections, exacerbations or hospitalisations in the previous month. Minimum of 10 smoking pack years. Outcomes: • All cause mortality (at ≥1year), • Mean rate of exacerbation (at ≥1year), • Hospitalisation (at ≥1year), • Rate of decline of FEV_1 (at ≥1year) • SRGQ QoL (6-12 months), • TDI score (≥ 6 month follow up) • Adverse events (specifically MI, arrhythmia, CHF, pneumonia, bone fracture, BMD)

	• The clinically important relative risk reduction (RRR) for mortality was 15%, exacerbations (20%), hospitalisation (20%), change in SGRQ (-4 points), FEV_1 (100 ml), and TDI (1 unit); adverse events (15%)
Search Strategy	Literature Search Strategy: **DRUG1,3,4,5,6 were run as one search**: Stable COPD **AND** (LABA OR LAMA OR ICS). Sources: MED,EMB,CIN,COCH. Limits: Study Types: RCTs, SRs, Years: 2003-20/8/09
Review Strategy	Original MA may be required or updating published MA Important subgroup analyses: study duration; type of run-in (either not stated; drug withdrawal; or drug optimisation) - lung function level: separate by FEV_1 < 50, <60, < 70 - exacerbations at baseline: separate those studies where people had exacerbations in previous year versus those who did not have exacerbations (or this detail is not stated in inclusion criteria)

	Research protocol DRUG 4a: LAMA + ICS vs LABA and DRUG 4b) LAMA + ICS vs. LAMA alone
Question	**DRUG 4a: LAMA + ICS vs. LABA** What is the clinical and cost effectiveness of long-acting antimuscarinic agents plus inhaled corticosteroids compared to long-acting beta2 agonists in the management of people with stable COPD? **DRUG 4b) LAMA + ICS vs. LAMA alone** What is the clinical and cost effectiveness of long-acting antimuscarinic agents plus inhaled corticosteroids compared to long-acting muscarinic antagonists in the management of people with stable COPD?
Objective	To determine if addition of ICS to long-acting antimuscarinic agents is clinically and economically beneficial compared with monotherapy with long-acting bronchodilators
Criteria	SRs and RCTs with minimum 6 month follow-up comparing LAMA + ICS with either LABA alone or LAMA alone in adults with stable COPD (without asthma) characterised by no recent infections, exacerbations or hospitalisations in the previous month. Minimum of 10 smoking pack years. Outcomes: • All cause mortality (at ≥1year), • Mean rate of exacerbation (at ≥1year), • Hospitalisation (at ≥1year), • Rate of decline of FEV_1 (at ≥1year) • SRGQ QoL (6-12 months), • TDI score (≥ 6 month follow up) • Adverse events (specifically MI, arrhythmia, CHF, pneumonia, bone fracture, BMD) • The clinically important relative risk reduction (RRR) for mortality was 15%, exacerbations (20%), hospitalisation (20%), change in SGRQ (-4 points), FEV_1 (100 ml), and TDI (1 unit); adverse events (15%)

Search Strategy	Literature Search Strategy: **DRUG1,3,4,5,6 were run as one search**: Stable COPD **AND** (LABA OR LAMA OR ICS). Sources: MED,EMB,CIN,COCH. Limits: Study Types: RCTs, SRs, Years: 2003-20/8/09
Review Strategy	Original MA may be required or updating published MA Important subgroup analyses: study duration; type of run-in (either not stated; drug withdrawal; or drug optimisation) - lung function level: separate by FEV_1 < 50, <60, < 70 - exacerbations at baseline: separate those studies where people had exacerbations in previous year versus those who did not have exacerbations (or this detail is not stated in inclusion criteria)

	Research protocol **DRUG 5a: LAMA + LABA vs LABA / DRUG 5b) LAMA + LABA vs. LAMA /** **DRUG 5c) LAMA + LABA vs LABA + ICS**
Question	**DRUG 5a: LAMA + LABA vs. LABA** What is the clinical and cost effectiveness of long-acting antimuscarinic agents plus long-acting beta2 agonists compared to long-acting beta2 agonists in the management of people with stable COPD? **DRUG 5b) LAMA + LABA vs. LAMA** What is the clinical and cost effectiveness of long-acting antimuscarinic agents plus long-acting beta2 agonists compared to long-acting muscarinic antagonists in the management of people with stable COPD? **DRUG 5c) LAMA + LABA vs. LABA + ICS** What is the clinical and cost effectiveness of long-acting antimuscarinic agents plus long-acting beta2 agonists compared to long-acting beta2 agonists plus inhaled corticosteroids in the management of people with stable COPD?
Objective	To determine if dual therapy with long-acting bronchodilators is clinically and economically beneficial compared with monotherapy with long-acting bronchodilators or dual therapy with LABA + ICS
Criteria	SRs and RCTs with minimum 6 month follow-up comparing LAMA + LABA with either LABA alone or LAMA alone or LABA + ICS in adults with stable COPD (without asthma) characterised by no recent infections, exacerbations or hospitalisations in the previous month. Minimum of 10 smoking pack years. Outcomes: • All cause mortality (at ≥1year), • Mean rate of exacerbation (at ≥1year), • Hospitalisation (at ≥1year),

	• Rate of decline of FEV_1 (at ≥1year) • SRGQ QoL (6-12 months), • TDI score (≥ 6 month follow up) • Adverse events (specifically MI, arrhythmia, CHF) (pneumonia, bone fracture, BMD for any comparison involving ICS) • The clinically important relative risk reduction (RRR) for mortality was 15%, exacerbations (20%), hospitalisation (20%), change in SGRQ (-4 points), FEV_1 (100 ml), and TDI (1 unit); adverse events (15%)
Search Strategy	Literature Search Strategy: **DRUG1,3,4,5,6 were run as one search**: Stable COPD **AND** (LABA OR LAMA OR ICS). Sources: MED,EMB,CIN,COCH. Limits: Study Types: RCTs, SRs, Years: 2003-20/8/09
Review Strategy	Original MA may be required or updating published MA Important subgroup analyses: study duration; type of run-in (either not stated; drug withdrawal; or drug optimisation) - lung function level: separate by FEV_1 < 50, <60, < 70 - exacerbations at baseline: separate those studies where people had exacerbations in previous year versus those who did not have exacerbations (or this detail is not stated in inclusion criteria)

	Research protocol DRUG 6a: LAMA + LABA + ICS vs LABA + ICS / DRUG 6b) LAMA + LABA + ICS vs. LAMA alone / DRUG 6c) LAMA + LABA + ICS vs LABA + LAMA
Question	**DRUG 6a: LAMA + LABA + ICS vs. LABA + ICS** What is the clinical and cost effectiveness of long-acting antimuscarinic agents plus long-acting beta2 agonists plus inhaled corticosteroids compared to long-acting beta2 agonists plus inhaled corticosteroids in the management of people with stable COPD? **DRUG 6b) LAMA + LABA + ICS vs. LAMA alone** What is the clinical and cost effectiveness of long-acting antimuscarinic agents plus long-acting beta2 agonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists alone in the management of people with stable COPD? **DRUG 6c) LAMA + LABA + ICS vs. LABA + LAMA** What is the clinical and cost effectiveness of long-acting antimuscarinic agents plus long-acting beta2 agonists plus inhaled corticosteroids compared to long-acting beta2 agonists plus long-acting antimuscarinic agents in the management of people with stable COPD?
Objective	To determine if triple therapy is clinically and economically beneficial compared with long-acting bronchodilators or dual therapy with LABA + ICS

Criteria	SRs and RCTs with minimum 6 month follow-up comparing triple therapy with either LABA + ICS or LABA + LAMA or LAMA alone in adults with stable COPD (without asthma) characterised by no recent infections, exacerbations or hospitalisations in the previous month. Minimum of 10 smoking pack years. Outcomes: • All cause mortality (at ≥1year), • Mean rate of exacerbation (at ≥1year), • Hospitalisation (at ≥1year), • Rate of decline of FEV_1 (at ≥1year) • SRGQ QoL (6-12 months), • TDI score (≥ 6 month follow up) • Adverse events (specifically MI, arrhythmia, CHF) (pneumonia, bone fracture, BMD for any comparison involving ICS) • The clinically important relative risk reduction (RRR) for mortality was 15%, exacerbations (20%), hospitalisation (20%), change in SGRQ (-4 points), FEV_1 (100 ml), and TDI (1 unit); adverse events (15%)
Search Strategy	Literature Search Strategy: **DRUG1,3,4,5,6 were run as one search**: Stable COPD **AND** (LABA OR LAMA OR ICS). Sources: MED,EMB,CIN,COCH. Limits: Study Types: RCTs, SRs, Years: 2003-20/8/09
Review Strategy	Original MA may be required or updating published MA Important subgroup analyses: study duration; type of run-in (either not stated; drug withdrawal; or drug optimisation) - lung function level: separate by FEV_1 < 50, <60, < 70 - exacerbations at baseline: separate those studies where people had exacerbations in previous year versus those who did not have exacerbations (or this detail is not stated in inclusion criteria)

	Research protocol Drug 8 LAMA vs SAMA
Question	What is the clinical and cost effectiveness of long-acting muscarinic antagonists compared to short-acting muscarinic antagonists in the management of people with stable COPD?
Objective	To determine if once a day LAMA is clinically and economically beneficial compared with four times a day SAMA in people with COPD
Criteria	SRs and RCTs with minimum 6 month follow-up comparing LAMA with SAMA in adults with stable COPD (without asthma) characterised by no recent infections, exacerbations or hospitalisations in the previous month. Outcomes of interest were mortality, exacerbations, hospitalisations, decline in FEV_1, change in health related quality of life (measured with total SGRQ), adverse events (MI or acute arrhythmia), and change in breathlessness score (measured with TDI). The clinically important relative risk reduction (RRR) for mortality was 15%, exacerbations (20%), hospitalisation (20%), change in SGRQ (-4 points), FEV_1 (100 ml), and TDI (1 unit); adverse events (15%)
Search Strategy	Literature Search Strategy: Stable COPD **AND** LAMA **AND** SAMA. Sources: MED,EMB,CIN,COCH. Limits: Study Types: RCTs, SRs, Years: 2003-20/8/09
Review Strategy	Original MA may be required or updating published MA Important subgroup analyses: study duration; type of run-in (either not stated; drug withdrawal; or drug optimisation) - lung function level: separate by FEV_1 < 50, <60, < 70 - exacerbations at baseline

	Research protocol **REHAB**
Question	Does early pulmonary rehabilitation (within one month of hospital discharge) in people who had an acute exacerbation improve outcomes compared with usual care (or no rehabilitation), in people with COPD?
Objective	To determine if early rehab (within 1 month of hospital discharge) in people who have suffered an exacerbation is clinically and economically beneficial compared with no rehab or usual care
Criteria	SRs and RCTs comparing early rehab (within 1 month of hospital discharge) in people who have suffered an exacerbation with no rehab or usual care. Outcomes: • All cause mortality (at ≥1year), • Mean rate of exacerbation (at ≥1year), • Hospitalisation (at ≥1year), • Rate of decline of FEV_1 (at ≥1year) • SRGQ QoL (6-12 months), shuttle walk distance; six minute walk distance • TDI score (≥ 6 month follow-up); • The clinically important relative risk reduction (RRR) for mortality was 15%, exacerbations (20%), hospitalisation (20%), change in SGRQ (-4 points), shuttle walk distance (48 meters), FEV_1 (100 ml), TDI (1 unit), and six minute walk distance (50 m).
Search Strategy	Literature Search Strategy: Stable COPD **AND** Pulmonary Rehabilitation. Sources: MED,EMB,CIN,COCH. Limits: Study Types: RCTs, SRs, Years: 2003-20/8/09
Review Strategy	Original MA may be required or updating published MA Important subgroup analyses: - rehab initiated in hospital - rehab initiated after hospital discharge

	Research protocol MULTI
Question	Is routine assessment using multidimensional severity assessment indices (e.g. BODE) more predictive of outcomes compared to FEV_1 alone?
Objective	To determine the prognostic ability of FEV_1 vs. multidimensional indices to predict outcomes in stable COPD patients
Criteria	Observational studies comparing FEV_1 with multidimensional indices in people with COPD. Exclusion criteria: retrospective studies, univariate analyses, multivariate analysis if it did not adjust for age and smoking, any index that was not multidimensional (i.e. it must include measures of different outcome combinations such as QoL + symptoms, not just multiple dimensions of one type of outcome measure such as QoL). Outcomes :mortality, hospitalisations and exacerbations
Search Strategy	Literature Search Strategy: Stable COPD **AND** Assessment Indices **AND** FEV_1. Sources: MED,EMB,CIN,COCH. Limits: Study Types: RCTs, SRs, Years: 2003-20/8/09
Review Strategy	Summary of study quality (no GRADE profiles)

Research protocol (Call for evidence)	
Question	The Guideline Development Group is seeking detailed unpublished data on patients entering published drug studies of long-acting bronchodilators and studies of combinations of long-acting bronchodilators with inhaled steroids. The data should be able to provide evidence for the following comparisons: 1) LABA + ICS v LABA 2) LAMA + ICS v LAMA 3) LAMA + ICS v LABA + LAMA 4) LABA + LAMA v LABA 5) LABA + LAMA v LAMA 6) LABA + LAMA + ICS v LABA + ICS 7) LABA + LAMA + ICS v LAMA 8) LABA + LAMA + ICS v LABA + LAMA
Objective	to identify subgroups of trials that have background combination therapy (i.e. LABA + LAMA+ ICS)
Criteria	With minimum 6 month follow-up comparing in adults with stable COPD (without asthma) characterised by no recent infections, exacerbations or hospitalisations in the previous month. Minimum of 10 smoking pack years. Outcomes: All cause mortality (at ≥1year), • Mean rate of exacerbation (at ≥1year), • Hospitalisation (at ≥1year), • Rate of decline of FEV_1 (at ≥1year) • SRGQ QoL (6-12 months), • TDI score (≥ 6 month follow up) • Adverse events (specifically MI, arrhythmia, CHF, pneumonia, osteoporosis)

Search Strategy	Letter to stakeholders - no search required
Review Strategy	RCTs with subgroup analysis by LABA/LAMA/ICS background which may inform clinical questions; baseline characteristics should be similar enough between groups; key trials with important background medication are: INSPIRE, TORCH, UPLIFT

Overall protocol		
	Inclusion	**Exclusion**
Types of Studies	Meta analyses / RCTs (parallel and crossover)	
Types of participants	Adults with stable COPD (without asthma) characterised by no recent infections, exacerbations or hospitalisations in the previous month. Minimum of 10 smoking pack years	Specific populations that are not relevant e.g. Japanese and African American
Types of intervention	LAMA vs SAMA LAMA vs LABA LABA + LAMA vs LAMA LABA+LAMA vs. LABA LAMA + ICS vs LAMA LAMA + ICS vs LABA LABA+ICS vs LABA LABA + ICS vs LAMA LABA+LAMA+ICS vs. LABA + LAMA LABA+LAMA+ICS vs. LABA + ICS LABA + LAMA + ICS vs LAMA	Nebulised route of delivery Short-acting LAMA or LABA

Types of Outcome measures	• All cause mortality (at ≥1year), • Mean rate of exacerbation (at ≥1year), • Hospitalisation (at ≥1year), • Rate of decline of FEV_1 (at ≥1year) • SRGQ QoL (6-12 months), • TDI score (≥ 6 month follow up) • Adverse events (cardiac, osteoporosis and pneumonia)	End exercise isotime Transdiaphragmatic pressure Dynamic hyperinflation Trough FEV_1/FVC Inspired capacity FEV_1 AUC 0-12
Follow up	≥ 6 months	

Research protocol Health economic literature review protocol	
Question	All clinical questions for guideline as specified in clinical review protocol
Objective	To identify economic evaluations that address the clinical questions as specified above
Criteria	**Population and Interventions** **Include:** Generally as for clinical review - patients with COPD **Setting** **Included:** UK NHS **Potentially includable (depending on availability and quality of other evidence; in hierarchical order):** OECD countries with predominantly public health insurance systems (e.g. France, Germany, Sweden); OECD countries with predominantly private health insurance systems (e.g. USA, Switzerland) **Excluded:** Non-OECD settings **Outcome** **Included:** Full economic evaluations; Cost-utility (QALYs) **Potentially includable (depending on availability and quality of other evidence; in hierarchical order):** Cost-effectiveness; Cost-benefit; Cost-consequences; Comparative costs (including cost minimisation analysis); QALYs (without cost); Willingness to pay (without cost)

	Excluded: Studies that report only cost per hospital (not cost per patient); Studies that report only average cost-effectiveness ratios and do not disaggregate the costs and effects to allow an incremental analysis to be conducted; Utility – i.e. quality of life on a zero-one score – (without cost); Resource use (e.g. hospitalisation; without cost) **Study design criteria** **Included:** Economic evaluations conducted alongside randomised controlled trials included in clinical review; Economic evaluation models where treatment effect is based on one or more randomised controlled trial where all are included in clinical review **Potentially includable (depending on availability and quality of other evidence):** Economic evaluation models where treatment effect is based on one or more randomised controlled trial where not all are included in clinical review; Economic evaluations based on non-randomised controlled trials or observational evidence (especially where include in clinical review or there are concerns over generalisability of RCT-based studies); Study quality rating = very serious limitations **Excluded:** Non-comparative studies (e.g. cost of illness studies); Comparative studies where only one intervention is within the scope of the question; Reviews of economic evaluations (recent reviews ordered and checked for references); Study applicability rating = not applicable **Publication status** **Included:** Published papers; Unpublished reports/papers submitted in response to a call for evidence **Excluded:** Unpublished reports/papers NOT submitted in response to a call for evidence; Abstract-only studies; Letters, editorials; Foreign language
Search Strategy	Literature Search Strategy: Stable COPD. Sources: MED,EMB, CRD (EED & HTA). Limits: Study Types: Economic, Years: MED & EMB 2007-24/7/09, CRD (EED & HTA) 2003-24/7/09
Review Strategy	• Economic GRADE profile if evidence identified. • Studies that are excluded that were potentially includable (as per above criteria) to be noted in methodological introduction.

21 Appendix J NEW 2010 update literature searches

Search Strategies

Search strategies used for COPD guideline update are outlined below.

The cut off date was: 20/8/09

Searches were run in Medline, Embase (OVID), the Cochrane Library and Cinahl (EBSCO) as per the NICE Guidelines Manual 2007
http://www.nice.org.uk/media/FA1/59/GuidelinesManualChapters2007.pdf and 2009
http://www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf .

Searches were constructed using the PICO format.

Population AND Intervention AND Comparison (if there was one) AND Search Filters (if used)

Outcomes were not used in the search strategy.

COPD Population search strategies

Medline search terms

1. exp Pulmonary Disease, Chronic Obstructive/

2. copd.ti,ab.

3. coad.ti,ab.

4. Bronchitis/

5. Chronic bronchitis/

6. (chronic adj5 (obstruct$ or limit#$)).ti.

7. (obstruct$ adj3 (airflow$ or airway$ or respirat$ or lung or pulmonary) adj2 (disease$ or disorder$)).ti,ab.

8. Pulmonary emphysema/

9. emphysema.ti,ab.

10. "chronic bronchitis".ti,ab.

11. or/1-10

12. bronchial neoplasms/ or exp bronchiectasis/ or exp bronchiolitis/ or cystic fibrosis/ or lung diseases, interstitial/ or lung neoplasms/

13. exp Sleep Apnea Syndromes/

14. Bronchopulmonary Dysplasia/

15. (cancer or neoplas$).ti.

16. "acute bronchitis".ti.

17. sleep apnea.ti.

18. (bronchiolitis or bronchiectasis).ti.

19. interstitial.ti.

20. (interstitial adj2 (lung or pulmonary or airway$ or airflow$)).ti.

21. exp Asthma/

22. asthma.ti.

23. or/12-22

24. 11 not 23

25. letter/

26. editorial/

27. exp historical article/

28. Anecdotes as Topic/

29. comment/

30. case report/

31. animal/ not (animal/ and human/)

32. Animals, Laboratory/

33. exp animal experiment/

34. exp animal model/

35. exp Rodentia/

36. or/25-35

37. 24 not 36

38. limit 37 to english language

39. (exp child/ or exp infant/) not exp adult/

40. 38 not 39

Embase search terms

1. exp Chronic Obstructive Lung Disease/

2. copd.ti,ab.

3. coad.ti,ab.

4. Bronchitis/

5. Chronic bronchitis/

6. (chronic adj5 (obstruct$ or limit#$)).ti.

7. (obstruct$ adj3 (airflow$ or airway$ or respirat$ or lung or pulmonary) adj2 (disease$ or disorder$)).ti,ab.

8. Lung emphysema/

9. emphysema.ti,ab.

10. "chronic bronchitis".ti,ab.

11. or/1-10

12. bronchial neoplasms/ or exp bronchiectasis/ or exp bronchiolitis/ or cystic fibrosis/ or lung diseases, interstitial/ or lung neoplasms/

13. exp Sleep Apnea Syndrome/

14. Lung Dysplasia/

15. (cancer or neoplas$).ti.

16. "acute bronchitis".ti.

17. sleep apnea.ti.

18. (bronchiolitis or bronchiectasis).ti.

19. interstitial.ti.

20. (interstitial adj2 (lung or pulmonary or airway$ or airflow$)).ti.

21. exp Asthma/

22. asthma.ti.

23. or/12-22

24. 11 not 23

25. letter.pt.

26. letter/

27. editorial.pt.

28. note.pt.

29. case report/

30. case study/

31. animal/ not (animal/ and human/)

32. nonhuman/

33. exp Animal Studies/

34. Animals, Laboratory/

35. exp experimental animal/

36. exp animal experiment/

37. exp animal model/

38. exp Rodent/

39. or/25-38

40. 24 not 39

41. limit 40 to english language

42. (exp child/ or exp newborn/) not exp adult/

43. 41 not 42

Cinahl search terms

S1 Pulmonary Disease, Chronic Obstructive or TX COPD or TX COAD or SU chronic bronchitis or TX chronic bronchitis or (TX obstruct* near airflow or TX obstruct* near airway* or TX obstruct* near respirat*) or TX obstruct* near lung or TX obstruct* near pulmonary

Cochrane search terms

#1 MeSH descriptor Pulmonary Disease, Chronic Obstructive explode all trees

#2 (COPD):ti or (COAD):ti

#3 MeSH descriptor Bronchitis, Chronic explode all trees

#4 MeSH descriptor Pulmonary Emphysema explode all trees

#5 (chronic near (obstruct* or limit*)):ab

#6 (chronic next bronchitis):ti

#7 (emphysema):ti

#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)

#9 MeSH descriptor Sleep Apnea Syndromes explode all trees

#10 MeSH descriptor Bronchopulmonary Dysplasia explode all trees

#11 MeSH descriptor Bronchial Neoplasms explode all trees

#12 MeSH descriptor Bronchiectasis explode all trees

#13 MeSH descriptor Bronchiolitis explode all trees

#14 MeSH descriptor Cystic Fibrosis explode all trees

#15 MeSH descriptor Lung Diseases, Interstitial explode all trees

#16 MeSH descriptor Lung Neoplasms explode all trees

#17 (cancer or neoplas*):ti

#18 (acute next bronchitis):ti

#19 sleep apnea:ti

#20 (bronchiolitis):ti or (bronchiectasis):ti or (interstitial):ti or (asthma):ti

#21 MeSH descriptor Asthma explode all trees

#22 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)

#23 (#8 AND NOT #22)

Randomised control trials and systematic reviews filters search strategies

Medline systematic reviews search terms

1. "review"/ or review.pt. or review.ti.

2. (systematic or evidence$ or methodol$ or quantitativ$ or analys$ or assessment$).ti,sh,ab.

3. 1 and 2

4. meta-analysis.pt.

5. Meta-Analysis/

6. exp Meta-Analysis as Topic/

7. (meta-analy$ or metanaly$ or metaanaly$ or meta analy$).mp.

8. ((systematic$ or evidence$ or methodol$ or quantitativ$) adj5 (review$ or survey$ or overview$)).ti,ab,sh.

9. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.

10. or/3-9

Medline randomised control trials search terms

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. double-blind method/ or random allocation/ or single-blind method/

4. exp Clinical Trial/

5. exp Clinical Trials as Topic/

6. clinical trial.pt.

7. random$.ti,ab.

8. ((clin$ or control$) adj5 trial$).ti,ab.

9. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.

10. Placebos/ or placebo$.ti,ab.

11. (volunteer$ or "control group" or controls or prospectiv$).ti,ab.

12. Cross-Over Studies/

13. ((crossover or cross-over or cross over) adj2 (design$ or stud$ or procedure$ or trial$)).ti,ab.

14. or/1-13

Medline randomised control trials including observational studies search terms

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. double-blind method/ or random allocation/ or single-blind method/

4. exp Clinical Trial/

5. exp Clinical Trials as Topic/

6. clinical trial.pt.

7. random.ti,ab.

8. (clin$ adj25 trial$).ti,ab.

9. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.

10. Placebos/ or placebo$.ti,ab.

11. Research Design/ or Comparative Study/

12. exp Evaluation Studies/ or follow-up studies/ or prospective studies/

13. (volunteer$ or "control group" or controls or prospectiv$).ti,ab.

14. exp epidemiological studies/

15. cohort stud$.ti,ab.

16. case control stud$.ti,ab.

17. ((crossover or cross-over or cross over) adj2 (design$ or stud$ or procedure$ or trial$)).ti,ab.

18. or/1-17

Embase systematic reviews search terms

1. "review"/ or review.pt. or review.ti.

2. (systematic or evidence$ or methodol$ or quantitativ$ or analys$ or assessment$).ti,sh,ab.

3. 1 and 2

4. Meta-Analysis/

5. "systematic review"/

6. (meta-analy$ or metanaly$ or metaanaly$ or meta analy$).mp.

7. ((systematic$ or evidence$ or methodol$ or quantitativ$) adj5 (review$ or survey$ or overview$)).ti,ab,sh.

8. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.

9. or/3-8

Embase randomised control trials search terms

1. controlled study/ or randomized controlled trial/

2. Clinical Trial/

3. clinical study/ or major clinical study/ or clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/

4. Placebo/

5. "Double Blind Procedure"/

6. ((clinical$ or control$ or compar$) adj3 (trial$ or study or studies)).mp.

7. "Clinical Article"/

8. Randomization/

9. placebo.tw.

10. randomi$.tw.

11. ((singl* or double$ or triple$ or treble$) adj5 (blind$ or mask$)).tw.

12. crossover procedure/

13. ((crossover or cross-over or cross over) adj2 (design$ or stud$ or procedure$ or trial$)).ti,ab.

14. or/1-13

15. compar$.tw.

16. control$.tw.

17. 15 and 16

18. 14 or 17

Embase randomised control trials including observational studies search terms

1. controlled study/ or randomized controlled trial/

2. Clinical Trial/

3. clinical study/ or major clinical study/ or clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/

4. Placebo/

5. "Double Blind Procedure"/

6. Randomization/

7. ((clinical$ or control$ or compar$) adj3 (trial$ or study or studies)).mp.

8. compar$.tw.

9. control$.tw.

10. 8 and 9

11. placebo.tw.

12. randomi$.tw.

13. (blind$ or mask$).tw.

14. crossover procedure/

15. (cross adj2 over adj2 (study or design)).ti,ab.

16. exp Cohort Analysis/

17. exp Longitudinal Study/

18. exp Prospective Study/

19. exp follow up/

20. cohort studies.ti,ab.

21. or/1-7,10-20

22. exp Case Control Study/

23. case control stud$.ti,ab.

24. or/22-23

25. 21 not 24

Cinhal and Cochrane search filters

None used

Clinical Questions search strategies

DRUG 1: LABA vs. LAMA

What is the clinical and cost effectiveness of long-acting beta$_2$ agonists compared long-acting muscarinic antagonists in the management of people with stable COPD?

DRUG 3a) LABA + ICS vs. LABA alone

What is the clinical and cost effectiveness of long-acting beta$_2$ agonists plus inhaled corticosteroids compared to long-acting beta$_2$ agonists in the management of people with stable COPD?

DRUG 3b)LABA + ICS vs. LAMA alone

What is the clinical and cost effectiveness of long-acting beta$_2$ agonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists in the management of people with stable COPD?

DRUG 4a) LAMA + ICS vs. LABA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus inhaled corticosteroids compared to long acting beta$_2$ agonists in the management of people with stable COPD?

DRUG 4b) LAMA + ICS vs. LAMA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists in the management of people with stable COPD?

DRUG 5a) LAMA + LABA vs. LABA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists compared to long-acting beta$_2$ agonists in the management of people with stable COPD?

DRUG 5b) LAMA + LABA vs. LAMA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists compared to long-acting muscarinic antagonists in the management of people with stable COPD?

DRUG 5 c) LAMA + LABA vs. LABA +ICS

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists compared to long-acting beta$_2$ agonists plus inhaled corticosteroids in the management of people with stable COPD?

DRUG 6a) LAMA + LABA + ICS vs. LABA + ICS

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists plus inhaled corticosteroids compared to long-acting beta$_2$ agonists plus inhaled corticosteroids in the management of people with stable COPD

DRUG 6b) LAMA + LABA + ICS vs. LAMA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists alone in the management of people with stable COPD?

DRUG 6c) LAMA + LABA + ICS vs. LABA + LAMA

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta$_2$ agonists plus inhaled corticosteroids compared to long-acting beta$_2$ agonists plus long-acting muscarinic antagonists in the management of people with stable COPD ?

Questions Drug 1,3,4,5,6 were run as one search

Population	Intervention	Comparison	Filters used	Date parameters
Stable COPD	LABA or LAMA or ICS		SRs,RCTs, (Medline and Embase only)	2003-20/8/09

Literature search strategy

Medline search terms

1. Adrenergic beta-Agonists/

2. ((agonist$ or adrenegenic) adj3 beta).ti,ab.

3. betamimetics.ti,ab.

4. ((agonist$ or adrenegenic) adj3 beta).ti.

5. Ethanolamines/

6. (ethanolamines or aminoethanols).ti,ab.

7. ((Formoterol or Eformoterol) adj fumarate).ti,ab.

8. (Atimos Modulite or Foradil or Oxis).ti,ab.

9. Albuterol/

10. albuterol.ti,ab.

11. (Salmeterol or Serevent or Accuhaler or Evohaler or Diskhaler).ti,ab.

12. Bronchodilator Agents/

13. or/1-12

14. Cholinergic Antagonists/

15. Muscarinic Antagonists/

16. (anti?muscarinic$ adj2 (agent$ or antagonist$)).ti,ab.

17. (anti?cholinergic$ adj2 (agent$ or antagonist$)).ti,ab.

18. (Tiotropium or Spiriva).ti,ab.

19. anticholinergic bronchodilator.ti,ab.

20. or/14-19

21. Adrenal Cortex Hormones/

22. Glucocorticoids/

23. (Glucocorticoid$ or Steroid$ or Corticosteroid$).ti,ab.

24. Budesonide/

25. (Novolizer or Pulmicort or Turbohaler or Respules or Symbicort).ti,ab.

26. fluticasone.ti,ab.

27. (Flixotide or Accuhaler or Diskhaler or Nebules or Seretide).ti,ab.

28. Beclomethasone/

29. (Budesonide or Beclomethasone or AeroBec or Asmabec Clickhaler or Beclazone Easi?breathe or Becodisks or Clenil Modulite or Qvar or Cyclohaler or Fostair).ti,ab.

30. or/21-29

31. 13 or 20 or 30

Embase search terms

1. Beta Adrenergic Receptor Stimulating Agent/

2. ((agonist$ or adrenegenic) adj3 beta).ti,ab.

3. betamimetics.ti,ab.

4. ((agonist$ or adrenegenic) adj3 beta).ti.

5. Ethanolamine/

6. Ethanolamine Derivative/

7. (ethanolamines or aminoethanols).ti,ab.

8. Formoterol/

9. Formoterol Fumarate/

10. ((Formoterol or Eformoterol) adj fumarate).ti,ab.

11. (Atimos Modulite or Foradil or Oxis).ti,ab.

12. Albuterol/

13. albuterol.ti,ab.

14. Salmeterol/

15. (Salmeterol or Serevent or Accuhaler or Evohaler or Diskhaler).ti,ab.

16. Bronchodilator Agent/

17. or/1-16

18. Cholinergic Receptor Blocking Agent/

19. Muscarinic Receptor Blocking Agent/

21. (anti?muscarinic$ adj2 (agent$ or antagonist$)).ti,ab.

22. (anti?cholinergic$ adj2 (agent$ or antagonist$)).ti,ab.

23. Tiotropium Bromide/

24. (Tiotropium or Spiriva).ti,ab.

25. anticholinergic bronchodilator.ti,ab.

26. or/18-25

27. Corticosteroid/

28. Glucocorticoid/

29. (Glucocorticoid$ or Steroid$ or Corticosteroid$).ti,ab.

30. Budesonide/

31. (Novolizer or Pulmicort or Turbohaler or Respules or Symbicort).ti,ab.

32. fluticasone.ti,ab.

33. (Flixotide or Accuhaler or Diskhaler or Nebules or Seretide).ti,ab.

34. Beclomethasone/

35. (Budesonide or Beclomethasone or AeroBec or Asmabec Clickhaler or Beclazone Easi?breathe or Becodisks or Clenil Modulite or Qvar or Cyclohaler or Fostair).ti,ab.

36. Budesonide Plus Formoterol/

37. or/27-45

38. 17 or 26 or 37

Cinahl search terms

S6 S2 or S3 or S4 or S5

S5 TX Becodisks or TX Clenil Modulite or TX Qvar or TX Cyclohale or TX Fostair

S4 TX Respules or TX Symbicort or TX fluticasone or TX Flixotide or TX Accuhaler or TX Nebules or TX Seretide or TX Beclomethasone or TX AeroBec or TX Asmabec Clickhaler or TX Beclazone Easi breathe or TX Diskhaler

S3 SU Bronchodilator Agents or SU Cholinergic Antagonists or TX Muscarinic Antagonist or TX Tiotropium or TX Spiriva or SU Adrenal Cortex Hormones or SU Glucocorticoids or TX Budesonide or TX Novolizer or TX Pulmicort or TX Pulmicort

S2 SU Adrenergic beta-Agonists or SU ethanolamines or TX Formoterol fumarte or TX Eformoterol fumarate or TX Atimos Modulite or TX Foradil or TX Oxis or TX Albuterol or TX Salmeterol or TX Serevent or TX Accuhaler or TX Evohaler

Cochrane search terms

#1 MeSH descriptor Adrenergic beta-Agonists, this term only

#2 MeSH descriptor Ethanolamines explode all trees

#3 Formoterol fumarate:ti,ab.

#4 Eformoterol fumarate:ti,ab.

#5 Atimos Modulite or Foradil or Oxis:ti,ab.

#6 MeSH descriptor Albuterol explode all trees

#7 Salmeterol or Serevent or Accuhaler or Evohaler or Diskhaler:ti,ab.

#8 MeSH descriptor Bronchodilator Agents, this term only

#9	MeSH descriptor Adrenal Cortex Hormones, this term only
#10	MeSH descriptor Glucocorticoids, this term only
#11	MeSH descriptor Budesonide explode all trees
#12	Novolizer or Pulmicort or Turbohaler or Respules or Symbicort:ti,ab.
#13	fluticasone:ti,ab
#14	Flixotide or Accuhaler or Diskhaler or Nebules or Seretide:ti,ab.
#15	MeSH descriptor Beclomethasone explode all trees
#16	Budesonide or Beclomethasone or AeroBec or Asmabec Clickhaler or Beclazone Easi breathe or Becodisks or Clenil Modulite or Qvar or Cyclohaler or Fostair:ti,ab.
#17	MeSH descriptor Cholinergic Antagonists, this term only
#18	MeSH descriptor Muscarinic Antagonists, this term only
#19	tiotropium or apiriva:ti,ab
#20	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR 18 OR #19)

DRUG 8: LAMA vs. SAMA

What is the clinical and cost effectiveness of long-acting muscarinic antagonists compared to short-acting muscarinic antagonists in the management of people with stable COPD?

Population	Intervention	Comparison	Filters used	Date parameters
Stable COPD	**LAMA**	**SAMA**	**SRs RCTs (Medline and Embase only)**	**2003-20/8/09**

Literature search strategy

Medline search terms

1. Cholinergic Antagonists/

2. Muscarinic Antagonists/

3. (anti?muscarinic$ adj2 (agent$ or antagonist$)).ti,ab.

4. (anti?cholinergic$ adj2 (agent$ or antagonist$)).ti,ab.

5. anticholinergic bronchodilator$.ti,ab.

6. Bronchodilator agents/

7. (Bronchodilat$ adj2 (drug$ or agent$)).ti,ab.

8. (Broncholytic adj2 (drug$ or agent$)).ti,ab.

9. or/1-8

10. (Tiotropium or Spiriva or respimat).ti,ab.

11. Ipratropium Bromide/

12. (Ipratropium or Atrovent or Aerocaps).ti,ab.

13. 11 or 12

14. 10 and 13

15. 9 or 14

Embase search terms

1. Cholinergic Receptor Blocking Agent/

2. Muscarinic Receptor Blocking Agent/

3. (anti?muscarinic$ adj2 (agent$ or antagonist$)).ti,ab.

4. (anti?cholinergic$ adj2 (agent$ or antagonist$)).ti,ab.

5. anticholinergic bronchodilator$.ti,ab.

6. *Bronchodilator agent/

7. (Bronchodilat$ adj2 (drug$ or agent$)).ti,ab.

8. (Broncholytic adj2 (drug$ or agent$)).ti,ab.

9. or/1-8

10. (Tiotropium or Spiriva or respimat).ti,ab.

11. Tiotropium/

12. 10 or 11

13. Ipratropium Bromide/

14. (Ipratropium or Atrovent or Aerocaps).ti,ab.

15. 13 or 15

16. 12 and 15

17. 9 or 16

Cinahl search terms

S6 S2 or S5

S5 S3 and S4

S4 SU Ipratropium or TX Ipratropium or TX Atrovent or TX Aerocaps

S3 SU Tiotropium or TX Tiotropium or TX Spiriva or TX respima

S2 SU Cholinergic antagonists or SU Muscarinic Antagonists or SU Bronchodilator agents or TX Bronchodilat* near agent* or TX Bronchodilat* near drug* or TX Broncholytic near agent* or TX Broncholytic near drug* or TX anti muscarinic* near agent* or TX anti muscarinic* near antagonist* or TX anti cholinergic* near agent* or TX anti cholinergic* near antagonist*

Cochrane search terms

#1 MeSH descriptor Bronchodilator Agents, this term only

#2 MeSH descriptor Cholinergic Antagonists, this term only

#3 MeSH descriptor Muscarinic Antagonists, this term only

#4 (#3 OR #4 OR #5)

#5 tiotropium or spiriva or respimat:ti,ab

#6 MeSH descriptor Ipratropium explode all trees

#7 Ipratropium or Atrovent or Aerocaps:ti,ab

#8 (#6 OR #7)

#9 (#5 AND #8)

#10 (#4 OR #9)

DIAG 1: How does post bronchodilator FEV_1 (forced expiratory volume in one second) compare with pre bronchodilator FEV_1 in terms of: a) sensitivity / specificity of FEV_1 for diagnosis; b) classification of severity of disease?

Population	Intervention	Comparison	Filters used	Date parameters
	FEV1	**bronchodilators**	**None**	**None**

Literature search strategy

Medline search terms

1. *Respiratory Function Tests/

2. *Lung function Test/

3. exp Spirometry/

4. Bronchospirometry/

5. ((respiratory or lung) adj2 function test$).ti,ab.

6. spirometry.ti,ab.

7. exp Forced Expiratory Volume/

8. FEV1.ti,ab.

9. (Forced adj2 expirat$ adj3 (maximum or test or index)).ti,ab.

10. Lung Forced Expiratory Volume.ti,ab.

11. "FEV(1)".ti,ab.

12. or/1-11

13. Bronchodilator Agents/

14. Bronchodilator$.ti,ab.

15. (broncholytic adj2 (agent$ or drugs$)).ti,ab.

16. or/13-15

17. 12 and 16

Embase search terms

1. *Respiratory Function Tests/

2. *Lung function Test/

3. exp Spirometry/

4. Bronchospirometry/

5. ((respiratory or lung) adj2 function test$).ti,ab.

6. spirometry.ti,ab.

7. exp Forced Expiratory Volume/

8. FEV1.ti,ab.

9. (Forced adj2 expirat$ adj3 (maximum or test or index)).ti,ab.

10. Lung Forced Expiratory Volume.ti,ab.

11. "FEV(1)".ti,ab.

12. or/1-11

13. Bronchodilator Agents/

14. Bronchodilator$.ti,ab.

15. (broncholytic adj2 (agent$ or drugs$)).ti,ab.

16. or/13-15

60. 12 and 16

Cinahl search terms

S4	S2 and S3
S3	TX Bronchodilator* or TX broncholytic near agent* or TX broncholytic near drug*
S2	Sh Respiratory Function Tests or sh Lung function Test or sh Spirometry or sh Bronchospirometry or TX respiratory near test or TX lung near test or TX spirometry or sh Forced Expiratory Volume or TX FEV1 or TX Lung Forced Expiratory Volume

Cochrane search terms

#1 MeSH descriptor Respiratory Function Tests, this term only

#2 MeSH descriptor Spirometry explode all trees

#3 MeSH descriptor Forced Expiratory Volume explode all trees

#4 (#1 OR #2 OR #3)

#5 MeSH descriptor Bronchodilator Agents explode all trees

#6 (#4 AND #5)

DIAG2: In individuals where the diagnosis of COPD is considered and spirometry is conducted, what is the sensitivity and specificity of a fixed ratio FEV_1 / FVC compared with lower limit of normal FEV_1 / FVC ratio to diagnose COPD?

Population	Intervention	Comparison	Filters used	Date parameters
	Fixed ratio FEV1	**Lower limit FEV1**	**None**	**None**

Literature search strategy

Medline search terms

1. *Respiratory Function Tests/

2. *Lung function Test/

3. exp Spirometry/

4. Bronchospirometry/

5. ((respiratory or lung) adj2 function test$).ti,ab.

6. spirometry.ti,ab.

7. exp Forced Expiratory Volume/

8. FEV1.ti,ab.

9. FVC.ti,ab.

10. (Forced adj2 expirat$ adj3 (volume or maximum or test or index)).ti,ab.

11. Lung Forced Expiratory Volume.ti,ab.

12. "FEV(1)".ti,ab.

13. or/1-12

14. (fixed adj2 ratio$).ti,ab.

15. (lower adj2 limit$).ti,ab.

16. "GOLD".ti,ab.

17. ("ATS" or "ERS").ti,ab.

18. or/14-17

19. 13 and 18

20. letter/

21. editorial/

22. exp historical article/

23. Anecdotes as Topic/

24. comment/

25. case report/

26. animal/ not (animal/ and human/)

27. Animals, Laboratory/

28. exp animal experiment/

29. exp animal model/

30. exp Rodentia/

31. or/20-30

32. 19 not 31

33. limit 32 to english language

Embase search terms

1. *Respiratory Function Tests/

2. *Lung function Test/

3. exp Spirometry/

4. Bronchospirometry/

5. ((respiratory or lung) adj2 function test$).ti,ab.

6. spirometry.ti,ab.

7. exp Forced Expiratory Volume/

8. FEV1.ti,ab.

9. FVC.ti,ab.

10. (Forced adj2 expirat$ adj3 (volume or maximum or test or index)).ti,ab.

11. Lung Forced Expiratory Volume.ti,ab.

12. "FEV(1)".ti,ab.

13. or/1-12

14. (fixed adj2 ratio$).ti,ab.

15. (lower adj2 limit$).ti,ab.

16. "GOLD".ti,ab.

17. ("ATS" or "ERS").ti,ab.

18. or/14-17

19. 13 and 18

20. letter.pt.

21. letter/

22. editorial.pt.

23. note.pt.

24. case report/

25. case study/

26. animal/ not (animal/ and human/)

27. nonhuman/

28. exp Animal Studies/

29. Animals, Laboratory/

30. exp experimental animal/

31. exp animal experiment/

32. exp animal model/

33. exp Rodent/

34. or/20-33

35. 19 not 34

36. limit 35 to english language

Cinahl search strategy

S3 S1 and S2

S2 fixed n2 ratio* or lower n2 limit* or "GOLD" or "ATS" or "ERS"

S1 mh Respiratory Function Tests or mh Spirometry+ or respiratory n2 function test* or lung n2 function test* or spirometry or mh Forced Expiratory Volume or FEV or FVC or Forced n2 expirat*

Cochrane search terms

#1 MeSH descriptor Respiratory Function Tests, this term only

#2 MeSH descriptor Spirometry explode all trees

#3 (respiratory or lung) near2 function test*:ti,ab,kw

#4 (spirometry):ti,ab,kw

#5 MeSH descriptor Forced Expiratory Volume explode all trees

#6 (FEV1):ti,ab,kw or (FVC):ti,ab,kw

#7 (Forced near2 expirat* near3 (volume or maximum or test or index))

#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)

#9 MeSH descriptor Bronchodilator Agents explode all trees

#10 Bronchodilator*:ti,ab.

#11 (broncholytic near (agent* or drugs*)):ti,ab,kw

#12 (#9 OR #10 OR #11)

#13 (#8 and #12)

MUCO: What is the clinical and cost effectiveness of mucolytic agents vs. placebo in people with stable COPD?

Population	Intervention	Comparison	Filters used	Date parameters
Stable COPD	Mucolytics		SRs RCTs	2003-20/8/09

Literature search strategy

Medline search terms

1. Expectorants/

2. Mucolytic$.ti,ab.

3. (Mucolytic$ adj2 (agent$ or drug$)).ti,ab.

4. Mucinolytic$.ti,ab.

5. Mucociliary clearance.ti,ab.

6. Secretolytic Agent$.ti,ab.

7. Carbocisteine.ti,ab.

8. (Carbocisteine or Carbocistine or Carbocysteine or Carboxymethylcysteine).ti,ab.

9. (Mecysteine or Cysteine Methylester or Cysteine Methyl Ester or Visclair or Methyl Cysteine or Methylcysteine).ti,ab.

10. (Erdosteine or Dithiosteine or Erdotin).ti,ab.

11. (Acetylcysteine or Acetyl Cystein or Acetylcystein or Acetyl Cysteine or Acetylcysteine or Acetyl l Cysteine).ti,ab.

12. Acetylcysteine/

13. or/1-12

Embase search terms

1. Expectorant agent/

2. Mucolytic agent/

3. Mucolytic$.ti,ab.

4. (Mucolytic$ adj2 (agent$ or drug$)).ti,ab.

5. Mucinolytic$.ti,ab.

6. Mucociliary clearance.ti,ab.

7. Secretolytic Agent$.ti,ab.

8. Carbocisteine/

9. Carbocisteine.ti,ab.

10. (Carbocisteine or Carbocistine or Carbocysteine or Carboxymethylcysteine).ti,ab.

11. Mecysteine/

12. (Mecysteine or Cysteine Methylester or Cysteine Methyl Ester or Visclair or Methyl Cysteine or Methylcysteine).ti,ab.

13. Erdosteine/

14. (Erdosteine or Dithiosteine or Erdotin).ti,ab.

15. Acetylcysteine/

16. (Acetylcysteine or Acetyl Cystein or Acetylcystein or Acetyl Cysteine or Acetylcysteine or Acetyl l Cysteine).ti,ab.

17. Acetylcysteine/

18. or/1-17

Cinahl search terms

S5 S4 or S3 or S2

S4 TX Acetylcysteine or TX Acetyl Cystein or TX Acetylcystein or TX Acetyl Cysteine or TX Acetylcysteine or TX Acetyl l Cysteine

S3 TX Mecysteine or TX Cysteine Methylester or TX Cysteine Methyl Ester or TX Methyl Cysteine or TX Methylcysteine or TX Erdosteine or TX Dithiosteine or TX Erdotin

S2 SU Expectorants or TX Mucolytic* or TX Mucinolytic* or TX Mucociliary clearance or TX Secretolytic Agent* or TX Carbocisteine or TX Carbocistine or TX Carbocysteine or TX Carboxymethylcysteine

Cochrane search terms

#1 MeSH descriptor Expectorants explode all trees

#2 (Mucolytic*):ti,ab,kw

#3 (Mucolytic* near (agent* or drug*)):ti,ab,kw

#4 (Secretolytic Agent*):ti,ab,kw

#5 (Mucociliary clearance):ti,ab,kw

#6 (Carbocisteine or Carbocistine or Carbocysteine or Carboxymethylcysteine):ti,ab,kw

#7 (Mecysteine or Cysteine Methylester or Cysteine Methyl Ester or Visclair or Methyl Cysteine or Methylcysteine):ti,ab,kw

#8 (Erdosteine or Dithiosteine or Erdotin):ti,ab,kw

#9 (Acetylcysteine or Acetyl Cystein or Acetylcystein or Acetyl Cysteine or Acetylcysteine or Acetyl l Cysteine):ti,ab,kw

#10 MeSH descriptor Acetylcysteine explode all trees

#12 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 or #10)

REHAB: Does early pulmonary rehabilitation (within one month of hospital discharge) in people who had an acute exacerbation improve outcomes compared with usual care (or no rehabilitation), in people with COPD?

Population	Intervention	Comparison	Filters used	Date parameters
Stable COPD	Pulmonary rehabilitation		SRs RCTs	2003-20/8/09

Literature search strategy

Medline search terms

1. *Rehabilitation/

2. (Pulmonary adj2 rehabilitat$).ti,ab.

3. *Exercise Therapy/

4. exp Exercise Movement Techniques/

5. *Exercise Test/

6. exp Exercise Tolerance/

7. (exercise adj (testing or tolerance or capacity)).ti,ab.

8. *Physical Endurance/

9. ((stress or treadmill or step) adj testing).ti,ab.

10. (shuttle adj2 walk$).ti,ab.

11. *Community Health Services/

12. *"Delivery of Health Care"/

13. or/1-12

Embase search terms

1. exp Pulmonary Rehabilitation/

2. *Rehabilitation/

3. Pulmonary Rehabilitation Program/

4. (Pulmonary adj2 rehabilitat$).ti,ab.

5. *Exercise/

6. *Exercise Test/

7. exp Exercise Tolerance/

8. Muscle training/

9. (exercise adj (testing or tolerance or capacity)).ti,ab.

10. ((stress or treadmill or step) adj testing).ti,ab.

11. (shuttle adj2 walk$).ti,ab.

12. *Community care/

13. *Health Program/

14. or/1-13

Cinahl search terms

S2 mh Rehabilitation or pulmonary n2 rehabilitat* or mh Exercise Therapy or mh Exercise Movement Techniques or mh Exercise Test or mh Exercise Tolerance or mh Physical Endurance or mh Community Health Services or mh Delivery of Health Care or shuttle n2 walk

Cochrane search terms

#1 MeSH descriptor Rehabilitation, this term only

#2 Pulmonary near rehabilitat*:ti,ab

#3 MeSH descriptor Exercise Therapy, this term only

#4 MeSH descriptor Exercise Movement Techniques explode all trees

#5 MeSH descriptor Exercise Test, this term only

#6 MeSH descriptor Exercise Tolerance explode all trees

#7 MeSH descriptor Physical Endurance, this term only

#8 MeSH descriptor Community Health Services, this term only

#9 MeSH descriptor Delivery of Health Care, this term only

#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)

MULTI: Is routine assessment using multidimensional severity assessment indices (eg BODE) more predictive of outcomes compared to FEV_1 alone?

Population	Intervention	Comparison	Filters used	Date parameters
Stable COPD	**Assessment indices**	**FEV1**	**SRs RCTs, Observational studies**	**2003-20/8/09**

Literature search strategy

Medline search terms

1. Body-Mass Index/

2. ("Body mass index" or BMI).ti,ab.

3. 1 or 2

4. Dyspnea/

5. (dyspnea or dyspnoea).ti,ab.

6. 4 or 5

7. Airway obstruction/

8. ((airflow or airway) adj2 obstruction).ti,ab.

9. 7 or 8

10. Exercise tolerance/

11. exercise capacity.ti,ab.

2. "6 adj2 walk$".ti,ab.

13. 10 or 11 or 12

14. 3 and 6 and 9 and 13

15. BODE.ti,ab.

16. mBODE.ti,ab.

17. assessment indice$.ti,ab.

18. Disease severity grad$.ti,ab.

19. CAT.ti,ab.

20. assessment tool$.ti,ab.

21. CCQ.ti,ab.

22. (COPD adj3 Questionnaire$).ti,ab.

23. St Georges respiratory questionnaire.ti,ab.

24. SGRQ.ti,ab.

25. *Questionnaires/

26. Predictive value of tests/

27. Severity of illness Index/

28. or/14-27

29. *Respiratory Function Tests/

30. *Lung function Test/

31. exp Spirometry/

32. Bronchospirometry/

33. ((respiratory or lung) adj2 function test$).ti,ab.

34. spirometry.ti,ab.

35. exp Forced Expiratory Volume/

36. FEV1.ti,ab.

37. (Forced adj2 expirat$ adj3 (maximum or volume or test or index)).ti,ab.

38. "FEV(1)".ti,ab.

39. or/29-88

40. 28 and 39

Embase search terms

1. Body Mass/

2. ("Body mass index" or BMI).ti,ab.

3. 1 or 2

4. Dyspnea/

5. (dyspnea or dyspnoea).ti,ab.

6. 4 or 5

7. Airway obstruction/

8. ((airflow or airway) adj2 obstruction).ti,ab.

9. 7 or 8

10. Exercise tolerance/

11. exercise capacity.ti,ab.

12. 10 or 11

13. 3 and 6 and 9 and 12

14. BODE index/

15. BODE.ti,ab.

16. mBODE.ti,ab.

17. assessment indice$.ti,ab.

18. Disease severity grad$.ti,ab.

19. Clinical assessment tool/

20. CAT.ti,ab.

21. assessment tool$.ti,ab.

22. CCQ.ti,ab.

23. (COPD adj3 Questionnaire$).ti,ab.

24. St Georges respiratory questionnaire.ti,ab.

25. SGRQ.ti,ab.

26. *Questionnaire/

27. "prediction and forecasting"/

28. Hospitalization/

29. or/13-28

30. *Respiratory Function Tests/

31. *Lung function Test/

32. exp Spirometry/

33. Bronchospirometry/

34. ((respiratory or lung) adj2 function test$).ti,ab.

35. spirometry.ti,ab.

36. exp Forced Expiratory Volume/

37. FEV1.ti,ab.

38. (Forced adj2 expirat$ adj3 (volume or maximum or test or index)).ti,ab.

39. "FEV(1)".ti,ab.

40. or/30-39

45. 29 and 40

Cinahl search terms

S10	S2 and S9
S9	S3 or S8
S8	S4 and S5 and S6 and S7
S7	MW Exercise capacity or exercise capacity or exercise capacity
S6	MW Airflow obstruction or Airflow obstruction or Airway obstruction
S5	MW Dyspnea or Dyspnea or Dysponea
S4	MW body mass index or body mass index
S3	BODE index or BODE score or mBODE or assessment tool* or assessment indice* or CAT or CCQ or SGRQ or St Georges respiratory questionnaire or COPD n3 questionnaire* or disease severity grad*
S2	mh Respiratory Function Tests or mh Spirometry+ or respiratory n2 function test* or lung n2 function test* or spirometry or mh Forced Expiratory Volume or FEV or Forced n2 expirat*

Cochrane search terms

#1	MeSH descriptor Body Mass Index explode all trees
#2	MeSH descriptor Dyspnea explode all trees
#3	MeSH descriptor Airway Obstruction explode all trees
#4	MeSH descriptor Exercise Tolerance explode all trees
#5	(#1 AND #2 AND #3 AND #4)
#6	MeSH descriptor Questionnaires, this term only
#7	MeSH descriptor Predictive Value of Tests, this term only
#8	MeSH descriptor Severity of Illness Index, this term only
#9	(BODE):ti,ab,kw or (assessment indice*):ti,ab,kw or (assessement tool*):ti,ab,kw or (CAT or CCQ or SGRQ):ti,ab,kw or (mBODE):kw
#10	(disease severity grad*):ti,ab,kw or (St Georges respiratory questionnaire):ti,ab,kw
#11	(#5 OR #6 OR #7 OR #8 OR #9 OR #10)

#12 MeSH descriptor Respiratory Function Tests explode all trees

#13 MeSH descriptor Spirometry explode all trees

#14 MeSH descriptor Forced Expiratory Volume explode all trees

#15 (#12 OR #13 OR #14)

#16 (#11 AND #15)

Economics Search

Economic searches were conducted in Medline, Embase and CRD for EED and HTA

Population	Intervention	Comparison	Filters used	Date parameters
Stable COPD			**Economic (Medline and Embase only**	**Medline and Embase 2007-24/7/09** **CRD EED and HTA 2003-24/7/09**

Medline economic filter search terms

1. costs.tw.
2. cost effective.tw.
3. economic.tw.
4. 1 or 2 or 3
5. (metabolic adj cost).tw.
6. ((energy or oxygen) adj cost).tw.

7. 5 or 6

8. 4 not 7

Embase economic filter search terms

1. costs.tw.

2. cost effective.tw.

3. economic.tw.

4. 1 or 2 or 3

5. (metabolic adj cost).tw.

6. ((energy or oxygen) adj cost).tw.

7. 5 or 6

8 4 not 7

COPD CRD search terms

chronic obstructive pulmonary disease or COPD

22 Appendix K NEW 2010 deleted sections from original guideline

Deleted sections from original guideline

Definition of chronic obstructive pulmonary disease

Airflow obstruction is defined as a reduced post-bronchodilator FEV1 (forced expiratory volume in 1 second) and a reduced post- bronchodilator FEV1/FVC ratio (where FVC is forced vital capacity), such that FEV1 is less than 80% predicted and FEV1/FVC is less than 0.7.

2 Methodology

2.1 Background

This chapter describes the people and techniques used to derive the clinical recommendations that follow in later chapters.

2.2 The developers

2.2.1 The National Collaborating Centre for Chronic Conditions (NCC-CC)

The NCC-CC is housed by the Royal College of Physicians (RCP) but governed by a multi-professional partners board inclusive of patient groups and NHS management. The Collaborating Centre was set up in 2001, to undertake commissions from the National Institute for Clinical Excellence (NICE), to develop clinical guidelines for the National Health Service.

2.2.2 The technical team

The technical team consisted of an information scientist, a systematic reviewer, a lead clinical advisor, and a health economist, supported by project management and administrative personnel. The clinical advisor also acted as the appointed Chair of the Guidelines Development Group (GDG, see below). The technical team met monthly in addition to partaking in the meetings of the GDG.

2.2.3 The Guideline Development Group (GDG)

The GDG met twelve times at monthly intervals to review the evidence identified by the technical team, to comment on its completeness, and to develop and refine clinical recommendations based on that evidence and other considerations.

Editorial responsibility for the guideline rested solely with the GDG, which also developed the audit criteria.

2.2.4 The Consensus Reference Group (CRG)

An extension of the GDG, the larger CRG, met three times throughout the process, once early in the development to ensure the aims and clinical questions were appropriate, once after three meetings of the GDG to confirm an operational definition of COPD and agree recommendations on diagnosis. Finally, at the end of the process to review the validity of the recommendations drafted by the GDG. The group employed formal consensus techniques for these latter meetings.

Nominations for all group members were invited from key stakeholder organisations, which were selected to ensure an appropriate mix of clinical professions and patient groups. Each nominee was expected to serve as an individual expert in their own right and not as a mandated representative, although they were encouraged to keep their parent organisation informed of the process. Group membership details can be found on the inside of the front cover of this document.

All group members made a formal "Declaration of Interests" at the start of the guideline development and provided updates throughout the process. The NCC-CC and the Group Chair monitored these.

2.2.5 Involvement of people with COPD

As part of the development process, the NCC CC was keen to ensure that the guideline development process was informed by the views of people with COPD and their carers. This was achieved in two ways:

- by securing patient organisation representation on the guideline development group
- by having a patient with COPD on the guideline development group

The patient and a representative of the British Lung Foundation's Breathe Easy patient support groups was present at every meeting of the GDG and CRG. They were therefore involved at every stage of the guideline development process and were able to consult with their wider constituencies throughout the process.

2.3 Searching for the evidence

There are four stages to evidence identification and retrieval:

i. The technical team set out a series of specific clinical questions (appendix A) that covered the issues identified in the project scope. The CRG met to discuss, refine and approve these questions as suitable for identifying appropriate evidence within the published literature.

ii. A total of 120 questions were identified. The technical team and project executive agreed that a full literature search and critical appraisal process could not be undertaken for all of these areas due to the time limitations within the guideline

development process. The technical team identified questions where it was felt that a full literature search and critical appraisal was essential.

iii. The Information Scientist developed a search strategy for each evidence-based question to identify the available evidence. Identified titles and abstracts were reviewed for relevance to the agreed clinical questions and full papers obtained as appropriate.

iv. The full papers were critically appraised and the pertinent data entered into evidence tables that were then reviewed and analysed by the GDG as the basis upon which to formulate recommendations. The evidence tables are available on request.

Limited details of the searches with regard to databases and constraints applied can be found in appendix A. In general no formal contact was made with authors of identified studies, but occasionally it was necessary to contact authors for clarification of specific points. Additional contemporary articles were identified by the GDG on an *ad hoc* basis. Stakeholder evidence identified via a process established by NICE[592] was incorporated where appropriate. Both were assessed for inclusion by the same criteria as evidence provided by the electronic searches.

Searches were re-run at the end of the guideline development process, thus including evidence published up to the end of May 2003. Studies recommended by stakeholders or GDG members that were published after this date were not considered for inclusion. This time-point should be the starting point for searching for new evidence for future updates to this guideline.

2.4 Synthesising the evidence

Abstracts of articles identified from the searches were screened for relevance. Hard copies were ordered of papers that appeared to provide useful evidence relevant to each clinical question. Each paper was assessed for its methodological quality against pre-defined criteria using a validated quality appraisal tool[593]. Papers that met the inclusion criteria were then assigned a level according to the evidence hierarchy as detailed on page 20. Owing to practical limitations, the selection, critical appraisal, and data extraction were undertaken by one reviewer only. Evidence was considered carefully by the GDG group for accuracy and completeness.

Each clinical question dictated the appropriate study design that was prioritised in the search strategy. In addition certain topics within any one clinical question at times required different evidence types to be considered. Randomised control trials (RCTs) were the most appropriate study design for a number of clinical questions as they lend themselves particularly well to research into medicines. They were not, however, the most appropriate study design for all clinical questions. For example, the evaluation of diagnostic tests is more

suited to alternative research designs. Furthermore, RCTs are more difficult to perform in areas such as rehabilitation and lifestyle, where interventions may be tailored to the needs of the individual. As such, pharmaceutical interventions tend to be placed higher in the evidence hierarchy than other equally important interventions. This should not be interpreted as a preference for a particular type of intervention or as a reflection of the quality of the evidence, particularly for those clinical areas where non-RCT evidence is valid and most appropriate.

Where available, evidence from well-conducted systematic reviews was appraised and presented. Trials included within these reviews are listed in the evidence table but were not critically appraised. Studies identified in addition to those included in the systematic review were included in the appraisal process.

The study populations considered varied between clinical questions. At times evidence was not available from studies that were specific to a COPD population; therefore, it was necessary to consider studies in either a heterogeneous respiratory disease population or other chronic conditions.

Study quality, although formally assessed, was not used as a basis for informing the evidence level assigned to evidence statements. Descriptive limitations of studies are included in the evidence statements as appropriate.

2.4.1 Expert papers

On occasion the GDG identified a clinical question that could not be appropriately answered through undertaking a systematic review (where the evidence was scarce, or where the question could not usefully be answered with the largely dichotomous output of a review). These questions were addressed via an expert-drafted discussion paper, subject to consideration by the GDG. In these instances Medline and Cochrane databases were searched together with a review of frequently cited papers and key review articles but there was no formal assessment of the studies cited. These review papers were developed and used as a basis for discussion by the GDG as a whole.

Finally, national and international evidence based guidelines were referred to during the development process. These were not formally appraised owing to the inherent difficulties of such a process, in that the consistency of process and of evidence base can be difficult to ascertain across such documents.

2.5 Health economic evidence

While evidence on cost effectiveness was extracted from the main searches wherever it existed, this was rare. It was necessary to undertake a separate search for information on the potential costs and benefits of the interventions and management strategies considered in this guideline. These searches were carried out by the health economist. The GDG realised that few formal cost effectiveness analyses would be identified, therefore the search for economic evidence was very broad and designed to identify information about the resources used in providing a service or intervention and/or the benefits that can be attributed to it. No study design criteria were imposed a priori i.e. the searches were not limited to RCTs or formal economic evaluations. Further details of the searches for economic evidence are given in section 15.

Identified titles and abstracts from the economics searches were reviewed by the health economist and full papers obtained as appropriate. The full papers were critically appraised by the health economist and the relevant data was conveyed to the GDG alongside the clinical evidence for each question. Given that the economics searches were broad and that no standard measure of assessing the quality of economic evidence is available, careful consideration was given to each study design and the applicability of the results to the guideline context. An important issue in this respect is that much of the evidence on costs and benefits comes from the health care systems around the world and is therefore of limited applicability to a guideline for England and Wales.

As well as presenting existing evidence on the costs and benefits of a broad range of interventions to the GDG, the issue of opportunistic case finding linked to targeted smoking cessation programmes was identified as an important area for further economic analysis. This choice was made on the grounds that this approach may be associated with:

- potentially large health benefits;
- a potentially large effect on NHS resources;
- uncertainty surrounding the benefits and resources;
- a potentially large service impact.

Health economic analysis can provide a framework for collating information from a variety of sources in order to estimate, and systematically compare, costs and benefits. This is a complex and labour intensive process and it does require a level of clinical evidence that is not always readily available. The results of this analysis are discussed briefly in section 15.

2.6 Drafting recommendations

Evidence for each topic was extracted into tables and summarised in evidence statements. The GDG reviewed the evidence tables and statements at each meeting and reached a group opinion. Recommendations were explicitly linked to the evidence supporting them and

graded according to the level of the evidence upon which they were based, using the grading system detailed in Section 0.

It should be noted that the level of evidence determines the grade assigned to each recommendation and as such does not necessarily reflect the clinical importance attached to the recommendation.

2.7 Agreeing recommendations

Once the evidence review had been completed and an early draft of the guideline produced, a one-day meeting of the CRG was held to finalise the recommendations. This included a pre-meeting vote on the recommendations and a further vote at the CRG meeting, where the group were asked to consider the draft guideline in 2 stages:

1) Are the evidence-based statements acceptable and is the evidence cited sufficient to justify the grading attached?

2) Are the recommendations derived from the evidence justified and are they sufficiently practical so that those at the clinical front line can implement them prospectively? There were 3 types of recommendation to be considered:

    (a) a recommendation from the GDG based on strong evidence - usually non controversial unless there was important evidence that had been missed or misinterpreted

    (b) a recommendation that was based on good evidence but where it was necessary to extrapolate the findings to make it useful in the NHS - the extrapolation approved by consensus

    (c) recommendations for which no evidence exists but which address important aspects of COPD care or management - and for which a consensus on best practice could be reached.

This formal consensus method has been established within the NCC CC, drawing on the knowledge set out in the Health Technology Appraisal[594], and practical experience. It approximates to a modification of the RAND Nominal Group process (as cited in the Health Technology Appraisal[594] and will be fully described in future publications.

2.8 Writing the guideline

The first formal version of the guideline was drawn up by the technical team in accord with the decisions of the Guideline Development Groups. The draft guideline was circulated to stakeholders according to the formal NICE stakeholder consultation and validation phase[18] prior to publication.

6.4 Spirometry

GDG consensus statements

A diagnosis of airflow obstruction can be made if the $FEV_1/FVC < 0.7$ (i.e. 70%) and $FEV_1 < 80\%$ predicted.	IV

6.8 Assessment of severity

GDG consensus statements

Currently there are no validated severity assessment tools that incorporate the variables quoted above.	IV

R18	Mild airflow obstruction can be associated with significant disability in patients with COPD. A true assessment of severity should include assessment of the degree of airflow obstruction and disability, the frequency of exacerbations and the following known prognostic factors: • FEV_1 • T_LCO • breathlessness (MRC scale) • health status • exercise capacity • body mass index (BMI) • partial pressure of oxygen in arterial blood (PaO_2) • cor pulmonale.	**Grade D**

R19 The severity of airflow obstruction should be assessed according to the reduction in FEV1 as shown in table 7

Table 7 Assessment of severity of airflow obstruction according to FEV_1 as a percentage of the predicted value

Severity	FEV_1
Mild airflow obstruction	50-79% predicted
Moderate airflow obstruction	30-49% predicted
Severe airflow obstruction	<30% predicted

7.2.2 Smoking cessation therapy

Recommendations

R26	Unless contraindicated, bupropion or nicotine replacement therapy combined with an appropriate support programme should be used to optimise smoking quit rates for people with COPD.	**Grade B**
R27	NICE Technology Appraisal Guidance No 39 recommends: '*If a smoker's attempt to quit is unsuccessful with treatment using either NRT or bupropion, the NHS should normally fund no further attempts within 6 months. However, if external factors interfere with a person's initial attempt to stop smoking, it may be reasonable to try again sooner'.*	**NICE**

7.3 Inhaled bronchodilator therapy

Although COPD is characterised by substantially irreversible airflow obstruction, bronchodilators have been the mainstay of pharmacotherapy [71,123]. $Beta_2$-agonists, anticholinergics and theophylline have all been used to treat COPD.

The structural changes in the airways prevent bronchodilators returning airway calibre to normal. Clinically relevant improvements in FEV_1 may be too small to identify against the background day to day variation in an individual patient. Inhaled agents are preferred to oral because of the reduction in systemic side effects. $Beta_2$ agonists act directly on bronchial smooth muscle to cause bronchodilation whereas anticholinergics act by inhibiting resting broncho-motor tone. As well as improving breathlessness through their direct bronchodilator effects, both classes of drugs also appear to work by reducing hyperinflation (both static and dynamic). This probably explains why clinical benefits may be seen without clear changes in the FEV_1.

R30	Patients who remain symptomatic should have their inhaled treatment intensified to include long-acting bronchodilators or combined therapy with a short-acting $beta_2$ agonist and a short-acting anticholinergic.	**Grade A**
R31	Long-acting bronchodilators should be used in patients who remain symptomatic despite treatment with short-acting bronchodilators because these drugs appear to have additional benefits over combinations of short-acting drugs.	**Grade A**
R32	Long-acting bronchodilators should also be used in patients who have 2 or more exacerbations per year.	**Grade D**

7.3.6.1 Beta$_2$-agonists and anticholinergics

Two randomised, double-blind, placebo-controlled parallel trials; Van Noord 2000[160] (n = 144), Chapman 2002 [595] (n = 409) and 3 randomised, double-blind, non placebo-controlled parallel trials; Auerbach 1997[596] (n = 652), Bone 1994[597] (n = 534), Gross 1998[598] (n = 863) and 1 randomised, double-blind, crossover; D'Urzo 2001[599] (n = 172). One study report[600] provided additional information about 2 critically appraised trials[596,597].

Evidence statements on combinations of beta$_2$-agonists and anticholinergics

During 12 weeks of treatment, **FEV$_1$** responses to ipratropium and salmeterol combination were significantly increased compared with salmeterol alone and placebo (n = 144) (p<0.01) [160].	Ib
Among salmeterol/anticholinergic treated patients, morning pre-treatment **FEV$_1$** levels improved significantly above baseline levels. This effect persisted during the six month treatment period. These improvements in lung function were significantly greater in the salmeterol /anticholinergic group than in the placebo/anticholinergic group for all but the last clinic visit. Analysis of adjusted treatment differences showed the mean improvement over the 24-week period was significantly higher in the salmeterol/anticholinergic group than in the placebo/anticholinergic group (p<0.01) [595].	Ib
Mean peak **FEV$_1$** responses to ipratropium + albuterol were significantly greater than those to each of the components on all test days (day 1, 29, 57 and 85)[596].	Ib
Mean peak **FEV$_1$** responses to ipratropium + albuterol were significantly greater than those to each of the components on all test days (day 1, 29, 57 and 85). Clinically significant mean **FEV$_1$ response** (>15% above baseline) was observed in all three treatment groups on all test days[597].	Ib
Mean change from pre-dose to peak **FEV$_1$** was significantly greater with ipratropium/albuterol combination compared with either albuterol alone or ipratropium alone in 863 participants over 12 weeks (p<0.001)[598].	Ib

Compared with baseline values, premedication **FEV_1** increased following 3 weeks treatment with formoterol/ipratropium and decreased following treatment with salbutamol/ipratropium (n = 172 participants treated over 6 weeks). Estimated treatment difference was 0.116 L (p<0.0001). Peak post medication FEV_1 was significantly higher with formoterol/ipratropium than with salbutamol/ipratropium (p<0.0001). AUC of FEV_1 for formoterol/ipratropium was much higher than for salbutamol/ipratropium (p<0.0001)[599].	Ib
During 12 weeks of treatment, **FVC** responses to ipratropium and salmeterol combination were significantly increased compared with salmeterol alone and placebo (p<0.01) [160].	Ib
Overall **FVC** response to ipratropium/albuterol combination was significantly greater than the response to either ipratropium or albuterol alone (p<0.01 to p=0.04) [597].	
During 12 weeks of treatment a significant decrease was seen in **daytime symptoms score** between both salmeterol alone (p<0.005) and salmeterol + ipratropium (p<0.001) compared with placebo. No significant difference was seen between salmeterol and combination groups. There were also no differences in **night symptoms** between ipratropium and salmeterol combination compared with salmeterol alone and placebo[160].	Ib
COPD **symptom scores** did not change and did not differ between ipratropium + albuterol combination and individual component groups [596 597].	Ib
Mean **total symptom score** was 0.6 points lower during 6 weeks treatment with formoterol/ipratropium than with salbutamol/ipratropium (p = 0.0042)[599].	Ib

Baseline PEFR and **PEFR** did not differ significantly between ipratropium/albuterol combination compared with either ipratropium or albuterol alone and did not change during 12 weeks of treatment [597].	Ib
Over 12 weeks improvements in **morning PEFR** were significantly better in both ipratropium/salmeterol combination group and salmeterol alone group than in the placebo group ($p<0.001$). No difference was observed between the salmeterol and combination treatment groups. Improvements in **evening PEFR** were significantly better in both ipratropium/salmeterol combination group compared with salmeterol alone ($p<0.01$). No difference was observed between the salmeterol and placebo treatment groups[160].	Ib
Morning PEFR did not differ significantly between ipratropium + albuterol combination and individual component groups and did not change during the study. **Evening PEFR** values in the ipratropium/albuterol group were significantly greater than those for the albuterol group [596].	Ib
Over 6 weeks, the mean morning premedication **PEFR** increased during both treatment periods; however the change in favour of formoterol/ipratropium was statistically significant compared with ipratropium/salbutamol ($p<0.001$) [599].	Ib
During 12 weeks of treatment, compared with placebo treatment with both salmeterol and ipratropium/salmeterol combination therapy were associated with a higher percentage of days and nights without use of **additional salbutamol** ($p<0.01$). No significant difference was observed between the two active treatments[160].	Ib

No significant difference between ipratropium and albuterol group and individual component groups in **use of concomitant respiratory medication** [596].	Ib
After 12 weeks treatment there were no significant differences between ipratropium/albuterol combination and either component alone in **distance walked** in 6 minutes [598].	Ib
Scores for the **SGRQ** were reduced from baseline for all components of the questionnaire (symptoms, activity, impact on daily life) among patients treated with salmeterol for 6 months, with a significant improvement in the symptom component ($p<0.005$), the impact on daily life component ($p = 0.05$) and the total score ($p<0.05$). There was no significant difference between the salmeterol/anticholinergic group and placebo anticholinergic group [595].	Ib
During 12 weeks of treatment, 35 patients experienced a COPD **exacerbation**, 18 (36%) in the placebo group, 11 (23%) in the salmeterol group and six (13%) in the salmeterol and ipratropium group ($p<0.01$ combination treatment v placebo) [160].	Ib
During the 6 month treatment period, 26% of salmeterol-treated patients and 33% of placebo-treated patients experienced at least one **exacerbation** of COPD ($p=0.117$). Fewer salmeterol-treated patients experienced more than 2 exacerbations (non significant) [595].	Ib
The number of patients with no COPD **exacerbations** during the 6 week treatment period was slightly higher with formoterol/ipratropium than with salbutamol/ipratropium: 55 patients (43.6%) and 49 patients (30.8%)[599].	Ib

During 12 weeks of treatment, no significant difference in **adverse events** was seen in salmeterol alone, placebo and ipratropium/salmeterol combination groups[160].	Ib
Incidence of **adverse events** recorded during a 6 month study were similar for both treatment groups, with at least one adverse event being reported by 72% of patients in the salmeterol group and 71% patients in the placebo group[595].	Ib
Most common **adverse events** were related to the respiratory system in both treatment groups, with exacerbations of COPD being the most common event reported by 44 patients (22%) receiving placebo and 41 patients (20%) receiving salmeterol. Events considered to be related to drug treatment were recorded in 11% of patients in the salmeterol group and 10% of the patients in the placebo group[595].	Ib
No significant differences were found in **adverse events** over 12 weeks in 863 patients treated with ipratropium/albuterol combination and either component alone [598].	Ib

Beta$_2$-agonists and inhaled steroids

Three randomised, double-blind, placebo-controlled parallel trials; Calverley 2003 [167] (n = 1465), Szanfranski 2003[166] (n = 812), Mahler 2002[165] (n = 691).

Factors for consideration within this topic include:

- considerable pre-screening of patients
- small patient populations in some studies
- only some studies are placebo controlled
- only some studies select both responders and non-responders to B-agonists
- concomitant medication is permitted in some studies, whereas in others it is restricted
- age limits differ e.g. >18yr and > 40yrs

- drug washout periods vary
- severity of COPD varies between studies.

Evidence statements on combinations of beta$_2$-agonists and inhaled steroids

In the study by Calverley et al.[167] the three active treatments increased pre-treatment **FEV$_1$** significantly compared with placebo (salmeterol/fluticasone p<0.0001; salmeterol p<0.0001; fluticasone p = 0.0063). This improvement was evident by week 2 and was sustained throughout treatment. The increase in FEV$_1$ associated with combination therapy was significantly greater than with either of its components separately. Ib

In the study by Szanfranski et al.[166] all active treatments (formoterol/budesonide combination, budesonide alone and formoterol alone) increased **FEV$_1$** compared with placebo. Budesonide/formoterol also increased FEV$_1$ compared with budesonide. There was no significant difference for budesonide/formoterol versus formoterol for FEV$_1$. Improvements in FEV$_1$ were sustained with budesonide/formoterol throughout the study period compared with budesonide and placebo. All active treatments improved **FVC** compared with placebo: budesonide/formoterol by 9% (p<0.001), budesonide by 4% (p<0.05) and formoterol by 11% (p<0.001). Ib

In the study by Mahler et al.[165] a significantly greater increase in **pre-dose FEV$_1$** at the endpoint was observed after treatment with salmeterol/fluticasone combination therapy (156ml) compared with salmeterol (107 ml) p = 0.012 and placebo (-4ml) (p<0.001). A significantly greater increase in pre-dose FEV$_1$ was also observed for treatment with fluticasone v placebo at the endpoint (109 v –4ml respectively p<0.001). There was no significant difference between the combination and fluticasone. Ib

A significantly greater increase in 2 hour **post-dose FEV$_1$** at the endpoint was observed after treatment with salmeterol/fluticasone combination therapy (261 ml) compared with fluticasone (138ml, p<0.001) and placebo (28ml, p<0.001)[165]. Significantly greater increases in 2 hour post-dose FEV$_1$ were observed at Day 1 and throughout the study during treatment with salmeterol/fluticasone combination therapy compared with fluticasone. Significantly greater increases in 2-hour post-dose FEV$_1$ were observed for the salmeterol group versus placebo (233 v 28ml, respectively p<0.024) at the Ib

endpoint and at all assessment points throughout the study [165].

Budesonide/formoterol significantly reduced all **symptom scores** within the first week of treatment compared with budesonide, formoterol and placebo. This significant effect was sustained for 12 months for budesonide/formoterol compared with placebo and budesonide regarding the total score and awakenings. For budesonide/formoterol compared with formoterol at 12 months the total symptom score was non significant.[166]	Ib
Budesonide/formoterol increased **days free from shortness of breath** by 12% compared with placebo (p<0.001). Budesonide/formoterol compared to budesonide also demonstrated a statistically significant effect for shortness of breath sustained for 12 months, this was non significant for budesonide/formoterol versus formoterol[166].	Ib
Budesonide/formoterol increased **awakening-free nights** by 14% compared with placebo (p<0.001). Awakening scores at 12 months were statistically significant for budesonide/formoterol versus placebo, budesonide alone and formoterol alone [166].	Ib
Budesonide/formoterol improved and maintained morning and evening **PEFR** compared with placebo, budesonide and formoterol alone (p<0.001)[166].	Ib
Increases in morning **PEFR** on Day 2, approximately 24 hours after the initiation of treatment, were greater for salmeterol/fluticasone combination treatment compared with fluticasone, salmeterol and placebo (p<0.005)[165].	Ib
Greater increases in morning PEF were observed throughout the 24 week treatment period with salmeterol/fluticasone combination treatment compared with fluticasone, salmeterol and placebo[165].	Ib
The overall change from baseline in morning **PEF** with combination treatment (31.9L/min) was greater than the sum of the mean changes from baseline observed with the individual components, 12.9 and 16.8L/min for fluticasone	Ib

(p<0.001) and salmeterol (p<0.001), respectively. Mean overall changes from baseline were also significantly greater for both fluticasone and salmeterol versus placebo (p<0.001)[165].

Budesonide/formoterol reduced use of **rescue medication** by 1.3 and 0.7 inhalations per 24h compared with placebo and budesonide respectively (both p<0.001)[166]. Ib

Significant reductions in **overall albuterol use** (number of inhalations per day and percentage of days without albuterol use) were observed during treatment with salmeterol/fluticasone combination compared with fluticasone and placebo. A significant reduction in overall albuterol use was also observed after treatment with salmeterol compared with placebo and with fluticasone compared with placebo[165]. There was no difference between the combination and salmeterol groups. Ib

A significant increase in the overall percentage of **nights with no awakenings** requiring albuterol was observed for treatment with salmeterol/fluticasone combination, fluticasone and salmeterol compared with placebo (p<0.001)[165]. Ib

At the endpoint, **breathlessness** (as assessed by the mean TDI score) in patients treated with the salmeterol/fluticasone combination (2.1) was greater than that after treatment with fluticasone (1.3, p = 0.033) and was significantly greater than that after treatment with salmeterol (0.9, p<0.001) and placebo (0.4, p<0.001). At the endpoint, TDI scores were significantly greater for fluticasone (1.3, p = 0.002), but not salmeterol, compared with placebo[165]. Ib

Calverley et al[167] showed a clinically significant improvement in **health status questionnaire** score by week 52. The raw mean changes in health status total score were –4.5 (12.9) at week 52. The change in SGRQ score in the combination group (salmeterol and fluticasone) over 52 weeks at the end of the study was significantly greater than that in both the placebo and fluticasone groups. Ib

In the study by Szanfranski et al. [166] compared with placebo, budesonide/formoterol showed clinically and statistically significant improvements in **SGRQ** symptoms score (mean difference 5.9, p<0.001) and impact score (mean difference 4.7, p=0.006) domains. Ib

In the study by Mahler et al. [165] after 6 months, treatment with salmeterol/fluticasone combination therapy resulted in a clinically important increase from baseline in mean overall **CRDQ** score (10) that was significantly greater compared with the placebo (5.0, p = 0.007) and fluticasone (4.8, p = 0.017) groups, but not with salmeterol (8.0). Ib

Clinically important increases in dyspnoea score (4.2), fatigue score (2.0) and physical summary score (6.1) were observed after treatment with salmeterol/fluticasone combination. These increases were also statistically significant versus the fluticasone and placebo treatment groups (p<0.016)[165]. Ib

In the study by Calverley et al[167] compared with placebo, all active treatments (salmeterol/fluticasone combination, salmeterol alone and fluticasone alone) significantly reduced the number of **exacerbations** per patient per year and the number of exacerbations that needed treatment with oral corticosteroids. Ib

The rate of exacerbations fell by 25% in the combination group (p<0.0001) and by 20% (p = 0.0027) and 19% (p = 0.0033) in the salmeterol and fluticasone groups respectively compared with placebo[167]. Ib

The treatment effect in relation to the number of exacerbations was more pronounced in patients with a baseline FEV_1 of <50% predicted who showed a 30% reduction with the combination compared with placebo, as against a 10% reduction in patients who had a baseline FEV_1 that was greater than 50% of that predicted[167]. Ib

Acute episodes of symptom exacerbation that required oral corticosteroids were reduced by 39% in the combination group (p<0.0001), 29% in the salmeterol group (p = 0.0003) and 34% in the fluticasone group (p = 0.0001) compared with placebo[167]. Ib

Szafranski et al[166] showed that compared with placebo, budesonide/formoterol combination significantly reduced the number of **severe exacerbations**. Ib

The mean number of severe exacerbations fell by 24% in the combination group (p=0.035) and by 15% (p=0.224) and 2% (p=0.895) in the budesonide and formoterol groups respectively versus placebo.

Budesonide/formoterol combination group also significantly reduced mean severe exacerbation rate versus formoterol (23% reduction; p=0.043).

Compared with placebo, the combination budesonide/formoterol and the budesonide group significantly reduced the number of oral steroid courses used in association with exacerbations (31%, p=0.027 and 29%, p=0.045 respectively).

In the study by Szanfranski et al. [166] the **adverse event** profile was similar in each group (formoterol/budesonide combination, budesonide alone and formoterol alone). The frequency of discontinuations due to other adverse events was similar in all groups. Ib

In the study by Calverley et al[167] there were no differences between groups in the number of patients reporting an **adverse event** apart from an increased frequency of oropharyngeal candidiasis (placebo 2%, salmeterol 2%, fluticasone 7%, and combination 8%). Ib

In the study by Mahler et al.[165] a greater percentage of patients in the fluticasone and the combination groups experienced candidiasis (mouth/throat) based on visual inspection compared with the placebo and salmeterol groups. Ib

R43	If patients remain symptomatic on monotherapy, their treatment should be intensified by combining therapies from different drug classes. Effective combinations include: • beta$_2$-agonist and anticholinergic* • long-acting beta$_2$ agonist and inhaled corticosteroid.*	**Grade A**
R44	The clinical effectiveness of combined treatments can be assessed by improvements in symptoms, activities of daily living, exercise capacity and lung function. Combination treatment should be discontinued if there is no benefit after 4 weeks.	**Grade D**

7.3.7 Delivery systems used to treat patients with stable COPD

R49	To ensure optimum efficacy for each patient with COPD, the dose of medication should be titrated according to individual clinical response.	**Grade D**

7.5.4 Oral mucolytics

Many patients with COPD cough up sputum [3]. Mucolytics are agents which are believed to increase the expectoration of sputum by reducing its viscosity. Some of these drugs, particularly N-acetylcysteine, may also have antioxidant effects which may contribute to their clinical effects.

In some European countries mucolytics are widely prescribed in the belief that they reduce the frequency of exacerbations and / or reduce symptoms in patients with chronic bronchitis. In contrast, in the U.K. mucolytics have not been recommended in previous guidelines and until recently were black listed and could not be prescribed on the NHS.

Three systematic reviews were found[265,601,602]. The studies included in these systematic reviews tended to be the same trials although the systematic review by Poole[265] did include additional papers. In addition to the trials included in the systematic reviews there were two other papers, an RCT [603] that compared mucolytic agents to placebo and a retrospective cohort study [604] that looked at the risk of re-hospitalisation among COPD patients using N-acetylcysteine compared to non-users.

Stey et al.[602] looked at the effect of oral N-acetylcysteine compared to placebo in chronic bronchitis (11 RCTs, N=2011) with treatment durations of 12 to 24 weeks.

Grandjean et al. [601] determined the efficacy of oral N-acetylcysteine compared to placebo in chronic bronchopulmonary disease (8 RCTs, N=1408) with a treatment duration ranging from three to six months.

Poole et al. [265] undertook a meta-analysis of mucolytics compared to placebo in the treatment of chronic bronchitis (22 RCTs, N=6,415) with a treatment duration of 2 to 24 months. The mucolytics included within this systematic review and meta-analysis include N-acetylcysteine (NAC), ambroxol, sobrerol, carbocysteine lysine, carbocysteine sobrerol, letosteine, cithiolone, iodinated glycerol, N-isobutyrylcysteine (NIC) and myrtol.

Most of the study participants in the three systematic reviews [601,602,605] had mild COPD, only McGavin 1995 and Petty 1990 included patients with an FEV_1 of <50% predicted. Most of the studies were carried out at least 10 years ago. There are differences between the studies in the definition of exacerbation that has been used but almost all used generally accepted definitions. This, together with the short duration of the studies makes it difficult to draw firm conclusions about effects on exacerbation rates.

The efficacy of mucolytic treatment needs to be considered in relation to the severity of COPD and duration of treatment.

Confounders not consistently accounted for in the studies include concomitant use of antibiotic therapy, drug concordance and drug type and dosage, except for the systematic review by Poole et al[265] which excluded combination mucolytics and antibiotics.

Other considerations include the degree of benefit that may be conferred for those who are repeatedly admitted to hospital with exacerbations of their COPD or those patients who have frequent or prolonged exacerbations. Poole et al. [265] highlighted that none of the studies reported the effect of treatment with mucolytics on hospitalisation due to COPD.

Oral mucolytic therapy was removed from schedules 10 and 11 (the so called “black” and “selected” lists) from 1st February 2003 and can now be prescribed. Carbocisteine is available in the UK.

Evidence statements

All three systematic reviews [265,601,602] demonstrate that compared to placebo, mucolytic therapy was associated with a significant reduction in the **number of exacerbations.**	Ia
The systematic review by Poole et al[265] also demonstrated that the odds ratio for having **no exacerbations** in the study period on a mucolytic compared to placebo was 2.22 (p<0.0001).	
In addition there was a significant reduction in the **number of days of COPD illness**, a benefit of 0.56 day per month 95% CI –0.77 to –0.35, (p<0.0001) and a reduction in the **number of days on prescribed antibiotics** of 0.53 days per month (p<0.0001); however both of these analyses relied on a smaller number of primary studies where these outcomes were reported.	
N-acetylcysteine (NAC) was significantly associated with a lower risk of **re hospitalisation**, RR=0.67 (95%CI; 0.53 to 0.85)[604].	IIb
There were no significant differences for **lung function** parameters (FEV_1 or % predicted or PEFR) between the treatment and placebo groups (meta-analysis of 10 RCTs[265].	Ia
Improvement of their **symptoms** was reported by 61% of patients receiving NAC compared to 35% receiving placebo (relative benefit 1.78 (95% CI; 1.54 to 2.05), NNT 3.7)[602].	Ia
Cattaneo [603] in an Italian RCT (N=60) found that there was a statistically significant improvement in dyspnoea (p<0.02), cough (p<0.02), and difficulty in expectorating (p<0.02) in patients treated with neltenexine (smokers and non smokers) compared with placebo. There was also a statistically significant improvement in sputum characteristics (p<0.02) and volume (p<0.01) in neltenexine treated patients when compared with placebo treated patients.	Ib

Petty et al.[606] in an eight-week study compared iodinated glycerol to placebo in patients (N=361) with severe COPD. Primary outcomes were based upon **symptom efficacy** parameters (cough frequency, severity, chest discomfort, ease in expectorating) and these were statistically significant (p<0.05) in favour of iodinated glycerol. There were no statistically significant differences between treatment groups for frequency of aerosol **bronchodilator use** or frequency of **concomitant medications**. Ib

There were no significant serious **adverse events** reported[265,601,602]. Ia

7.6.1 Inhaled corticosteroids

Recommendations

R39 Inhaled corticosteroids should be prescribed for patients v
$FEV_1 \leq 50\%$ predicted, who are having 2 or more exacerba
requiring treatment with antibiotics or oral corticosteroids
month period. The aim of treatment is to reduce exacerba
rates and slow the decline in health status and not to impr
function per se.

R40 Clinicians should be aware of the potential risk of develop
osteoporosis and other side effects in patients treated wit
dose inhaled corticosteroids (especially in the presence of
risk factors) and should discuss the risk with patients.

LAMA vs. LABA

Evidence statements

Over 6 months, there was no statistically significant difference in **exacerbation rates** [164].

7.6.2 Ambulatory oxygen therapy

Table 7.3 Duration of oxygen supply from a size DD portable oxygen cylinder at different flow rates

Used at a flow rate of	A portable cylinder without an oxygen conserving device will last
1 l/min	7 hours 40 minutes
2 l/min	3 hours 50 minutes
4 l/min	1 hour 55 minutes
6 l/min	57 minutes

(N.B. The usual regulator only delivers at 2 l/min and 4 l/min)

Table 7.4 Appropriate equipment for ambulatory oxygen therapy

Usage	Equipment
For a duration of use of less than 90 minutes	Small cylinder
For a duration of use of less than 4 hours but more than 90 min	Small cylinder with oxygen conserving device
For duration of use of more than 4 hours	Liquid oxygen
For flow rates greater than 2 l/min and duration of use of	Liquid oxygen

more than 30 min	

7.7 Combination therapy

There are similar theoretical advantages in combining a bronchodilator with its effects on symptoms, with an inhaled steroid with its effects on exacerbations to produce additive or synergistic clinical benefits.

The following four types of combination therapy were considered and evidence is presented for each combination separately:

- beta$_2$-agonist and anticholinergic
- beta$_2$-agonist and theophylline
- anticholinergic and theophylline
- long-acting beta$_2$ agonist and inhaled steroid.
- A full literature search was also undertaken for anticholinergic and inhaled steroid but no evidence was found for this combination.
- For each of these combinations, no systematic reviews were found, however a good body of RCT data was identified:

7.12 Pulmonary rehabilitation

R83	Pulmonary rehabilitation should be made available to all appropriate patients with COPD.	**Grade A**

7.13 Vaccination and anti-viral therapy

National policy for 2003/2004 is that influenza immunisation should be offered to all patients with chronic obstructive pulmonary disease and pneumococcal vaccine should be offered to those with chronic lung disease[240].

Detailed information regarding both the influenza and pneumococcal vaccine is available in the HMSO publication on Immunisation against Infectious Disease (1996) otherwise known as the "Green Book"[607]. This publication includes a new (draft) pneumococcal replacement chapter (November 2003)[608].

R89	NICE Technology Appraisal Guidance No. 58 [376] makes the following recommendation: *Within licensed indications, zanamivir and oseltamivir are recommended for the treatment of at-risk adults who present with influenza like illness and who can start therapy within 48 hours of the onset of symptoms.* The technology appraisal also notes that zanamivir should be used with caution in people with COPD because of risk of bronchospasm. If people with COPD are prescribed zanamivir they should be made aware of the risks and have a fast-acting bronchodilator available.	**NICE**

7.13.3 Identifying and managing anxiety and depression

R104	The presence of anxiety and depression in patients with COPD can be identified using validated assessment tools.	**Grade D**
R105	Patients found to be depressed or anxious should be treated with conventional pharmacotherapy.	**Grade A**
R106	For antidepressant treatment to be successful, it needs to be supplemented by spending time with the patient explaining why depression needs to be treated alongside the physical disorder.	**Grade C**

7.15 Follow-up of patients with COPD

R131	Patients with mild or moderate COPD should be reviewed at least once per year, or more frequently if indicated, and the review should cover the issues listed in table 7.7.	**Grade D**

8.12 Oxygen therapy during exacerbations of COPD

R165	If necessary, oxygen should be given to keep the SaO_2 greater than 90%.	**Grade C**
R167	In the interim period while the recommendation on the availability of oximeters is implemented, oxygen should be given to all patients with an exacerbation of COPD who are breathless, if the oxygen saturations are not known.	**Grade D**
R168	During the transfer to hospital the following points should be considered: • It is not desirable to exceed an oxygen saturation of 93%. Oxygen therapy should be commenced at approximately 40% and titrated upwards if saturation falls below 90% and downwards if the patient becomes drowsy or if the saturation exceeds 93-94%. • Patients with known type II respiratory failure need special care, especially if they require a long ambulance journey or if they are given oxygen at home for a	**Grade D**

	prolonged period before the ambulance arrives.	
R170	The aim of supplemental oxygen therapy in exacerbations of COPD is to maintain adequate levels of oxygenation (SaO_2>90%), without precipitating respiratory acidosis or worsening hypercapnia. Patients with pH<7.35 should be considered for ventilatory support.	**Grade D**

23 Appendix L NEW 2010 update criteria for selecting high-priority research recommendations

Criteria for selecting high-priority research recommendations				
Criterion	**FRR1 – Timing of pulmonary rehabilitation**	**FRR2 – Multi dimensional assessment**	**FRR3 – Triple therapy**	**FRR4 – Mucolytics**
Importance to the patients of the population	Impacts upon patient quality of life	Impacts upon assessment of disease severity	Impacts upon severity of disease and quality of life	Impacts upon quality of life
Relevance to NICE guidance	Medium, the research is relevant to the recommendations in the guideline	Medium, the research is relevant to the recommendations in the guideline	High, the research is essential to inform future updates of key recommendations in the guideline	Low, the research is of interest and will fill exiting evidence gaps
Relevance to NHS	Facilities already exist therefore benefits are to people with COPD	Would impact upon both primary and secondary care	Clinical and cost effectiveness issues of relevance to NHS	Clinical and cost effectiveness issues of relevance to NHS
National priorities	National Strategy for COPD yet to be published	National Strategy for COPD yet to be published	National Strategy for COPD yet to be published	National Strategy for COPD yet to be published
Current evidence base	Nil found on timing	BODE index felt by the GDG to be time-consuming and impractical for use in a primary care setting	Limited evidence base. Needs adequate powering and study duration	Limited evidence base. Requires trial design stratification re concomitant therapies
Equality	No special considerations – applies to all with	No special considerations – applies to all with	No special considerations – applies to all with	No special considerations

	COPD	COPD	COPD	
Feasibility	No identified ethical or technical issues	No identified ethical or technical issues	No identified ethical (equipoise demonstrable) or technical issues	No identified ethical or technical issues
Other comments	Would benefit from cluster randomised design	Important to both primary and secondary care settings	Focus on differential dropout rates would be prudent	Baseline severity needs well defining out the outset

24 Appendix M NEW 2010 update cost effectiveness modelling

A cost-effectiveness model comparing LAMA, LABA+ICS, and LAMA+LABA+ICS (triple therapy) in people with severe/very severe COPD requiring initial maintenance therapy

> Model overview

The GDG were interested in the following question: Is LAMA, LABA+ICS or triple therapy more cost-effective as initial therapy in COPD patients with an FEV_1 <50% predicted (severe to very severe COPD)?

A cost-utility analysis was undertaken where costs and quality-adjusted life-years (QALYs) were considered from a UK NHS perspective. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance[37].

Topic selection for modelling

Areas were prioritised for new analysis by the GDG. The GDG was interested in assessing the cost-effectiveness of alternative regular maintenance therapies (or combinations of such therapies) for people with stable COPD. Due to complexities in the clinical data it was judged unfeasible to adequately conduct an analysis looking at all possible inhaled interventions in all treatment scenarios within the scope of the guideline update. This included the following issues:

- There were inconsistencies in the clinical evidence network i.e. seemingly contradictory relative risks
- The maintenance therapy decision is not a one off decision – there is the initial decision and then subsequent decisions about adding in additional therapy. Clinical trials generally do not match a particular scenario, i.e. initial maintenance treatment or patients on a specific treatment who are experiencing symptoms, but instead recruit COPD patients meeting variable criteria and randomise to therapy – this makes explicit consideration of the initial decision and subsequent decisions muddied (for example we have information about using triple therapy but not separately for using it straight away and using it after using other therapies but still experiencing symptoms).

The aim was to therefore undertake a focussed analysis that would be useful to the guideline and inform decision making. Following review of the clinical evidence and published economic literature it was considered that examining the following question was the highest priority: is LAMA, LABA+ICS or triple therapy more cost-effective as initial therapy in COPD patients with an FEV_1 <50% predicted (severe to very severe COPD)?

These treatment options were selected as those that represent the most appropriate possible clinical options for people with COPD and an FEV_1 <50% predicted. The GDG felt that the clinical and cost-effectiveness literature suggested that LAMA or LABA+ICS were probably the appropriate options for initial maintenance therapy for patients with an FEV_1 <50% predicted. However, it was felt that if triple therapy could be justified on cost-effectiveness terms that it might be considered as an initial therapy. Therefore these options were incorporated into the model. It was felt unnecessary to include LABA as there was good existing evidence that use of LABA+ICS over LABA alone was more effective and cost-effective in this patient group. No data was available for LAMA+ICS as a treatment option and so it was considered inappropriate to include in the model. Clinical effectiveness data for LAMA+LABA was considered insufficient for it to be considered a primary treatment option and it was felt that it would only be appropriate to consider in patients in whom ICS was declined or not tolerated. On this basis, it was felt that inclusion of LAMA+LABA was also not a priority for inclusion in the model.

It was felt that in less severe patients ($FEV_1 \geq$50% predicted) the key issue was whether to use LAMA or LABA in initial therapy but that issues with the available clinical data would mean that new health economic modelling would be unlikely to reduce uncertainty around this decision and so was considered less of a priority for modelling.

The analysis aimed to consider initial maintenance treatment. It did not incorporate changes to therapy over time. This was judged to be a pragmatic approach given the available data.

Approach to modelling

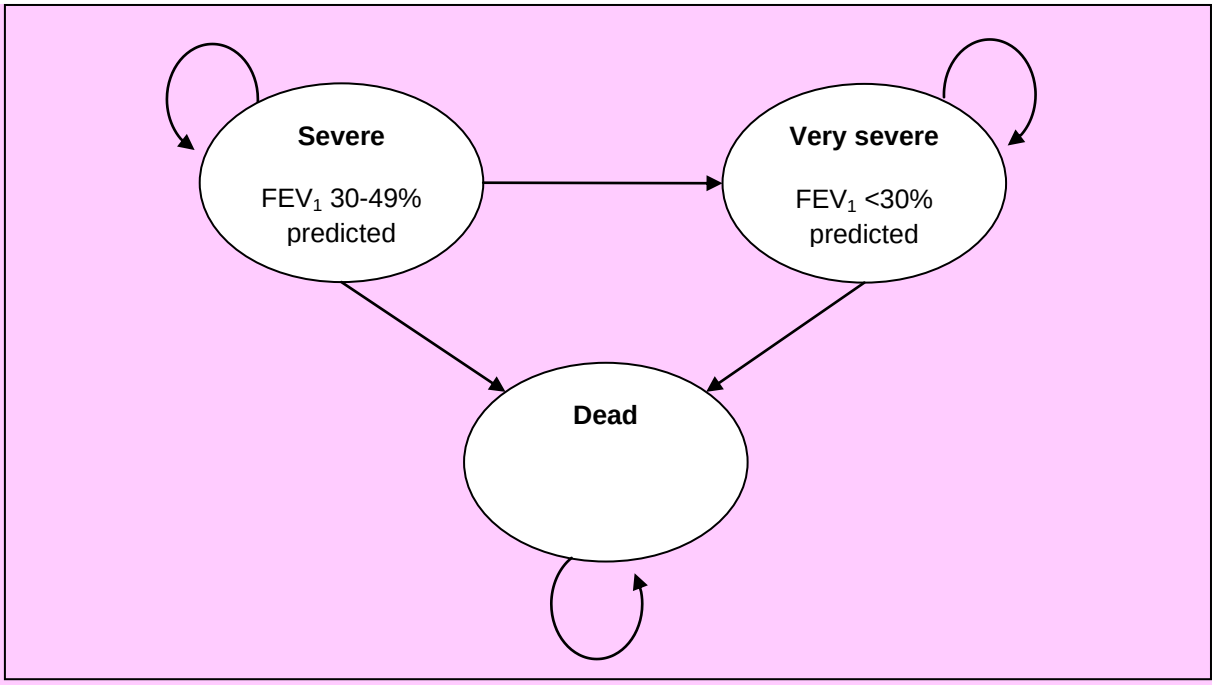
A Markov model was constructed describing how a population with COPD changes over time. Specifically, this represents an increase in mortality and exacerbations over time, and a reduction in quality of life, as patients' lung function declines. The Markov model consisted of three mutually exclusive health states: severe COPD (FEV_1 30 to <50% predicted), very severe COPD (FEV_1 <30% predicted) and dead. Patients can progress from severe to very severe COPD; they cannot regress in COPD severity. A cycle length of one year was used. Different exacerbation and hospitalisation rates, mortality rates, utilities and maintenance costs are assigned to each COPD severity stage.

For the baseline, we populated the model with data relating to the LABA+ICS treatment group. Running the model estimates outcomes over a specified time period. By applying cost and utility weights we estimated mean costs and QALYs over the whole time period.

To compare the impact of treating the same population with a different treatment option we applied relative treatment effects from RCTs for each treatment option to the baseline estimates in the model, reran the model and then recalculated mean costs and mean QALYs.

Comparing these mean results for the three different treatment options allowed us to identify which was the most cost-effective.

Table 1: Markov model depiction



> Analyses undertaken

Outcomes incorporated into the model were based on the systematic review of the clinical effectiveness data and GDG discussion. The aim was to incorporate key outcomes that are differentially impacted by treatment across the treatment options being considered by the model and that result in differences in costs and/or QALYs.

The basecase analysis incorporates a differential treatment effect in terms of exacerbations. Exacerbations in the model are attributed a cost and a utility loss (quality of life impact) and so impact costs and QALYs. This was considered the most robust assessment that could be made based on the available data. Some EQ-5D utility data was available from the literature to inform the estimate of the impact of exacerbations.

- **Basecase analysis (exacerbation effect only):**
  - Outcomes impacted by treatment:
    - exacerbations (non-hospitalised)
    - exacerbations (hospitalised)
  - Costs will vary between treatment options due to differences in drug costs and exacerbations between treatment options.
  - QALYs will vary between treatment options due to differences in exacerbations between treatment options – each exacerbation is associated with a QALY loss; so if the number of exacerbations varies between treatments then so will the QALYs.

An alternative analysis was undertaken that incorporated a differential treatment effect in terms of stable utility (quality of life) as well as exacerbations. This was not included in the basecase due to concerns regarding estimating this effect. Model inputs are discussed in detail in subsequent sections.

- **Alternative analysis 1 (exacerbation and stable utility effect):**
    - Outcomes impacted by treatment:
        - exacerbations (non-hospitalised)
        - exacerbations (hospitalised)
        - quality of life during stable COPD (due to improved symptoms with treatment)
    - Costs will vary between treatments as in the basecase analysis.
    - QALYs will vary as in the basecase analysis but also due to the difference in utility between treatment arms whilst patients are stable.

Careful consideration was given to whether or not it was appropriate to incorporate a differential treatment effect in terms of mortality. It was generally considered that there was not currently strong evidence to support a differential mortality effect between the treatments being considered in the model but that it was plausible given the effect of treatments on exacerbations. Many studies were also not powered to detect a mortality effect. It was concluded that it would be most appropriate to run the analysis both excluding and including mortality. As such, a second sensitivity analysis was undertaken where mortality was differentially impacted between the treatments in the model, in addition to exacerbations.

- **Alternative analysis 2 (exacerbations and mortality effect):**
    - Outcomes impacted by treatment:
        - exacerbations (non-hospitalised)
        - exacerbations (hospitalised)
        - mortality
    - Costs will vary due as in primary analysis but COPD maintenance costs will also vary between treatment options as there will be different numbers of people alive with each treatment option due to differences in mortality.
    - QALYs will vary as in primary analysis but there will also be a difference in life years between treatment options due to the different mortality with the treatment options.

Note that progression was assumed not to be impacted differentially between the treatments being compared.

Time horizon

In all the above analyses, a treatment duration of four years was examined. This matches the longest follow-up of the clinical trials that inform the comparisons in this model.

As sensitivity analyses, we also examined the effect of using a shorter time horizon of 1 year (matching the shortest follow-up of the clinical trials that inform the comparisons in this model) and a longer time horizon of a lifetime (35 cycles).

In the basecase and first alternative analysis, where a differential treatment effect on mortality was not incorporated, it was expected that the time horizon would not have a large impact on results. In the analysis that included mortality however it was considered that it may have a greater impact. When mortality is impacted differentially between treatments there are a different numbers of people alive at the end of the four year treatment period. Due to this, even assuming no further differential treatment impact, costs and QALYs therefore vary between treatment options beyond 4-years.

Uncertainty

The model was built probabilistically in order to take account of the uncertainty around input parameter point estimates. A probability distribution is defined for each model input parameter. When the model is run a value for each input is randomly selected from its respective probability distribution simultaneously and costs and QALYs are calculated using these values. The model is run repeatedly – in this case 5000 times – and results are summarised. Probability distributions in the analysis were based on error estimates from data sources, for example confidence intervals around relative risk estimates.

In addition to the sensitivity analyses already described above around the outcomes incorporated in the model and the time horizon, various additional sensitivity analyses, where one or more inputs were varied, were undertaken to test the robustness of model assumptions and data sources.

> Model inputs

Inputs summary table

Model inputs were selected following a review of the literature and validated with the GDG. Note that healthcare utilisation defined exacerbations were used in the model. Point estimates and the 95% confidence interval for inputs are shown in the table; the latter to illustrate the range of values taken in the probabilistic analysis. Confidence intervals are as reported from the data where available (for COPD utility and relative treatment effects for exacerbations, hospitalisations and mortality), where not reported or where the input value in the table below is the result of a calculation the confidence interval shown is generated from 10,000 simulations of the probabilistic analysis. Where no confidence interval is presented the input was not varied in the probabilistic analysis. More details about sources and any calculations can be found in the sections following this summary table. Details of the probability distributions used for the probabilistic analysis are also included in subsequent sections.

Table 2: Summary of model inputs – point estimates and 95% confidence intervals*

Input	Data		Sources
Comparators	• LAMA • LABA+ICS • Triple therapy (LAMA+LABA+ICS)		
Population	COPD, FEV_1 <50% predicted, requiring initial maintenance therapy		
Initial cohort *Severity:*	Age (a) Female (b) Severe (c) Very severe (c)	66 years 46% 67% 33%	(a) Mean across RCTs used to inform treatment effects[200,201,219] (b) Analysis of UK GP records[15] (c) DH analysis[609]
Progression			
Annual probability	Severe to very severe	0.064 (0.053-0.076)	Derived from mean decline in FEV_1 of 39ml/year[610]
Baseline event rates (LABA+ICS)			
Exacerbation/ year	Severe Very severe	0.91 (0.87-0.96) 1.54 (1.44-1.64)	LABA+ICS arm in TORCH analysis by GOLD stage[207]
Hospitalisation/ year	Severe Very severe	0.17 (0.16-0.18) 0.29 (0.27-0.31)	Based on 19% of exac requiring hospitalisation with LABA+ICS[197]
Mortality RR vs. gen pop	Severe Very severe	3.1 (2.6-4.1) 5.0 (3.5-11.8)	Mortality risk by GOLD stage vs. non-COPD population[611] (applied to age dependent mortality rates for the UK general population[612])
Utilities			
COPD utility	Severe Very severe	0.750 (0.731-0.768) 0.647 (0.598-0.695)	EQ-5D utilities reported by Rutten van Molken[613]
QALY loss per exacerbation	Non-hospitalised Hospitalised	0.011 (0.006-0.018) 0.020 (0.015-0.027)	Derived from O'Reilly[614], Paterson[615], Spencer[616], Starkie[617]

Costs			
Drug costs	LAMA LABA+ICS Triple therapy	£395.18 £488.76 £883.94	Based on recommended dosing[221,618-621], UK prices[622], and the Prescription Cost Analysis 2007[623]
Cost per exacerbation	Non-hospitalised Hospitalised	£34 (22-48) £2403 (2063-2771)	O'Reilly et al.†[624] Derived from NHS reference costs[625], UK COPD audit[626], PSSRU costs[627], ICU estimates[174,628]
Maintenance costs/year (excl. exacerbations)	Severe Very severe	£273 (208-347) £896 (735-1079)	Derived from Britton et al. 2003†[33]

Relative treatment effects				
	LABA+ICS vs. LAMA	Triple vs. LABA+ICS	Triple vs. LAMA	LABA+ICS vs LAMA: INSPIRE[219] Triple vs LAMA: OPTIMAL[200] Triple vs LABA+ICS: UPLIFT RCT subgroup[201]
Exacerbations	0.97 (0.84-1.12)	0.85 (0.79-0.92)	0.85 (0.65-1.11)	
Hospitalisations	1.08 (0.73-1.59)	0.89 (0.75-1.07)	0.53 (0.33-0.86)	
Mortality	0.56 (0.33-0.94)	0.91 (0.76-1.15)	1.61 (0.46-5.60)	
Stable utility	+0.023 (0.001-0.046)	+0.021 (0.006-0.036)	+0.040 (0.007-0.075)	Observed SGRQ from above RCTs mapped to EQ-5D[617]

*Confidence intervals are as reported from the data where available (for COPD utility and relative treatment effects for exacerbations, hospitalisations and mortality), where not reported or where the input value shown is the results of a calculation the confidence interval shown is generated from 10,000 simulations of the probabilistic analysis; where no confidence interval is presented the input was not varied in the probabilistic analysis.

†Inflated to 2007/8 costs using healthcare inflation index[627]

Initial cohort setting

The cohort is assumed to have a starting age of 66 years and be 46% female. The former is based on the average age in the three trials utilised in the model for treatment effects[197,200,219]. The latter is based on a published analysis of UK GP records[15].

The analysis considers a population of people with COPD and an FEV_1 less than 50% predicted (that is people with more severe disease). On entering the model the cohort is distributed as 67% severe (FEV_1 30 to <50% predicted) and 33% very severe (FEV_1 <30% predicted). This was based on the estimated distribution of severity stages in people diagnosed with COPD in England from an analysis undertaken by the Department of Health[609].

Progression

The annual transition probability for progression from severe (FEV_1 30% to <50% predicted) to very severe (FEV_1 <30%) in the model was derived based on a mean decline in FEV_1 of 39ml/year (SE 0.003) as reported in the TORCH study in the LABA+ICS arm[610]. The mean annual decline was incorporated into the probabilistic analysis using a gamma distribution. Details of calculations and data selection are provided below.

Note that no differential effect between the three treatment options in the model was applied to disease progression as the GDG felt that current evidence did not support this. This means that the time spent in the severe and very severe severity states only varied between treatment options in the secondary analysis where mortality was impacted.

A non-systematic review of the literature identified a variety of potential sources of data for the annual decline in lung function, including cohort studies and randomised controlled trials. Data from a selection of key studies are summarised in Table 3. There is some evidence of a significant difference in decline in FEV with pharmacological treatment compared to no treatment (notably in the TORCH study)[610]. On this basis it was considered that an 'on-treatment' rate of decline was most appropriate to use in the model as all comparators were active treatments. Given that TORCH was a large study with 3-years of follow-up this was considered an appropriate source of data.

Table 3: Selected studies of COPD lung function decline

COPD populations	**Annual FEV_1 decline**
Lung Health Study 5-year FU (Scanlon 2000)[118]	52ml/year (SD 55)
East London Cohort (Donaldson 2003)[629]	34.5ml/year
Anthonisen (Anthonisen 1986)[41]	44ml/year (SD 129)
Fletcher and Peto (1977)[583]	48 (SE 2)
Treatment specific	**Annual FEV_1 decline (post-bronchodilator)**
TORCH RCT (3-year follow-up; n = 5343)[610]	LABA+ICS 39.0ml/year (SE 3.0) LABA 42.3ml/year (SE 3.1) ICS 42.3ml/year (SE 3.1) Placebo 55.3ml/year (SE 3.2)
UPLIFT RCT (4-year follow-up n = 4993)[224]	Current treatment +placebo 42ml/year (SE 1) Current treatment +LAMA 40ml/year (SE 1)

The probability of transitioning from severe (FEV_1 30 to <50% predicted) to very severe (FEV_1 <30% predicted) was calculated as follows.

A typical patient in the severe (FEV_1 30 to <50% predicted) was attributed the following characteristics:

- male – based on UK GP records[15]
- aged 66 years – the average in the trials used in this analysis for treatment effects[197,200,219]
- 1.75m tall – the average male height in the UK[630]
- an FEV_1 40% of predicted – the midpoint of the range in this group and the mean in this group in the TORCH study[207].

A male, aged 66 years, of height 1.75m and with an FEV_1 of 40% his predicted FEV_1 must have an FEV_1 of 1.27 according to the European Respiratory Society 1993 reference equations[45]. Assuming a decline of 39ml/year in FEV_1 we calculated his FEV_1 for subsequent years. His predicted FEV_1 in corresponding years was also calculated using the same reference equations as above. His resulting FEV_1 % predicted was then calculated for each year by dividing his FEV_1 by his predicted FEV_1. The resulting figures are displayed in Table 4. On this basis, he would reach the very severe stage (FEV_1<30%) in 10.4 years.

It was then assumed he represents the median patient and that on average 50% of the population would have progressed by 10.4 years. Therefore in the population there would be a 50% probability of progressing in 10.4 years. Assuming a constant hazard the instantaneous rate was calculated as:

$$Annual\,rate = -\frac{\ln(1-p)}{t} = -\frac{\ln(1-0.5)}{10.4} = 0.0664$$

Where: p = the proportion of patients that progress over time period t.

This was then converted from an annual rate to an annual transition probability using the standard formula:

$$\begin{aligned} Probability\ of\ progressing\ (moderate\ to\ severe) &= 1-e^{-rt} \\ &= 1-e^{-0.0664\times 1} \\ &= 0.0642 \end{aligned}$$

Where: r = rate; t = time period

Table 4: Modelled FEV_1 decline for male aged 66, height 1.76m, FEV_1 40% predicted and a decline of 39ml/year

Age	FEV_1	Predicted FEV_1	FEV_1 % predicted
66	1.27	3.16	40.0%
67	1.23	3.14	39.1%
68	1.19	3.11	38.2%
69	1.15	3.08	37.3%
70	1.11	3.05	36.4%
71	1.07	3.02	35.5%
72	1.03	2.99	34.5%
73	0.99	2.96	33.5%
74	0.95	2.93	32.5%
75	0.91	2.90	31.5%
76	0.88	2.87	30.5%
77	0.84	2.85	29.4%
78	0.80	2.82	28.3%
79	0.76	2.79	27.2%
80	0.72	2.76	26.1%
81	0.68	2.73	24.9%
82	0.64	2.70	23.8%
83	0.60	2.67	22.6%
84	0.56	2.64	21.3%
85	0.52	2.61	20.1%
86	0.49	2.58	18.8%

Baseline event rates with LABA+ICS

The model must be populated with appropriate event rates for one of the comparators in the model (baseline events). Event rates for the other comparators are then calculated in the model by applying relative effect figures from randomised controlled trials. The model was populated with baseline event rates for LABA+ICS.

Exacerbations

Overall average annual exacerbation rates of 0.91 (SE 0.023) per person per year for severe (FEV_1 30 to <50% predicted) and 1.54 (SE 0.051) per person per year for very severe (FEV_1 <30% predicted) were applied in the model for people treated with LABA+ICS. This was based on rates observed in the TORCH study LABA+ICS arm in these FEV_1 groups and imputed error estimates (see below)[207]. Hospitalisation rates for exacerbations were not reported by GOLD stage and it was assumed that 19% of all exacerbations required hospitalisation as observed in the TORCH LABA+ICS arm[197]. This equated to an average of 0.17 per patient per year and 0.29 per patient per year for severe and very severe respectively. Note that healthcare utilisation defined exacerbations were used in the model. Exacerbation rates were incorporated into the probabilistic analysis using log normal distributions.

Error estimates were not reported for the exacerbations rates by FEV_1 severity stage. In order to incorporate uncertainty around the exacerbation rate into the model a standard error was imputed based on the reported mean rate for each severity stage and the estimated total patient years. Total patient years were estimated using the number of patients for each severity stage (GOLD 3 = 728; GOLD 4 = 243) multiplied by the average patient follow-up for the TORCH study as a whole (2.4 years). The following formula for the standard error of a rate was then used:

$$SE\,rate = \sqrt{\frac{rate}{total\ patient\ years}}$$

Baseline exacerbation rate data stratified by FEV_1 was sought through a non-systematic review of the literature. The TORCH study data was selected as it provided stratified rates from a large cohort for people treated with LABA+ICS[207]. Rates were also similar to those observed in the clinical trials being used in the model for relative treatment effect. It included 728 LABA+ICS patients FEV_1 30-49% predicted and 243 FEV_1 <30% predicted. Donaldson et al. also reported stratified rates from a UK cohort however the population was smaller and rates were not specific to any one treatment[631]. A Spanish and a Swedish cohort study were also identified[496,632].

Mortality

Age-dependant mortality was incorporated into the model using life tables for England and Wales and severity specific COPD mortality data[611,612]. A relative risk for mortality with COPD was applied of 3.1 and 5.0 for severe (FEV_1 30 to <50% predicted) and very severe (FEV_1 <30%) stage respectively[611].

COPD severity specific mortality data was reported by Ekberg et al. based on a Swedish population study with 22,044 people[611]. Relative risks were presented for smokers, former smokers and never smokers stratified by GOLD COPD severity stage and gender compared to the general population without symptoms of chronic bronchitis and with normal pulmonary function (see Table 5). A weighted average of the reported GOLD stage 3 (FEV_1 30 to <50% predicted) and GOLD stage 4 (FEV_1 <30% predicted) figures were used in the model. These inputs were incorporated into the probabilistic analysis using log normal distributions.

Table 5: COPD mortality risks in GOLD stages 3 and 4 compared with the general population

	GOLD 3 (FEV_1 30 to <50%)				GOLD 4 (FEV_1 <30%)			
	RR	**LCI**	**UCI**	**N**	**RR**	**LCI**	**UCI**	**N**
Men – smoker	2.42	1.84	3.18	101	3.57	2.23	5.71	27
Men - former smoker	2.42	1.44	4.08	33	2.59	0.83	8.07	8
Men - never smoker	3.93	1.86	8.3	15	1.04	0.15	7.39	7
Female - smoker	5.11	3.09	8.45	36	10.26	4.53	23.25	9
Female - former smoker	-	-	-	-	-	-	-	-
Female never smoker	3.91	0.96	15.8	7	18.1	2.53	129.6	3
Weighted average	**3.1**			**192**	**5.0**			**54**

Source: Ekberg et al. 2005[611]

COPD mortality rates stratified by FEV_1 were sought through a non-systematic review of the literature. The Ekberg et al. data was selected as it provided relative estimates of COPD mortality by FEV_1 group compared with a general population[611]. Soriano et al. also reported stratified COPD mortality rates compared to a matched control group from a UK cohort[15]. COPD severity was however classified as mild, severe and very severe by prescribed drugs and the Ekberg FEV_1 stratified data was considered more appropriate for the model. Both studies found higher COPD mortality in the more severe groups. Other COPD mortality data was identified but was either not stratified, not compared with a control non-COPD group or the source of estimates was unclear.

Utilities (health-related quality of life)

QALY loss per exacerbation

Exacerbations drive the differences in QALYs between treatment options in the basecase analysis. Each hospitalised exacerbation was attributed a QALY loss of 0.020 and each non-hospitalised exacerbation was attributed a QALY loss of 0.011. The basis for this is described below.

In order to estimate the impact of COPD exacerbations on QALYs, information was required on the magnitude of effect on utility during an exacerbation and the duration of effect.

COPD utility data was sought by searching Medline using COPD and EQ-5D specific terms and reviewing previous cost-utility analyses. As limited data was identified further ad hoc searches looked more broadly for information about the impact of COPD exacerbations on quality of life. A review of health-related quality of life data (including utility and non-utility measures) in COPD was identified and checked for useful papers[633].

Two studies were identified that looked at utility change during exacerbations of COPD:

- Paterson and colleagues evaluated utility using EQ-5D in patients with an established diagnosis of chronic bronchitis and who presented at a general practice clinic with an acute exacerbation[kkk615]. The study enrolled 81 patients at a single centre in Glasgow, UK. The UK tariff for the EQ-5D was used. They reported a mean increase in EQ-5D of 0.17 (SD 0.24) from initial presentation for an acute exacerbation and at a second visit within one week of treatment completion. Average treatment duration is not reported but typically treatment with antibiotics/oral corticosteroids would be for 7-14 days.

- O'Reilly and colleagues evaluated utility using EQ-5D in patients hospitalised for an acute exacerbation of COPD[614]. The study enrolled 222 patients at a single hospital in Blackpool, UK. Patients had a diagnosis of COPD and were admitted for an acute exacerbation[lll]. The UK tariff for the EQ-5D was used. Patients were assessed at admission, then every other day

[kkk] An increase in at least two of the following: increased frequency and/or severity of cough; increase in sputum volume, dyspnoea or increased dyspnoea; increase in chest congestion as indicated by adventitious sounds, and chills and/or fever. Patients also had to be able to produce mucopurulent or purulent sputum and had to be able to provide a suitable sample for laboratory analysis and microbiological confirmation.

[lll] No specific definition of an exacerbation was used; it was based on the physician and respiratory nurse's determination.

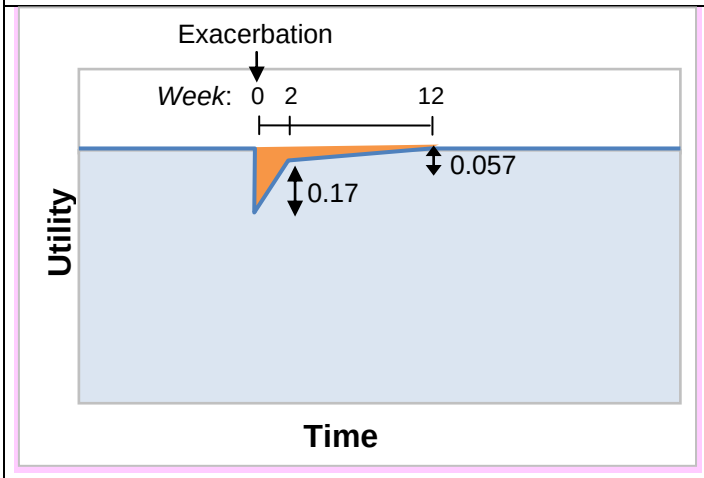
during their hospital stay. A group that entered the study following a protocol amendment were also assessed at 3 months after discharge (n = 40). They reported a mean increase in EQ-5D of 0.653 (SD 0.434) between admission and discharge, and a decrease of 0.240 (SD 0.373) between discharge and 3-month follow-up. Average length of stay in hospital was eleven days.

Limited information was identified regarding the duration of impact on utility. As described above, O'Reilly and colleagues reported a reduction in utility between discharge and 3-month follow-up, however this result is difficult to interpret and may reflect new exacerbations that occur during the 3-month follow-up. Spencer and Jones used the SGRQ (a disease specific measure of health-related quality of life) to examine the time course of recovery of health status following an acute exacerbation[616]. They reported the biggest improvement between presentation and 4 weeks. But SGRQ score continued to improve beyond this. In patients that did not experience another exacerbation SGRQ continued to improve (although at a slower rate) 4 to 12 weeks and even up to 26 weeks. In patients that did experience another exacerbation, SGRQ showed a minor improvement beyond 4 weeks. This suggests that the impact of COPD exacerbation on patients extends beyond the treatment phase.

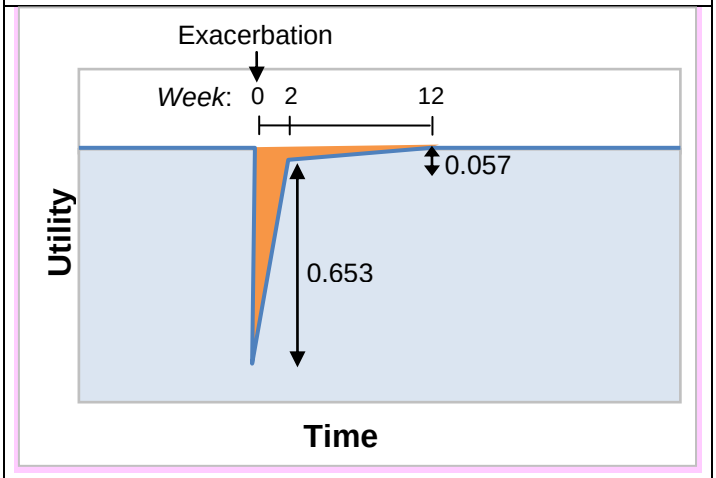
QALY loss due to an exacerbation was modelled in two parts – the first 2 weeks following an exacerbation and then following this up to 12 weeks (3 months). For non-hospitalised exacerbations, the change in utility from the start of an exacerbation to 2 weeks is based on that reported by Paterson and colleagues (0.17) as this was from exacerbations presenting in general practice[615]. For hospitalised exacerbations the figure reported by O'Reilly and colleagues is used (0.653) for the corresponding period[614]. These decrements were incorporated into the probabilistic analysis using a gamma distribution. The utility change over the period 2-12 weeks was estimated based on the rate of change in SGRQ between week 4 and 12 for people not experiencing a new exacerbation reported by Spencer and Jones. SQRG values at week 4 and 12 (42.5 and 37.8 – mean difference 4.7) were mapped to EQ-5D using a published algorithm[617]. The average change in EQ-5D per week was then calculated. This rate of utility change was then applied for the 2-12 week period resulting in a change in utility of 0.057 over the latter 10 week period of the 12 week period modelled. This parameter was incorporated into the probabilistic analysis using a gamma distribution for the mean SGRQ difference. QALY loss was then calculated for a non-hospitalised and hospitalised exacerbation using the EQ5D decrements and the durations stated. Figure 2 illustrates this graphically. Using this approach the QALY loss is the same irrespective of starting utility and so does not vary with COPD severity. Note that more detail regarding the mapping of SGRQ to EQ5D is given later in this report.

Figure 2: QALY loss during an exacerbation

Non-hospitalised exacerbation:



Hospitalised exacerbation:



Key:

Blue line = person's utility

Blue fill (area under blue line) = person's QALYs

Orange fill = QALY loss during exacerbation

Previous approaches to modelling the impact of exacerbations on utility

Previous cost-utility analyses in COPD were also reviewed for methods employed for estimating the impact of exacerbations in terms of utility as part of the model development. These are summarised in Table 6.

Table 6: Approaches to exacerbations in cost-utility analyses in the literature

	Approach to exacerbations		**Sources**	
	Utility during exacerbation	***Duration***	***Utility during exacerbation***	***Duration***
Spencer et al. 2005[634]	ATS 1/2/3: Minor = 0.72/0.658/0.475 Major = 0.519/0.447/0.408[mmm]	3 months	Based on area under curve assuming initial utility low and logarithmic recovery curve over 3 months to within 0.03 of stable utility. Utility low points based on expert panel (n=27) who completed EQ-5D from patient perspective. Non-linear recovery and prolonged improvement period based on Spencer and Jones, 2003[616].	
Borg et al. 2004[635]	Mild = -5% Moderate = -15% Severe = -70%[nnn]	GOLD 1: mild 12.64 days, moderate 12.55, severe 4.67 GOLD 2a: mild 12.64, moderate 12.55, severe 4.67 GOLD 2b: mild 12.64, moderate 14.06, severe 8.49 GOLD 3: mild 10.20, moderate 12.58, severe 9.33[ooo]	Mild and moderate – expert panel estimation (n=3) Severe – assumed to be equal to severe asthma exacerbation; UK asthma patient data (n=100)[636]	Symptom duration by GOLD severity and exacerbation type (n=138)[631]
Oostenbrink et al. 2005[173] Rutten-van Molken et al. 2007[174]	Non-severe = -15% Severe = -50%[ppp]	1 month	Non-severe – derivation unclear, referenced to Paterson et al. 2000[615] Severe – derivation unclear, referenced to Spencer & Jones 2003[616]	Assumption

[mmm] minor = requiring oral corticosteroids and/or antibacterials; major = hospitalisation
[nnn] mild = patient manages in normal environment including telephone call to doctor and possibly antibiotics or oral steroids; moderate = patient must make an unscheduled visit to DR; severe = requires hospitalisation or ER visit
[ooo] GOLD 1 = FEV1 >80% predicted; GOLD 2a = FEV1 50-80% predicted; GOLD 2b = FEV1 30 to <50% predicted; GOLD 3 = FEV1 <30% predicted
[ppp] Non-severe = awareness of sign or symptom AND discomfort that interferes with usual activities; severe = inability to do work or usual activities

Maniadakis et al. 2006[637]				
Sin et al. 2004[638]	-0.32	Mild = 1 week Moderate = 2 weeks Severe = 4 weeks[qqq]	Utility weight for 'cough, wheeze or trouble breathing' from US stated preference experiment[639]	Assumption
Brady et al. 2007[210]	Mild = -0.17 Moderate = -0.47 Severe = -0.47[qqq]	3 months	Mild – estimate reported by Paterson et al. 2000[615] Moderate and severe – derivation unclear, reference to Spencer et al. 2001[640]	Assumption

[qqq] Mild = worsening of symptoms requiring outpatient physician services and institution of systemic corticosteroids or antimicrobial agents; moderate = requiring emergency department utilisation or urgent physician office visits; severe = requiring inpatient care

Utility by COPD severity

In the model, utilities of 0.750 (CI: 0.731-0.768) and 0.647 (CI: 0.598-0.695) are used for severe (FEV_1 30 to <50% predicted) and very severe (FEV_1 <30%) stages respectively based on data collected pre-randomisation in the UPLIFT study[613]. These inputs are incorporated into the probabilistic analysis with a beta distribution.

COPD EQ-5D utility data was sought by searching Medline using COPD and EQ-5D specific terms and reviewing previous cost-utility analyses. A review of the use of EQ-5D in COPD was identified and checked for additional papers[641]. A number of studies were identified that reported EQ-5D estimates of COPD utility – nine reported overall COPD utility and four reported utility by severity stratification. These are summarised in Table 7. Two studies reported COPD utilities stratified into FEV_1 30 to <50% predicted and FEV_1 <50% predicted. Rutten-van Molken et al. reports EQ-5D data using the UK tariff collected in the multinational UPLIFT trial[613]. Questionnaires were administered at randomisation and patients therefore weren't on LAMA but could be on other drugs. At baseline 65% were on LABA and 62% were on ICS. Stahl et al. reports EQ-5D data using the UK tariff from a Swedish population [642]. Data from the Rutten-van Molken study was selected for use in the model as the population was larger.

Table 7: COPD EQ-5D data

	Studies	Population	EQ-5D tariff	Stratification[†]	N	EQ-5D index
Overall COPD	Rutten-van Molken[613]	Multinational	UK	n/a	1235	0.76 (SD 0.21)
	Punekar[643]	Multinational	UK	n/a	2703	0.62-0.71 (range across countries)
	Sullivan[644]	USA	US	n/a	1609	0.797 (IQR 0.76-0.83)
	Harper[584]*	UK	NR	n/a	125	0.524 (SD 0.157)
	Hazell[645]	UK	UK	n/a	1054	0.63
	Stavem[646]	Norway	UK	n/a	59	0.73 (IQR 0.62-0.81)
	Polley[647]	UK	NR	n/a	18	0.45 (SD 0.31)
	Szende[648]	Sweden	European	n/a	176	0.76 (SD 0.22)
	Johansson[649]	Sweden	NR	n/a	21	0.52 (SD 0.30)
By severity	Rutten-van Molken[613]	Multinational	UK	GOLD 2	622	0.787 (CI: 0.771-0.802)
				GOLD 3	513	0.750 (CI: 0.731-0.768)
				GOLD 4	91	0.647 (CI: 0.598-0.695)
	Stahl[642]**	Sweden	UK	GOLD 1	26	0.84 (SD 0.15)
				GOLD 2	91	0.73 (SD 0.23)
				GOLD 3	33	0.74 (SD 0.25)
				GOLD 4	9	0.52 (SD 0.26)
				BTS 0	26	0.84 (SD 0.15)
				BTS 1	63	0.74 (SD 0.21)
				BTS 2	47	0.72 (SD 0.28)
				BTS 3	23	0.63 (SD 0.25)
	Punekar[643]	Multinational	UK	GOLD 1	92/218	PCP[‡] 0.77 (CI: 0.73-0.81) / RS[‡] 0.68 (CI: 0.64-0.72)
				GOLD 2	77/314	0.68 (CI:0.62-0.74) / 0.72 (CI:0.69-0.75)
				GOLD 3/4	79/340	0.62 (CI:0.56-0.68) / 0.64 (CI:0.61-0.67)
	Spencer[634]	UK	UK	ATS 1	283	0.81 (SE 0.02)
				ATS 2		0.72 (SE 0.03)
				ATS 3		0.67 (SE 0.05)

*Brazier et al.[650] also reports on the same dataset[641] and is not included above. **Szende[648] also reports on the same dataset and is not included above.

[†] FEV_1 % predicted: GOLD 1/2/3/4 = ≥80/79-50/49-30/<30; ATS 1/2/4 = 80-50/50-35/<35; BTS 0/1/2/3 = ≥80/79-60/59-40/<40. [‡] PCP = patients treated by a primary care physician; RS patients treated by a respiratory specialist.

Costs

Drug costs

The annual costs applied for the treatment options in the model were £395.18 for LAMA alone, £488.76 for LABA+ICS and £883.94 for triple therapy.

Treatment costs were estimated based on recommended licensed dosing from summaries of product characteristics, costs from the NHS Drug Tariff and relative usage of different drugs and preparations within each class of therapy (that is: LAMA, LABA+ICS) based on the Prescription Cost Analysis for England 2007[221,222,618-623]. Table 8 presents a summary of included drug preparations, costs and usage used to calculate costs.

Note the following for costing purposes:

- LABA+ICS are assumed to be administered only as a combination inhaler product (rather than separate inhalers for each mono-component) as all clinical evidence reviewed used the combination products and the GDG felt it was therefore only appropriate to recommend use of combination products.
- LAMA and LABA+ICS products are available in a number of different inhalers. As the different inhalers have slightly different prices, an average cost was used in the model based on the relative usage of the different available inhalers from the Prescription Cost Analysis[623].
- Two LABA+ICS combination products are available that are licensed for use in COPD – salmeterol/fluticasone and formoterol/budenoside. The cost of LABA+ICS used in the model was therefore based on a weighted average of the two drug costs.
- Salmeterol/fluticasone and formoterol/budenoside are also licensed in asthma. A range of different preparations (that is different inhalers/doses) are available, some have a COPD and asthma indication and some only asthma. Inhalers without a COPD indication will generally not be suitable to fulfil the recommended COPD dose. Information was not available in the Prescription Cost Analysis regarding what a prescription was used for and so asthma and COPD usage could not be separated. The average cost of salmeterol/fluticasone and formoterol/budenoside for a patient with COPD was based on the usage of preparations with a COPD indication only.
- Taking the usage only from preparations of salmeterol/fluticasone and formoterol/budenoside with a COPD indication gave a relative usage between the two products of 74% and 26% respectively. However, GDG members considered this likely to be unrepresentative of true usage, probably due to misprescribing. On this basis a relative usage between the agents was calculated based on overall usage of the drugs which results in 26% salmeterol/fluticasone and 74% formoterol/budenoside. This relative split between the agents was used for costing purposes.

Table 8: Drug unit costs for LAMA and LABA+ICS

Drug	Within class use*	Formulation	Preparation	Units/ pack	Cost/ pack†	Cost/ unit	Units/ dose‡	Doses / day‡	Cost/ day	Cost/ year	Preparation use %**	Av. cost
LAMA												
Tiotropium	100%	Spiriva® (Boehringer Ingelheim)	HandiHaler® (inhalation powder), device + capsules, 18 micrograms	30	£34.87	£1.16	1	1	£1.16	£424.25	20%	
			HandiHaler® (inhalation powder), capsules, 18 micrograms	30	£31.89	£1.06	1	1	£1.06	£388.00	80%	**£395.18**
LABA+ICS												
Budesonide/ formoterol	26%	Symbicort® (AstraZeneca)	200/6 Turbohaler® (dry powder inhaler), metered dose, 200/6 micrograms	120	£38.00	£0.32	2	2	£1.27	£462.33	72%	
			400/12 Turbohaler® (dry powder inhaler), metered dose, 400/12 micrograms	60	£38.00	£0.63	1	2	£1.27	£462.33	28%	
Fluticasone/ salmeterol	74%	Seretide® (A&H)	500 Accuhaler® (dry powder for inhalation), device + blisters, 500/50 micrograms	60	£40.92	£0.68	1	2	£1.36	£497.86	100%	**£488.76**

Based on usage of all preparations of drugs within each class (e.g. LABA+ICS) reported in Prescription Cost Analysis 2007 – each class sums to 100% **Based on use of the specific drug preparations shown that have an indication for COPD reported in Prescription Cost Analysis 2007 – each drug (e.g. budenoside/formoterol) sums to 100%. Sources: †NHS Drug Tariff February 2010[622], ‡product licences[221,618,620,621], */ Prescription Cost Analysis 2007[623]*

Acute COPD exacerbation costs

Costs of £2403 per hospitalised COPD exacerbation and £34 per non-hospitalised COPD exacerbation were applied in the model. The cost per hospitalised exacerbation was based primarily based on 2007/8 NHS reference costs[625]. The cost per non-hospitalised exacerbation was based on the results of a UK costing study inflated using UK healthcare inflation indices to 2007/8 prices (latest indices available at time of analysis)[624,627]. Further details are provided below. Cost parameters were incorporated into the probabilistic analysis using gamma distributions.

Hospitalised exacerbation cost

A cost of £2403 per hospitalised exacerbation of COPD was estimated as follows.

The NHS reference costs provide average UK costs per hospitalisation by HRG code. A weighted average of the costs for all categories of COPD hospitalisation (HRG DZ21A-K) from the 2007/2008 NHS reference costs (latest available at time of analysis) were used to estimate the cost of a hospitalisation for a COPD exacerbation[625].

Costs for accident and emergency (A&E) services, paramedic services and critical care are reported unbundled from hospital costs by HRG code in the NHS reference costs and so needed to be added to the above basic hospitalisation cost[625]. Resource use for these services for a COPD admission was not available from the NHS reference costs and so was sought elsewhere.

It was estimated that 67% of patients would come to hospital by ambulance. This was based on data from the 2008 National COPD audit that reported data regarding admission route for a group of patients hospitalised for COPD an exacerbation[626]. This reported that 34% of patients saw their GP and were sent to hospital, 12% went to A&E via their own steam and 41% didn't see their GP but called an ambulance (16% had an 'other' route and 1% did not state a route). Information was not given about what proportion of patients who saw a GP and were sent to hospital used an ambulance. Based on discussion with a GP representative from the GDG it was judged reasonable to assume that ambulance use would be the same as among those who did not see a GP (that is of the 53% of people who did not see a GP 12% went to A&E via own stream and 41% called an ambulance). The estimate of 67% ambulance use for the model was therefore based on the 41% of patients who didn't see a GP but called an ambulance plus 26% who saw their GP and were sent to hospital by ambulance. The cost of coming to hospital by ambulance was based on a weighted average of the costs for all categories of 'Paramedic services' for breathing difficulties (HRG PS06A-C) from the NHS reference costs[625].

It was assumed that all patients attended A&E. The cost of A&E was based on the weighted average of the costs for all categories of 'A&E services leading to admitted' from the NHS reference costs[625].

UK data regarding the use of critical care services per hospitalisation for a COPD exacerbation was not identified. Two studies (one from Italy and one from Spain) were identified from the literature that provided estimates of time spent in ICU per COPD hospitalisation and so an average of these estimates was used; 0.6 days[174,628]. The cost per day in ICU was based on a weighted average of the costs per day for all categories of 'Critical care services – Adult: intensive therapy unit' (HRG XC01Z-XC07Z) from the NHS reference costs[625].

The 2008 National COPD Audit indicated that 34% of patients would see their GP prior to coming to hospital and so this cost was also incorporated[626]. The cost of a GP visit was based on the 2008 average UK cost (latest available at time of analysis)[627].

Non-hospitalised exacerbation cost

A cost of £34 per non-hospitalised exacerbation was based on the results of a UK costing study inflated using UK healthcare inflation indices to 2007/8 prices (latest indices available at time of analysis)(before inflated £30.69, SD 111.4)[624,627]. Details of the selection of the data source are provided below.

The literature was reviewed for estimates of resource use and/or the costs of non-hospitalised COPD exacerbations. Studies that were identified are summarised in Table 9. Original reports of resource or costing studies are included in this table, including those reported within cost-effectiveness study reports. Cost-effectiveness studies that utilise data reported elsewhere are not included in the table (as this would be duplication) nor are those that use estimates based on assumptions or expert opinion. Note that studies that only reported in-hospital costs for patients with COPD exacerbations are also not included in the table.

Estimates of cost for a non-hospitalised exacerbation from the studies varied considerably. A number of considerations were relevant in selecting a source for the model. The definition of exacerbations varied between studies and did not necessarily match up with the categorisation being used in this analysis; we were looking for an estimate where hospitalised exacerbations were not included. Most studies were not in a UK setting and management may vary between countries. For example, in the UK access to healthcare is generally via a GP but in other countries this may not be the case.

Only one study was identified that was conducted in a UK setting and the exacerbation definition in this study also matched that being used in the model[624]. On this basis this source was utilised. It was noted that this cost estimate was quite low compared with the overseas estimates. However, it was difficult to judge if it was inaccurate or if it represented a genuine difference in management between countries. This issue was discussed with the GDG and consideration was given to the cost of drugs used to treat an exacerbation and the average cost of typical healthcare contacts. It was concluded that while it did appear possibly too low it was not unfeasible and, in the absence of other data, should be used in the model. Sensitivity analysis was planned to explore the impact of this cost on results.

Table 9: COPD exacerbation costing studies

Study reference	Setting and study design	Exacerbation definitions	Cost/exacerbation (2007/8 £)[rrr]	Resource use reported?
Lucioni et al 2005[628]	• Italy (resource use and unit costs) • People diagnosed with COPD hospitalised for an exacerbation; followed-up prospectively for 6 months post-discharge • Data collection via patient questionnaires • N = 570 (282 with ≥1 exacerbation) • Exacerbations = 282	• Not reported (includes exacerbations requiring hospitalisation and not)	• £1085[sss] Resource use included: medical visits, hospital admission, tests, drugs, oxygen therapy, ventilation, rehabilitation.	No
Andersson et al 2002[496]	• Sweden (resource use and unit costs) • People diagnosed with COPD who had experienced had experienced an exacerbation the previous winter • Data collection via patient questionnaires; visits and hospitalisations verified via medical records • N = 61 • Exacerbations = 75	• Mild = self-managed by increasing dose of current medication (including adding OTC medication) • Mild-moderate = telephone contact and/or antibiotics/systemic corticosteroids • Moderate = requiring GP/outpatient visit • Severe = requiring A&E visit or hospitalisation	• Mild = £11 • Mild/moderate = £34 • Moderate = £202 • Severe = £2092 Resource use included: drugs, healthcare contacts, A&E visits, hospitalisation, transportation.	No
Miravitlles et al. 2002[651]	• Spain (resource use and unit costs) • People diagnosed with COPD who presented to GP with exacerbation; followed-up at 1 month • Data collection by GP at planned follow-up visits • N = 2414	• Exacerbation = presence of increased dyspnoea, and/or increased production and/or purulence that led to a change or increase in treatment	• £144 Resource use included: drugs, clinic visits, A&E visits, hospitalisation, oxygen (cost of exacerbation includes treatment failure defined as new GP/A&E visit or hospitalisation in month following exacerbation)	No

[rrr] All costs are converts to UK £ using PPP for the appropriate year, and then inflated to 2007/8 costs using the PSSRU healthcare inflation indices[177,627]. Reported to nearest whole £.
[sss] Direct cost only presented here; calculated by dividing exacerbation costs/year by exacerbations/year

Rutten-van Molken 2007[174]	• Spain (resource use and unit costs) • Reanalysis of data from Miravitlles et al 2002 above.	• Exacerbation = as per Miravitlles et al. 2002 above • Severe = unspecified but appears to be requiring A&E visit or hospitalisation	• Non-severe = £75[ttt] • Severe = £1940[ttt,uuu] Resource use included: healthcare contacts, A&E visits, hospitalisation, drugs, oxygen	Yes
O'Reilly et al. 2006[624]	• UK (resource use and unit costs) • People diagnosed with COPD registered in a PCT; followed-up prospectively for 1 year • Data collection by daily diary cards • N = 848 • Exacerbations: symptom-defined = 296; healthcare defined = 351	• Symptom-defined = increased symptoms for ≥2days • Healthcare-defined = requiring antibiotics and/or oral corticosteroids for chest problems	• Symptom-defined = £18 • Healthcare-defined = £34 Resource use included: drugs, healthcare contacts, A&E visits, hospitalisation Note: no patients were hospitalised during study	Partly
Price et al (1999)[652]	• Resource use from RCT – country unspecified (UK unit costs) • Symptomatic COPD patients enrolled in fluticasone propionate RCT; resource use collected prospectively • Exacerbations: mild = 64; moderate = 112; severe = 18	• Mild = self-managed by patient • Moderate = physician-treated • Severe = hospitalised	• Mild = £21 • Moderate = £136 • Severe = £2362	No
Oostenbrink et al. 2004[176]	• Netherlands/Belgium (86%/14%) (Netherlands unit costs) • People with stable COPD enrolled in 2 tiotropium vs. ipratropium RCTs; prospective follow-up for 1 year • N = 519 (207 with ≥1 exacerbation) • Exacerbations = 364	• Mild = awareness of a sign or symptom which is easily tolerated[vvv] • Moderate = causing discomfort enough to cause interference with usual activity[vvv] • Severe = incapacitating or causing inability to do work or usual activity[vvv]	• Mild = £74 • Moderate = £498[www] • Severe = £3448[www] Resource use included: hospitalisation, A&E visits, healthcare contacts, ambulance transportation, tests, drugs	Partly

[ttt] Direct medical costs only included here; NHS sick leave benefit and other excluded.
[uuu] 52% of severe exacerbations required hospital admission.
[vvv] Classification of exacerbations based on ratings by the physician-investigator.
[www] Hospitalisation was 16% and 78% in moderate and severe exacerbations respectively.

Oostenbrink et al. 2005[173]	• Canada[xxx] (resource use and unit costs) • Original resource use data reported as part of CEA. People with COPD; prospective follow-up for 1 year • N = 598 • Exacerbations = NR	Canada • Exacerbation = NR • Severe = hospitalisation or A&E visit	Canada • Non severe = £58 • Severe = £4036 Resource use included: hospitalisation, A&E visits, healthcare visits, drugs, oxygen	Yes
Maniadakis et al. 2006[637]	• Greece (resource use and unit costs) • Original resource use data reported as part of CEA. Analysis of medical records at the University General Hospital of Heraklion in Greece. • N = NR • Exacerbations = NR	• NR	Non-severe = £477 Severe = £882 Resource use included: hospitalisation, A&E visits, healthcare visits, drugs, oxygen	Yes

[xxx] This CEA also reports Netherlands estimates using different data but as this is based on Oostenbrink 2004 detailed above this is not included here.

COPD maintenance costs

Annual maintenance costs for COPD of £273 (SE 35.0) and £896 (SE 79.5) for severe (FEV_1 30 to <50% predicted) and very severe (FEV_1 <30% predicted) stages respectively were applied in the model. Mean estimates were derived from a UK COPD costing study[33]; error estimates were imputed (see below for details). Details of derivation and data selection are provided below.

Note that in the model, maintenance costs only vary between treatment arms in the secondary analyses where a mortality impact of treatment is incorporated.

The literature was reviewed for estimates of per patient annual maintenance costs for stable COPD stratified by severity. Studies that were identified are summarised in Table 10. Original reports of resource or costing studies were included. This included estimates reported within a cost-effectiveness analysis. Cost-effectiveness studies that utilise data reported elsewhere are not included in the table (as this would be duplication) nor are those that use estimates based on assumptions or expert opinion. Only estimates stratified by severity are included. If this did not include stratification of the <50% group they are also not included in the table.

Estimates of annual costs excluding those associated with exacerbations were required for the model as exacerbations are costed separately. This would therefore cover healthcare contact such as regular follow-up visits and additional medications and therapies, such as oxygen. Ideally resource use would have been collected in a UK setting.

Only one study reported costs from a UK setting[33]. Severity classification was by self-designation or dyspnoea scale (into mild, moderate and severe) rather than FEV_1 cut-offs as used in the model. Exacerbations costs were included in the estimates however the study also reported that 60% of costs in the overall population are due to unscheduled care. Some data were available that reported by FEV_1 based severity groups and excluded exacerbation costs but from non-UK settings[173,174]. The UK data was prioritised. The figures for moderate and severe COPD defined by dyspnoea score with 60% of costs subtracted to remove unscheduled care (i.e. treatment of exacerbations) were used for severe and very severe COPD in the model respectively.

These parameters were incoporated into the probabilistic analysis using the cost for severe COPD (£723) and the difference in cost between severe and very severe COPD (£623). Gamma distributions were assigned. No error esimates were reported for the cost estimates and so a standard error was imputed that would generate a confidence interval half that of the mean cost estimate.

Table 10: COPD maintenance costing studies

	Study design	Maintenance cost/year (2007/8 £)[yyy]	Resource use reported?
Lucioni et al 2005[628]	• Italy (resource use and unit costs) • People diagnosed with COPD hospitalised for an exacerbation; followed-up prospectively for 6 months post-discharge • Data collection via patient questionnaires • N = 570	• GOLD 2 = £2544[zzz] • GOLD 3 = £3489 • GOLD 4 = £6740 Resource use included: medical visits, hospital admission, tests, drugs, oxygen therapy, ventilation, rehabilitation. Includes exacerbation costs; in whole population costs not related to exacerbations = 48%.	No
Miravitlles et al. 2003[653]	• Spain (resource use and unit costs) • People diagnosed with COPD who presented to GP with exacerbation; followed-up at 1 year • Data collection by GP at planned follow-up visits • N = 766	• ATS 1 = £1236 • ATS 2 = £1704 • ATS 3 = £2424 Resource use included: drugs, clinic visits, A&E visits, hospitalisation, oxygen. Includes exacerbation costs	No
Rutten-van Molken 2005[174]	• Spain (resource use and unit costs) • Reanalysis of data from Miravitlles et al 2003 above.	• GOLD 2 = £393 • GOLD 3 = £537 • GOLD 4 = £748 Resource use included: healthcare contacts, tests, drugs, oxygen. Excludes exacerbation costs.	Yes
Oostenbrink et al. 2005[173]	• Netherlands/Belgium (86%/14%) (Netherlands unit costs) • People with stable COPD enrolled in 2 tiotropium vs. ipratropium RCT; prospective follow-up for 1 year (reanalysis of data from RCT) • N = 519	Netherlands • GOLD 2 = £352 • GOLD 3 = £617 • GOLD 4 = £1363	Yes

[yyy] All costs are converts to UK £ using PPP for the appropriate year, and then inflated to 2007/8 costs using the PSSRU healthcare inflation indices[627]. Reported to nearest whole £. FEV_1 % predicted: GOLD 1/2/3/4 = ≥80/79-50/49-30/<30; ATS 1/2/4 = 80-50/50-35/<35.

[zzz] Direct cost only presented here; calculated by dividing exacerbation costs/year by exacerbations/year.

	• Canada (resource use and unit costs) • Original resource use data reported as part of CEA. People with COPD; prospective follow-up for 1 year • N = 598	Canada • GOLD 2 = £330 • GOLD 3 = £797 • GOLD 4 = £1594 Resource use included: healthcare contacts, tests, drugs, oxygen. Excludes exacerbation costs.	
Maniadakis et al. 2006[637]	• Greece (resource use and unit costs) • Original resource use data reported as part of CEA. Analysis of medical records at the University General Hospital of Heraklion in Greece. • N = NR	• GOLD 2 = £355 • GOLD 3 = £431 • GOLD 4 = £562 Resource use included: healthcare contacts, spirometry, drugs. Excludes exacerbation costs.	Yes
Tynan 2005[654]	• Ireland • People with COPD diagnosis attending an outpatients clinic • Data collected by patient interview for previous 6 months and annualised • N = 150 (GOLD 0/1/2/3/4 = 20/14/46/38/24)	• GOLD 0 = £1637 • GOLD 1 = £2000 • GOLD 2 = £2753 • GOLD 3 = £4004 • GOLD 4 = £6703 Resource use included: healthcare contacts, hospitalisation, drugs, tests. Includes exacerbation costs	
Britton 2003[33aaaa]	• UK • N = 400 • Data from telephone interviews • Recorded info about the past year • People with COPD	• Mild = £171 / £291[bbbb] • Moderate = £352 / £683 • Severe = £1494 / £2239 Mild, moderate, severe = Self reported severity / MRC dyspnoea 0-2, 3-4, 5. Resource use included: healthcare contacts, tests, drugs, oxygen. Includes exacerbation costs; in whole population costs not related to unscheduled care = 40%.	

[aaaa] Other country reports of same study available but not reported as same format as for UK.
[bbbb] Direct costs only presented here

Jansson 2002[655]	• Sweden (resource use and costs) • People with COPD; followed-up over 1 year • Data collected via telephone interviews every 3 months • N = 212	• FEV_1 ≥80% predicted = £173 • FEV_1 60-79% predicted = £384 • FEV_1 40-59% predicted = £1297 • FEV_1 <40% predicted = £4258 Resource use included: drugs, healthcare contacts, hospitalisation, oxygen. Includes exacerbation costs.	Partly

Relative treatment effects

As described above, baseline event rates for the LABA+ICS arm of the model were obtained from the literature. The impact of alternative treatment combinations were then modelled by applying relevant relative treatment effects from randomised controlled trials to these baseline event rates.

In the base case analysis only exacerbations are impacted differentially by treatment in the model. Two alternative analyses also incorporate: a) a difference in utility when stable; b) mortality.

Relative treatment effect data were sought from the randomised controlled trials identified in the systematic evidence reviews undertaken for the guideline. Three studies were identified that each compared two of the three treatment options that are incorporated into the model:

- INSPIRE study[219]: LAMA vs LABA+ICS
- UPLIFT subgroup analysis[201]: triple therapy vs LABA+ICS
- OPTIMAL study[200]: triple therapy vs. LAMA

All three studies provide direct comparisons of two treatment options in the model. However, the studies form an evidence loop and cannot all be used at the same time to inform the model. For example, if we know the relative number of exacerbations with LAMA compared to LABA+ICS from one study, and the relative number of exacerbations with triple therapy compared to LABA+ICS from another study, the relative number of exacerbations with triple therapy compared in LAMA is therefore implicit without the use of the study that compares triple and LAMA.

There are three possible pairs of trials that can therefore be used in provide the estimates of relative treatment effect for the model (see also Figure 3 below):

1. INSPIRE and UPLIFT subgroup
2. INSPIRE and OPTIMAL
3. UPLIFT subgroup and OPTIMAL

Figure 3: Trials data combinations for estimates of relative effect

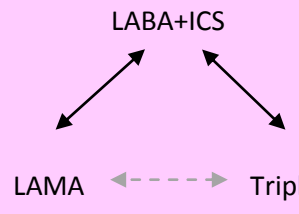
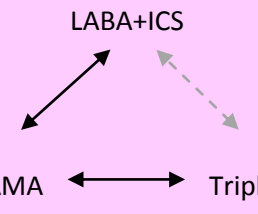
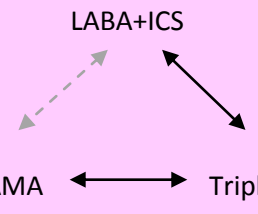
1. INSPIRE, UPLIFT	2. INSPIRE, OPTIMAL	3. UPLIFT, OPTIMAL
		
Solid black line = comparison in trial; Dashed grey line = implicit comparison		

Table 11 below summarises the resulting treatment effect estimates using each of the three pairs of trials. Rate ratios are used for exacerbations, and exacerbations requiring hospitalisation. Risk ratios are used for mortality. Mean difference is used for EQ-5D – this is obtained by mapping mean SQRQ data to EQ5D and calculating the difference. Note that more detail regarding the mapping of SGRQ to EQ5D is given later in this report.

Table 11: Relative effect estimates used in model for each three pairs of trials

	LABA+ICS vs. LAMA	Triple vs. LABA+ICS	Triple vs. LAMA
Exacerbations: rate ratio (95% confidence interval); grey/italic = implicit value			
1. INSPIRE, UPLIFT	0.97 (0.84-1.12)	0.85 (0.78-0.92)	*0.82*
2. INSPIRE, OPTIMAL	0.97 (0.84-1.12)	*0.88*	0.85 (0.65-1.11)
3. UPLIFT, OPTIMAL	*1.00*	0.85 (0.78-0.92)	0.85 (0.65-1.11)
Hospitalisations: rate ratio (95% confidence interval); grey/italic = implicit value			
1. INSPIRE, UPLIFT	1.08 (0.73-1.59)	0.89 (0.75-1.07)	*0.96*
2. INSPIRE, OPTIMAL	1.08 (0.73-1.59)	*0.49*	0.53 (0.33-0.86)
3. UPLIFT, OPTIMAL	*0.60*	0.89 (0.75-1.07)	0.53 (0.33-0.86)
Stable utility (EQ-5D): mean difference mapped from SGRQ*; grey/italic = implicit value			
1. INSPIRE, UPLIFT	0.023 (0.001-0.046)	0.021 (0.006-0.036)	*0.044*
2. INSPIRE, OPTIMAL	0.023 (0.001-0.046)	*0.017*	0.040 (0.007-0.075)
3. UPLIFT, OPTIMAL	*0.019*	0.021 (0.006-0.036)	0.040 (0.007-0.075)
Mortality: risk ratio (95% confidence interval); grey box = implicit value			
1. INSPIRE, UPLIFT	0.56 (0.33-0.94)	0.91 (0.76-1.11)	*0.51*
2. INSPIRE, OPTIMAL	0.56 (0.33-0.94)	*2.88*	1.61 (0.46-0.56)
3. UPLIFT, OPTIMAL	*1.72*	0.91 (0.76-1.11)	1.61 (0.46-0.56)

*Confidence intervals reflect uncertainty in mean difference in SGRQ translated to uncertainty in EQ-5D. Confidence interval generated from 10,000 simulations of probabilistic analysis
Sources: INSPIRE[219], UPLIFT subgroup[201], OPTIMAL[200]

The model was run using each of the three pairs of trials so that the impact on results and conclusions could be examined. As LABA+ICS data had been used to populate the model, relative treatment effects were calculated and applied in the model for LAMA and triple therapy compared to LABA+ICS using the above data. In the probabilistic analysis log normal distributions were used for rate ratios and risk ratios. Normal distributions were used for the mean SGRQ differences that were used calculate the mean EQ5D differences.

Mapping SGRQ to EQ-5D

Due to a lack of utility data, SGRQ data were mapped to EQ-5D where required. This was done as part of the estimation of QALY loss with an exacerbation (direct utility data was available for the initial impact but not over the longer term) and also to estimate the impact of treatment on stable utility as described in the relevant sections above.

The SGRQ (St Georges Respiratory Questionnaire) is a widely used measure of health impairment in COPD and asthma. SGRQ is not a utility measure and so cannot be used directly to calculate QALYs. There have however been some reports of mapping of SGRQ to EQ-5D. Two algorithms were identified that mapped total SGRQ score to EQ-5D utility[175,617]. These were compared and the Starkie method was selected in preference to the Oba method as the latter resulted in impossible values at the extreme ends[175,617]. However, it is noted that both approaches yielded similar values in the middle. The Starkie formula is displayed below.

$$Predicted\,utility\,score = 1 - 0.0335 + 0.0017T + 0.0001T^2 - 0.0279G$$

Where: T = total SGRQ score; G = gender (0=female, 1=male)

The GDG highlighted that they were aware of some issues with mapping SGRQ to EQ-5D when examined at a patient level and it was judged inferior to direct utility data. However, in the absence of alternatives this was considered a reasonable approach to fill in gaps in the data.

In addition, the SGRQ reflects exacerbations as well as stable symptoms. This is likely to more of an issue when used as an approximation of the difference in stable utility between treatment options than when estimating the rate of recovery following an exacerbation. In particular because the data used for the rate of recovery is in patients who do not have a new exacerbation and is also non-comparative.

> Computations

The model was constructed in Microsoft Excel and was evaluated by cohort simulation.

Patients start in cycle 0 distributed amongst the model health states (severe, very severe, dead) as described above. Patients were redistributed amongst the model health states over time as follows. Each cycle, the age-dependant COPD-severity specific death rates were applied to alive patients and the probability of progressing from severe to very severe was then applied to the remaining alive patients in the severe severity group in order to recalculate the number of people in each state. Life years in severe and very severe COPD states for the cohort are computed each cycle. A half-cycle correction is applied.

Each cycle, the number of exacerbations the cohort experienced was calculated by applying the severity-specific exacerbation rates to the number of life years in each severity state. The number of hospitalised exacerbations experienced was calculated by applying the

severity-specific hospitalisation rates to the number of life years in each severity state. The number of non-hospitalised exacerbations was calculated by subtracting the number of hospitalised exacerbations from the total exacerbations.

Total QALYs were calculated from the above information as follows. Each cycle, the time spent (i.e. 1 year) in each state of the model was weighted by the utility for that state. This gives the QALYs for each state for the cycle. The number of non-hospitalised and hospitalised exacerbations that occurred was multiplied by the relevant QALY loss due to an exacerbation. These were combined to give the QALYs per cycle, Q(t), and discounted to reflect time preference (discount rate = r). QALYs during year 1 were not discounted. The total discounted QALYs was the sum of the discounted QALYs per cycle.

$$Total\,discounted QALYs = \sum_{t=1}^{i} \frac{Q(t)}{(1+r)^{t-1}}$$

Where: t = cycle number; i = maximum cycle number; Q(t) = QALYs in cycle t; r = discount rate

Total costs were calculated from the above information as follows. Each cycle, the time spent (i.e. 1 year) in each state of the model was multiplied by the maintenance costs for that state and the relevant drug cost. The number of non-hospitalised and hospitalised exacerbations that occurred was multiplied by the respective costs. These were combined to give the costs per cycle, C(t), and discounted to reflect time preference (discount rate = r). Costs during year 1 were not discounted. The total discounted costs was the sum of the discounted costs per cycle.

$$Total\,discounted\,costs = \sum_{t=1}^{i} \frac{C(t)}{(1+r)^{t-1}}$$

Where: t = cycle number; i = maximum cycle number; C(t) = Costs in cycle t; r = discount rate

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs/QALYs(X) = total discounted costs/QALYs for option X

- Cost-effective if: ICER < Threshold

When there are more than two comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net benefit (NB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs. The decision rule then applied is that the comparator with the highest NB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost. For ease of computation NB is used to identify the optimal strategy in the probabilistic analysis simulations.

$$Net\ Benefit(X) = QALYs(X) \times D - Costs(X)$$

Where: Costs/QALYs(X) = total discounted costs/QALYs for option X; D = threshold

The probabilistic analysis was run for 5000 simulations. Each simulation, mean discounted costs and mean discounted QALYs were calculated for each treatment option. The net benefit was also calculated and the most cost-effective option identified (that is, the one with the highest net benefit), at a threshold of £20,000 and £30,000 per QALY gained. The results of the probabilistic analysis are summarised in terms of mean costs, mean QALYs and mean net benefit for each treatment option, where each is the average of the 5000 simulated estimates. The option with the highest mean net benefit (averaged across the 5000 simulations) is the most cost-effective at the specified threshold. The percentage of simulations where each strategy was the most cost-effective gives an indication of the strength of evidence in favour of that strategy being cost-effective.

Results are also presented on the cost-effectiveness plane where the difference in mean costs and the difference in mean QALYs between treatment options are plotted. All differences are calculated relative to LABA+ICS and so LABA+ICS is always at the origin of the cost-effectiveness plane. Results could have equally been presented with differences calculated relative to LAMA or triple therapy. This would make no difference to the cost effectiveness results it would simply mean that the axis would move so that a different treatment option is at zero. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio, the magnitude of which is labelled.

> Results

Detailed results are presented over the next few pages for the basecase scenario and various sensitivity analyses including the alternative treatment effect analyses. All results are means from the probabilistic analysis unless otherwise specified.

Basecase analysis – exacerbation effect only

In the basecase analysis only exacerbations (non-hospitalised and hospitalised) varied between treatment options. A four-year treatment period was considered. Three analyses were undertaken using different pairs of clinical trials to calculate relative treatment effects.

The results of these analyses are presented in Table 12 and Figure 4. A break down of costs is presented in Table 13. LAMA or LABA+ICS was found to be the most cost-effective strategy depending on the clinical trial data used to calculate relative treatment effects.

When INSPIRE and UPLIFT subgroup data were used, LAMA was found to be the most cost-effective option. Triple therapy was the most effective (that is it had the highest number of QALYs) but had a high ICER when compared with LAMA at £187,697 per QALY gained. LABA+ICS was more effective than LAMA (higher QALYs) but also with higher costs and was ruled out by extended dominance. LAMA was the optimal strategy at a threshold of £20,000 per QALY gained in 84% of simulations, LABA+ICS in 16% and triple therapy in 0%. When INSPIRE and OPTIMAL data were used instead results were similar although the ICER for triple therapy compared to LABA+ICS was lower at £93,737 per QALY gained.

When UPLIFT subgroup and OPTIMAL data were used LABA+ICS was found to be the most cost-effective option. LAMA was ruled out by dominance – it was more expensive with lower QALYs than LABA+ICS. Triple therapy was the most effective (that is, it had the highest number of QALYs) but had a high ICER when compared with LABA+ICS at £159,353 per QALY gained. LABA+ICS was the optimal strategy at a threshold of £20,000/QALY in 92% of simulations, LAMA in 8% and triple therapy in 0%.

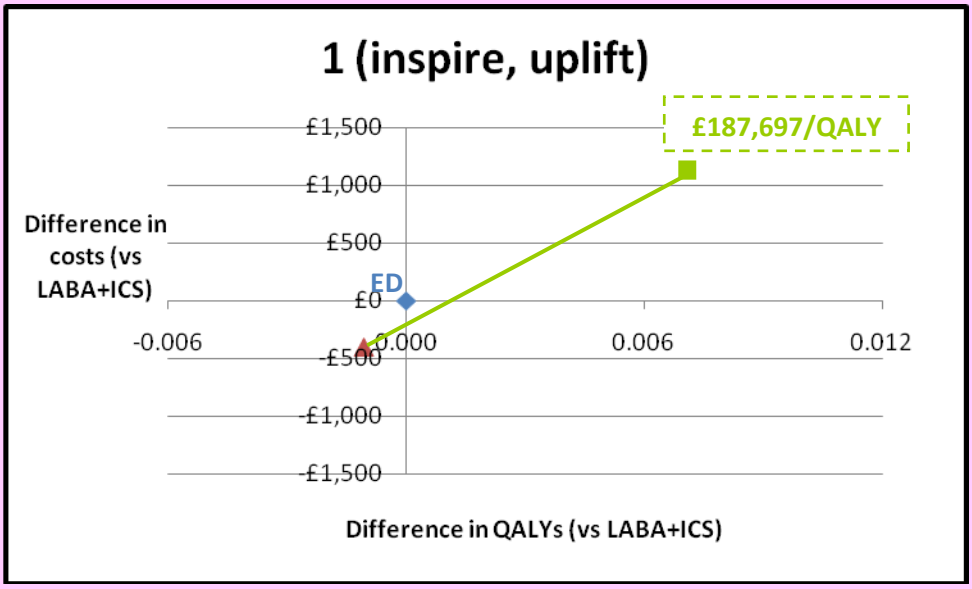
The results indicate fairly low uncertainty within individual analyses. However, the fact that between analyses there is a disagreement about the most cost-effective option indicates considerable uncertainty based on the available clinical evidence.

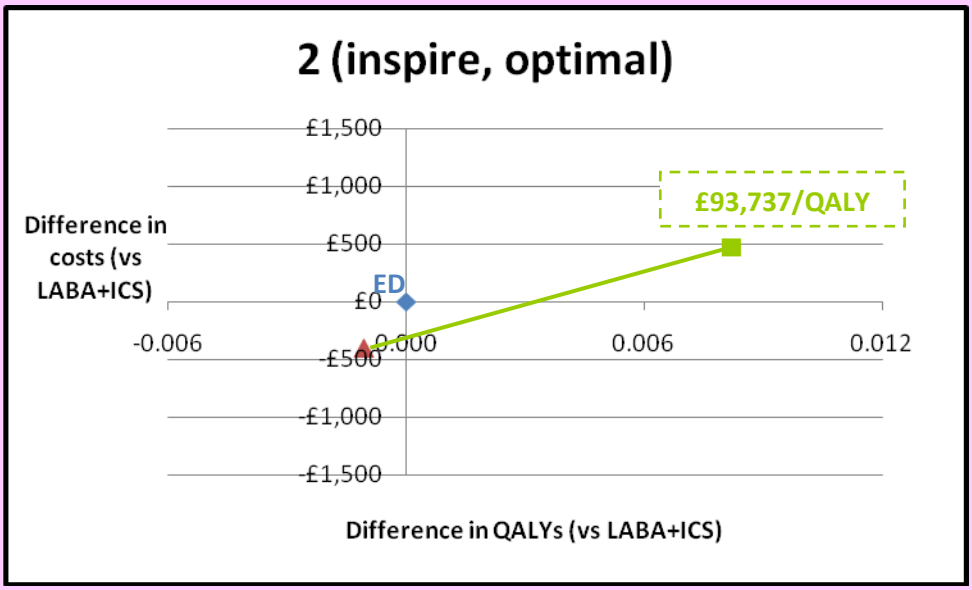
Table 12: Basecase results (exacerbation effect only; 4 years)

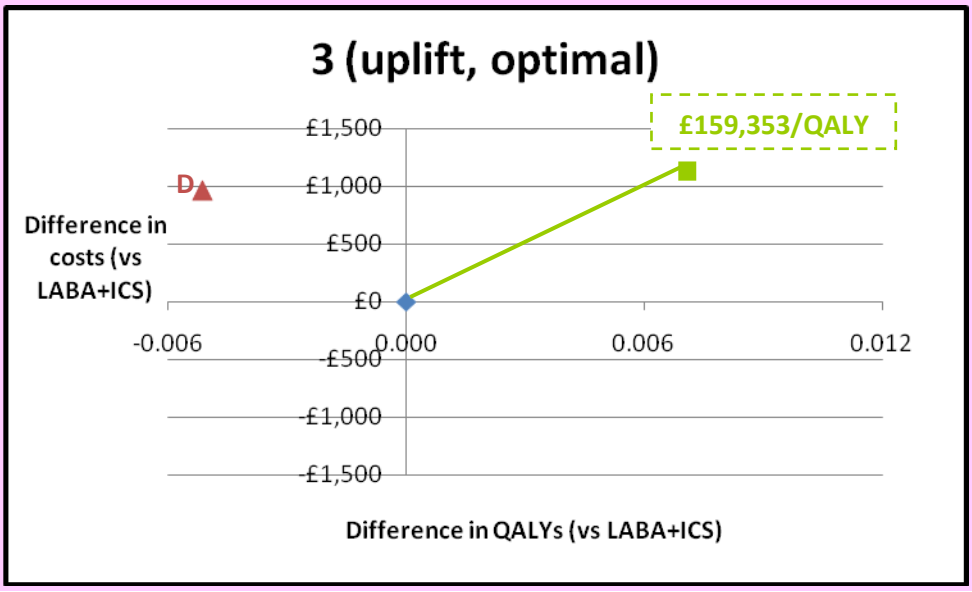
	Mean Cost	Mean QALYs	Net benefit* (threshold= £20,000 per QALY)	Probability that strategy is most cost-effective (threshold= £20,000 per QALY)	Net benefit* (threshold= £30,000 per QALY)	Probability that strategy is most cost-effective (threshold= £30,000 per QALY)
1. INSPIRE, UPLIFT data						
LABA+ICS	£5296	2.350	£41,709	16%	£65,211	17%
LAMA	£4896	2.349	£42,087	84%	£65,579	83%
Triple	£6426	2.357	£40,721	0%	£64,294	0%
2. INSPIRE, OPTIMAL data						
LABA+ICS	£5296	2.350	£41,709	15%	£65,211	16%
LAMA	£4896	2.349	£42,087	84%	£65,579	81%
Triple	£5764	2.358	£41,405	1%	£64,989	3%
3. UPLIFT, OPTIMAL data						
LABA+ICS	£5296	2.350	£41,709	92%	£65,211	92%
LAMA	£6260	2.345	£40,643	8%	£64,094	8%
Triple	£6426	2.357	£40,721	0%	£64,294	0%

*Highest net benefit = most cost effective option at stated threshold

Figure 4: Basecase results on the cost-effectiveness plane (exacerbation effect only; 4 years)







LABA+ICS

LAMA

Triple therapy

ED = ruled out by extended dominance

D = ruled out by dominance

Table 13: Basecase cost breakdown (exacerbations effect only; 4 years) – totals for a cohort of 1000 people (deterministic analysis)

	Exacerbations				Cost of treating exacerbations				Total cost	
	Total	*Non-hospitalised*	*Hospitalised*	Drug costs (intervention)	Total	*Non-hospitalised*	*Hospitalised*	COPD maintenance cost	Undiscounted	Discounted
1. INSPIRE, UPLIFT data										
LABA+ICS	4161	3370	791	£1,753,181	£2,015,084	£114,403	£1,900,681	£1,866,173	£5,634,438	£5,364,238
LAMA	4286	3551	735	£1,417,488	£1,888,152	£120,519	£1,767,633	£1,866,173	£5,171,814	£4,923,524
Triple	3537	2833	704	£3,170,669	£1,787,775	£96,169	£1,691,606	£1,866,173	£6,824,617	£6,498,454
2. INSPIRE, OPTIMAL data										
LABA+ICS	4161	3370	791	£1,753,181	£2,015,084	£114,403	£1,900,681	£1,866,173	£5,634,438	£5,364,238
LAMA	4286	3551	735	£1,417,488	£1,888,152	£120,519	£1,767,633	£1,866,173	£5,171,814	£4,923,524
Triple	3643	3253	390	£3,170,669	£1,047,273	£110,427	£936,846	£1,866,173	£6,084,115	£5,793,414
3. UPLIFT, OPTIMAL data										
LABA+ICS	4161	3370	791	£1,753,181	£2,015,084	£114,403	£1,900,681	£1,866,173	£5,634,438	£5,364,238
LAMA	4149	2832	1317	£1,417,488	£3,263,358	£96,122	£3,167,235	£1,866,173	£6,547,019	£6,232,870
Triple	3537	2833	704	£3,170,669	£1,787,775	£96,169	£1,691,606	£1,866,173	£6,824,617	£6,498,454

Sensitivity analyses

Alternative analysis one – exacerbation and stable quality of life effects

In this alternative analysis stable utility is differentially impacted between comparators as well as exacerbations. As in the basecase a four-year treatment period was considered and three analyses were undertaken using different pairs of clinical trials to calculate relative treatment effects.

Results of these analyses are presented in Table 14 and Figure 5. Triple therapy was found to be the most effective (highest number of QALYs) and most cost-effective strategy irrespective of the clinical trial data used to calculate relative treatment effects. LABA+ICS was found to be the next most effective and cost-effective option also irrespective of clinical data used. LAMA was less effective but also less expensive than LABA+ICS, except for when the data pair of UPLIFT and OPTIMAL was used and it was dominated. The ICER for triple therapy compared to LABA+ICS was in the range £7000 to £15,000 depending on the clinical trial data pair used. At a threshold of £20,000 per QALY gained, triple therapy was optimal in 71% to 76% of simulations, LABA+ICS was optimal in the majority of the remaining simulations and LAMA was very rarely optimal.

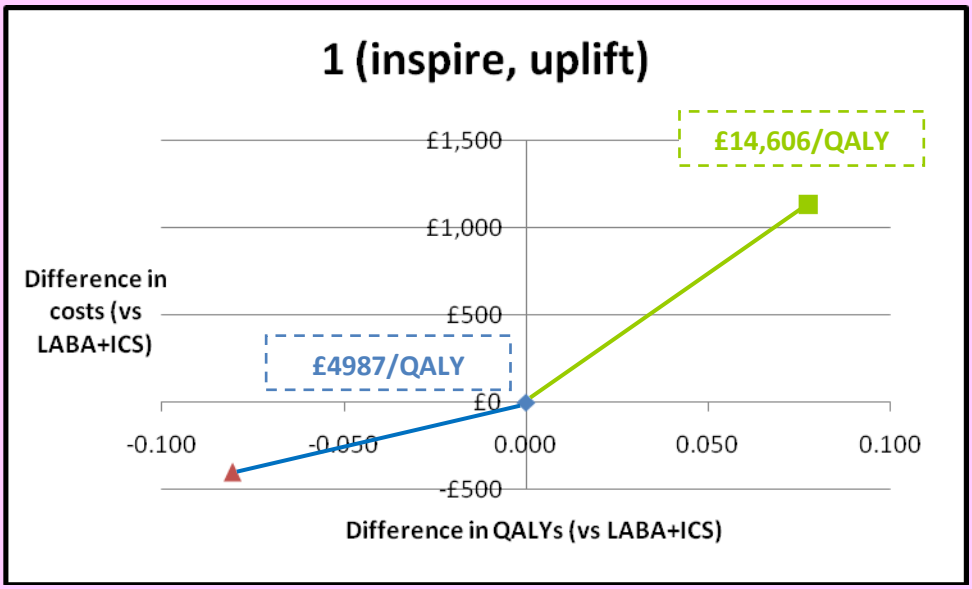
In this sensitivity analysis there was fairly low uncertainty within and between analyses that triple therapy is the optimal strategy. That is it provided the greatest health gain at an acceptable cost.

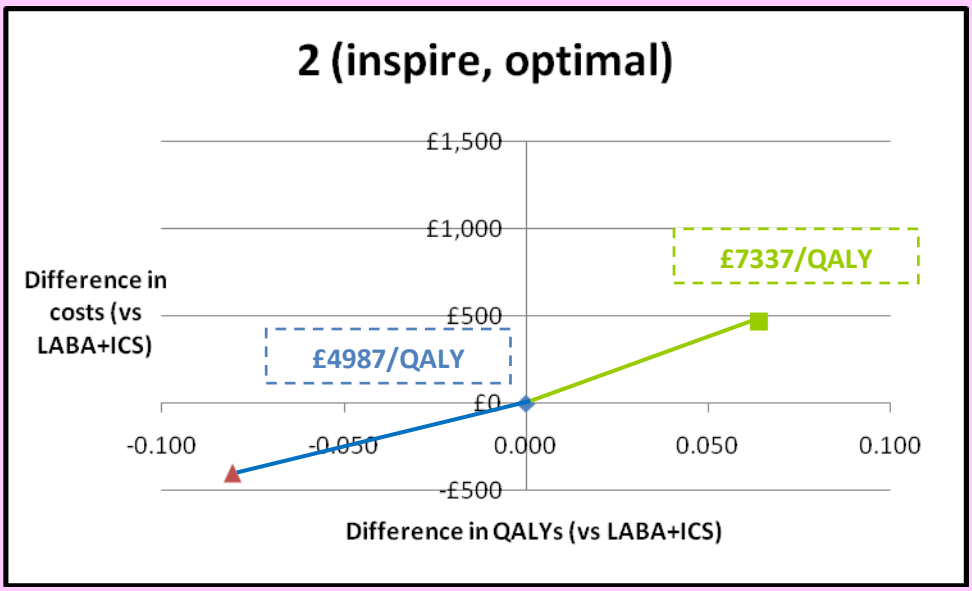
Table 14: Alternative analysis 1 results (exacerbation and stable quality of life effects; 4 years)

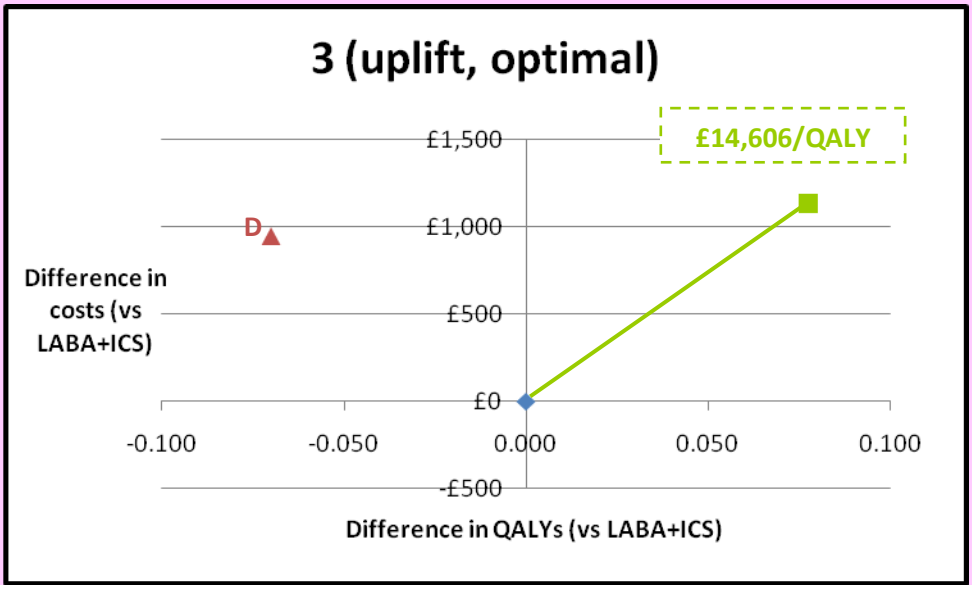
	Mean Cost	Mean QALYs	Net benefit* (threshold= £20,000 per QALY)	Probability that strategy is most cost-effective (threshold= £20,000 per QALY)	Net benefit* (threshold= £30,000 per QALY)	Probability that strategy is most cost-effective (threshold= £30,000 per QALY)
1. INSPIRE, UPLIFT data						
LABA+ICS	£5298	2.349	£41,688	21%	£65,180	6%
LAMA	£4895	2.268	£40,475	4%	£63,160	1%
Triple	£6429	2.427	£42,105	76%	£66,373	93%
2. INSPIRE, OPTIMAL data						
LABA+ICS	£5298	2.349	£41,688	29%	£65,180	25%
LAMA	£4895	2.268	£40,475	0%	£63,160	0%
Triple	£5766	2.413	£42,496	71%	£66,628	75%
3. UPLIFT, OPTIMAL data						
LABA+ICS	£5298	2.349	£41,688	22%	£65,180	6%
LAMA	£6244	2.279	£39,340	2%	£62,131	1%
Triple	£6429	2.427	£42,105	76%	£66,373	93%

*Highest net benefit = most cost effective option at stated threshold

Figure 5: Alternative analysis 1 results on the cost-effectiveness plane (exacerbation and stable quality of life effects; 4 years)







LABA+ICS

LAMA

Triple therapy

ED = ruled out by extended dominance

D = ruled out by dominance

Alternative analysis two – exacerbations and mortality effects

In this second alternative analysis mortality is differentially impacted between comparators as well as exacerbations. As in the basecase a four-year treatment period was considered and three analyses were undertaken using different pairs of clinical trials to calculate relative treatment effects.

Results of these analyses are presented in Table 15 and Figure 6.

When INSPIRE and UPLIFT subgroup data were used LABA+ICS was the the most cost-effective option. LAMA was less effective but also with lower costs. The ICER for LABA+ICS versus LAMA was low at £4302. Triple therapy was the most effective (that is it had the highest number of QALYs) but had an ICER of £40,722 when compared to the next most effective strategy, LABA+ICS, and so was not considered cost-effective. LABA+ICS was the optimal strategy at a threshold of £20,000 per QALY gained in 89% of simulations, LAMA in 4% and triple therapy in 7%.

When INSPIRE and OPTIMAL data were used instead results were quite different. LABA+ICS was still the most cost-effective option but was now also the most effective option (highest QALYs). LAMA was again less effective and with lower costs than LABA+ICS, and the ICER for LABA+ICS vs LAMA was low. Triple therapy was however now dominated by LAMA as it was less effective (lower QALYs) with higher costs. LABA+ICS was the optimal strategy at a threshold of £20,000 per QALY gained in 92% of simulations, LAMA in 3% and triple therapy in 5%.

When UPLIFT subgroup and OPTIMAL data were used results were again different. LAMA was now the most effective (that is it had the highest number of QALYs) and cost-effective option. LABA+ICS was less effective and less costly than LAMA and triple therapy was ruled out by extended dominance. The ICER for LAMA versus LABA+ICS was £15,566. LAMA was the optimal strategy in 64% of simulations, LABA+ICS in 34% and triple therapy in 2%.

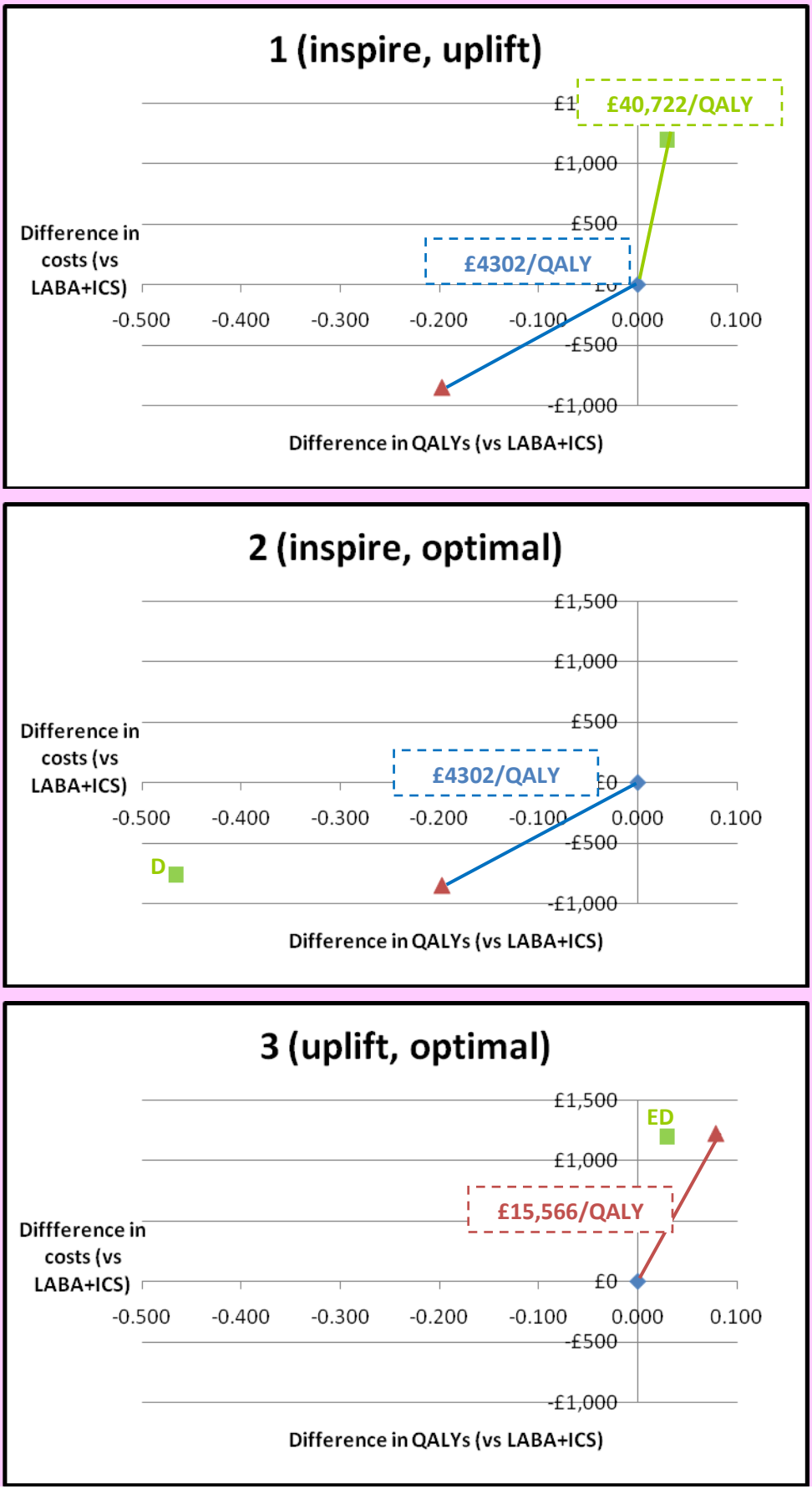
Results indicate fairly low uncertainty within individual analyses. However, there are considerable differences between results based on difference clinical data indicating high uncertainty in this sensitivity analysis.

Table 15: Alternative analysis 2 results (exacerbation and mortality effects; 4 years)

	Mean Cost	Mean QALYs	Net benefit* (threshold= £20,000 per QALY)	Probability that strategy is most cost-effective (threshold= £20,000 per QALY)	Net benefit* (threshold= £30,000 per QALY)	Probability that strategy is most cost-effective (threshold= £30,000 per QALY)
1. INSPIRE, UPLIFT data						
LABA+ICS	£5293	2.350	£41,714	89%	£65,218	66%
LAMA	£4443	2.153	£38,614	4%	£60,142	2%
Triple	£6491	2.380	£41,104	7%	£64,902	31%
2. INSPIRE, OPTIMAL data						
LABA+ICS	£5293	2.350	£41,714	92%	£65,218	93%
LAMA	£4443	2.153	£38,614	3%	£60,142	2%
Triple	£4531	1.885	£33,166	5%	£52,014	5%
3. UPLIFT, OPTIMAL data						
LABA+ICS	£5293	2.350	£41,714	34%	£65,218	22%
LAMA	£6519	2.429	£42,064	64%	£66,355	69%
Triple	£6491	2.380	£41,104	2%	£64,902	8%

*Highest net benefit = most cost effective option at stated threshold

Figure 6: Alternative analysis 2 results on the cost-effectiveness plane (exacerbation and mortality effects; 4 years)



Time horizon

Sensitivity analysis explored the impact of the time horizon on results. The time horizon did not greatly impact results for the base case analysis or the first alternative analysis described above and conclusions remained the same. There was a small decrease in the magnitude of the ICERs as the time horizon increased.

The time horizon had a greater impact in the second alternative analysis where a treatment effect on mortality was incorporated. Results for this analysis for a 1 year, 4 year and lifetime analysis are summarised in Table 16.

In the 4-year analysis of option 1, LABA+ICS was the most cost-effective option; triple therapy had the highest QALY but was not cost-effective. However when this 4-year treatment period was extrapolated to a lifetime impact triple became a cost-effective option.

In the 4-year analysis of option 3, LAMA was the most effective option (hightest QALYs) and the most cost-effective option. When the time horizon was reduced to 1 year LAMA was still the most effective but was no longer the most cost-effective and LABA+ICS was.

Table 16: Time horizon sensitivity analysis: alternative analysis 2 results (exacerbation and mortality effects)

	1 (inspire, uplift):			2 (inspire, optimal):			3 (uplift, optimal):		
	Cost	QALYs	Probability that strategy is most cost-effective (threshold= £20,000 per QALY)	Cost	QALYs	Probability that strategy is most cost-effective (threshold= £20,000 per QALY)	Cost	QALYs	Probability that strategy is most cost-effective (threshold= £20,000 per QALY)
1 year									
LABA+ICS	£1,483	0.681	79%	£1,483	0.681	78%	£1,483	0.681	75%
LAMA	£1,337	0.666	21%	£1,337	0.666	20%	£1,770	0.685	25%
Triple	£1,815	0.684	0%	£1,520	0.642	2%	£1,815	0.684	0%
4 years									
LABA+ICS	£5,293	2.350	89%	£5,293	2.350	92%	£5,293	2.350	34%
LAMA	£4,443	2.153	4%	£4,443	2.153	3%	£6,519	2.429	64%
Triple	£6,491	2.380	7%	£4,531	1.885	5%	£6,491	2.380	2%
Lifetime (4-years differential treatment period with lifetime extrapolation)*									
LABA+ICS	£11,788	4.972	38%	£11,788	4.972	93%	£11,788	4.972	11%
LAMA	£9,729	4.311	1%	£9,729	4.311	2%	£13,590	5.267	75%
Triple	£13,133	5.057	61%	£8,470	3.509	6%	£13,133	5.057	14%
Lifetime (lifetime differential treatment period)*									
LABA+ICS	£11,772	4.965	34%	£11,772	4.965	92%	£11,772	4.965	9%
LAMA	£7,976	3.751	1%	£7,976	3.751	1%	£18,431	6.293	76%
Triple	£14,845	5.197	65%	£7,449	3.026	6%	£14,845	5.197	15%

*Minor discrepancies in LABA+ICS figures between the two lifetime analyses are due to them being generated by different runs of the probabilisitc model.

Exacerbation rate

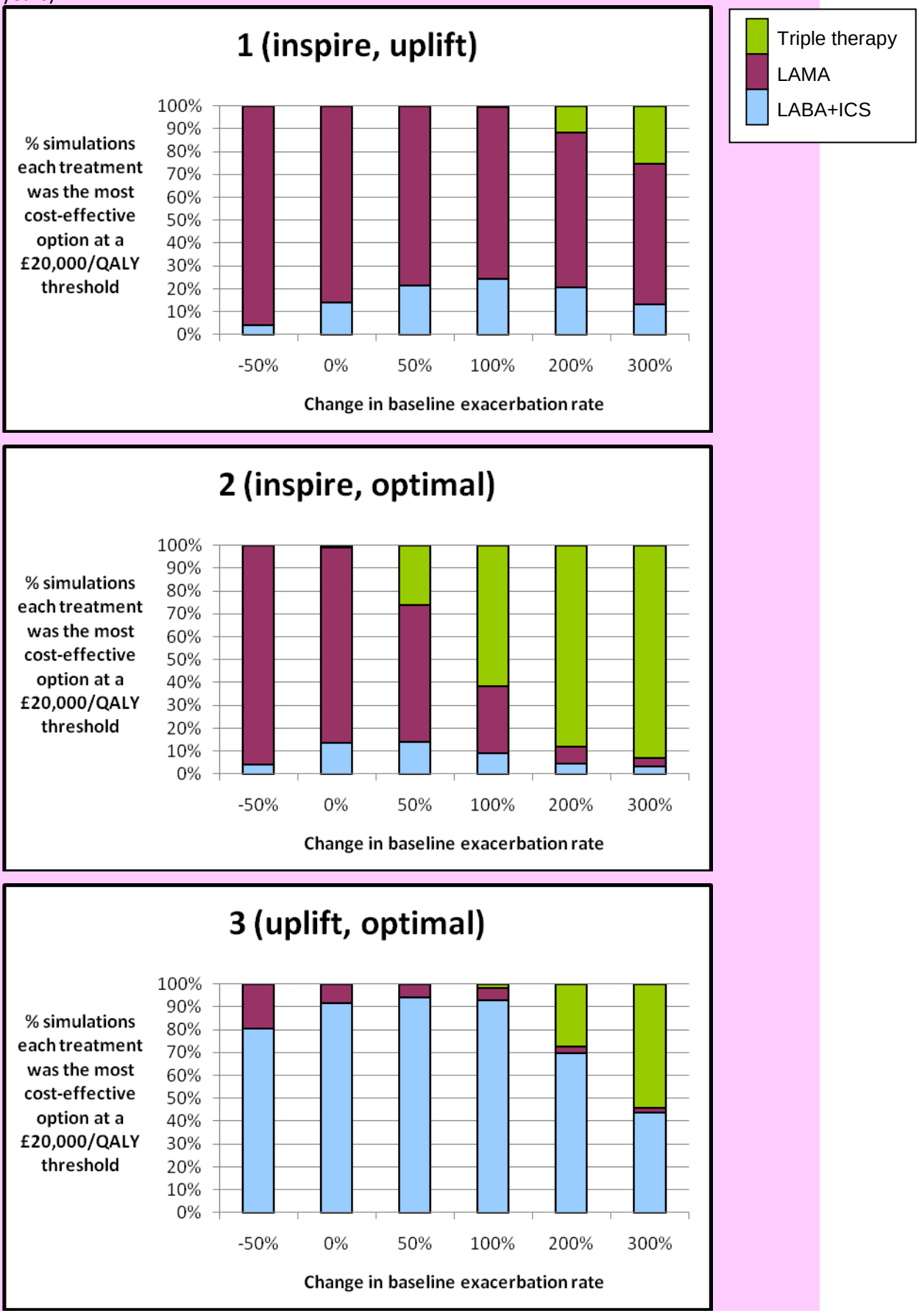
A sensitivity analysis was undertaken to look at the impact of varying the baseline exacerbation rate on the basecase analysis. Rates were varied by a factor of -50% to +300% – the resulting baseline exacerbation rates used in the sensitivity analysis are presented in Table 17. Results are presented in Figure 7. We found that as the exacerbation rate increases so the percentage of simultations where triple therapy was optimal increased.

Table 17: Exacerbation rates used in sensitivity analysis

Change from baseline exacerbation rate	COPD stage	Exacacerbations/ year	Hospitalisations/ year
-50%	**Severe**	0.46	0.09
	Very severe	0.77	0.15
0% (baseline)	**Severe**	0.91	0.17
	Very severe	1.54	0.29
100%	**Severe**	1.82	0.35
	Very severe	3.08	0.59
200%	**Severe**	2.73	0.52
	Very severe	4.62	0.88
300%	**Severe**	3.64	0.69
	Very severe	6.16	1.17

Severe = FEV_1 30% to <50% predicted; Very severe = FEV_1 <30% predicted

Figure 7: Exacerbation rate sensitivity analysis: basecase analysis (exacerbation effect only; 4 years)



Cost of non-hospitalised exacerbations

Sensitivity analysis around the cost of a non-hospitalised exacerbation was undertaken due to uncertainty about the cost being too low. In one analysis the cost was doubled from £34 to £68. This had very little impact on the basecase analysis results.

A threshold analysis was also undertaken (using the deterministic analysis) to see at what cost of a non-hospitalised exacerbation would triple therapy become the favoured option (i.e. with an ICER of under £20,000/QALY) in the basecase analysis. The result was that triple therapy was cost-effective only when the cost of treating a non-hospitalised exacerbation was assumed to be around £2000 or higher. The exact theshold varied depending on the clinical trial data pair used.

> Discussion

Summary and GDG interpretation

The aim of this analysis was to evaluate which was the most cost-effective option from LABA+ICS, LAMA and triple therapy for initial management of people with COPD and an FEV_1 <50%.

The base case analysis, which is driven by differences in exacerbations between treatments, found that LABA+ICS or LAMA was the most cost-effective option depending on which clinical data was used to inform the differences between treatments. Triple therapy was the most effective option (highest QALYs) but was not cost-effective. The GDG considered this analysis to be the most robust in terms of the available data. However, it was also considered likely to be conservative in terms of the benefits of treatment and may underestimate the value of triple therapy. The fact that either LABA+ICS or LAMA was the favoured option depending on the clinical data used in the analysis highlights an inconsistency in the clinical data but one that could not be resolved and so therefore was considered to represent an uncertainty over the preferred option.

In the sensitivity analysis which also incorporates a difference between treatments in terms of stable utility (quality of life), triple therapy was found to be the most effective (highest QALYs) and the most cost-effective option, irrespective of which clinical data was used to inform the differences between treatments. The GDG considered that a scenario where treatment impacted utility due to stable symptom improvement as well as exacerbations to be a realistic one but given the limitations of the estimate of treatment effect on stable utility they interpreted the results with caution.

A sensitivity analysis that looked at the impact of exacerbation rates found that as the baseline exacerbation rate increased so did the probability that triple therapy was cost-effective.

In the sensitivity analysis where a treatment effect in terms of mortality was incorporated, results varied greatly depending on the clinical data used and were sensitive to the time horizon taken. This reflected considerable inconsistency in the clinical data for this outcome.

The GDG concluded that this result was difficult to interpret and it was not used to inform decision making.

Limitations

The availability of utility data to inform the estimation of QALYs was somewhat limited. EQ-5D utility data was identified for the initial impact of hospitalised and non-hospitalised exacerbations. Mapping of SGRQ data to EQ-5D utility was used to supplement this where necessary. GDG members indicated that they were aware of problems with mapping SGRQ to EQ-5D and were generally not in favour of an approach that primarily based QALY impact on this. For this reason, in the base case analysis we attributed a QALY loss to hospitalised and non-hospitalised exacerbations, which minimised the reliance on mapped data. This lack of direct utility data impacts most analyses in the area of COPD. A notable exception being a cost-utility analysis using patient level TORCH data where EQ5D utility data was collected at various time points throughout the trial and so could be used as a basis for QALY calculations.

In the model we assumed that an exacerbation impacted a patient (to a diminishing extent) for 3 months but then stable utility will return to the same level as prior to the exacerbation. The GDG noted that there is evidence that exacerbations may permanently impact quality of life and this assumption is likely to be somewhat conservative. It was however accepted as a reasonable simplification for modelling purposes.

As described in the model input section, there was discussion regarding whether the cost of a non-hospitalised exacerbation identified in the literature was too low. Sensitivity analysis showed however that the model was not especially sensitive to the cost of a non-hospitalised exacerbation and this uncertainty was therefore not considered a major limitation.

Note that other more minor data limitations were discussed throughout the model inputs section.

Conclusions

Based on the limitations of the clinical evidence for triple therapy and the results of the cost-effective model, the GDG concluded that patients with an FEV_1 <50% should be offered LAMA or LABA+ICS as initial maintenance therapy. The GDG considered that while triple therapy was potentially effective and cost-effective, the evidence was not strong enough to warrant a recommendation that all patients with an FEV_1 <50% be routinely started on triple therapy. Triple therapy was instead recommended if symptoms or exacerbations persisted. They noted that triple therapy was most likely to be cost-effective in patients who will obtain a benefit in terms of exacerbation reduction and symptom relief.

25 Appendix N NEW 2010 COPD update GDG declarations of interest register

GDG declarations of Interest Register

GDG MEMBER	Declarations of Interest
Margaret Barnard	
24/08/2008	I have COPD
Graham Burns	
07.08.08 x1 GDG deputy	I have received fees for delivering educational lectures to respiratory specialists, GPs and nurses from a number of companies: Passtest BMJ, TEVA, GSK, AZ, Pfizer and Boehringer-Ingelheim. I received subsistence (hotel/food) from Boehringer-Ingelheim allowing me to attend the British Thoracic Society summer meeting in York (June 2008). GSK and MSD have supported meetings of the North of England Thoracic Society in the form of unrestricted educational grants.
Peter Calverley	
28.08-08	In the last 12 months I have attended one advisory board for AstraZeneca to consider future drug treatments in COPD, one for Daxas to review progress on an unlicensed therapy in development and one for Roche to design a study for testing retinoids in emphysema. I have agreed to be the UK principal investigator for a study comparing inhaled corticosteroids plus bronchodilators with bronchodilators alone which is supported by Boehringer-Ingelheim. I have led a research team supported by Chiesi comparing long-acting beta-agonists with and without inhaled corticosteroids. This project ends this autumn. I have spoken at 3 meetings (one UK, 2 overseas) about current drug treatment, all supported by GSK. I do not have any regular paid employment by any party other than the University of Liverpool and I hold no shares or other pecuniary interests in the pharmaceutical or medical suppliers industries. My department currently receives funds from GSK to conduct a non-commercial prospective study evaluating the phenotypic differences in COPD. This supports a medical research fellows salary. At present we do not receive funding from any other pharmaceutical or company source.
Barbara Foggo	
22.04.09 x1 GDG deputy	Dec 08 - GSK One-day Nurse Advisory Board for pulmonary arterial hypertension. Dec 08 - Pfizer one-hour talk on sildenafil/congenital heart disease associated pulmonary arterial hypertension. Honorariums paid.

Kevin Grufydd Jones	
25.07.08	In the last 12 months I have carried out advisory work and educational talks for the following pharmaceutical companies; Astra Zeneca, Glaxo Smith Kline, Boehringer Ingelheim, Galen, MSD, Novartis, Triniti Chiesi. My practice has carried out comercial trial work for Astra Zeneca, Boehringer Ingelheim (cardiovascular drug), Servier (vaccine). I have been sponsored by Astra Zeneca and Boehringer Ingelheim to attend the International Primary Care Respiratory Congress and European Respiratory Congress respectively. Astra Zeneca have provided a research grant for a study to validate the Asthma Control questionnaire in Children (no direct product involvement). I am a member of the British Thoracic Society and General Practice Airways Group.
Erica Haines	
12.1.09 x1GDG deputy	Attended ATS conference in May 2008 on GPIAG respiratory leaders programme sponsored by GSK. Attended speaker meetings in current role for AstraZeneca and BPIAG. Attended Novartis Head Office in Basel Switzerland as Advisory Board Member (November 2008). Currently working with GSK to develop 10 roadshows across the UK about asthma management. Starts next week.
David Halpin (Invited expert)	
23.7.08	I have received sponsorship to attend international meetings, and honoraria for lecturing, attending advisory boards and preparing educational materials from Altana, AstraZeneca, GlaxoSMithKline and Boehringer Ingelheim. I am the principle investigator of study of the efficacy of health forecasting which is being funded by AstraZeneca.
Karen Heslop	
Date? 2008	I provide consultancy for training in psychological management of anxiety and depression, which is common in COPD. Consultancy fees have been received in the last 12 months. I also provide non-promotional training for COPD management e.g. to practice nurses on behalf of the pharmaceutical industry. I have received travel fellowships from GSK in May to attend the American Thoracic Society meeting.
24.06.09	Boehringer Ingelheim - consultancy work for workshop on CBT in COPD; Astra Zeneca - consultancy fee for workshop on CBT.
16.9.09	Presentation on CBT in COPD for GSK on 11.9.09. Presentation on oxygen guidelines and inhaler workshop on 23.9.09 for AZ
Kevin Holton	
07.01.09 x1 GDG	NONE

Melvyn Jones	
22.05.09	The practice has joined Assura GP co, which will potentially benefit from primary care commissioned services. As yet no services have been commissioned. I work for UCL as a senior lecturer. This organisation I suspect receives grant income from the health sector, but I have no direct involvement or benefits from this. I have published a letter in the BMJ which was critical of implementation of a NICE guideline *(Mannan R, Jones M. What's the evidence that NICE guidance has been implemented? Maybe NICE Needs to do more to ensure implementation of guidelines. BMJ 2005;330:1085)*
10.12.08	Family member is a consultant radiologist who reports CT scans for the GSK emphysema trial, but she has no financial or academic involvement in the trial
Katherine Leach	
8.10.08	NONE
Christine Loveridge	
24.10.08	I regularly speak or take part in advisory boards for the following companies as part of my role in education for health and in recognition of my experience on a personal level. They include GSK, AZ, Teva, Boehringer Ingelheim, Pfizer. Education for Health as a not for profit charity work with the healthcare industry in an advisory and educational capacity. These include GSK, AZ, Teva, Trinity Chieri, Boehringer Ingelheim, Pfizer.
Phyo Kyan Myint	
17.10.08	NONE
John O'Reilly	
05.08.08	NONE
19.09.08	I have received honoraria for lectures at educational meetings from Boehringer Ingelheim, TEVA, GSK, AstraZeneca, Cephalon, UCB, Respironics prior to September 2007. I have subsequently received support for travel and accommodation to attend educational conferences but not honoraria or other payments for COPD-related meetings.
Fiona Phillips	
12.07.09 x2 GDGs	NONE

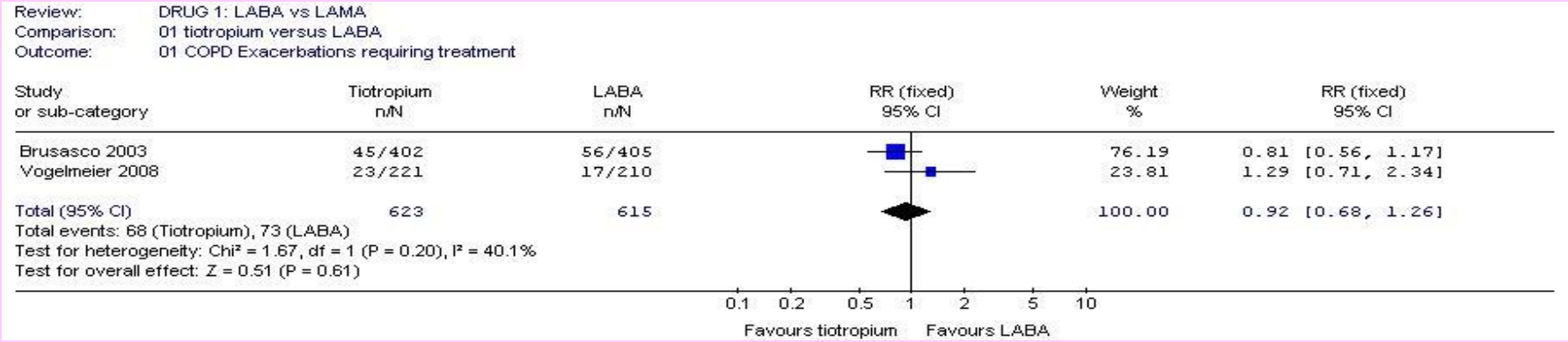
Michael Rudolf	
31.07.08	I have received support for travel and accommodation to attend international meetings from Boehringer Ingelheim and TEVA. I have received payment for chairing/speaking at educational meetings sponsored by AstraZeneca, GSK, Pfizer, Novartis, MSD, Boehringer Ingelheim & TEVA. My department has received financial support for running departmental meetings from AstraZeneca and TEVA. From 1997-2004 I was chairman of the BTS COPD Consortium which helped to raise awareness of COPD and played a major role in implementing both the BTS COPD Guidelines and the NICE COPD Guidelines.
Sally Singh	
07.08.08	NONE
Jadwiga Wedzicha	
9.08.08	In the past 12 months I have received honoraria for lectures or participation in advisory boards from the following pharmaceutical companies: Novartis, Kyorin Japan, GSK, AstraZeneca, Wyeth, Boehringer Ingelheim. Grant from GSK for ECLIPSE cohort study - approx £500,000 over 4 years from 2006-2010. Grant from AstraZeneca for study of susceptibility to COPD exacerbation - approx £225,000 from 2007-2009.

26 Appendix O NEW 2010 COPD update forest plots

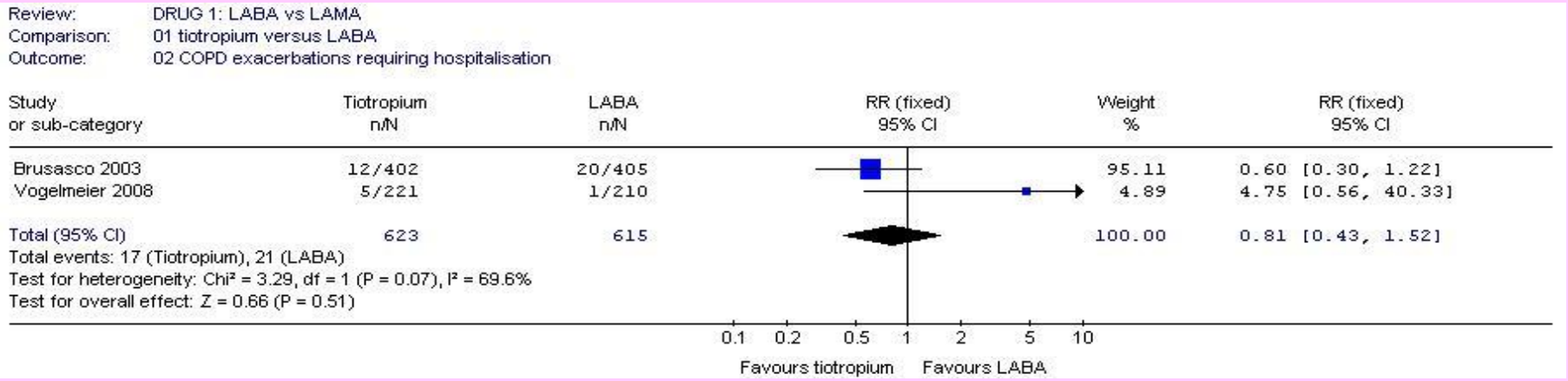
From section 7.3.4 Long-acting anticholinergics (long-acting muscarinic antagonists or LAMA)

LAMA versus LABA

Number of people with COPD exacerbations requiring additional therapy



Number of people with COPD exacerbations requiring hospitalisation

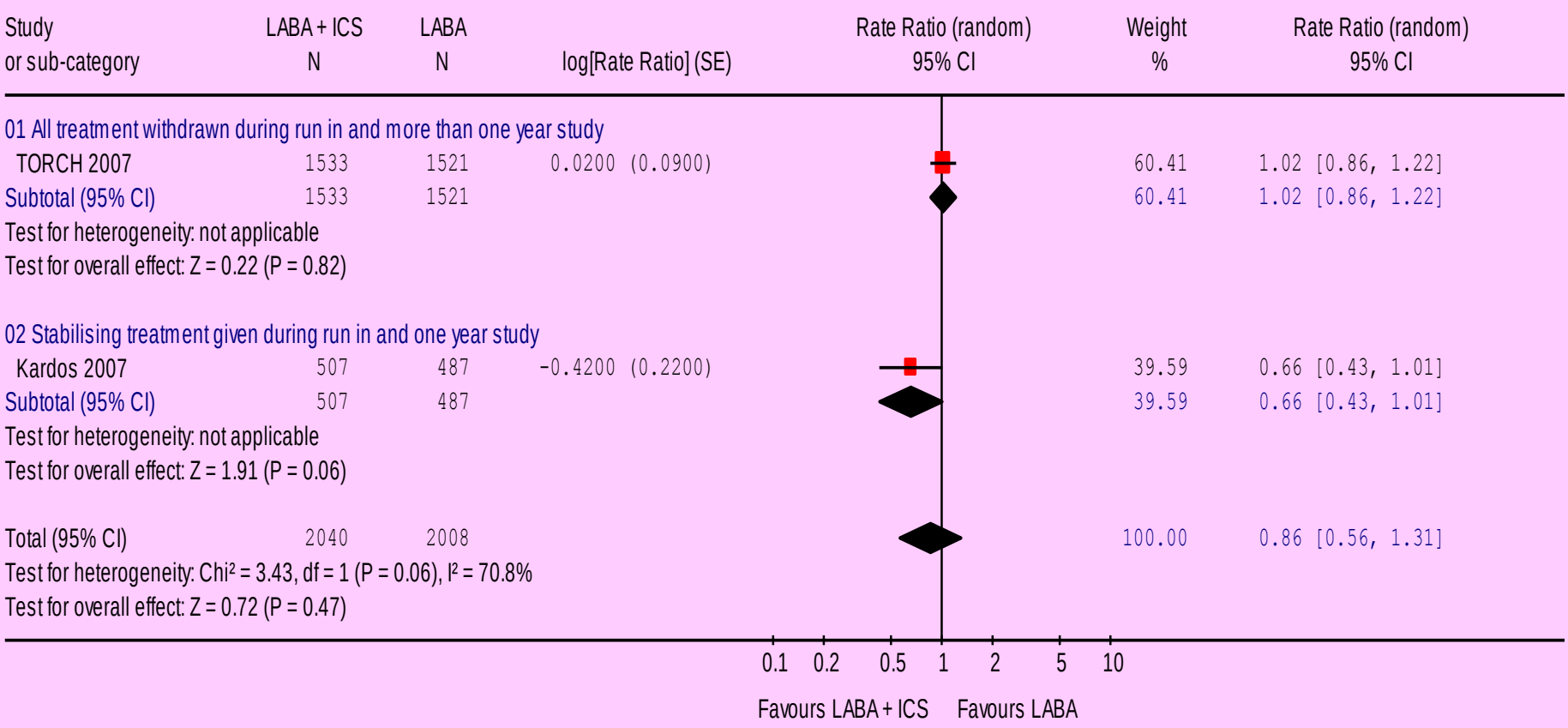


From section 7.3.6.1 Long-acting beta$_2$ agonists (LABA) and inhaled corticosteroids (ICS)

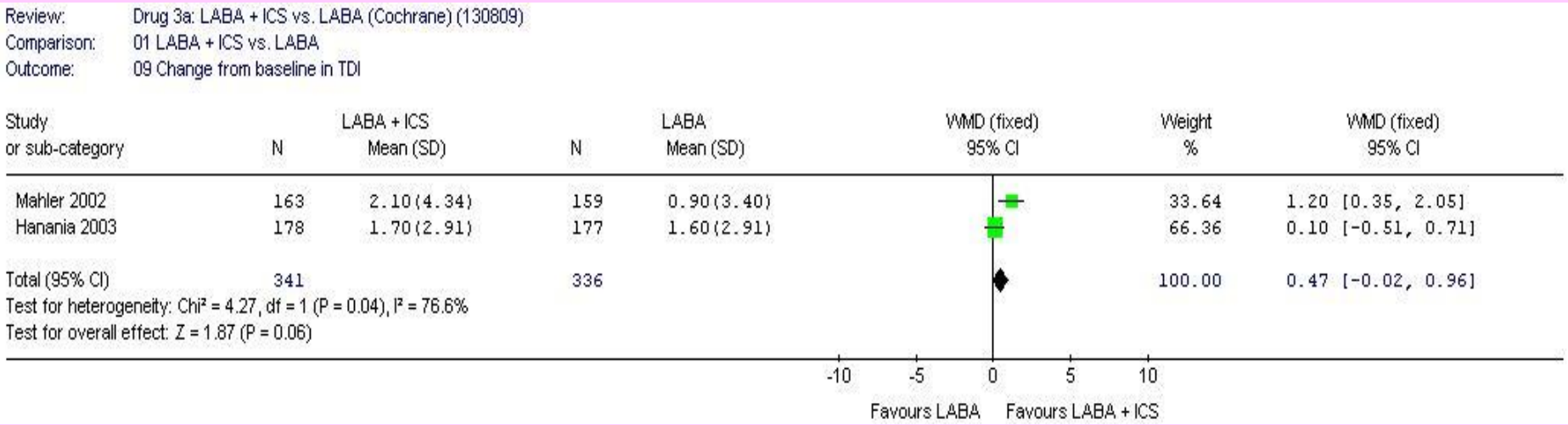
Drug 3a LABA + ICS versus LABA

Exacerbations requiring hospitalisation

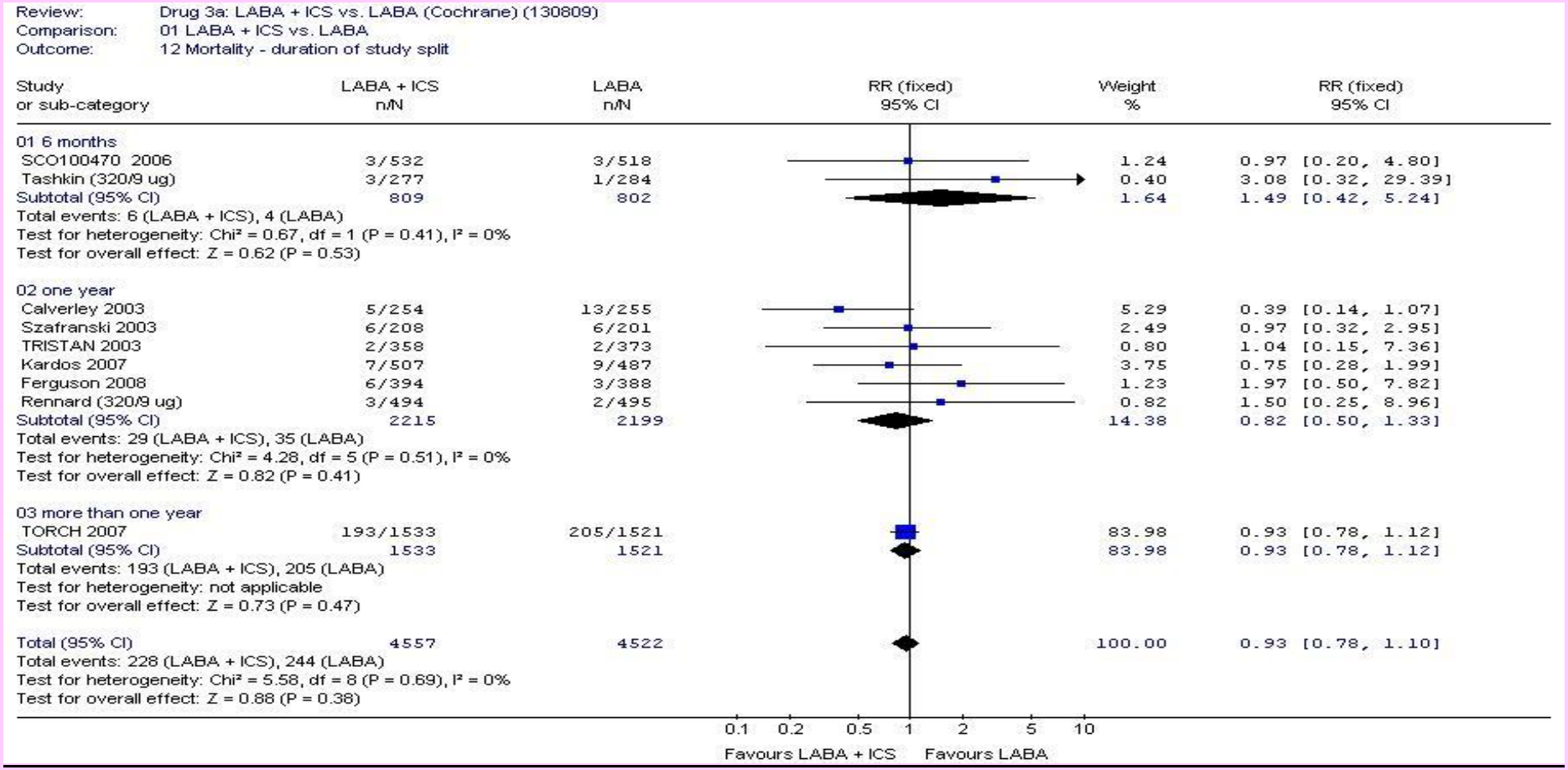
Review: Drug 3a: LABA + ICS vs. LABA (Cochrane) (latest 300309)
Comparison: 01 LABA + ICS vs. LABA
Outcome: 07 Exacerbations requiring hospitalisation



Change from baseline in breathlessness score (TDI)

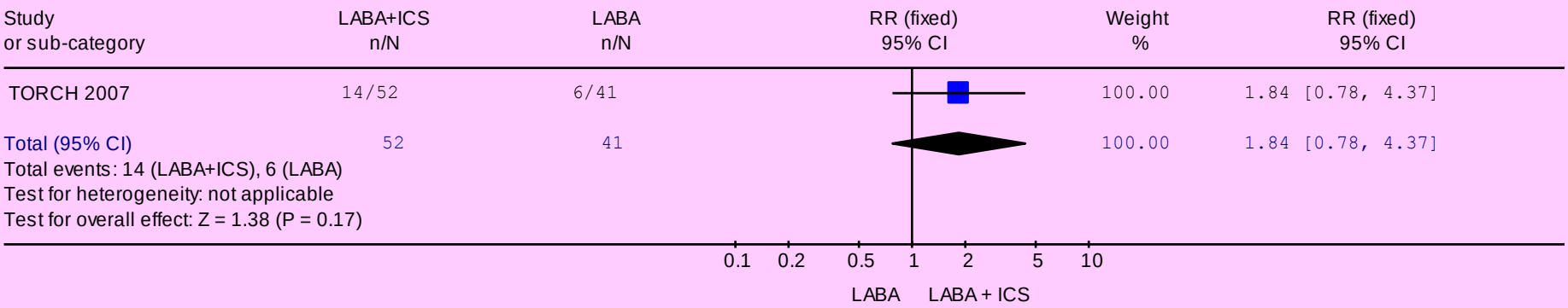


Mortality

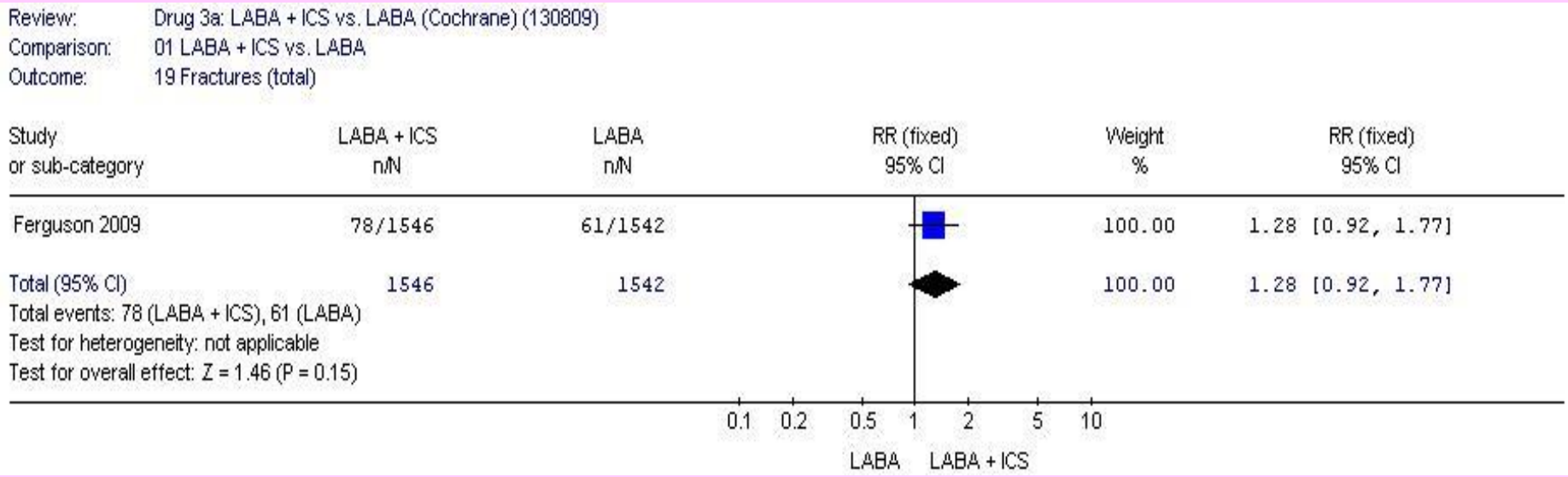

Review: Drug 3a: LABA + ICS vs. LABA (Cochrane) (130809)
Comparison: 01 LABA + ICS vs. LABA
Outcome: 12 Mortality - duration of study split
Study or sub-category
LABA + ICS n/N
LABA n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
01 6 months
SCO100470 2006 3/532 3/518 1.24 0.97 [0.20, 4.80]
Tashkin (320/9 ug) 3/277 1/284 0.40 3.08 [0.32, 29.39]
Subtotal (95% CI) 809 802 1.64 1.49 [0.42, 5.24]
Total events: 6 (LABA + ICS), 4 (LABA)
Test for heterogeneity: Chi² = 0.67, df = 1 (P = 0.41), I² = 0%
Test for overall effect: Z = 0.62 (P = 0.53)
02 one year
Calverley 2003 5/254 13/255 5.29 0.39 [0.14, 1.07]
Szafranski 2003 6/208 6/201 2.49 0.97 [0.32, 2.95]
TRISTAN 2003 2/358 2/373 0.80 1.04 [0.15, 7.36]
Kardos 2007 7/507 9/487 3.75 0.75 [0.28, 1.99]
Ferguson 2008 6/394 3/388 1.23 1.97 [0.50, 7.82]
Rennard (320/9 ug) 3/494 2/495 0.82 1.50 [0.25, 8.96]
Subtotal (95% CI) 2215 2199 14.38 0.82 [0.50, 1.33]
Total events: 29 (LABA + ICS), 35 (LABA)
Test for heterogeneity: Chi² = 4.28, df = 5 (P = 0.51), I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)
03 more than one year
TORCH 2007 193/1533 205/1521 83.98 0.93 [0.78, 1.12]
Subtotal (95% CI) 1533 1521 83.98 0.93 [0.78, 1.12]
Total events: 193 (LABA + ICS), 205 (LABA)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.73 (P = 0.47)
Total (95% CI) 4557 4522 100.00 0.93 [0.78, 1.10]
Total events: 228 (LABA + ICS), 244 (LABA)
Test for heterogeneity: Chi² = 5.58, df = 8 (P = 0.69), I² = 0%
Test for overall effect: Z = 0.88 (P = 0.38)
0.1 0.2 0.5 1 2 5 10
Favours LABA + ICS
Favours LABA

Cataracts

Review: Drug 3a: LABA + ICS vs. LABA (Cochrane) (latest 300309)
Comparison: 01 LABA + ICS vs. LABA
Outcome: 18 Cataracts



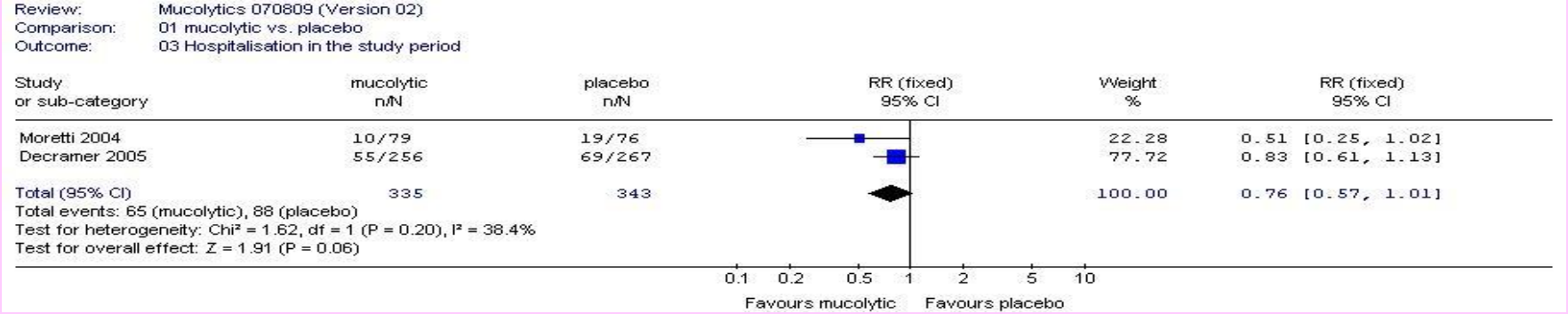
Fractures


Review: Drug 3a: LABA + ICS vs. LABA (Cochrane) (130809)
Comparison: 01 LABA + ICS vs. LABA
Outcome: 19 Fractures (total)
Study or sub-category
LABA + ICS n/N
LABA n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Ferguson 2009 78/1546 61/1542 100.00 1.28 [0.92, 1.77]
Total (95% CI) 1546 1542 100.00 1.28 [0.92, 1.77]
Total events: 78 (LABA + ICS), 61 (LABA)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.46 (P = 0.15)
0.1 0.2 0.5 1 2 5 10
LABA LABA + ICS

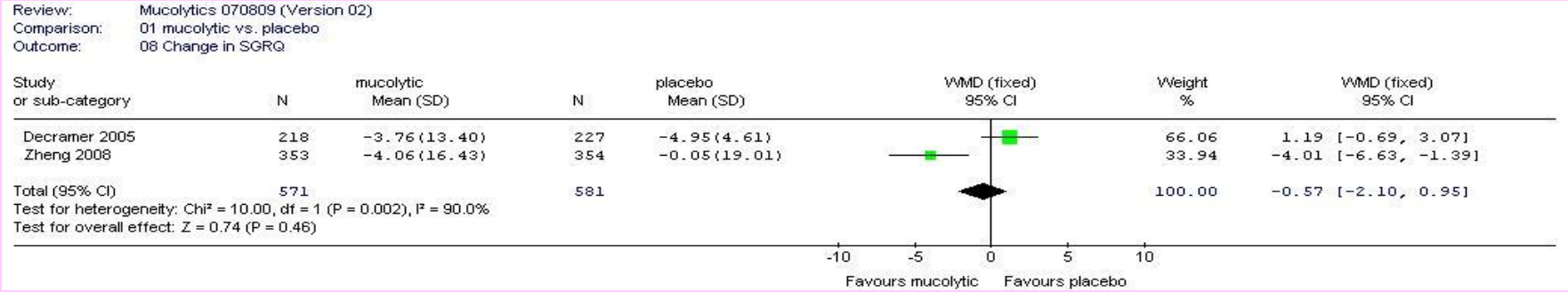
From section 7.4.4 Oral mucolytics

Mucolytics versus Placebo

Number of people hospitalised

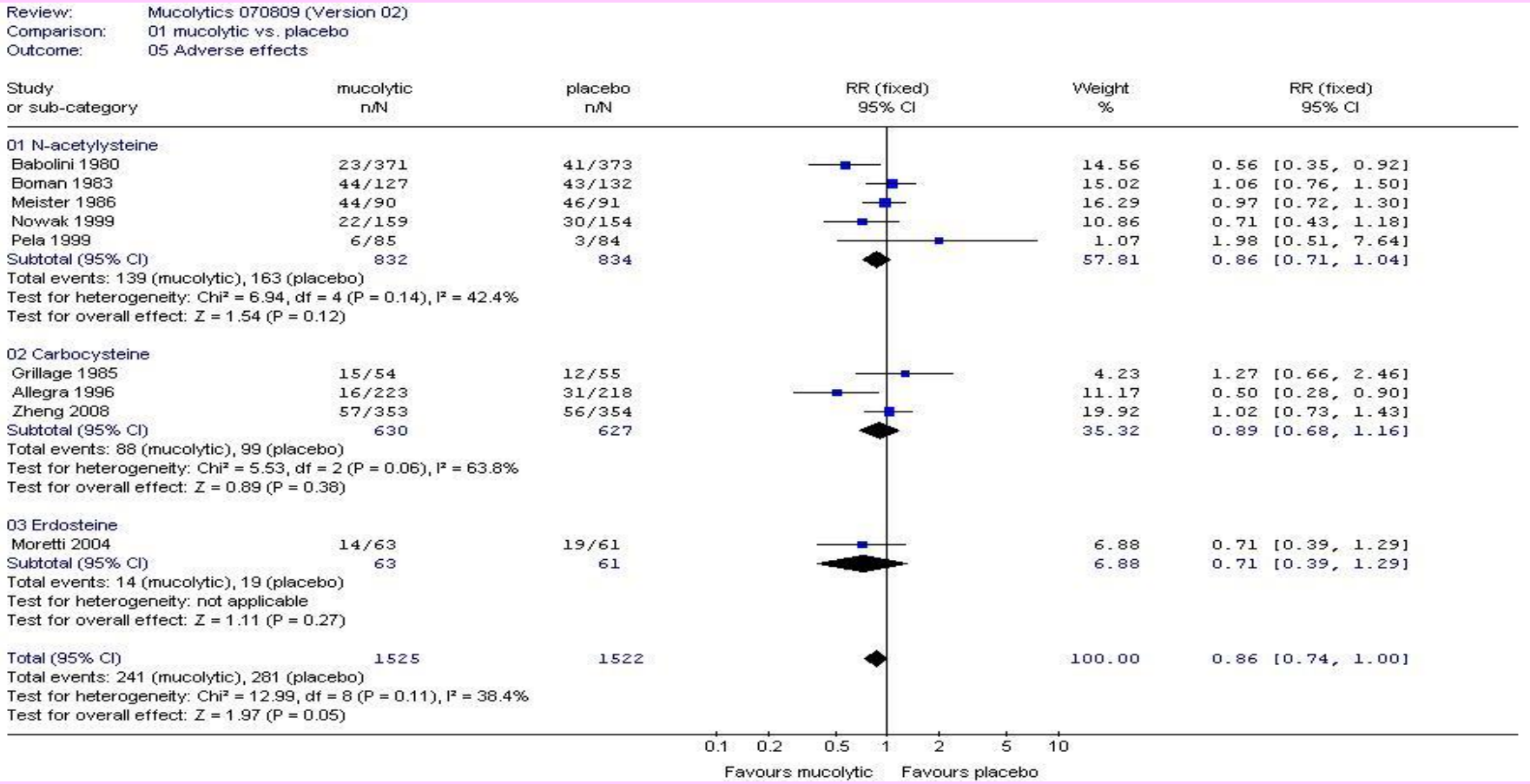


Change from baseline in health related quality of life (total SGRQ score)

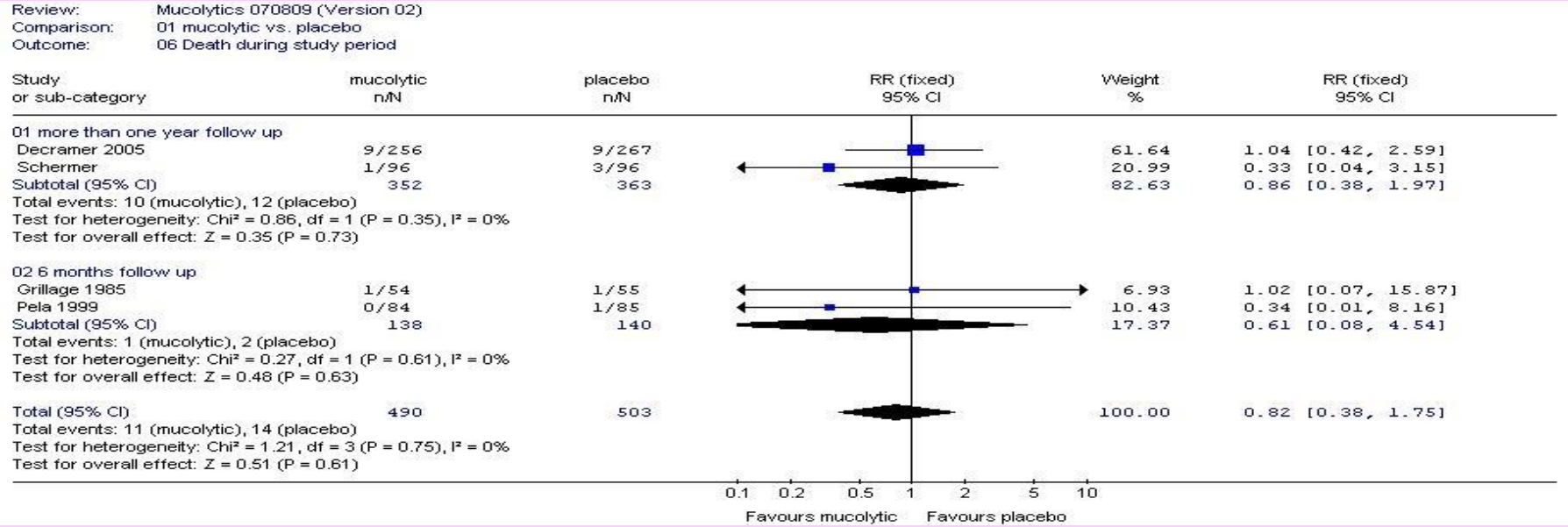


Total who completed SGRQ in Decramer study is 445. Assumed that the 78 drop outs were evenly distributed between the intervention and placebo arms. NCC calculated SD from the mean and 95% CI that were provided in the paper.

Adverse events



Mortality

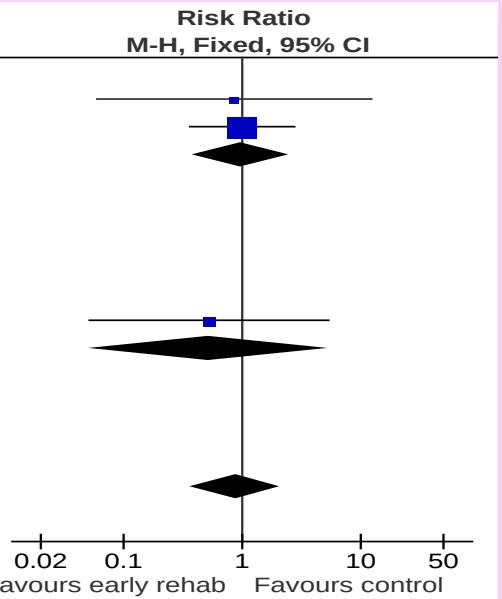

Review: Mucolytics 070809 (Version 02)
Comparison: 01 mucolytic vs. placebo
Outcome: 06 Death during study period
Study or sub-category
mucolytic n/N
placebo n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
01 more than one year follow up
Decramer 2005 9/256 9/267 61.64 1.04 [0.42, 2.59]
Schermer 1/96 3/96 20.99 0.33 [0.04, 3.15]
Subtotal (95% CI) 352 363 82.63 0.86 [0.38, 1.97]
Total events: 10 (mucolytic), 12 (placebo)
Test for heterogeneity: Chi² = 0.86, df = 1 (P = 0.35), I² = 0%
Test for overall effect: Z = 0.35 (P = 0.73)
02 6 months follow up
Grillage 1985 1/54 1/55 6.93 1.02 [0.07, 15.87]
Pela 1999 0/84 1/85 10.43 0.34 [0.01, 8.16]
Subtotal (95% CI) 138 140 17.37 0.61 [0.08, 4.54]
Total events: 1 (mucolytic), 2 (placebo)
Test for heterogeneity: Chi² = 0.27, df = 1 (P = 0.61), I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Total (95% CI) 490 503 100.00 0.82 [0.38, 1.75]
Total events: 11 (mucolytic), 14 (placebo)
Test for heterogeneity: Chi² = 1.21, df = 3 (P = 0.75), I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)
0.1 0.2 0.5 1 2 5 10
Favours mucolytic
Favours placebo

From section 7.9.5 Timing of rehabilitation programmes

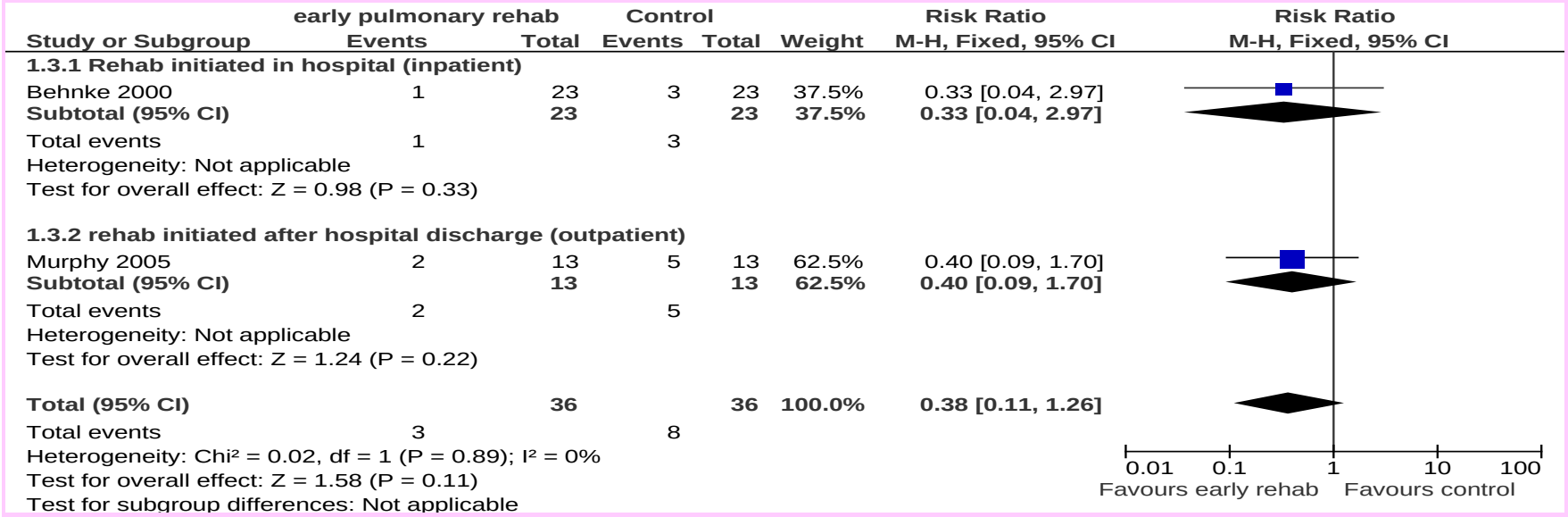
Early pulmonary rehabilitation post exacerbation compared with usual care/control

Mortality

Study or Subgroup	early pulmonary rehab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Rehab initiated in hospital (inpatient)						
Behnke 2000	1	14	1	12	11.9%	0.86 [0.06, 12.28]
Nava 1998	12	60	4	20	66.5%	1.00 [0.36, 2.75]
Subtotal (95% CI)		**74**		**32**	**78.4%**	**0.98 [0.38, 2.52]**
Total events	13		5			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
1.2.2 rehab initiated after hospital discharge (outpatient)						
Man 2004	1	20	2	21	21.6%	0.53 [0.05, 5.35]
Subtotal (95% CI)		**20**		**21**	**21.6%**	**0.53 [0.05, 5.35]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)		**94**		**53**	**100.0%**	**0.88 [0.37, 2.11]**
Total events	14		7			
Heterogeneity: Chi² = 0.25, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Test for subgroup differences: Not applicable						



Exacerbations



27 Reference List

1 Healthcare Commission. *Clearing the air: A national study of chronic obstructive pulmonary disease.* Healthcare Commission, 2006.

2 Cox BD. Blood pressure and respiratory function. In: The health and lifestyle survey. Preliminary report of a nationwide survey of the physical and mental health, attitudes and lifestyle of a random sample of 9003 British adults. London: 1987: 17-33.

3 Renwick DS, Connolly MJ. *Prevalence and treatment of chronic airways obstruction in adults over the age of 45*. *Thorax.* 51(2); 164-168. 1996.

4 Seamark DA, Williams S, Timon S et al. Home or surgery based screening for chronic obstructive pulmonary disease (COPD)? *Primary Care Respiratory Journal.* 2001; 10(2):30-33.

5 Pride NB, Soriano JB. Chronic obstructive pulmonary disease in the United Kingdom: trends in mortality, morbidity and smoking. *Current Opinion in Pulmonary Medicine.* 2002; 8(2):95-101.

6 Office for National Statistics. *Health Statistics Quarterly.* (8). London: HMSO, 2000.

7 NHS Information Centre for Health and Social Care. *Quality Outcomes Framework: Prevalence Data Tables 2008/9*. Available from: http://www.ic.nhs.uk/statistics-and-data-collections/supporting-information/audits-and-performance/the-quality-and-outcomes-framework/qof-2008/09/data-tables/prevalence-data-tables. Last accessed on: 2010 May 5.

8 Shahab L, Jarvis MJ, Britton J et al. Chronic obstructive pulmonary disease: Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. *Thorax.* 2006; 61(12):1043-1047.

9 Department of Health. *Chronic Obstructive Pulmonary Disease (COPD) Indicator set: Dataset and Business Rules: new GMS Contract QOF Implemenation.* (version14.0). London: Department of Health, 1-5-2009.

10 Department of Health. *On the state of the public health: Annual Report of the Chief Medical Officer 2004.* 2005.

11 Mannino DM, Gagnon RC, Petty TL et al. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. *Arch Intern Med.* 2000; 160(11):1683-1689.

12 British Thoracic Society. *The Burden of Lung Disease.* (2nd edition). British Thoracic Society, 2006.

13 Burney, P. and Jarvis, D. *The burden of COPD in the UK.* NHS National Library for Health: Respiratory Specialist Library, 2006.

14 Nacul LC, Soljak M, Meade T. Model for estimating the population prevalence of chronic obstructive pulmonary disease: cross sectional data from the Health Survey for England. *Population Health Metrics.* 2007; 5:8.

15 Soriano JB, Maier WC, Egger P et al. Recent trends in physician diagnosed COPD in women and men in the UK. *Thorax.* 2000; 55(9):789-794.

16 Royal College of Physicians, British Thoracic Society, and British Lung Foundation. *Report of the National Chronic Obstructive Pulmonary Disease Audit 2008: Clinical audit of COPD exacerbations admitted to acute NHS trusts across the UK.* London: Royal College of Physicians, 2008.

17 British Lung Foundation. *Breathing fear - the COPD effect.* 2003.

18 Royal College of Physicians and British Thoracic Society. *Report of the 2003 National COPD Audit.* 2004.

19 Hansell A, Hollowell J, McNiece R et al. Validity and interpretation of mortality, health service and survey data on COPD and asthma in England. *Eur Respir J.* 2003; 21(2):279-286.

20 Eachus J, Williams M, Chan P et al. Deprivation and cause specific morbidity: evidence from the Somerset and Avon survey of health. *Br Med J.* 1996; 312(7026):287-292.

21 British Lung Foundation. *Invisible lives: Chronic Obstructive Pulmonary Disease (COPD) finding the missing millions.* 2007.

22 Hansell AL, Walk JA, Soriano JB. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. *Eur Respir J.* 2003; 22(5):809-814.

23 Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.* 2008.

24 Sin DD, Anthonisen NR, Soriano JB et al. Mortality in COPD: Role of comorbidities. *Eur Respir J.* 2006; 28(6):1245-1257.

25 Damiani, M. and Dixon, J. *Managing the pressure. Emergency hospital admissions in London 1997 - 2001.* London: King's Fund, 2002.

26 Buist SA. Consequences and Comorbidities of Cigarette-induced Lung Injury: Lung Cancer, COPD, and Cardiovascular disease. Introduction. *Proceedings of the American Thoracic Society.* 2008; 5(8):796-799.

27 Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease.* GOLD, 2006.

28 Wasswa-Kintu S, Gan WQ, Man SF et al. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. *Thorax.* 2005; 60(7):570-575.

29 Mannino DM. COPD and lung cancer have come a long way ...baby. *American Journal of Respiratory & Critical Care Medicine.* 2007; 176(2):108-109.

30 Boyd CM, Darer J, Boult C et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *Journal of the American Medical Association.* 2005; 294(6):716-724.

31 Fabbri LM, Luppi F, Beghe B et al. Complex chronic comorbidities of COPD. *Eur Respir J.* 2008; 31(1):204-212.

32 van Weel C., Schellevis FG. Comorbidity and guidelines: conflicting interests. *Lancet.* 2006; 367(9510):550-551.

33 Britton M. The burden of COPD in the U.K.: results from the Confronting COPD survey. *Respir Med.* 2003; 97(Suppl C):S71-S79.

34 British Thoracic Society. *The Burden of Lung Disease.* (2nd edition). British Thoracic Society, 2006.

35 Anon. Appendix D: Economics costs of COPD to the NHS. *Thorax.* 2004; 59(Suppl):i192-i194.

36 National Institute for Health and Clinical Excellence. *The Guidelines Manual 2007.* National Institute for Health and Clincal Excellence, 2007.

37 National Institute for Health and Clinical Excellence. *The Guidelines Manual.* London: UK: National Institute for Health and Clinical Excellence, 2009.

38 Fletcher CM, Elmes PC, Fairbairn MB et al. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *Br Med J.* 1959; 2(5147):257-266.

39 Nolan D, White P, Pearson MG. FEV-1 and PEF in COPD management. *Thorax.* 1999; 54(5):468-469.

40 Jones PW. Health status measurement in chronic obstructive pulmonary disease. *Thorax.* 2001; 56(11):880-887.

41 Anthonisen NR, Wright EC, Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1986; 133(1):14-20.

42 Burrows B. The course and prognosis of different types of chronic airflow limitation in a general population sample from Arizona: comparison with the Chicago "COPD" series. *Am Rev Respir Dis.* 1989; 140(3 Pt 2):S92-S94.

43 Perez PR, Hallal PC, Vazquez GJ et al. Impact of bronchodilator use on the prevalence of COPD in population-based samples. *COPD: Journal of Chronic Obstructive Pulmonary Disease.* 2007; 4(2):113-120.

44 Calverley PMA, Burge PS, Spencer S et al. Bronchodilator reversibility testing in chronic obstructive pulmonary disease. *Thorax.* 2003; 58(8):659-664.

45 Quanjer PH, Tammeling GJ, Cotes JE et al. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *European Respiratory Journal Supplement.* 1993; 16:5-40.

46 Global Initiative for Chronic Obstructive Lung Disease. *Global strategy for the diagnosis, management and prevention of COPD (2007 update)*.:[1-109] Available from: http://www goldcopd com/.

47 Johannessen A, Lehmann S, Omenaas ER et al. Post-bronchodilator spirometry reference values in adults and implications for disease management. *American Journal of Respiratory & Critical Care Medicine.* 2006; 173(12):1316-1325.

48 Schermer TRJ, Quanjer PH. COPD screening in primary care: Who is sick? *Primary Care Respiratory Journal.* 2007; 16(1):49-53.

49 Falaschetti E, Laiho J, Primatesta P et al. Prediction equations for normal and low lung function from the Health Survey for England. *Eur Respir J.* 2004; 23(3):456-463.

50 Viegi G, Pedreschi M, Pistelli F et al. Prevalence of airways obstruction in a general population: European Respiratory Society vs American Thoracic Society definition. *Chest.* 2000; 117(5 SUPPL. 2):339S-345S.

51 Hardie JA, Buist AS, Vollmer WM et al. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. *Eur Respir J.* 2002; 20(5):1117-1122.

52 Celli BR, Halbert RJ, Isonaka S et al. Population impact of different definitions of airway obstruction. *Eur Respir J.* 2003; 22(2):268-273.

53 Hnizdo E, Glindmeyer HW, Petsonk EL et al. Case definitions for chronic obstructive pulmonary disease. *COPD: Journal of Chronic Obstructive Pulmonary Disease.* 2006; 3(2):95-100.

54 Culver BH. Interpretation of spirometry: we can do better than the GOLD standard. *Respir Care.* 2006; 51(7):719-721.

55 Roberts SD, Farber MO, Knox KS et al. FEV1/FVC ratio of 70% misclassifies patients with obstruction at the extremes of age. *Chest.* 2006; 130(1):200-206.

56 Shirtcliffe P, Weatherall M, Marsh S et al. COPD prevalence in a random population survey: a matter of definition. *Eur Respir J.* 2007; 30(2):232-239.

57 Enright P, Quanjer P. Spirometry for COPD is both underutilized and overutilized. *Chest.* 2007; 132(2):368-370.

58 Medbo A, Melbye H. Lung function testing in the elderly--can we still use FEV1/FVC<70% as a criterion of COPD? *Respir Med.* 2007; 101(6):1097-1105.

59 Hansen JE, Sun XG, Wasserman K. Spirometric criteria for airway obstruction: Use percentage of FEV1/FVC ratio below the fifth percentile, not < 70%. *Chest.* 2007; 131(2):349-355.

60 Pellegrino R, Brusasco V, Viegi G et al. Definition of COPD: based on evidence or opinion? *Eur Respir J.* 2008; 31(3):681-682.

61 Swanney MP, Ruppel G, Enright PL et al. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax.* 2008; 63(12):1046-1051.

62 Akhtar R, Wilson A. A comparison of spirometry in general practice and a pulmonary function laboratory. *Primary Care Respiratory Journal.* 2005; 14(4):215-220.

63 Schermer TR, Smeele IJ, Thoonen BP et al. Current clinical guideline definitions of airflow obstruction and COPD overdiagnosis in primary care. *Eur Respir J.* 2008; 32(4):945-952.

64 Cerveri I, Corsico AG, Accordini S et al. Underestimation of airflow obstruction among young adults using FEV1/FVC <70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. *Thorax.* 2008; 63(12):1040-1045.

65 Pellegrino R, Viegi G, Brusasco V et al. Interpretative strategies for lung function tests. *Eur Respir J.* 2005; 26(5):948-968.

66 American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis.* 1991; 144(5):1202-1218.

67 Ko FW, Woo J, Tam W et al. Prevalence and risk factors of airflow obstruction in an elderly Chinese population. *Eur Respir J.* 2008; 32(6):1472-1478.

68 Roche N, Dalmay F, Perez T et al. FEV1/FVC and FEV1 for the assessment of chronic airflow obstruction in prevalence studies: do prediction equations need revision? *Respir Med.* 2008; 102(11):1568-1574.

69 Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J.* 2004; 23(6):932-946.

70 National Institute for Health and Clinical Excellence. *Chronic Obstructive Pulmonary Disease- management of chronic obstructive pulmonary disease in adults in primary and secondary care.* (CG12)., 2004.

71 COPD Guidelines Group of the Standards of Care Committee of the BTS. BTS guidelines for the management of chronic obstructive pulmonary disease. *Thorax.* 1997; 52(Suppl 5):S1-28.

72 Global Initiative for Chronic Obstructive Lung Disease. *Global strategy for the diagnosis, management and prevention of COPD.* 2001.

73 British Thoracic Society, Scottish Intercollegiate Guidelines Network. British Guideline on the management of asthma. *Thorax.* 2003; 58(Suppl 1):1-94.

74 Anthonisen NR, Wright EC. Bronchodilator response in chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1986; 133(5):814-819.

75 Nisar M, Walshaw M, Earis JE et al. Assessment of reversibility of airway obstruction in patients with chronic obstructive airways disease. *Thorax.* 1990; 45(3):190-194.

76 Nisar M, Earis JE, Pearson MG et al. Acute bronchodilator trials in chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1992; 146(3):555-559.

77 Hadcroft J, Calverley PM. Alternative methods for assessing bronchodilator reversibility in chronic obstructive pulmonary disease. *Thorax.* 2001; 56(9):713-720.

78 Brand PL, Quanjer PH, Postma DS et al. Interpretation of bronchodilator response in patients with obstructive airways disease. The Dutch Chronic Non-Specific Lung Disease (CNSLD) Study Group. *Thorax.* 1992; 47(6):429-436.

79 Tweeddale PM, Alexander F, McHardy GJR. Short-term variability in fev1 and bronchodilator responsiveness in patients with obstructive ventilatory defects. *Thorax.* 1987; 42(7):487-490.

80 Fabbri LM, Romagnoli M, Corbetta L et al. *Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease*. *American Journal of Respiratory & Critical Care Medicine.* 167(3); 418-424. 2003.

81 Santus P, Pecchiari M, Carlucci P et al. Bronchodilation test in COPD: effect of inspiratory manoeuvre preceding forced expiration. *Eur Respir J.* 2003; 21(1):82-85.

82 Burge PS, Calverley PMA, Jones PW et al. Prednisolone response in patients with chronic obstructive pulmonary disease: results from the ISOLDE study. *Thorax.* 2003; 58:1-5.

83 Celli BR, Cote CG, Lareau SC et al. Predictors of Survival in COPD: more than just the FEV1. *Respir Med.* 2008; 102 Suppl 1:S27-35, 2008 Jun.:S27-S35.

84 Fan VS, Curtis JR, Tu S et al. Using quality of life to predict hospitalization and mortality in patients with obstructive lung diseases. *Chest.* 2002; 122(2):429-436.

85 Almagro P, Calbo E, Ochoa de EA et al. Mortality after hospitalization for COPD. *Chest.* 2002; 121(5):1441-1448.

86 Chen H, Eisner MD, Katz PP et al. Measuring disease-specific quality of life in obstructive airway disease: validation of a modified version of the airways questionnaire 20. *Chest.* 2006; 129(6):1644-1652.

87 Yohannes AM, Baldwin RC, Connolly M. Mortality predictors in disabling chronic obstructive pulmonary disease in old age. *Age & Ageing.* 2002; 31(2):137-140.

88 Osman IM, Godden DJ, Friend JA et al. Quality of life and hospital re-admission in patients with chronic obstructive pulmonary disease. *Thorax.* 1997; 52(1):67-71.

89 Ramsey SD, Sullivan SD. The burden of illness and economic evaluation for COPD. *Eur Respir J.* 2003; 21(41):29s-35s.

90 Oga T, Nishimura K, Tsukino M et al. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *American Journal of Respiratory & Critical Care Medicine.* 2003; 167(4):544-549.

91 Singh S, Loke YK, Furberg CD et al. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Pulmonary Pharmacology & Therapeutics.* 2008; 300(12):1439-1450.

92 Antonelli-Incalzi R, Pedone C, Scarlata S et al. Correlates of mortality in elderly COPD patients: Focus on health-related quality of life. *Respirology.* 2009; 14(1):98-104.

93 Esteban C, Quintana JM, Aburto M et al. Predictors of mortality in patients with stable COPD. *J Gen Intern Med.* 2008; 23(11):1829-1834.

94 Oga T, Nishimura K, Tsukino M et al. Health status measured with the CRQ does not predict mortality in COPD. *Eur Respir J.* 2002; 20(5):1147-1151.

95 Gudmundsson G, Gislason T, Janson C et al. Risk factors for rehospitalisation in COPD: role of health status, anxiety and depression. *Eur Respir J.* 2005; 26(3):414-419.

96 Halpin DM, Peterson S, Larsson TP et al. Identifying COPD patients at increased risk of mortality: predictive value of clinical study baseline data. *Respir Med.* 2008; 102(11):1615-1624.

97 Briggs A, Spencer M, Wang H et al. Development and validation of a prognostic index for health outcomes in chronic obstructive pulmonary disease. *Arch Intern Med.* 2008; 168(1):71-79.

98 Ong KC, Earnest A, Lu SJ. A multidimensional grading system (BODE index) as predictor of hospitalization for COPD. *Chest.* 2005; 128(6):3810-3816.

99 Esteban C, Quintana JM, Aburto M et al. A simple score for assessing stable chronic obstructive pulmonary disease. *QJM: An International Journal of Medicine.* 2006; 99(11):751-759.

100 Casanova C, Cote C, de Torres JP et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 2005; 171(6):591-597.

101 de Torres JP, Pinto Plata V., Casanova C et al. C-reactive protein levels and survival in patients with moderate to very severe COPD.[see comment]. *Chest.* 2008; 133(6):1336-1343.

102 Marin JM, Carrizo SJ, Casanova C et al. Prediction of risk of COPD exacerbations by the BODE index. *Respir Med.* 2009; 103(3):373-378.

103 Celli BR, Cote CG, Marin JM et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.* 2004; 350(10):1005-1012.

104 Bridevaux PO, Gerbase MW, Probst HN et al. Long-term decline in lung function, utilisation of care and quality of life in modified GOLD stage 1 COPD. *Thorax.* 2008; 63(9):768-774.

105 National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax.* 2004; 59 Suppl 1:1-232.

106 Freeman D. COPD prevalence in asymptomatic smokers - The first 100. *Primary Care Respiratory Journal.* 2000; 9:41.

107 van Schayck CP, Loozen JM, Wagena E et al. Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. *Br Med J.* 2002; 324(7350):1370-1374.

108 Humerfelt S, Eide G, Aaro L et al. Effectiveness of postal smoking cessation advice: a randomised controlled trial in young men with reduced FEV1 and asbestos exposure. *Eur Respir J.* 1998; 11:284-290.

109 Risser NL, Belcher DW. Adding spirometry, carbon-monoxide, and pulmonary symptom results to smoking cessation counseling - a randomized trial. *J Gen Intern Med.* 1990; 5(1):16-22.

110 Jonsson JS, Gislason T, Gislason D et al. Acute bronchitis and clinical outcome three years later: prospective cohort study. *Br Med J.* 1998; 317(7170):1433.

111 British Thoracic Society. *BTS guidelines for the management of COPD. The COPD Guielines Group of the Standards of Care Committee of the BTS*. *Thorax.* 52(Suppl 5); S1-S28. 1997.

112 van der Meer RM, Wagena EJ, Ostelo RWJG et al. Smoking cessation for chronic obstructive pulmonary disease. *The Cochrane Library.* 2003; Issue 3(3)

113 Anthonisen NR, Connett JE, Kiley JP et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *Journal of the American Medical Association.* 1994; 272(19):1497-1505.

114 Brandt CJ, Ellegaard H, Joensen M et al. Effect of diagnosis of "smoker's lung". RYLUNG Group. *Lancet.* 1997; 349(9047):253.

115 Crowley TJ, Macdonald MJ, Walter MI. Behavioral anti-smoking trial in chronic obstructive pulmonary disease patients. *Psychopharmacology.* 1995; 119:193-204.

116 Pederson LL, Wanklin JM, Lefcoe NM. The effects of counseling on smoking cessation among patients hospitalized with chronic obstructive pulmonary disease: a randomized clinical trial. *International Journal of the Addictions.* 1991; 26(1):107-119.

117 Tashkin D, D., Kanner et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet.* 2001; 357(9268):1571-1575.

118 Scanlon PD, Connett JE, Waller LA et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease - The Lung Health Study. *American Journal of Respiratory & Critical Care Medicine.* 2000; 161(2):381-390.

119 Kanner RE, Connett JE, Williams DE et al. Effects of randomized assignment to a smoking cessation intervention and changes in smoking habits on respiratory symptoms in smokers with early chronic obstructive pulmonary disease: the Lung Health Study. *Am J Med.* 1999; 106:410-416.

120 National Institute for Health and Clinical Excellence. *Smoking cessation services: guidance.* (PH 10). London: UK: National Institute for Health and Clinical Excellence, 2008.

121 Woolacott NF, Jones L, Forbes CA et al. *The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation*. *Health Technology Assessment.* 6(16); 1-245. 2002. PM:12269277

122 National Institute for Clinical Excellence. *Varenicline for smoking cessation.* (TA123)., 2007.

123 Pauwels RA, Buist AS, Calverley PM et al. 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. *American Journal of Respiratory & Critical Care Medicine.* 2001; 163(5):1256-1276.

124 Corris PA, Neville E, Nariman S et al. Dose-response study of inhaled salbutamol powder in chronic air-flow obstruction. *Thorax.* 1983; 38(4):292-296.

125 Teale C, Morrison JFJ, Page RL et al. Dose-response to inhaled salbutamol in chronic obstructive airways disease. *Postgraduate Medical Journal.* 1991; 67(790):754-756.

126 Sestini P, Renzoni E, Robinson S et al. Short-acting beta 2 agonists for stable chronic obstructive pulmonary disease. *The Cochrane Library.* 2003; Issue 3(3)

127 Dullinger D, Kronenberg R, Niewoehner DE. Efficacy of inhaled metaproterenol and orally-administered theophylline in patients with chronic airflow obstruction. *Chest.* 1986; 89(2):171-173.

128 Guyatt GH, Townsend M, Pugsley SO et al. Bronchodilators in chronic air-flow limitation. Effects of airway function, exercise capacity, and quality of life. *Am Rev Respir Dis.* 1987; 135(5):1069-1074.

129 Guyatt GH, Townsend M, Nogradi S et al. Acute response to bronchodilator. An imperfect guide for bronchodilator therapy in chronic airflow limitation. *Arch Intern Med.* 1988; 148(9):1949-1952.

130 Guyatt GH, Townsend M, Keller JL et al. Should study subjects see their previous responses: data from a randomized control trial. *J Clin Epidemiol.* 1989; 42(9):913-920.

131 Hansen NC, May O. Domiciliary nebulised terbutaline in severe chronic airways obstruction. *Eur Respir J.* 1990; 3(4):463-464.

132 Jaeschke R, Guyatt GH, Singer J et al. Mechanism of bronchodilator effect in chronic airflow limitation. *Canadian Medical Association Journal.* 1991; 144(1):35-39.

133 Klock LE, Miller TD, Morris AH et al. A comparative study of atropine sulphate and isoproterenol hydrochloride in chronic bronchitis. *Am Rev Respir Dis.* 1975; 112(3):371-376.

134 Light RW, Summer WR, Luchsinger PC. Response of patients with chronic obstructive lung disease to the regular administraion of nebulised isoproterenol. *Chest.* 1975; 67(6):634-639.

135 Shah SS, Johnsonton D, Woodcock AA et al. Breathlessness and exercise tolerance in chronic airflow obstruction: 2-hourly versus 4-hourly salbutamol by inhalation. *Current Medical Research and Opinion.* 1983; 8(5):345-349.

136 Silins RA, Marlin GE. Evaluation of domiciliary treament with terbutaline by wet nebulisation in patients with chronic bronchitis and emphysema. *Australian & New Zealand Journal of Medicine.* 1985; 15(2):230-240.

137 Tandon MK, Kailis SG. Bronchodilator treatment for partially reversible chronic obstructive airways disease. *Thorax.* 1991; 46(4):248-251.

138 Taylor DR, Buick B, Kinney C. The efficacy of orally administered theophylline, inhaled salbutamol, and a combination of the two as chronic therapy in the management of chronic bronchitis with reversible air-flow obstruction. *Am Rev Respir Dis.* 1985; 131(5):747-751.

139 Wilson RSE, Connellan SJ. Domiciliary nebulized salbutamol solution in severe chronic airway obstruction in severe chronic airway obstruction. *Thorax.* 1980; 35:873-876.

140 Cook D, Guyatt G, Wong E et al. Regular versus as-needed short-acting inhaled beta-agonist therapy for chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 2001; 163(1):85-90.

141 Gross NJ, Co E, Skorodin MS. Cholinergic bronchomotor tone in COPD. Estimates of its amount in comparison with that in normal subjects. *Chest.* 1989; 96(5):984-987.

142 Ikeda A, Nishimura K, Koyama H et al. Bronchodilating effects of combined therapy with clinical dosages of ipratropium bromide and salbutamol for stable copd - comparison with ipratropium bromide alone. *Chest.* 1995; 107(2):401-405.

143 Ikeda A, Nishimura K, Koyama H et al. Comparative dose-response study of 3 anticholinergic agents and fenoterol using a metered-dose inhaler in patients with chronic obstructive pulmonary-disease. *Thorax.* 1995; 50(1):62-66.

144 Higgins BG, Powell RM, Cooper S et al. Effect of salbutamol and ipratropium bromide on airway caliber and bronchial reactivity in asthma and chronic-bronchitis. *Eur Respir J.* 1991; 4(4):415-420.

145 Braun SR, McKenzie WN, Copeland C et al. A comparison of the effect of ipratropium and albuterol in the treatment of chronic obstructive airway disease. *Arch Intern Med.* 1989; 149(3):544-547.

146 Campbell S. For COPD a combination of ipratropium bromide and albuterol sulfate is more effective than albuterol base. *Arch Intern Med.* 1999; 159(2):156-160.

147 Colice GL. Nebulized bronchodilators for outpatient management of stable chronic obstructive pulmonary disease. *Am J Med.* 1996; 100(1A):11S-18S.

148 Rennard SI, Serby CW, Ghafouri M et al. Extended therapy with ipratropium is associated with improved lung function in patients with COPD: A retrospective analysis of data from seven clinical trials. *Chest.* 1996; 110(1):62-70.

149 Taylor J, Kotch A, Rice K et al. Ipratropium bromide hydrofluoroalkane inhalation aerosol is safe and effective in patients with COPD. *Chest.* 2001; 120(4):1253-1261.

150 Rennard SI, Anderson W, Zu Wallack R et al. Use of a long-acting inhaled beta(2)-adrenergic agonist, salmeterol xinafoate, in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 2001; 163(5):1087-1092.

151 Dahl R, Greefhorst LAPM, Nowak D et al. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 2001; 164(5):778-784.

152 Mahler DA, Donohue JF, Barbee RA et al. Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest.* 1999; 115(4):957-965.

153 Appleton S, Smith B, Veale A et al. Long-acting beta2-agonists for chronic obstructive pulmonary disease. *The Cochrane Library.* 2003; Issue 3(3)

154 Boyd G, Morice AH, Pounsford JC et al. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). *Eur Respir J.* 1997; 10(4):815-821.

155 Goodwin B, Cox F, Anderson W et al. *Comparision of salmeterol 42ug BID (SLG) versus ipratropium bromide 36ug q.i.d. vs placebo on disease specific quality of life in COPD patients: reversible or non-reversible to ventolin*. *ALA/ATS Abstract 1997-1999.* 1997.

156 Grove A, Lipworth BJ, Reid P et al. Effects of regular salmeterol on lung function and exercise capacity in patients with chronic obstructive airways disease. *Thorax.* 1996; 51(7):689-693.

157 Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. *American Journal of Respiratory & Critical Care Medicine.* 1997; 155(4):1283-1289.

158 Rutten-Van M, Roos B, van N. An empirical comparison of the St George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Disease Questionnaire (CRQ) in a clinical trial setting. *Thorax.* 1999; 54(11):995-1003.

159 Ulrik CS. Efficacy of inhaled salmeterol in the management of smokers with chronic obstructive pulmonary disease: a single centre randomised, double blind, placebo controlled, crossover study. *Thorax.* 1995; 50(7):750-754.

160 van Noord JA, de Munck DRAJ, Bantje TA et al. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. *Eur Respir J.* 2000; 15(5):878-885.

161 Shukla, V. K., Husereau, D. R., Boucher, M., Mensunkai, S., and Dales, R. *Long-acting beta2-agonists for maintenance therapy of stable chronic obstructive pulmonary disease: a systematic review.* (39). Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA)., 2002.

162 Aalbers R, Ayres J, Backer V et al. Formoterol in patients with chronic obstructive pulmonary disease: A randomized, controlled, 3-month trial. *Eur Respir J.* 2002; 19(5):936-943.

163 Rossi A, Kristufek P, Levine BE et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. *Chest.* 2002; 121(4):1058-1069.

164 Brusasco V, Hodder R, Miravitlles M et al. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax.* 2003; 58:399-404.

165 Mahler DA, Wire P, Horstman D et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 2002; 166(8):1084-1091.

166 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(1):74-81.

167 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(9356):449-456.

168 Donohue JF, van Noord JA, Bateman ED et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest.* 2002; 122(1):47-55.

169 Littner MR, Ilowite JS, Tashkin DP et al. Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 2000; 161(4):1136-1142.

170 Casaburi R, Briggs DD, Donohue JF et al. The spirometric efficacy of once-daily dosing with tiotropium in stable COPD - A 13-week multicenter trial. *Chest.* 2000; 118(5):1294-1302.

171 Casaburi R, Mahler DA, Jones PW et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J.* 2002; 19(2):217-224.

172 Vincken W, van Noord JA, Greefhorst APM et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J.* 2002; 19(2):209-216.

173 Oostenbrink JB, Rutten-van Molken MP, Monz BU et al. Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries. *Value in Health.* 2005; 8(1):32-46.

174 Rutten-van Mölken MP, Oostenbrink JB, Miravitlles M et al. Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. *European Journal of Health Economics.* 2007; 8(2):123-135.

175 Oba Y. Cost-effectiveness of long-acting bronchodilators for chronic obstructive pulmonary disease. *Mayo Clin Proc.* 2007; 82(5):575-582.

176 Oostenbrink JB, Rutten vMM, Al MJ et al. One-year cost-effectiveness of tiotropium versus ipratropium to treat chronic obstructive pulmonary disease. *Eur Respir J.* 2004; 23(2):241-249.

177 Organisation for Economic Co-operation and Development (OECD). *Purchasing Power Parities (PPPs) for OECD countries since 1980*. *http://www oecd org/.* 2008. OECD. http://www.oecd.org/

178 Vogelmeier C, Kardos P, Harari S et al. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study. *Respir Med.* 2008; 102(11):1511-1520.

179 Keatings VM, Jatakanon A, Worsdell YM et al. Effects of inhaled and oral glucocorticoids on inflammatory indices in asthma and COPD. *American Journal of Respiratory & Critical Care Medicine.* 1997; 155(2):542-548.

180 Hattotuwa KL, Gizycki MJ, Ansari TW et al. The effects of inhaled fluticasone on airway inflammation in chronic obstructive pulmonary disease: a double-blind, placebo-controlled biopsy study. *American Journal of Respiratory & Critical Care Medicine.* 2002; 165(12):1592-1596.

181 Peperell K, Rudolf M, Pearson M et al. General practitioner prescribing habits in asthma/COPD. *Asthma in General Practice.* 1997; 5(2):29-30.

182 Alsaeedi A, Sin DD, McAlister FA. The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: A systematic review of randomized placebo-controlled trials. *Am J Med.* 2002; 113(1):59-65.

183 Burge PS, Calverley PMA, Jones PW et al. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *Br Med J.* 2000; 320(7245):1297-1303.

184 The Lung Health Study Research Group, Altose MD, Redline S et al. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med.* 2000; 343(26):1902-1909.

185 Vestbo J, Sorensen T, Lange P et al. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet.* 1999; 353(9167):1819-1823.

186 Pauwels RA, Lofdahl CG, Laitinen LA et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. *N Engl J Med.* 1999; 340(25):1948-1953.

187 van Grunsven PM, van Schayck CP, Derenne JP et al. Long term effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a meta-analysis. *Thorax.* 1999; 54(1):7-14.

188 Derenne JP. *Effects of high dose inhaled beclomethasone in the rate of decline in FEV1 in patients with chronic obstructive pulmonary disease: results of a 2 year prospective multicentre study*. *American Journal of Respiratory & Critical Care Medicine.* 151. 1995.

189 Johnell O, Pauwels R, Lofdahl C-G et al. Bone mineral density in patients with chronic obstructive pulmonary disease treated with budesonide Turbuhaler. *Eur Respir J.* 2002; 19(6):1058-1063.

190 Jones PW, Willits LR, Burge PS et al. Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations. *Eur Respir J.* 2003; 21(1):68-73.

191 Soriano JB, Vestbo J, Pride NB et al. Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice. *Eur Respir J.* 2002; 20(4):819-825.

192 Sin DD, Tu JV. Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 2001; 164:580-584.

193 Sin DD, Man SFP. Inhaled corticosteroids and survival in chronic obstructive pulmonary disease: Does the dose matter? *Eur Respir J.* 2003; 21(2):260-266.

194 Renkema TE, Schouten JP, Koeter GH et al. *Effects of long-term treatment with corticosteroids in COPD*. *Chest.* 109(5); 1156-1162. 1996.

195 Paggiaro PL, Dahle R, Bakran I et al. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. *Lancet.* 1998; 351(9105):773-780.

196 Dragonetti ME, Groth ML. Inhaled cortiocsteroids in chronic obstructive pulmonary disease: Are they cost-effect? *Clinical Pulmonary Medicine.* 2000; 7

197 Calverley PM, Anderson JA, Celli B et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med.* 2007; 356(8):775-789.

198 Ferguson GT, Calverley PM, Anderson JA et al. Prevalence and progression of osteoporosis in patients with COPD. Results from the towards a revolution in COPD health study. Chest. 2009; 136(6):1456-1465.

199 Sin DD, Tashkin D, Zhang X et al. Budesonide and the risk of pneumonia: a meta-analysis of individual patient data. *Lancet.* 2009; 374(9691):712-719.

200 Aaron S, Vandemheen K, Fergusson D et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med.* 2007; 146(8):545-555.

201 Boehringer Ingelheim Ltd. UPLIFT subgroup analyses (Number 5 - RIGHT DATA). Boehringer Ingelheim Ltd, 2009:

202 Nannini LJ, Cates CJ, Lasserson TJ et al. Combined corticosteroid and long-acting beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews.* 2007;(4):CD006829.

203 Ferguson GT, Calverley PM, Anderson JA et al. Prevalence and progression of osteoporosis in patients with COPD. Results from the towards a revolution in COPD health study. Chest. 2009; 136(6):1456-1465.

204 Ferguson GT, Anzueto A, Fei R et al. Effect of fluticasone propionate/salmeterol (250/50mug) or salmeterol (50mug) on COPD exacerbations. *Respir Med.* 2008; 102(8):1099-1108.

205 Rennard SI, Tashkin DP, McElhattan J et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs.* 2009; 69(5):549-565.

206 Tashkin DP, Rennard SI, Martin P et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. *Drugs.* 2008; 68(14):1975-2000.

207 Jenkins C, Jones P, Calverley P et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. *Respiratory Research.* 2009; 10(1):59.

208 Dal Negro RR, Eandi M, Pradelli L et al. Cost-effectiveness and healthcare budget impact in Italy of inhaled corticosteroids and bronchodilators for severe and very severe COPD patients. *International Journal of Copd.* 2007; 2(2):169-176.

209 Lofdahl CG, Ericsson A, Svensson K et al. Cost effectiveness of budesonide/formoterol in a single inhaler for COPD compared with each monocomponent used alone. *Pharmacoeconomics.* 2005; 23(4):365-375.

210 Mayers, I., Jacobs, P., Marciniuk, D. D., Chuck, A., and Varney, J. *Long-acting Beta2-agonists (LABA) plus corticosteroids versus LABA alone for chronic obstructive pulmonary disease.* (83). Canada: Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH), 2007.

211 Briggs A, Glick H, Lozano-Ortega G et al. Is treatment with ICS and LABA cost-effective for COPD? Multinational economic analysis of the TORCH study. *Eur Respir J.* 2009;09031936.

212 Earnshaw SR, Wilson MR, Dalal AA et al. Cost-effectiveness of fluticasone propionate/salmeterol (500/50 microg) in the treatment of COPD. *Respir Med.* 2009; 103(1):12-21.

213 Oba Y. Cost-effectiveness of salmeterol, fluticasone, and combination therapy for COPD. *Am J Manag Care.* 2009; 15(4):226-232.

214 Akazawa M, Hayflinger DC, Stanford RH et al. Economic assessment of initial maintenance therapy for chronic obstructive pulmonary disease. *Am J Manag Care.* 2008; 14(7):438-448.

215 Rascati KL, Akazawa M, Johnsrud M et al. Comparison of hospitalizations, emergency department visits, and costs in a historical cohort of Texas Medicaid patients with chronic obstructive pulmonary disease, by initial medication regimen. *Clin Ther.* 2007; 29(6):1203-1213.

216 Gagnon YM, Levy AR, Spencer MD et al. Economic evaluation of treating chronic obstructive pulmonary disease with inhaled corticosteroids and long-acting beta 2-agonists in a health maintenance organization. *Respir Med.* 2005; 99(12):1534-1545.

217 Delea TE, Hagiwara M, Dalal AA et al. Healthcare use and costs in patients with chronic bronchitis initiating maintenance therapy with fluticasone/salmeterol vs other inhaled maintenance therapies. *Current Medical Research & Opinion.* 2009; 25(1):1-13.

218 Calverley PM, Boonsawat W, Cseke Z et al. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J.* 2003; 22(6):912-919.

219 Wedzicha JA, Calverley PM, Seemungal TA et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *American Journal of Respiratory & Critical Care Medicine.* 2008; 177(1):19-26.

220 Najafzadeh M, Marra CA, Sadatsafavi M et al. Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD. *Thorax.* 2008; 63(11):962-967.

221 electronic Medicines Compendium. *Seretide 100, 250, 500 Accuhaler*. 2008. UK: Middlesex, Allen & Hanbury. http://emc.medicines.org.uk/medicine/2317/SPC/Seretide+100%2c+250%2c+500+Accuhaler/#USEHANDLING

222 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary*. 57 ed. UK: BMJ Group and RPS Publishing; 2009.

223 Kardos P, Wencker M, Glaab T et al. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 2007; 175(2):144-149.

224 Tashkin DP, Celli B, Senn S et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med.* 2008; 359(15):1543-1554.

225 Brocklebank DM, Ram FSF, Wright J et al. *Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature*. *Health Technology Assessment.* 5(26). 2001. The National Coordinating Centre for Health Technology Assessment (NCCHTA). http://www.ncchta.org/ProjectData/3_project_record_published.asp?PjtId=1106

226 Ram FSF, Brocklebank DM, Muers M et al. Pressurised metered-dose inhalers versus all other hand-held inhalers devices to deliver bronchodilators for chronic obstructive pulmonary disease. *The Cochrane Library.* 2003; Issue 3(3)

227 Cuvelier A, Muir J, Benhamou D et al. Dry powder ipratropium bromide is as safe and effective as metered-dose inhaler formulation: a cumulative dose-response study in chronic obstructive pulmonary disease patients. *Respir Care.* 2002; 47(2):159-166.

228 Eiser N, Angus K, McHale S. The role of domiciliary nebulizers in managing patients with severe COPD. *Respir Med.* 2001; 95(4):265-274.

229 O'Driscoll BR, Kay EA, Taylor RJ et al. A long-term prospective assessment of home nebulizer treatment. *Respir Med.* 1992; 86(4):317-325.

230 Allen SC. Competence thresholds for the use of inhalers in people with dementia. *Age & Ageing.* 1997; 26(2):83-86.

231 Hodkinson HM. Evaluation of a mental test score for assessment of mental impairment in the elderly. *Age & Ageing.* 1972; 1(4):233-238.

232 Connolly MJ. Inhaler technique of elderly patients: comparison of metered-dose inhalers and large volume spacer devices. *Age & Ageing.* 1995; 24(3):190-192.

233 Allen SC, Prior A. What determines whether an elderly patient can use a metered dose inhaler correctly? *British Journal of Diseases of the Chest.* 1986; 80(1):45-49.

234 Armitage JM, Williams SJ. Inhaler technique in the elderly. *Age & Ageing.* 1988; 17(4):275-278.

235 Selroos O, Halme M. Effect of a volumatic spacer and mouth rinsing on systemic absorption of inhaled corticosteroids from a metered dose inhaler and dry powder inhaler. *Thorax.* 1991; 46(12):891-894.

236 Diggory P, Bailey R, Vallon A. Effectiveness of inhaled bronchodilator delivery systems for elderly patients. *Age & Ageing.* 1991; 20(5):379-382.

237 Harvey J, Williams JG. Randomised cross-over comparison of five inhaler systems for bronchodilator therapy. *British Journal of Clinical Practice.* 1992; 46(4):249-251.

238 Allen SC, Ragab S. Ability to learn inhaler technique in relation to cognitive scores and tests of praxis in old age. *Postgraduate Medical Journal.* 2002; 78(915):37-39.

239 Teale C, Jones A, Patterson CJ et al. Community survey of home nebulizer technique by elderly people. *Age & Ageing.* 1995; 24(4):276-277.

240 O'Driscoll BR. Nebulisers for chronic obstructive pulmonary disease. *Thorax.* 1997; 52(Suppl 2):S49-S52.

241 Boe J, Dennis JH, O'Driscoll BR et al. European Respiratory Society Guidelines on the use of nebulizers. *Eur Respir J.* 2001; 18(1):228-242.

242 Formgren H, Sjokvist A, Stahl E et al. Terbutaline in COPD comparison between Turbuhaler and chlorofluorocarbon (CFC) inhaler. *Lung.* 1994; 172(5):271-280.

243 Ikeda A, Nishimura K, Koyama H et al. Comparison of the bronchodilator effects of salbutamol delivered via a metered-dose inhaler with spacer, a dry-powder inhaler, and a jet nebulizer in patients with chronic obstructive pulmonary disease. *Respiration.* 1999; 66(2):119-123.

244 Iacono P, Velicitat P, Guemas E et al. Improved delivery of ipratropium bromide using Respimat (a new soft mist inhaler) compared with a conventional metered dose inhaler: cumulative dose response study in patients with COPD. *Respir Med.* 2000; 94(5):490-495.

245 Callahan CM, Dittus RS, Katz BP. Oral corticosteroid therapy for patients with stable chronic obstructive pulmonary disease. A meta-analysis. *Ann Intern Med.* 1991; 114(3):216-223.

246 Corden Z, Rees PJ. The effect of oral corticosteroids on bronchodilator responses in COPD. *Respir Med.* 1998; 92(2):279-282.

247 Weiner P, Weiner M, Rabner M et al. The response to inhaled and oral steroids in patients with stable chronic obstructive pulmonary disease. *Journal of Internal Medicine.* 1999; 245(1):83-89.

248 Weir DC, Robertson AS, Gove RI et al. Time course of response to oral and inhaled corticosteroids in nonasthmatic chronic air-flow obstruction. *Thorax.* 1990; 45(2):118-121.

249 Weir DC, Gove RI, Robertson AS et al. Corticosteroid trials in non-asthmatic chronic airflow obstruction: A comparison of oral prednisolone and inhaled beclomethasone dipropionate. *Thorax.* 1990; 45(2):112-117.

250 Royal College of Physicians. *Osteoporosis. Clinical guidelines for prevention and treatment*. 1999.

251 Vassallo R, Lipsky JJ. Theophylline: recent advances in the understanding o fits mode of action and uses in clinical practice. *Mayo Clin Proc.* 1998; 73(4):346-354.

252 Murciano D, Aubier M, Lecocguic Y et al. Effects of theophylline on diaphragmatic strength and fatigue in patients with chronic obstructive pulmonary disease. *N Engl J Med.* 1984; 311(6):349-353.

253 Ziment I. Theophylline and mucociliary clearance. *Chest.* 1987; 92(Suppl 1):38S-43S.

254 Matthay RA, Mahler DA. Theophylline improves global cardiac function and reduces dyspnea in chronic obstructive lung disease. *Journal of Allergy & Clinical Immunology.* 1986; 78(4 II Suppl):793-799.

255 Upton RA. Pharmacokinetic interactions between theophylline and other medication. *Clinical Pharmacokinetics.* 1991; 20(Part 1):66-80.

256 Aronson JK, Hardman M, Reynolds DJ. ABC of monitoring drug therapy. Theophylline. *Br Med J.* 1992; 305(6865):1355-1358.

257 Ram FSF, Jones PW, Castro AA et al. Oral theophylline for chronic obstructive pulmonary disease. *The Cochrane Library.* 2003; Issue 3(3)

258 Fink G, Kaye C, Sulkes J et al. Effect of theophylline on exercise performance in patients with severe chronic obstructive pulmonary disease. *Thorax.* 1994; 49(4):332-334.

259 Newman D, Tamir J, Speedy L et al. Physiological and neuropsychological effects of theophylline in chronic obstructive pulmonary disease. *Israel Journal of Medical Sciences.* 1994; 30(11):811-816.

260 Alexander MR, Dull WL, Kasik JE. Treatment of chronic obstructive pulmonary disease with orally administered theophylline. A double-blind, controlled study. *Journal of the American Medical Association.* 1980; 244(20):2286-2290.

261 Mulloy E, McNicholas WT. Theophylline improves gas exchange during rest, exercise, and sleep in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1993; 148(4):1030-1036.

262 Compton CH, Gubb J, Nieman R et al. Cilomilast, a selective phosphodiesterase-4 inhibitor for treatment of patients with chronic obstructive pulmonary disease: a randomised, dose-ranging study. *Lancet.* 2001; 358(9278):265-270.

263 Bachh AA, Shah NN, Bhargava R et al. Effect of oral N-acetylcysteine in COPD - A randomised controlled trial. *JK Practitioner.* 2007; 14(1):12-16.

264 Zheng JP, Kang J, Huang SG et al. Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study. *Lancet.* 2008; 371(9629):2013-2018.

265 Poole PJ, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *The Cochrane Library.* 2003; Issue 3(3)

266 Poole P, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews.* 2006;(Black Peter N. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews: Reviews 2006 Issue 3 John Wiley & Sons)

267 Schermer T, Chavannes N, Dekhuijzen R et al. Fluticasone and N-acetylcysteine in primary care patients with COPD or chronic bronchitis. *Respir Med.* 2009; 103(4):542-551.

268 Grandjean EM, Berthet P, Ruffmann R et al. Cost-effectiveness analysis of oral N-acetylcysteine as a preventive treatment in chronic bronchitis. *Pharmacological Research.* 2000; 42(1):39-50.

269 Grassi C, Morandini GC. A controlled trial of intermittent oral acetylcysteine in the long-term treatment of chronic bronchitis
18. *European Journal of Clinical Pharmacotherapy.* 1976; 09(5-6):393-396.

270 Boman G, Backer U, Larsson S et al. Oral acetylcysteine reduces exacerbation rate in chronic bronchitis: report of a trial organized by the Swedish Society for Pulmonary Diseases
1. *European Journal of Respiratory Diseases.* 1983; 64(6):405-415.

271 Meister R. Langzeittherapie mit Acetylcystein Retard-Tabletten bei Patienten mit chronischer Bronchitis. *Forum prackt Allg Arzt.* 1986; 25:18-25.

272 Parr GD, Huitson A. Oral Fabrol (oral N-acetyl-cysteine) in chronic bronchitis. *British Journal of Diseases of the Chest.* 1987; 81(4):341-348.

273 Rasmussen JB, Glennow C. Reduction in days of illness after long-term treatment with N-acetylcysteine controlled-release tablets in patients with chronic bronchitis
4. *Eur Respir J.* 1988; 1(4):351-355.

274 MacNee W. Oxidants/antioxidants and chronic obstructive pulmonary disease: pathogenesis to therapy. *Novartis Foundation Symposium.* 2001; 234:169-185.

275 Rahman I, MacNee W. Regulation of redox glutathione levels and gene transcription in lung inflammation: therapeutic approaches. *Free Radical Biology and Medicine.* 2000; 28(9):1405-1420.

276 Rautalahti M, Virtamo J, Haukka J et al. The effect of alpha-tocopherol and beta-carotene supplementation on COPD symptoms. *American Journal of Respiratory & Critical Care Medicine.* 1997; 156(5):1447-1452.

277 The ATBC Cancer Prevention Study Group. The alpha tocopherol, beta carotene lung cancer prevention study: design, methods, participant characteristics, and compliance. *Ann Epidemiol.* 1994; 4(1):1-10.

278 Aversa C, Cazzola M, Clini V et al. Clinical trial of the efficacy and safety of moguisteine in patients with cough associated with chronic respiratory diseases. *Drugs Under Experimental & Clinical Research.* 1993; 19(6):273-279.

279 Barnabe R, Berni F, Clini V et al. The efficacy and safety of moguisteine in comparison with codeine phosphate in patients with chronic cough. *Monaldi Arch Chest Dis.* 1995; 50(2):93-97.

280 Del Donno M, Aversa C, Corsico R et al. Efficacy and safety of moguisteine in comparison with dextromethorphan in patients with persistent cough. *Drug Investigation.* 1994; 7(2):93-100.

281 Sergysels R, Art G. A double-masked, placebo-controlled polysomnographic study of the antitussive effects of helicidine. *Current Therapeutic Research, Clinical & Experimental.* 2001; 62(1):35-47.

282 Wojcicki J, Szwed G, Drozdowska KD. The antitussive and expectorant drug Duopect evaluated by the preferential test. *Archivum Immunologiae et Therapiae Experimentalis.* 1976; 24(4):549-552.

283 Staykova T, Black P, Chacko E et al. Prophyactic antibiotic therapy for chronic bronchitis. *The Cochrane Library.* 2003; Issue 3(3)

284 Francis R. Chemotherapy in chronic bronchitis. Influence of daily penicillin and tetracycline on exacerbations and their cost. *Br Med J.* 1960; 1(5169):297-303.

285 Gosling WRO, Djajadinigrat RJ, Bergstein PGM et al. *Continuous suppressive antimicrobial treament in chronic infected bronchitis during the winter months*. *Diseases of the Chest.* (376); 380. 1967.

286 Johnston RN, Lockhart W, Smith DH et al. A trial of phenethicillin in chronic bronchitis. *Br Med J.* 1961; 2(5258):985-986.

287 Johnston RN, McNeill RS, Smith DH et al. Five-year winter chemoprophylaxis for chronic bronchitis. *Br Med J.* 1969; 4(678):265-269.

288 Liippo K, Pelliniemi TT, Lehto H. Trimethoprim prophylaxis of acute exacerbations in chronic obstructive pulmonary disease. *Acta Medica Scandinavica.* 1987; 221(5):455-459.

289 Moyes EN, Kershaw RA. *Long-continued treatment with tetracycline and prednisolone in chronic bronchitis*. *Lancet.* 270(7007); 1187-1191. 1957.

290 Murdoch JM, Leckie WJH, Downie J et al. *An evaluation of continuous antibiotic therapy in chronic bronchitis*. *British Medical Journal.* 2(5162); 1277-1285. 1959.

291 Pridie R. A trial of continuous winter chemotherapy in chronic bronchitis. *Lancet.* 1960; 2(7153):723-727.

292 Working Party of the Medical Research Council. *Value of chemoprophylaxis and chemotherapy in early chronic bronchitis. A report to the Medical Reserach Council by their Working Party on Trials of Chemotherapy in Early Chronic Bronchitis*. *British Medical Journal.* 1(5499); 1317-1322. 1966.

293 Haas H, Morris JF, Samson S. Effect of oral penicillin on pneumococcal carriage in elderly men with chronic bronchitis. *Clin Ther.* 1986; 8(3):301-308.

294 Suzuki T, Yanai M, Yamaya M et al. Erythromycin and common cold in COPD. *Chest.* 2001; 120(3):730-733.

295 Medical Research Council, Fletcher. Value of chemoprophylaxis and chemotherapy in early chronic bronchitis. A report to the Medical Research Council by their working party on trials of chemotherapy in early chronic bronchitis. *Br Med J.* 1966; 1(5499):1317-1322.

296 Pines A. Controlled trials of a sulphonamide given weekly to prevent exacerbations of chronic bronchitis. *Br Med J.* 1967; 3(5559):202-204.

297 Moher D, Schulz K, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet.* 2001; 357(9263):1191-1194.

298 Hahn HH, MacGregor RR, Avent CK et al. Ampicillin and tetracycline in the treatment and prophylaxis of chronic bronchitis. *Antimicrobial Agents & Chemotherapy.* 1972; 2(1):45-48.

299 Grob PR, White E, Gargan R et al. The use of erythromycin as prophylaxis in chronic bronchitis: a cohort study from general practice. *Journal of International Medical Research.* 1980; 8(Suppl):50.

300 Pugh DL, Holland EE. Chemoprophylaxis in chronic bronchitis. *Antiseptic.* 1974; 71:261-267.

301 McVay L. Antibiotic prophylaxis in chronic respiratory diseases. *Arch Intern Med.* 1953; 92(6):833-846.

302 Buchanan J. Long-term prophylactic administration of tetracycline to chronic bronchitics. *Lancet.* 1958; 2(7049):719-723.

303 Cherniack N. Long-term treatment of bronchiectasis and chronic bronchitis. *Arch Intern Med.* 1959; 103(March 1959):345-353.

304 Francis R. Chemotherapy of bronchitis. Influence of penicillin and tetracycline administered daily, or intermittently for exacerbations. *Br Med J.* 1961; 2(5258):979-985.

305 Cooper J, Inman J, Currie W. Prophylactic treatment of chronic bronchitis comparing cotrimoxazole and amoxycillin. *British Journal of Clinical Practice.* 1975; 29(11):307-310.

306 Zu Walalck RL, Mahler DA, Reilly D et al. Salmeterol plus theophylline combination therapy in the treatment of COPD. *Chest.* 2001; 119(6):1661-1670.

307 Bellia V, Foresi A, Bianco S et al. Efficacy and safety of oxitropium bromide, theophylline and their combination in COPD patients: a double-blind, randomized, multicentre study (BREATH Trial). *Respir Med.* 2002; 96(11):881-889.

308 Nishimura K, Koyama H, Ikeda A et al. The additive effect of theophylline on a high-dose combination of inhaled salbutamol and ipratropium bromide in stable COPD. *Chest.* 1995; 107(3):718-723.

309 Royal College of Physicians. *Domiciliary oxygen therapy services. Clinical guidelines and advice for prescribers*. London: Royal College of Physicians; 1999.

310 Medical Research Council Working Party, Flenley DC. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet.* 1981; 1(8222):681-686.

311 Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med.* 1980; 93(3):391-398.

312 Timms RM, Khaja FU, Williams GW. Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. *Ann Intern Med.* 1985; 102(1):29-36.

313 Cooper CB, Waterhouse J, Howard P. Twelve year clinical study of patients with hypoxic cor pulmonale given long term domiciliary oxygen therapy. *Thorax.* 1987; 42(2):105-110.

314 Cooper CB, Howard P. An analysis of sequential physiologic changes in hypoxic cor pulmonale during long-term oxygen therapy. *Chest.* 1991; 100(1):76-80.

315 Zielinski J, MacNee W, Wedzicha J et al. Causes of death in patients with COPD and chronic respiratory failure. *Monaldi Arch Chest Dis.* 1997; 52(1):43-47.

316 PPA. *Drug Tariff National Health Service, England and Wales*. THE STATIONERY OFFICE BOOKS; 2003.

317 Heaney LG, McAllister D, MacMahon J. Cost minimisation analysis of provision of oxygen at home: are the drug tariff guidelines cost effective?
29. *Br Med J.* 1999; 319(7201):19-23.

318 Eaton T, Garrett JE, Young P et al. Ambulatory oxygen improves quality of life of COPD patients: A randomised controlled study. *Eur Respir J.* 2002; 20(2):306-312.

319 Crockett AJ, Cranston JM, Moss JR et al. A review of long-term oxygen therapy for chronic obstructive pulmonary disease. *Respir Med.* 2001; 95(6):437-443.

320 Andersson A, Strom K, Brodin H et al. Domiciliary liquid oxygen versus concentrator treatment in chronic hypoxaemia: a cost-utility analysis. *Eur Respir J.* 1998; 12(6):1284-1289.

321 Okubadejo AA, Paul EA, Wedzicha JA. Domiciliary oxygen cylinders: indications, prescription and usage. *Respir Med.* 1994; 88(10):777-785.

322 Woodcock AA, Gross ER, Geddes DM. Oxygen relieves breathlessness in "pink puffers". *Lancet.* 1981; 1(8226):907-909.

323 Evans TW, Waterhouse JC, Carter A et al. Short burst oxygen treatment for breathlessness in chronic obstructive airways disease. *Thorax.* 1986; 41(8):611-615.

324 Swinburn CR, Mould H, Stone TN et al. Symptomatic benefit of supplemental oxygen in hypoxemic patients with chronic lung disease. *Am Rev Respir Dis.* 1991; 143(5 Pt 1):913-915.

325 Ambrosino N, Montagna T, Nava S et al. Short term effect of intermittent negative pressure ventilation in COPD patients with respiratory failure. *Eur Respir J.* 1990; 3(5):502-508.

326 Meecham Jones DJ, Paul EA, Jones PW et al. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. *American Journal of Respiratory & Critical Care Medicine.* 1995; 152(2):538-544.

327 Plant PK, Elliott MW. Management of ventilatory failure in COPD. *Thorax.* 2003; 58(6):537-542.

328 Clini E, Sturani C, Rossi A et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J.* 2002; 20(3):529-538.

329 Behnke RH, Blount SG, Bristow JD et al. Primary prevention of pulmonary heart disease. *Circulation.* 1970; 41(6):A17-A23.

330 Chetty KG, Brown SE, Light RW. Identification of pulmonary hypertension in chronic obstructive pulmonary disease from routine chest radiographs. *Am Rev Respir Dis.* 1982; 126(2):338-341.

331 Miller MR, Gorecka DM, Bishop JM. Radiological prediction of pulmonary hypertension in chronic obstructive pulmonary disease. *European Heart Journal.* 1984; 5(7):581-587.

332 Oswald-Mammosser M, Oswald T, Nyankiye E et al. Non-invasive diagnosis of pulmonary hypertension in chronic obstructive pulmonary disease. Comparison of ECG, radiological measurements, echocardiography and myocardial scintigraphy. *European Journal of Respiratory Diseases.* 1987; 71(5):419-429.

333 MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part One. *American Journal of Respiratory & Critical Care Medicine.* 1994; 150(3):833-852.

334 Weitzenblum E, Zielinski J, Bishop JM. The diagnosis of "cor pulmonale" by non-invasive methods: a challenge for pulmonologists and cardiologists. *Bulletin Europeen De Physiopathologie Respiratoire.* 1983; 19(5):423-426.

335 Danchin N, Cornette A, Henriquez A et al. Two-dimensional echocardiographic assessment of the right ventricle in patients with chronic obstructive lung disease. *Chest.* 1987; 92(2):229-233.

336 Starling MR, Crawford MH, Sorensen SG et al. A new two-dimensional echocardiographic technique for evaluating right ventricular size and performance in patients with obstructive lung disease. *Circulation.* 1982; 66(3):612-620.

337 Turnbull LW, Ridgway JP, Biernacki W et al. Assessment of the right ventricle by magnetic resonance imaging in chronic obstructive lung disease. *Thorax.* 1990; 45(8):597-601.

338 Altschule MD. Limited usefulness of the so-called ejection fraction measurement in clinical practice. *Chest.* 1986; 90(1):134-135.

339 MacNee W, Morgan AD, Wathen CG et al. Right ventricular performance during exercise in chronic obstructive pulmonary disease. The effects of oxygen. *Respiration.* 1985; 48(3):206-215.

340 Zielinski J, Hawrylkiewicz I, Gorecka D et al. Captopril effects on pulmonary and systemic hemodynamics in chronic cor pulmonale. *Chest.* 1986; 90(4):562-565.

341 Kiely DG, Cargill RI, Wheeldon NM et al. Haemodynamic and endocrine effects of type 1 angiotensin II receptor blockade in patients with hypoxaemic cor pulmonale. *Cardiovascular Research.* 1997; 33(1):201-208.

342 Saadjian AY, Philip-Joet FF, Vestri R et al. Long-term treatment of chronic obstructive lung disease by Nifedipine: an 18-month haemodynamic study. *Eur Respir J.* 1988; 1(8):716-720.

343 Johnson DC, Joshi RC, Mehta R et al. Acute and long term effect of nifedipine on pulmonary hypertension secondary to chronic obstructive airways disease. *European Journal of Respiratory Diseases Supplement.* 1986; 146:495-502.

344 Gould L, Zahir M, DeMartino A et al. Haemodynamic effects of phentolamine in chronic obstructive pulmonary disease. *British Heart Journal.* 1971; 33(4):445-450.

345 Van Mieghem W, De Backer G, De Wispelaere B et al. Phentolamine infusion in cor pulmonale due to chronic obstructive pulmonary disease. *Acta Cardiologica.* 1978; 33(4):253-262.

346 Vik-Mo H, Walde N, Jentoft H et al. Improved haemodynamics but reduced arterial blood oxygenation, at rest and during exercise after long-term oral prazosin therapy in chronic cor pulmonale. *European Heart Journal.* 1985; 6(12):1047-1053.

347 Green LH, Smith TW. The use of digitalis in patients with pulmonary disease. *Ann Intern Med.* 1977; 87(4):459-465.

348 Jezek V, Schrijen F. Haemodynamic effect of deslanoside at rest and during exercise in patients with chronic bronchitis. *British Heart Journal.* 1973; 35(1):2-8.

349 Brown SE, Pakron FJ, Milne N et al. Effects of digoxin on exercise capacity and right ventricular function during exercise in chronic airflow obstruction. *Chest.* 1984; 85(2):187-191.

350 British Thoracic Society Standards of Care Subcommittee on Pulmonary Rehabilitation. Pulmonary rehabilitation. *Thorax.* 2001; 56(11):827-834.

351 Ries AL, Carlin BW, Carrieri-Kohlman V et al. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based guidelines. *Chest.* 1997; 112(5):1363-1396.

352 Salman GF, Mosier MC, Beasley BW et al. Rehabilitation for patients with chronic obstructive pulmonary disease: Meta-analysis of randomized controlled trials. *J Gen Intern Med.* 2003; 18(3):213-221.

353 Toshima MT, Blumberg E, Ries AL et al. Does rehabilitation reduce depression in patients with chronic obstructive pulmonary disease? *Journal of Cardiopulmonary Rehabilitation.* 1992; 12(4):261-269.

354 Griffiths TLB. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet.* 2000; 355(9201):362-368.

355 Lacasse Y, Brosseau L, Milne S et al. Pulmonary Rehabilitation for Chronic Obstructive Pulmonary Disease. *The Cochrane Library.* 2003; Issue 3(3)

356 Ries AL, Kaplan RM, Limberg TMK et al. Effects of pulmonary rehabilitation on physiological and psychosocial outcomes in patients with chronic obstructive pulmonary-disease. *Ann Intern Med.* 1995; 122(11):823-832.

357 Bestall JC, Paul EA, Garrod R et al. Longitudinal trends in exercise capacity and health status after pulmonary rehabilitation in patients with COPD. *Respir Med.* 2003; 97(2):173-180.

358 The Wessex Institute. *Hospital based pulmonary rehabilitation programmes for patients with severe chronic obstructive pulmonary disease.* 1999.

359 Griffiths TL, Phillips CJ, Davies S et al. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax.* 2001; 56(10):779-784.

360 Smith K, Cook D, Guyatt GH et al. Respiratory muscle training in chronic airflow limitation: a meta-analysis. *Am Rev Respir Dis.* 1992; 145(3):533-539.

361 Lotters F, van Tol B, Kwakkel G et al. Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. *Eur Respir J.* 2002; 20(3):570-576.

362 Ortega F, Toral J, Cejudo P et al. Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 2002; 166(5):669-674.

363 Puente-Maestu L, Sanz ML, Sanz P et al. Comparison of effects of supervised versus self-monitored training programmes in patients with chronic obstructive pulmonary disease. *Eur Respir J.* 2000; 15(3):517-525.

364 Berry MJ, Rejeski WJ, Adair NE et al. A randomized, controlled trial comparing long-term and short-term exercise in patients with chronic obstructive pulmonary disease. *Journal of Cardiopulmonary Rehabilitation.* 2003; 23(1):60-68.

365 Young P, Dewse M, Fergusson W et al. Respiratory rehabilitation in chronic obstructive pulmonary disease: Predictors of nonadherence. *Eur Respir J.* 1999; 13(4):855-859.

366 Foglio K, Bianchi L, Ambrosino N. Is it really useful to repeat outpatient pulmonary rehabilitation programs in patients with chronic airway obstruction? A 2-year controlled study. *Chest.* 2001; 119(6):1696-1704.

367 Puhan M, Scharplatz M, Troosters T et al. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews.* 2009;(Scharplatz Madlaina):CD005305.

368 Eaton T, Young P, Fergusson W et al. Does early pulmonary rehabilitation reduce acute health-care utilization in COPD patients admitted with an exacerbation? A randomized controlled study. *Respirology.* 2009; 14(2):230-238.

369 Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Am J Med.* 2000; 109(3):207-212.

370 Behnke M, Jorres RA, Kirsten D et al. Clinical benefits of a combined hospital and home-based exercise programme over 18 months in patients with severe COPD. *Monaldi Arch Chest Dis.* 2003; 59(1):44-51.

371 Behnke M, Taube C, Kirsten D et al. Home-based exercise is capable of preserving hospital-based improvements in severe chronic obstructive pulmonary disease. *Respir Med.* 2000; 94(12):1184-1191.

372 Kirsten DK, Taube C, Lehnigk B et al. Exercise training improves recovery in patients with COPD after an acute exacerbation. *Respir Med.* 1998; 92(10):1191-1198.

373 Nava S. Rehabilitation of patients admitted to a respiratory intensive care unit. *Archives of Physical Medicine & Rehabilitation.* 1998; 79(7):849-854.

374 Man WD, Polkey MI, Donaldson N et al. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. *Br Med J.* 2004; 329(7476):1209.

375 Murphy N, Bell C, Costello RW. Extending a home from hospital care programme for COPD exacerbations to include pulmonary rehabilitation. *Respir Med.* 2005; 99(10):1297-1302.

376 National Institute for Clinical Excellence. *Guidance on the use of zanamivir, amantadine and oseltamivir for the treatment of influenza.* (NICE technology appraisal guidance- No.58)., 2003.

377 Poole PJ, Chacko E, Wood-Baker RWB et al. Influenza vaccine for patients with chronic obstructive pulmonary disease. *The Cochrane Library.* 2003; Issue 3(3)

378 Nichol KL, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. *Ann Intern Med.* 1999; 130(5):397-403.

379 National Institute of Clinical Excellence. *Guidance on the use of Zanamivir (Relenza) in the treatment of influenza.* (NICE technology appraisal guidance- No.15). National Institute of Clinical Excellence (NICE), 2000.

380 Turner, D., Wailoo, A., Nicholson, K., Cooper, N., Sutton, A., Abrams, K., and NICE. *Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.* University of Leciester; ScHARR at University of Sheffield: NICE, 28-4-2002.

381 Nichol KL, Baken L, Wuorenma J et al. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. *Arch Intern Med.* 1999; 159(20):2437-2442.

382 Nichol KL. The additive benefits of influenza and pneumococcal vaccinations during influenza seasons among elderly persons with chronic lung disease. *Vaccine.* 1999; 17 Suppl 1:S91-S93.

383 Leech JA, Gervais A, Ruben FL. Efficacy of pneumococcal vaccine in severe chronic obstructive pulmonary disease. *Canadian Medical Association Journal.* 1987; 136(4):361-365.

384 Tandon MK, Gebski V. A controlled trial of a killed Haemophilus influenzae vaccine for prevention of acute exacerbations of chronic bronchitis. *Australian & New Zealand Journal of Medicine.* 1991; 21(4):427-432.

385 Hak E, Van Essen GA, Buskens E et al. Is immunising all patients with chronic lung disease in the community against influenza cost effective? Evidence from a general practice based clinical prospective cohort study in Utrecht, the Netherlands. *Journal of Epidemiology and Community Health.* 1998; 52(2):120-125.

386 Snider GL. Reduction pneumoplasty for giant bullous emphysema. Implications for surgical treatment of nonbullous emphysema. *Chest.* 1996; 109(2):540-548.

387 Stirling GR, Babidge WJ, Peacock MJ et al. Lung volume reduction surgery in emphysema: a systematic review. *Annals of Thoracic Surgery.* 2001; 72(2):641-648.

388 Pompeo E, Marino M, Nofroni I et al. Reduction pneumoplasty versus respiratory rehabilitation in severe emphysema: a randomized study. Pulmonary Emphysema Research Group. *Annals of Thoracic Surgery.* 2000; 70(3):948-953.

389 National Emphysema Treatment Trial Research Group. A randomised trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med.* 2003; 348(21):2059-2073.

390 Zenati M, Keenan RJ, Courcoulas AP et al. Lung volume reduction or lung transplantation for end-stage pulmonary emphysema? *European Journal of Cardiothoracic Surgery.* 1998; 14(1):27-31.

391 Gaissert HA, Trulock EP, Cooper JD et al. Comparison of early functional results after volume reduction or lung transplantation for chronic obstructive pulmonary disease. *Journal of Thoracic and Cardiovascular Surgery.* 1996; 111(2):296-306.

392 Keller CA, Naunheim KS, Osterloh J et al. Hemodynamics and gas exchange after single lung transplantation and unilateral thoracoscopic lung reduction. *Journal of Heart and Lung Transplantation.* 1997; 16(2):199-208.

393 Hosenpud JD, Bennett LE, Keck BM et al. The Registry of the International Society for Heart and Lung Transplantation: eighteenth Official Report-2001. *Journal of Heart and Lung Transplantation.* 2001; 20(8):805-815.

394 Cassivi SD, Meyers BF, Battafarano RJ et al. Thirteen-year experience in lung transplantation for emphysema. *Annals of Thoracic Surgery.* 2002; 74(5):1663-1669.

395 American Thoracic Society, Aris R, Barbers RG et al. International guidelines for the selection of lung transplant candidates. *American Journal of Respiratory & Critical Care Medicine.* 1998; 158:335-339.

396 Geddes D, Davies M, Koyama H et al. Effect of lung-volume-reduction surgery in patients with severe emphysema. *N Engl J Med.* 2000; 343(4):239-245.

397 National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. *N Engl J Med.* 2001; 345(15):1075-1083.

398 Trulock EP, III. Lung Transplantation for COPD. *Chest.* 1998; 113(Suppl 4):269S-276S.

399 Eriksson S. A 30-year perspective on alpha(1)-antitrypsin deficiency. *Chest.* 1996; 110(6):S237-S242.

400 Dirksen A, Dijkman JH, Madsen F et al. A randomized clinical trial of alpha1-antitrypsin augmentation therapy. *American Journal of Respiratory & Critical Care Medicine.* 1999; 160(5 I):1468-1472.

401 The Alpha 1-Antitrypsin Deficiency Registry Study Group. Survival and FEV1 decline in individuals with severe deficiency of alpha 1-antitrypsin. *American Journal of Respiratory & Critical Care Medicine.* 1998; 158:49-59.

402 Seersholm N, Wencker M, Banik N et al. Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group. *Eur Respir J.* 1997; 10(10):2260-2263.

403 Hay JW, Robin ED. Cost-effectiveness of alpha-1 antitrypsin replacement therapy in treatment of congenital chronic obstructive pulmonary disease. *American Journal of Public Health.* 1991; 81(4):427-433.

404 *Specialist Nurse Innovations for COPD Review*. *Barts and The London.* 2003. **http://www.smd.qmul.ac.uk/gp/copdreview/copdreview.html**

405 Thomas M, McKinley RK, Freeman E et al. Breathing retraining for dysfunctional breathing in asthma: a randomised controlled trial. *Thorax.* 2003; 58(2):110-115.

406 Rivington-Law BA, Epstein SW, Thompson GL et al. Effect of chest wall vibrations on pulmonary function in chronic bronchitis. *Chest.* 1984; 85(3):378-381.

407 Kurabayashi H, Machida I, Tamura K et al. Breathing out into water during subtotal immersion: A therapy for chronic pulmonary emphysema. *American Journal of Physical Medicine & Rehabilitation.* 2000; 79(2):150-153.

408 Mohsenifar Z, Rosenberg N, Goldberg HS et al. Mechanical vibration and conventional chest physiotherapy in outpatients with stable chronic obstructive lung disease. *Chest.* 1985; 87(4):483-485.

409 Olseni L, Midgren B, Hornblad Y et al. Chest physiotherapy in chronic obstructive pulmonary disease: Forced expiratory technique combined with either postural drainage or positive expiratory pressure breathing. *Respir Med.* 1994; 88(6):435-440.

410 Savci S, Ince DI, Arikan H. A comparison of autogenic drainage and the active cycle of breathing techniques in patients with chronic obstructive pulmonary diseases. *Journal of Cardiopulmonary Rehabilitation.* 2000; 20(1):37-43.

411 Van Hengstum M, Festen J, Beurskens C et al. Effect of positive expiratory pressure mask physiotherapy (PEP) versus forced expiration technique (FET/PD) on regional lung clearance in chronic bronchitis. *Eur Respir J.* 1991; 4(6):651-654.

412 Kolaczkowski W, Taylor R, Hoffstein V. Improvement in oxygen saturation after chest physiotherapy in patients with emphysema. *Physiotherapy Canada.* 1989; 41(1):18-23.

413 Christensen EF, Nedergaard T, Dahl R. Long-term treatment of chronic bronchitis with positive expiratory pressure mask and chest physiotherapy. *Chest.* 1990; 97(3):645-650.

414 Casciari RJ, Fairshter RD, Harrison A. Effects of breathing retraining in patients with chronic obstructive pulmonary disease. *Chest.* 1981; 79(4):393-398.

415 van Ede L, Yzermans CJ, Brouwer HJ. Prevalence of depression in patients with chronic obstructive pulmonary disease: a systematic review. *Thorax.* 1999; 54(8):688-692.

416 Rose C, Wallace L, Dickson R et al. The most effective psychologically-based treatments to reduce anxiety and panic in patients with chronic obstructive pulmonary disease (COPD): A systematic review. *Patient Education & Counseling.* 2002; 47(4):311-318.

417 Borson S, McDonald GJ, Gayle T et al. Improvement in mood, physical symptoms, and function with nortriptyline for depression in patients with chronic obstructive pulmonary-disease. *Psychosomatics.* 1992; 33(2):190-201.

418 Kunik ME, Braun U, Stanley MA et al. One session cognitive behavioural therapy for elderly patients with chronic obstructive pulmonary disease. *Psychological Medicine.* 2001; 31(4):717-723.

419 Man GC, Hsu K, Sproule BJ. Effect of alprazolam on exercise and dyspnea in patients with chronic obstructive pulmonary disease. *Chest.* 1986; 90(6):832-836.

420 Kozora E, Vu Tran Z, Make B. Neurobehavioral improvement after brief rehabilitation in patients with chronic obstructive pulmonary disease. *Journal of Cardiopulmonary Rehabilitation.* 2002; 22(6):426-430.

421 van Manen JG, Bindels PJ, Dekker FW et al. Risk of depression in patients with chronic obstructive pulmonary disease and its determinants. *Thorax.* 2002; 57(5):412-416.

422 Yohannes AM, Roomi J, Baldwin RC et al. Depression in elderly outpatients with disabling chronic obstructive pulmonary disease. *Age & Ageing.* 1998; 27(2):155-160.

423 Yohannes AM, Baldwin RC, Connolly MJ. Depression and anxiety in elderly outpatients with chronic obstructive pulmonary disease: Prevalence, and validation of the BASDEC screening questionnaire. *International Journal of Geriatric Psychiatry.* 2000; 15(12):1090-1096.

424 Lacasse Y, Rousseau L, Maltais F. Prevalence of depressive symptoms and depression in patients with severe oxygen-dependent chronic obstructive pulmonary disease. *Journal of Cardiopulmonary Rehabilitation.* 2001; 21(2):80-86.

425 Crockett AJ, Cranston JM, Moss JR et al. The impact of anxiety, depression and living alone in chronic obstructive pulmonary disease. *Qual Life Res.* 2002; 11(4):309-316.

426 Dowson C, Laing R, Barraclough R et al. The use of the Hospital Anxiety and Depression Scale (HADS) in patients with chronic obstructive pulmonary disease: a pilot study. *New Zealand Medical Journal.* 2001; 114(1141):447-449.

427 Withers NJ, Rudkin ST, White RJ. Anxiety and depression in severe chronic obstructive pulmonary disease: The effects of pulmonary rehabilitation. *Journal of Cardiopulmonary Rehabilitation.* 1999; 19(6):362-365.

428 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica.* 1983; 67(6):361-370.

429 Okubadejo AA, Paul EA, Jones PW et al. Does long-term oxygen therapy affect quality of life in patients with chronic obstructive pulmonary disease and severe hypoxaemia? *Eur Respir J.* 1996; 9(11):2335-2339.

430 Yohannes AM, Connolly MJ, Baldwin RC. A feasibility study of antidepressant drug therapy in depressed elderly patients with chronic obstructive pulmonary disease. *International Journal of Geriatric Psychiatry.* 2001; 16(5):451-454.

431 National Collaborating Centre for Mental Health. *Depression in Adults with a Chronic Physical Health Problem: treatment and management (final draft).* (91). London: National Institute for Health and Clinical Excellence, 2009.

432 Schols AM, Wouters EF. Nutritional abnormalities and supplementation in chronic obstructive pulmonary disease. *Clinics in Chest Medicine.* 2000; 21(4):753-762.

433 Agusti AG. Systemic effects of chronic obstructive pulmonary disease. *Novartis Foundation Symposium.* 2001; 234:242-249.

434 Ferreira IM, Brooks D, Lacasse Y et al. Nutritional supplementation for stable chronic obstructive pulmonary disease. *The Cochrane Library.* 2003; Issue 3(3)

435 Otte KE, Ahlburg P, D'Amore F et al. Nutritional repletion in malnourished patients with emphysema. *Journal of Parenteral & Enteral Nutrition.* 1989; 13(2):152-156.

436 Slinde F, Gronberg AM, Engstrom CR et al. Individual dietary intervention in patients with COPD during multidisciplinary rehabilitation. *Respir Med.* 2002; 96(5):330-336.

437 Schols AMWJ, Mostert R, Soeters PB et al. Nutritional state and exercise performance in patients with chronic obstructive lung disease. *Thorax.* 1989; 44(11):937-941.

438 Baarends EM, Schols AM, Mostert R et al. Peak exercise response in relation to tissue depletion in patients with chronic obstructive pulmonary disease. *Eur Respir J.* 1997; 10(12):2807-2813.

439 Engelen MP, Schols AM, Baken WC et al. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. *Eur Respir J.* 1994; 7(10):1793-1797.

440 Landbo C, Prescott E, Lange P et al. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 1999; 160(6):1856-1861.

441 Marquis K, Debigare R, Lacasse Y et al. Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 2002; 166(6):809-813.

442 Prescott E, Almdal T, Mikkelsen KL et al. Prognostic value of weight change in chronic obstructive pulmonary disease: results from the Copenhagen City Heart Study. *Eur Respir J.* 2002; 20(3):539-544.

443 Sahebjami H, Doers JT, Render ML et al. Anthropometric and pulmonary function test profiles of outpatients with stable chronic obstructive pulmonary disease. *Am J Med.* 1993; 94(5):469-474.

444 Wilson DO, Rogers RM, Wright EC et al. Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. *Am Rev Respir Dis.* 1989; 139(6):1435-1438.

445 Gray-Donald K, Gibbons L, Shapiro SH et al. Effect of nutritional status on exercise performance in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1989; 140(6):1544-1548.

446 Schols AMWJ, Soeters PB, Dingemans AMC et al. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis.* 1993; 147(5):1151-1156.

447 Sahebjami H, Sathianpitayakul E. Influence of body weight on the severity of dyspnea in chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 2000; 161(3 I):886-890.

448 Schols AMWJ, Slangen J, Volovics L et al. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 1998; 157(6):1791-1797.

449 Palange P, Forte S, Felli A et al. Nutritional state and exercise tolerance in patients with COPD. *Chest.* 1995; 107(5):1206-1212.

450 Rogers RM, Donahoe M, Costantino J. Physiologic effects of oral supplemental feeding in malnourished patients with chronic obstructive pulmonary disease. A randomized control study. *Am Rev Respir Dis.* 1992; 146(6):1511-1517.

451 Koplemann, P. G. and The members of the working party. *Nutrition and patients a doctors responsibility.* London: RCP, 2002.

452 Roberts CM, Lowe D, Bucknall CE et al. Clinical audit indicators of outcome following admission to hospital with acute exacerbation of chronic obstructive pulmonary disease. *Thorax.* 2002; 57(2):137-141.

453 Elkington H, White P, Higgs R et al. GPs' views of discussions of prognosis in severe COPD. *Fam Pract.* 2001; 18(4):440-444.

454 Sullivan KE, Hebert PC, Logan J et al. What do physicians tell patients with end-stage COPD about intubation and mechanical ventilation? *Chest.* 1996; 109(1):258-264.

455 Rhodes P. Focus on palliative care. Palliative care: the situation of people with chronic respiratory disease. *British Journal of Community Nursing.* 1999; 4(3):131-136.

456 Heffner JE, Fahy B, Hilling L et al. Attitudes regarding advance directives among patients in pulmonary rehabilitation. *American Journal of Respiratory & Critical Care Medicine.* 1996; 154(6 Pt 1):1735-1740.

457 Jennings AL, Davies AN, Higgins JPT et al. Opioids for the palliation of breathlessness in terminal illness. *The Cochrane Library.* 2003; Issue 3(3)

458 Ramsdell JW, Henderson S, Renvall MJ et al. Effects of theophylline and ipratropium on cognition in elderly patients with chronic obstructive pulmonary disease. *Annals of Allergy Asthma & Immunology.* 1996; 76(4):335-340.

459 Hunt A. *The elderly at home. A study of elderly people living in the community in England in 1976*. London: OPCS; 1976.

460 Yohannes AM, Roomi J, Connolly MJ. Elderly people at home disabled by chronic obstructive pulmonary disease. *Age & Ageing.* 1998; 27(4):523-525.

461 Yohannes AM, Greenwood YA, Connolly MJ. Reliability of the Manchester respiratory activities of daily living questionnaire as a postal questionnaire. *Age & Ageing.* 2002; 31(5):355-358.

462 Yohannes AM, Roomi J, Winn S et al. The Manchester Respiratory Activities of Daily Living questionnaire: development, reliability, validity, and responsiveness to pulmonary rehabilitation. *Journal of the American Geriatrics Society.* 2000; 48(11):1496-1500.

463 Garrod R, Bestall JC, Paul EA et al. Development and validation of a standardized measure of activity of daily living in patients with severe COPD: the London Chest Activity of Daily Living scale (LCADL). *Respir Med.* 2000; 94(6):589-596.

464 Garrod R, Paul EA, Wedzicha JA. An evaluation of the reliability and sensitivity of the London Chest Activity of Daily Living Scale (LCADL). *Respir Med.* 2002; 96(9):725-730.

465 Law M, Polatajko H, Pollock N et al. Pilot testing of the Canadian Occupational Performance Measure: clinical and measurement issues. *Canadian Journal of Occupational Therapy.* 1994; 61(4):191-197.

466 Sewell L, Singh SJ. The Canadian Occupational Performance Measure: Is it a reliable measure in clients with chronic obstructive pulmonary disease? *British Journal of Occupational Therapy.* 2001; 64(6):305-310.

467 British Thoracic Society. Managing passengers with respiratory disease planning air travel: British Thoracic Society recommendations. *Thorax.* 2002; 57(4):289-304.

468 Zaugg M, Kaplan V, Widmer U et al. Fatal air embolism in an airplane passenger with a giant intrapulmonary bronchogenic cyst. *American Journal of Respiratory & Critical Care Medicine.* 1998; 157(5 Pt 1):1686-1689.

469 Sassi-Dambron DE, Eakin EG, Ries AL et al. Treatment of dyspnea in COPD. A controlled clinical trial of dyspnea management strategies. *Chest.* 1995; 107(3):724-729.

470 Howland J, Nelson EC, Barlow PB et al. Chronic obstructive airway disease. Impact of health education. *Chest.* 1986; 90(2):233-238.

471 Gallefoss F, Bakke PS, Rsgaard PK. Quality of life assessment after patient education in a randomized controlled study on asthma and chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 1999; 159(3):812-817.

472 Gallefoss F, Bakke PS. How does patient education and self-management among asthmatics and patients with chronic obstructive pulmonary disease affect

medication? *American Journal of Respiratory & Critical Care Medicine.* 1999; 160(6):2000-2005.

473 Devine EC, Pearcy J. Meta-analysis of the effects of psychoeducational care in adults with chronic obstructive pulmonary disease. *Patient Education & Counseling.* 1996; 29(2):167-178.

474 Monninkhof EM, van der Valk PDLPM, van der Palen J et al. Self-management education for patients with chronic obstructive pulmonary disease. *The Cochrane Library.* 2003; Issue 3(3)

475 Bourbeau J, Julien M, Maltais F et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease - A disease-specific self- management intervention. *Arch Intern Med.* 2003; 163(5):585-591.

476 Emery CF, Schein RL, Hauck ER et al. Psychological and cognitive outcomes of a randomized trial of exercise among patients with chronic obstructive pulmonary disease. *Health Psychology.* 1998; 17(3):232-240.

477 Blake RL, Jr., Vandiver TA, Braun S et al. A randomized controlled evaluation of a psychosocial intervention in adults with chronic lung disease. *Family Medicine.* 1990; 22(5):365-370.

478 Littlejohns P, Baveystock CM, Parnell H et al. Randomised controlled trial of the effectiveness of a respiratory health worker in reducing impairment, disability, and handicap due to chronic airflow limitation. *Thorax.* 1991; 46(8):559-564.

479 Cockcroft A, Bagnall P, Heslop A et al. Controlled trial of respiratory health worker visiting patients with chronic respiratory disability. *Br Med J.* 1987; 294(6566):225-228.

480 Solomon DK, Portner TS, Bass GE et al. Clinical and economic outcomes in the hypertension and COPD arms of a multicenter outcomes study. *Journal of the American Pharmaceutical Association.* 1998; 38(5):574-585.

481 Gourley GA, Portner TS, Gourley DR et al. Humanistic outcomes in the hypertension and COPD arms of a multicenter outcomes study. *Journal of the American Pharmaceutical Association.* 1998; 38(5):586-597.

482 Watson PB, Town GI, Holbrook N et al. Evaluation of a self-management plan for chronic obstructive pulmonary disease. *Eur Respir J.* 1997; 10(6):1267-1271.

483 Gallefoss F, Bakke PS. Impact of patient education and self-management on morbidity in asthmatics and patients with chronic obstructive pulmonary disease. *Respir Med.* 2000; 94(3):279-287.

484 The Australian Lung Foundation. *Chronic Obstructive Pulmonary Disease (COPD). Australian and New Zealand Management Guidelines.* Lutwyche, 2002.

485 *Extremes of age. The 1999 report of the national confidential enquiry into perioperative deaths*. London: NCEPOD; 1999.

486 Appleberg M, Gordon L, Fatti LP. Preoperative pulmonary evaluation of surgical patients using the vitalograph. *British Journal of Surgery.* 1974; 61(1):57-59.

487 Kocabas A, Kara K, Ozgur G et al. Value of preoperative spirometry to predict postoperative pulmonary complications. *Respir Med.* 1996; 90(1):25-33.

488 Celli BR, Rodriguez KS, Snider GL. A controlled trial of intermittent positive pressure breathing, incentive spirometry, and deep breathing exercises in preventing pulmonary complications after abdominal surgery. *Am Rev Respir Dis.* 1984; 130(1):12-15.

489 Saklad M. Grading of patients for surgical procedures. *Anaesthesiology.* 1941; 2(3):281-284.

490 Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest.* 2000; 117(5):398S-401S.

491 Garcia-Aymerich J, Monso E, Marrades RM et al. Risk factors for hospitalization for a chronic obstructive pulmonary disease exacerbation - EFRAM Study. *American Journal of Respiratory & Critical Care Medicine.* 2001; 164(6):1002-1007.

492 Connors AF, Dawson NV, Thomas C et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. *American Journal of Respiratory & Critical Care Medicine.* 1996; 154(4):959-967.

493 Seemungal TAR, Donaldson GC, Bhowmik A et al. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 2000; 161(5):1608-1613.

494 Donaldson GC, Seemungal TA, Bhowmik A et al. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax.* 2002; 57(10):847-852.

495 Seemungal TAR, Donaldson GC, Paul EA et al. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 1998; 157(5):1418-1422.

496 Andersson F, Borg S, Jansson S-A et al. The costs of exacerbations in chronic obstructive pulmonary disease (COPD). *Respir Med.* 2002; 96(9):700-708.

497 Price MJ, Hurrell C. Health care costs of treating exacerbations of COPD. *Eur Respir J.* 1999; 14(380s)

498 Wedzicha JA. Exacerbations: etiology and pathophysiologic mechanisms. *Chest.* 2002; 121(Suppl 5):136S-141S.

499 Gravil JH, Al Rawas OA, Cotton MM et al. Home treatment of exacerbations of chronic obstructive pulmonary disease by an acute respiratory assessment service. *Lancet.* 1998; 351(9119):1853-1855.

500 Killen J, Ellis H. Assisted discharge for patients with exacerbations of chronic obstructive pulmonary disease: safe and effective. *Thorax.* 2000; 55(11):885.

501 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(11):907-912.

502 Davies L, Wilkinson M, Bonner S et al. "Hospital at home" versus hospital care in patients with exacerbations of chronic obstructive pulmonary disease: prospective randomised controlled trial. *Br Med J.* 2000; 321(7271):1265-1268.

503 Ojoo JC, Moon T, McGlone S et al. Patients' and carers' preferences in two models of care for acute exacerbations of COPD: results of a randomised controlled trial. *Thorax.* 2002; 57(2):167-169.

504 Hernandez C, Casas A, Escarrabill J et al. Home hospitalisation of exacerbated chronic obstructive pulmonary disease patients. *Eur Respir J.* 2003; 21(1):58-67.

505 Fried TR, Van Doorn C, Tinetti ME et al. Older persons' preferences for site of treatment in acute illness. *J Gen Intern Med.* 1998; 13(8):522-527.

506 Fried TR, Van Doorn C, O'Leary JR et al. Older persons' preferences for home vs hospital care in the treatment of acute illness. *Arch Intern Med.* 2000; 160(10):1501-1506.

507 Cotton MM, Bucknall CE, Dagg KD et al. Early discharge for patients with exacerbations of chronic obstructive pulmonary disease: a randomised controlled trial. *Thorax.* 2000; 55(11):902-906.

508 Shepperd S, Harwood D, Jenkinson C et al. Randomised controlled trial comparing hospital at home care with inpatient hospital care. I: three month follow up of health outcomes. *Br Med J.* 1998; 316(7147):1786-1791.

509 Turner MO, Patel A, Ginsburg S et al. Bronchodilator delivery in acute airflow obstruction: A meta-analysis. *Arch Intern Med.* 1997; 157(15):1736-1744.

510 McCrory, D. C., Brown, C., Gray, R. N., Goslin, R. E., MacIntyre, N. R., Kolimaga, J. T., Oddone, E. Z., and Matchar, D. *Management of acute exacerbations of chronic obstructive pulmonary disease.* (256.). Rockville, MD, USA: Agency for Healthcare Research and Quality., 2001.

511 Wood-Baker R, Walters EH, Gibson P. Oral corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *The Cochrane Library.* 2003; Issue 3(3)

512 Singh JM, Palda VA, Stanbrook MB et al. Corticosteroid therapy for pts with acute exacerbations of COPD: a systematic review. *Arch Intern Med.* 2002; 162(22):2527-2536.

513 Bullard MJ, Liaw SJ, Tsai YH et al. Early corticosteroid use in acute exacerbations of chronic airflow obstruction. *American Journal of Emergency Medicine.* 1996; 14(2):139-143.

514 Maltais F, Ostinelli J, Bourbeau J et al. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic

obstructive pulmonary disease: A randomized controlled trial. *American Journal of Respiratory & Critical Care Medicine.* 2002; 165(5):698-703.

515 Davies L, Angus RM, Calverley PMA. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet.* 1999; 354(9177):456-460.

516 Niewoehner DE, Erbland ML, Deupree RH et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *N Engl J Med.* 1999; 340(25):1941-1947.

517 Thompson WH, Nielson CP, Carvalho P et al. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *American Journal of Respiratory & Critical Care Medicine.* 1996; 154(2):407-412.

518 Albert RK, Martin TR, Lewis SW. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. *Ann Intern Med.* 1980; 92(6):753-758.

519 Stockley RA, O'Brien C, Pye A et al. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest.* 2000; 117(6):1638-1645.

520 *Community management of lower respiratory tract infection in adults.* (SIGN publication No 59.)., 2002.

521 Saint S, Bent S, Vittinghoff E et al. Antibiotics in chronic obstructive pulmonary-disease exacerbations - a metaanalysis. *Journal of the American Medical Association.* 1995; 273(12):957-960.

522 Nouira S, Marghli S, Belghith M et al. Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: A randomised placebo-controlled trial. *Lancet.* 2001; 358(9298):2021-2025.

523 Sin DD, Tu JV. Outpatient antibiotic therapy and short term mortality in elderly patients with chronic obstructive pulmonary disease. *Can Respir J.* 2000; 7(6):466-471.

524 Allegra L, Blasi F, de Bernardi B et al. Antibiotic treatment and baseline severity of disease in acute exacerbations of chronic bronchitis: a re-evaluation of previously published data of a placebo-controlled randomized study. *Pulmonary Pharmacology & Therapeutics.* 2001; 14:149-155.

525 Anthonisen NR, Manfreda J, Warren CPW et al. Antibiotic-therapy in exacerbations of chronic obstructive pulmonary-disease. *Ann Intern Med.* 1987; 106(2):196-204.

526 Elmes PC, King TK, Langlands JH et al. Value of ampicillin in the hospital treatment of exacerbations of chronic bronchitis. *Br Med J.* 1965; 2(5467):904-908.

527 Berry DG, Fry J, Hindley CP. Exacerbations of chronic bronchitis: treatment with oxytetracycline. *Lancet.* 1960; 275(7116):137-139.

528 Davies BI, Maesen FP. Quinolones in chest infections. *Journal of Antimicrobial Chemotherapy.* 1986; 18(3):296-299.

529 Morris S, Anderson P, Irwin DE. Acute exacerbations of chronic bronchitis: a pharmacoeconomic review of antibacterial use. *Pharmacoeconomics.* 2002; 20(3):153-168.

530 Backhouse R, Shakespeare A, Hutton J. Economic evaluation of alternative antibiotic regimens in the management of acute exacerbations of chronic bronchitis. *British Journal of Medical Economics.* 1995; 8:1-25.

531 Torrance G, Walker V, Grossman R et al. Economic evaluation of ciprofloxacin compared with usual antibacterial care for the treatment of acute exacerbations of chronic bronchitis in patients followed for 1 year. *Pharmacoeconomics.* 1999; 16(5 Pt 1):499-520.

532 Lakshminarayan S, Sahn SA, Weil JV. Effect of aminophylline on ventilatory responses in normal man. *Am Rev Respir Dis.* 1978; 117(1):33-38.

533 Sanders JS, Berman TM, Bartlett MM et al. Increased hypoxic ventilatory drive due to administration of aminophylline in normal men. *Chest.* 1980; 78(2):279-282.

534 Sharp JT. Theophylline in chronic obstructive pulmonary disease. *Journal of Allergy & Clinical Immunology.* 1986; 78(Part 2):800-805.

535 Barr RG, Rowe BH, Camargo CA, Jr. Methylxanthines for exacerbations of chronic obstructive pulmonary disease. *The Cochrane Library.* 2003; Issue 3(3)

536 Murata GH, Gorby MS, Chick TW et al. Aminophylline in the outpatient management of decompensated chronic obstructive pulmonary disease. *Chest.* 1990; 98(6):1346-1350.

537 Murciano D, Auclair MH, Pariente R et al. A randomized, controlled trial of theophylline in patients with severe chronic obstructive pulmonary-disease. *N Engl J Med.* 1989; 320(23):1521-1525.

538 Barbera JA, Reyes A, Roca J et al. Effect of intravenously administered aminophylline on ventilation/perfusion inequality during recovery from exacerbations of chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1992; 145(6):1328-1333.

539 Rice KL, Leatherman JW, Duane PG et al. Aminophylline for acute exacerbations of chronic obstructive pulmonary disease. A controlled trial. *Ann Intern Med.* 1987; 107(3):305-309.

540 Seidenfeld JJ, Jones WN, Moss RE et al. Intravenous aminophylline in the treatment of acute bronchospastic exacerbations of chronic obstructive pulmonary disease. *Annals of Emergency Medicine.* 1984; 13(4):248-252.

541 Wrenn K, Slovis CM, Murphy F et al. Aminophylline therapy for acute bronchospastic disease in the emergency room. *Ann Intern Med.* 1991; 115(4):241-247.

542 Ram FSF, Poole PJ, Bagg W et al. *Randomised, controlled trial of theophylline for the treatment of exacerbations of chronic obstructive pulmonary disease*. *American Journal of Respiratory & Critical Care Medicine.* 161(Suppl); A489. 2000.

543 Greenstone M, Lasserson T. Doxapram for ventilatory failure due to exacerbations of chronic obstructive pulmonary disease. *The Cochrane Library.* 2003; (4)(4)

544 Bardsley PA, Tweney J, Morgan N et al. Oral almitrine in treatment of acute respiratory failure and cor pulmonale in patients with an exacerbation of chronic obstructive airways disease. *Thorax.* 1991; 46(7):493-498.

545 Moser K. Respiratory stimulation with intravenous doxapram in respiratory failure. A double blind co-operative study. *N Engl J Med.* 1973; 288(9):427-431.

546 Angus RM, Ahmed AA, Fenwick LJ et al. Comparison of the acute effects on gas exchange of nasal ventilation and doxapram in exacerbations of chronic obstructive pulmonary disease. *Thorax.* 1996; 51(10):1048-1050.

547 Edwards. A double blind trial of five respiratory stimulants in patients with acute ventialtion failure. *Lancet.* 1967; 2(7509):226-229.

548 Newman WJ, Banham SJ, Barr J et al. *A randomised trial comparing non-invasive ventilation with the respiratory stimulant, doxapram, in the treament of acute hypercapnic respiratory failure complicating exacerbations of chronic obstructive pulmonary disease*. 2001.

549 Murphy R, Driscoll P, O'Driscoll R. Emergency oxygen therapy for the COPD patient. *Emergency Medicine Journal.* 2001; 18(5):333-339.

550 Murphy R, Mackway-Jones K, Sammy I et al. Emergency oxygen therapy for the breathless patient. Guidelines prepared by the North West Oxygen Group. *Emergency Medicine Journal.* 2001; 18(6):421-423.

551 Hutchison DCS, Flenley DC, Donald KW. Controlled oxygen therapy in respiratory failure. *Br Med J.* 1964; 2(5417):1159-1166.

552 Bone RC, Pierce AK, Johnson RL, Jr. Controlled oxygen administration in acute respiratory failure in chronic obstructive pulmonary disease: a reappraisal. *Am J Med.* 1978; 65(6):896-902.

553 Agusti AG, Carrera M, Barbe F et al. Oxygen therapy during exacerbations of chronic obstructive pulmonary disease. *Eur Respir J.* 1999; 14(4):934-939.

554 King TK, Ali N, Briscoe WA. Treatment of hypoxia with 24 percent oxygen. A new approach to the interpretation of data collected in a pulmonary intensive care unit. *Am Rev Respir Dis.* 1973; 108(1):19-29.

555 Plant PK, Owen JL, Elliott MW. One year period prevalence study of respiratory acidosis in acute exacerbations of COPD: implications for the provision of non-invasive ventilation and oxygen administration. *Thorax.* 2000; 55(7):550-554.

556 DeGaute JP, Domenighetti G, Naeije R et al. Oxygen delivery in acute exacerbation of chronic obstructive pulmonary disease. Effects of controlled oxygen therapy. *Am Rev Respir Dis.* 1981; 124(1):26-30.

557 Smith JP, Stone RW, Muschenheim C. Acute respiratory failure in chronic lung disease. *Am Rev Respir Dis.* 1968; 97(5):791-803.

558 Eldridge F, Gherman C. Studies of oxygen administration in respiratory failure. *Ann Intern Med.* 1968; 68(3):569-578.

559 Prime FJ, Westlake EK. The respiratory response to CO2 in emphysema. *Clinical Science.* 1954; 13(3):321-332.

560 Aubier M, Murciano D, Milic-Emili J et al. Effects of the administration of O2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. *Am Rev Respir Dis.* 1980; 122(5):747-754.

561 Fajac I, Texereau J, Rivoal V et al. Blood gas measurement during exercise: a comparative study between arterialized earlobe sampling and direct arterial puncture in adults. *Eur Respir J.* 1998; 11(3):712-715.

562 Dall'Ava-Santucci J, Dessanges JF, Dinh Xuan AT et al. Is arterialized earlobe blood PO2 an acceptable substitute for arterial blood PO2? *Eur Respir J.* 1996; 9(6):1329-1330.

563 Pitkin AD, Roberts CM, Wedzicha JA. Arterialised earlobe blood gas analysis: an underused technique. *Thorax.* 1994; 49(4):364-366.

564 Sauty A, Uldry C, Debetaz LF et al. Differences in PO2 and PCO2 between arterial and arterialized earlobe samples. *Eur Respir J.* 1996; 9(2):186-189.

565 Peter JV, Moran JL, Phillips-Hughes J et al. Noninvasive ventilation in acute respiratory failure--a meta-analysis update. *Critical Care Medicine.* 2002; 30(3):555-562.

566 Keenan SP, Kernerman PD, Cook DJ et al. Effect of noninvasive positive pressure ventilation on mortality in patients admitted with acute respiratory failure: a meta-analysis. *Critical Care Medicine.* 1997; 25(10):1685-1692.

567 Ram FSF, Lightowler JVJ, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *The Cochrane Library.* 2003; Issue 3(3)

568 Thys F, Roeseler J, Reynaert M et al. Noninvasive ventilation for acute respiratory failure: A prospective randomised placebo-controlled trial. *Eur Respir J.* 2002; 20(3):545-555.

569 Conti G, Antonelli M, Navalesi P. Noninvasive vs conventional mechanical ventilation in pts with COPD after failure of medical treatment in the ward; a randomised trial. *Intensive Care Medicine.* 2002; 28(12):1701-1707.

570 Keenan SP, Gregor J, Sibbald WJ et al. Noninvasive positive pressure ventilation in the setting of severe, acute exacerbations of chronic obstructive pulmonary disease: more effective and less expensive. *Critical Care Medicine.* 2000; 28(6):2094-2102.

571 Plant PK, Owen JL, Parrott S et al. Cost effectiveness of ward based non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease: economic analysis of randomised controlled trial. *Br Med J.* 2003; 326(7396):956.

572 Seneff MG, Wagner DP, Wagner RP et al. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. *Journal of the American Medical Association.* 1995; 274(23):1852-1857.

573 Esteban A, Anzueto A, Frutos F et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *Journal of the American Medical Association.* 2002; 287(3):345-355.

574 Rieves RD, Bass D, Carter RR et al. Severe COPD and acute respiratory failure. Correlates for survival at the time of tracheal intubation. *Chest.* 1993; 104(3):854-860.

575 Nevins ML, Epstein SK. Predictors of outcome for patients with COPD requiring invasive mechanical ventilation. *Chest.* 2001; 119(6):1840-1849.

576 Nava S, Ambrosino N, Clini E et al. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. *Ann Intern Med.* 1998; 128(9):721-728.

577 Bellone A, Lascioli R, Raschi S et al. Chest physical therapy in patients with acute exacerbation of chronic bronchitis: Effectiveness of three methods. *Archives of Physical Medicine & Rehabilitation.* 2000; 81(5):558-560.

578 Newton DA, Bevans HG. Physiotherapy and intermittent positive-pressure ventilation of chronic bronchitis. *Br Med J.* 1978; 2(6151):1525-1528.

579 Bellone A, Spagnolatti L, Massobrio M et al. Short-term effects of expiration under positive pressure in patients with acute exacerbation of chronic obstructive pulmonary disease and mild acidosis requiring non-invasive positive pressure ventilation. *Intensive Care Medicine.* 2002; 28(5):581-585.

580 Wollmer P, Ursing K, Midgren B et al. Inefficiency of chest percussion in the physical therapy of chronic bronchitis. *European Journal of Respiratory Diseases.* 1985; 66(4):233-239.

581 Brown PM, Manfreda J, McCarthy D et al. The effect of mechanical vibration in patients with acute exacerbations of COPD. *Physiotherapy Canada.* 1987; 39:371-374.

582 *National COPD audit*. *Royal College of Physicians.* 2003. http://www.rcplondon.ac.uk/college/ceeu/ceeu_copd_home.htm.

583 Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J.* 1977; 1(6077):1645-1648.

584 Harper R. Comparison of outcome measures for patients with chronic obstructive pulmonary disease (COPD) in an outpaitent setting. *Thorax.* 1997; 52(10):879-887.

585 Netten, A. and Curtis, L. *Unit costs of health and social care.* The University of Kent: 2003.

586 Guest JF. The annual cost of chronic obstructive pulmonary disease to the UK's National Health Service. *Disease Management and Health Outcomes.* 1999; 5(2):2-100.

587 Sullivan SD, Ramsey SD, Lee TA. The economic burden of COPD. *Chest.* 2000; 117(Suppl 2):5S-9S.

588 Calverley P, Sondhi S. *The burden of obstructive lung disease in the UK - COPD and asthma*. *Thorax.* 1996.

589 NHS executive. *Burdens of disease. A discussion document.* 1996.

590 Gibson PG, Wlodarczyk JH, Wilson AJ et al. Severe exacerbation of chronic obstructive airways disease: health resource use in general practice and hospital. *Journal of Quality in Clinical Practice.* 1998; 18(2):125-133.

591 McGuire A, Irwin DE, Fenn P et al. The excess cost of acute exacerbations of chronic bronchitis in patients aged 45 and older in England and Wales. *Value in Health.* 2001; 4(5):370-375.

592 National Institute for Clinical Excellence. *Information for National Collaborating Centres and Guideline Development Groups.* (The Guideline Development Process Series No. 3.). London: National Institute for Clinical Excellence, 2001.

593 Scottish Intercollegiate Guidelines Network. *SIGN 50 A guideline developers' handbook*. 2001. **http://www.sign.ac.uk/guidelines/fulltext/50/**

594 Murphy, M. K., Black, N. A., Lamping, D. L., McKee, C. M., Sanderson, C. F., and Askham, J. et al. *Consensus development methods, and their use in clinical guideline development.* (Health Technology Assessment. Vol. 2.)., 1998.

595 Chapman, Arvidsson PC. The addition of salmeterol 50 mg bid to anticholinergic treatment in patients with COPD: A randomized, placebo controlled trial. *Can Respir J.* 2002; 9(3):178-185.

596 Auerbach D, Hill C, Baughman R et al. Routine nebulized ipratropium and albuterol together are better than either alone in COPD. *Chest.* 1997; 112(6):1514-1521.

597 Bone R, Boyars M, Braun SR et al. In chronic obstructive pulmonary-disease, a combination of ipratropium and albuterol is more effective than either agent alone - an 85-day multicenter trial. *Chest.* 1994; 105(5):1411-1419.

598 Gross N, Tashkin D, Miller R et al. Inhalation by nebulization of albuterol-ipratropium combination (Dey combination) is superior to either agent alone in the treatment of chronic obstructive pulmonary disease. *Respiration.* 1998; 65(5):354-362.

599 D'Urzo AD, De Salvo MC, Ramirez-Rivera A et al. In patients with COPD, treatment with a combination of formoterol and ipratropium is more effective than a combination of salbutamol and ipratropium : a 3-week, randomized, double-blind, within-patient, multicenter study. *Chest.* 2001; 119(5):1347-1356.

600 Friedman M, Serby CW, Menjoge SS et al. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. *Chest.* 1999; 115(3):635-641.

601 Grandjean EM, Berthet P, Ruffmann R et al. Efficacy of oral long-term N-acetylcysteine in chronic bronchopulmonary disease: a meta-analysis of published double-blind, placebo-controlled clinical trials. *Clin Ther.* 2000; 22(2):209-221.

602 Stey C, Steurer J, Bachmann S et al. The effect of oral N-acetylcysteine in chronic bronchitis: A quantitative systematic review. *Eur Respir J.* 2000; 16(2):253-262.

603 Cattaneo C. Neltenexine tablets in smoking and non-smoking patients with COPD. A double-blind, randomised, controlled study versus placebo. *Minerva Medica.* 2001; 92(4):277-284.

604 Gerrits CMJM, Herings RMC, Leufkens HGM et al. N-acetylcysteine reduces the risk of re-hospitalisation among patients with chronic obstructive pulmonary disease. *Eur Respir J.* 2003; 21(5):795-798.

605 Poole PJ, Black PN. Oral mucolytic drugs for exacerbations of chronic obstructive pulmonary disease: systematic review. *Br Med J.* 2001; 322(7297):1271-1274.

606 Petty TL. The national mucolytic study. Results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. *Chest.* 1990; 97(1):75-83.

607 *Immunisation against infectious disease ("The Green Book")*. London: Department of Health; 1996.

608 DOH. Pneumococcal (draft replacement chapter). *Immunisation Against Infectious Disease ("The Green Book")*, London: Department of Health, 2003:

609 Department of Health. *COPD prevalence in England - analysis of the 2001 Health Survey for England*. 2009. Department of Health.

610 Celli BR, Thomas NE, Anderson JA et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *American Journal of Respiratory & Critical Care Medicine.* 2008; 178(4):332-338.

611 Ekberg-Aronsson M, Pehrsson K, Nilsson JA et al. Mortality in GOLD stages of COPD and its dependence on symptoms of chronic bronchitis. *Respiratory Research.* 2005; 6:98.

612 Office for National Statistics. *Interim Life Tables England and Wales 2005-2007*. *http://www statistics gov uk/*. 2009. Office for National Statistics. http://www.statistics.gov.uk/StatBase/Product.asp?vlnk=14459

613 Rutten-van Molken MP, Oostenbrink JB, Tashkin DP et al. Does quality of life of COPD patients as measured by the generic EuroQol five-dimension questionnaire differentiate between COPD severity stages? *Chest.* 2006; 130(4):1117-1128.

614 O'Reilly JF, Williams AE, Rice L. Health status impairment and costs associated with COPD exacerbation managed in hospital. *Int J Clin Pract.* 2007; 61(7):1112-1120.

615 Paterson C, Langan CE, McKaig GA et al. Assessing patient outcomes in acute exacerbations of chronic bronchitis: the measure your medical outcome profile (MYMOP), medical outcomes study 6-item general health survey (MOS-6A) and EuroQol (EQ-5D). *Qual Life Res.* 2000; 9(5):521-527.

616 Spencer S, Jones PW, GLOBE Study Group. Time course of recovery of health status following an infective exacerbation of chronic bronchitis. *Thorax.* 2003; 58(7):589-593.

617 Starkie HJ. Mapping the St George's respiratory questionnaire to utility values using the EQ5D. 08 Oct 20; 2008.

618 electronic Medicines Compendium. *Spiriva 18 microgram inhalation powder, hard capsule*. 2008. UK: Middlesex, Allen & Hanbury. http://emc.medicines.org.uk/medicine/10039/SPC/Spiriva+18+microgram+inhalation+powder%2c+hard+capsule/

619 electronic Medicines Compendium. *Spiriva Respimat 2.5 micrograms solution for inhalation*. 2009. UK: Middlesex, Allen & Hanbury. http://emc.medicines.org.uk/medicine/20134/SPC/Spiriva+Respimat+2.5+micrograms+solution+for+inhalation/

620 electronic Medicines Compendium. *Symbicort Turbohaler 200/6 Inhalation powder*. 2009. UK: Middlesex, Allen & Hanbury. http://emc.medicines.org.uk/medicine/4821/SPC/Symbicort+Turbohaler+200+6+Inhalation+powder/

621 electronic Medicines Compendium. *Symbicort Turbohaler 400/12, Inhalation powder*. 2009. UK: Middlesex, Allen & Hanbury. http://emc.medicines.org.uk/medicine/11882/SPC/Symbicort+Turbohaler+400+12%2c+Inhalation+powder./

622 compiled on behalf of the Department of Health by the NHS Business Services Authority NPS. *National Health Service Drug Tariff for England and Wales*. Available from: Presecription Pricing Division.

623 Department of Health. *Prescription Cost Analysis 2007*. 2009. UK, Department of Health. http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/prescription-cost-analysis-2007

624 O'Reilly JF, Williams AE, Holt K et al. Defining COPD exacerbations: impact on estimation of incidence and burden in primary care. *Primary Care Respiratory Journal.* 2006; 15(6):346-353.

625 Department of Health. *NHS Reference Costs 2007/8*. *Department of Health.* Gateway reference 11485. 2009.

626 Royal College of Physicians, British Thoracic Society, and British Lung Foundation. *Report 4 of the National Chronic Obstructive Pulmonary Disease Audit 2008: Patient Survey.* London: Royal College of Physicians, 2008.

627 Curtis, L. *Unit Costs of Health and Social Care.* Personal Social Services Research Unit, 2008.

628 Lucioni C, Donner CF, De Benedetto F. I costi della broncopneumopatia cronica ostruttiva: la fase prospettica dello studio ICE (Italian Costs for Exacerbations in COPD). *Pharmacoeconomics Italian research articles.* 2005; 7:119-1134.

629 Donaldson GC, Seemungal TA, Patel IS et al. Longitudinal changes in the nature, severity and frequency of COPD exacerbations
6. *Eur Respir J.* 2003; 22(6):931-936.

630 NHS Information Centre. *Health Survey for England Latest Trends 2007*. *The Information Centre for Health and Social Care.* 2007. The Information Centre for Health and Social Care. www.ic.nhs.uk

631 Donaldson G, Seemungal TAR, Wilkinson TM et al. Exacerbation types by COPD severity: risk of hospitalisation by patients not seeking treatment. *Eur Respir J.* 2003; 22(Suppl 45):S353.

632 Izquierdo Alonso JL, de Miguel Diez J. Economic impact of pulmonary drugs on direct costs of stable chronic obstructive pulmonary disease. *Journal of Chronic Obstructive Pulmonary Disease.* 2004; 1(2):215-223.

633 Doll H, Miravitlles M. Health-related QOL in acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease: a review of the literature. *Pharmacoeconomics.* 2005; 23(4):345-363.

634 Spencer M, Briggs AH, Grossman RF et al. Development of an economic model to assess the cost-effectiveness of treatment interventions for chronic obstructive pulmonary disease. *Pharmacoeconomics.* 2005; 23(6):619-637.

635 Borg S, Ericsson A, Wedzicha J et al. A computer simulation model of the natural history and economic impact of chronic obstructive pulmonary disease. *Value in Health.* 2004; 7(2):153-167.

636 Andersson F, Borg S, Stahl E. The impact of exacerbations on the asthmatic patient's preference scores. *J Asthma.* 2003; 40(6):615-623.

637 Maniadakis N, Tzanakis N, Fragoulakis V et al. Economic evaluation of tiotropium and salmeterol in the treatment of chronic obstructive pulmonary disease (COPD) in Greece. *Current Medical Research & Opinion.* 2006; 22(8):1599-1607.

638 Sin DD, Golmohammadi K, Jacobs P. Cost-effectiveness of inhaled corticosteroids for chronic obstructive pulmonary disease according to disease severity. *Am J Med.* 2004; 116(5):325-331.

639 United States Congress Office of Technology Assessment. *Evaluation of the Oregon Medicaid Proposal.* (OTA-H-531). Washington,DC: US Government Printing Office, 1992.

640 Spencer S, Calverley PM, Sherwood Burge P et al. Health status deterioration in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine.* 2001; 163(1):122-128.

641 Pickard AS, Wilke C, Jung E et al. Use of a preference-based measure of health (EQ-5D) in COPD and asthma. *Respir Med.* 2008; 102(4):519-536.

642 Stahl E, Lindberg A, Jansson SA et al. Health-related quality of life is related to COPD disease severity. *Health Qual Life Outcomes.* 2005; 3:56.

643 Punekar YS, Rodriguez RR, Sculpher M et al. Implications of chronic obstructive pulmonary disease (COPD) on patients' health status: a western view. *Respir Med.* 2007; 101(3):661-669.

644 Sullivan PW, Lawrence WF, Ghushchyan V. A national catalog of preference-based scores for chronic conditions in the United States. *Medical Care.* 2005; 43(7):736-749.

645 Hazell M, Frank T, Frank P. Health related quality of life in individuals with asthma related symptoms. *Respir Med.* 2003; 97(11):1211-1218.

646 Stavem K. Reliability, validity and responsiveness of two multiattribute utility measures in patients with chronic obstructive pulmonary disease. *Qual Life Res.* 1999; 8(1-2):45-54.

647 Polley L, Yaman N, Heaney L et al. Impact of cough across different chronic respiratory diseases: comparison of two cough-specific health-related quality of life questionnaires. *Chest.* 2008; 134(2):295-302.

648 Szende A, Leidy NK, Stahl E et al. Estimating health utilities in patients with asthma and COPD: evidence on the performance of EQ-5D and SF-6D. *Qual Life Res.* 2009; 18(2):267-272.

649 Johansson PM, Tillgren PE, Guldbrandsson KA et al. A model for cost-effectiveness analyses of smoking cessation interventions applied to a quit-and-win contest for mothers of small children. *Scandinavian Journal of Public Health.* 2005; 33(5):343-352.

650 Brazier J, Roberts J, Tsuchiya A et al. A comparison of the EQ-5D and SF-6D across seven patient groups. *Health Econ.* 2004; 13(9):873-884.

651 Miravitlles M, Murio C, Guerrero T et al. Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. *Chest.* 2002; 121(5):1449-1455.

652 Price MJ, Hurrell C, Efthimiou J et al. Health care costs of treating exacerbations of chronic obstructive pulmonary disease (COPD). *Eur Respir J.* 1999; 14(Suppl 30):380s.

653 Miravitlles M, Murio C, Guerrero T et al. Costs of chronic bronchitis and COPD: a 1-year follow-up study. *Chest.* 2003; 123(3):784-791.

654 Tynan AJ, Lane SJ. COPD: illness severity, resource utilisation and cost. *Irish Medical Journal.* 2005; 98(2):41-45.

655 Jansson SA, Andersson F, Borg S et al. Costs of COPD in Sweden according to disease severity. *Chest.* 2002; 122(6):1994-2002.