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.

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Acknowledgements for the original guideline

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Acknowledgements for the update guideline

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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 FEV₁/FVC ratio (where FEV₁ is forced expiratory volume in 1 second and FVC is forced vital capacity), such that FEV₁/FVC is less than 0.7.

- If FEV₁ 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. 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 FEV₁. A postal study 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 FEV₁ and respiratory symptoms was around 9%. Prevalence increases with increasing age 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.

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. The diagnosed prevalence of COPD is 1.5% of the population in 2007/08 according to the Quality Outcome Framework (QOF) statistical bulletin.

Approximately 835,000 people in England have been diagnosed with COPD in 2008-9. 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.

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) 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.

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. 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. 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. 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. All cause mortality is increased in patients with COPD.

The inpatient mortality rate in 2008 was 7.7% compared with 7.5% in 2003. 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.

Mortality from COPD in England shows a strong urban rural gradient with high mortality rates in the large conurbations in the North of England. 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. People in urban and deprived areas are more likely to be at risk.

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

COPD is an important co-morbidity in those dying from other smoking related diseases, most commonly ischaemic heart disease and lung cancer\textsuperscript{12,22}. COPD is the fifth leading cause of death in the UK and fourth worldwide\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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)\textsuperscript{21}. Respiratory disease accounts for 5.2 million bed days, nearly 10\% of all hospital
COPD (update)

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.\textsuperscript{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.\textsuperscript{13} About 30% of patients admitted with COPD for the first time will be readmitted within three months.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsubscript{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.\textsuperscript{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 FEV₁, 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\textsuperscript{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\textsuperscript{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. 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).


The developer’s role and remit is summarised below:

<table>
<thead>
<tr>
<th>National Clinical Guidelines Centre for Acute and Chronic Conditions (NCGC-ACC)</th>
<th>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).</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCGC-ACC Technical Team</td>
<td>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.</td>
</tr>
<tr>
<td>Guideline Development Group</td>
<td>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.</td>
</tr>
<tr>
<td>Guideline Project Executive (PE)</td>
<td>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.</td>
</tr>
<tr>
<td>Formal consensus</td>
<td>At the end of the guideline development process the GDG met to review and agree the guideline recommendations.</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question</td>
<td>The review question as agreed by the GDG.</td>
</tr>
<tr>
<td>Objectives</td>
<td>Short description; for example ‘To estimate the effects and cost effectiveness of...’ or ‘To estimate the diagnostic accuracy of...’.</td>
</tr>
<tr>
<td>Criteria for considering studies for the review</td>
<td>Using the PICO (population, intervention, comparison and outcome) framework. Including the study designs selected.</td>
</tr>
<tr>
<td>How the information will be searched</td>
<td>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.)</td>
</tr>
<tr>
<td>The review strategy</td>
<td>The methods that will be used to review the evidence, outlining exceptions and subgroups. Indicate if meta-analysis will be used.</td>
</tr>
</tbody>
</table>

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’.

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.


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](http://thorax.bmj.com/content/59/suppl_1)

The following versions of the guideline are available:
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:**

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

4 Glossary of terms
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACBT</td>
<td>Active Cycle of Breathing Technique</td>
</tr>
<tr>
<td>ACCP</td>
<td>American College of Chest Physicians</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>Angiotensin-Converting Enzyme inhibitor</td>
</tr>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>Ads</td>
<td>Advanced Directives</td>
</tr>
<tr>
<td>Adverse event</td>
<td>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.</td>
</tr>
<tr>
<td>Allied health professionals</td>
<td>Healthcare professionals, other than doctors and nurses, directly involved in the provision of healthcare. (Also known as professions allied to medicine or PAMs.)</td>
</tr>
<tr>
<td>Anticholinergic drugs</td>
<td>Anticholinergic drugs are also referred to as muscarinic antagonists e.g. short-acting muscarinic antagonist (SAMA) in the update guideline</td>
</tr>
<tr>
<td>Appraisal of evidence</td>
<td>Formal assessment of the quality of research evidence and its relevance to the clinical question or guideline under consideration, according to predetermined criteria.</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>ARF</td>
<td>Acute Respiratory Failure</td>
</tr>
<tr>
<td>ARR</td>
<td>Adjusted risk ratio</td>
</tr>
<tr>
<td>ASA Scoring System</td>
<td>American Society of Anaesthesiologists</td>
</tr>
<tr>
<td>ATBC</td>
<td>Alpha-Tocopherol and Beta-Carotene Supplementation</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BD</td>
<td>Bronchodilator</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BORG</td>
<td>Tool for measuring dyspnoea or the state of being short of breath</td>
</tr>
<tr>
<td>BTS</td>
<td>British Thoracic Society</td>
</tr>
<tr>
<td>Case-control study (CCT)</td>
<td>A study that starts with the identification of a group of individuals sharing the same characteristics and a suitable comparison (control) group. All participants</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>are then assessed with respect to things that happened to them in the past.</td>
<td></td>
</tr>
<tr>
<td>CEN</td>
<td>European Committee for Standardization</td>
</tr>
<tr>
<td>CES-D</td>
<td>Centre for Epidemiological Studies Depression Scale</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CLD</td>
<td>Chronic Lung Disease</td>
</tr>
<tr>
<td>Clinical audit</td>
<td>A systematic process for setting and monitoring standards of clinical care.</td>
</tr>
<tr>
<td>Clinical effectiveness</td>
<td>How well a drug, treatment or package of care works to produce good outcomes for patients?</td>
</tr>
<tr>
<td>Clinician</td>
<td>A health care professional providing patient care, e.g. doctor, nurse, physiotherapist.</td>
</tr>
<tr>
<td>CMC</td>
<td>Clinically Meaningful Change</td>
</tr>
<tr>
<td>CNS</td>
<td>Clinical Nurse Specialist</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>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.</td>
</tr>
<tr>
<td>Cochrane review</td>
<td>Reviews of randomised controlled trials prepared by the Cochrane Collaboration.</td>
</tr>
<tr>
<td>Cohort study</td>
<td>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.</td>
</tr>
<tr>
<td>Concordance</td>
<td>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.</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>COPM</td>
<td>Canadian Occupational Performance Measure</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>Comparative analysis of the costs and health benefits of a treatment or care pathway.</td>
</tr>
<tr>
<td>CRG</td>
<td>Consensus Reference Group</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>CRQ / CRDQ</td>
<td>Chronic Respiratory Diseases Questionnaire</td>
</tr>
<tr>
<td>CT scan</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest X-Ray</td>
</tr>
<tr>
<td>Dco</td>
<td>Diffusing Capacity of Carbon Dioxide</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined Daily Dosage</td>
</tr>
<tr>
<td>Diagnostic study</td>
<td>Any research study aimed at evaluating the utility of a diagnostic procedure.</td>
</tr>
<tr>
<td>DLCO</td>
<td>Carbon Monoxide Diffusing Capacity</td>
</tr>
<tr>
<td>DPI</td>
<td>Dry Powdered Inhaler</td>
</tr>
<tr>
<td>DPTC</td>
<td>Disabled Person’s Tax Credit</td>
</tr>
<tr>
<td>ECCS</td>
<td>European Coal &amp; Steel Community</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>Evidence table</td>
<td>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.</td>
</tr>
<tr>
<td>Evidence-based</td>
<td>The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.</td>
</tr>
<tr>
<td>Experimental study</td>
<td>A research study designed to test if a treatment or intervention has an effect on the course or outcome of a condition or disease.</td>
</tr>
<tr>
<td>FET</td>
<td>Forced Expiratory Time</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced Expiratory Volume in 1 second</td>
</tr>
<tr>
<td>FFM</td>
<td>Fat Free Mass Index</td>
</tr>
<tr>
<td>FFMPIBW</td>
<td>Fat-Free Mass as a Percentage of Ideal Body Weight</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced Vital Capacity</td>
</tr>
<tr>
<td>GDG</td>
<td>Guidelines Development Group</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
</tr>
<tr>
<td>Grade of recommendation</td>
<td>A code (e.g. A, B, C) linked to a guideline recommendation, indicating the strength of the evidence supporting that recommendation.</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HAM-D</td>
<td>Hamilton Depression Rating Scale</td>
</tr>
<tr>
<td>Health technology</td>
<td>Health technologies include medicines, medical devices, diagnostic techniques, surgical procedures, health promotion and other therapeutic interventions.</td>
</tr>
<tr>
<td>Health Technology Appraisal (HTA)</td>
<td>A focused review of evidence around a newly emerging health technology, produced by NICE.</td>
</tr>
<tr>
<td>Hierarchy of evidence</td>
<td>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.</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>HRQL</td>
<td>Health Related Quality of Life</td>
</tr>
<tr>
<td>IBW</td>
<td>Ideal Body Weight</td>
</tr>
<tr>
<td>ICS</td>
<td>Inhaled corticosteroid</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>ILI</td>
<td>Influenza Like Illness</td>
</tr>
<tr>
<td>IPPV</td>
<td>Intermittent Positive Pressure Ventilation</td>
</tr>
<tr>
<td>IQR</td>
<td>Inter Quartile range</td>
</tr>
<tr>
<td>IRR</td>
<td>Incident Rate Ratio</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to Treat Analysis</td>
</tr>
<tr>
<td>ITU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>KPa</td>
<td>Kilopascal – A unit of pressure</td>
</tr>
<tr>
<td>LABA</td>
<td>Long-acting beta₂ agonist</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>LAMA</td>
<td>Long-acting muscarinic antagonist</td>
</tr>
<tr>
<td>LCADL</td>
<td>London Chest Activity of Daily Living scale</td>
</tr>
<tr>
<td>Level of evidence</td>
<td>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.</td>
</tr>
<tr>
<td>Literature review</td>
<td>A process of collecting, reading and assessing the quality of published (and unpublished) articles on a given topic.</td>
</tr>
<tr>
<td>LTOT</td>
<td>Long Term Oxygen Therapy</td>
</tr>
<tr>
<td>LVRS</td>
<td>Lung Volume Reduction Surgery</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>A statistical technique for combining (pooling) the results of a number of studies that address the same question to produce a summary result.</td>
</tr>
<tr>
<td>MID</td>
<td>Minimally important difference</td>
</tr>
<tr>
<td>MRADL</td>
<td>Manchester Respiratory Activities of Daily Living</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>Muscarinic antagonist drugs</td>
<td>Muscarinic antagonists e.g. long-acting muscarinic antagonists (LAMA) are also referred to as Anticholinergic drugs in the original guideline.</td>
</tr>
<tr>
<td>MV</td>
<td>Mechanical Ventilation</td>
</tr>
<tr>
<td>NAC</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>NCC-CC</td>
<td>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</td>
</tr>
<tr>
<td>NCEPOD</td>
<td>National Confidential Enquiry into Perioperative Deaths</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Clinical Excellence</td>
</tr>
<tr>
<td>NIV</td>
<td>Non Invasive Ventilation</td>
</tr>
<tr>
<td>NNT</td>
<td>Number Needed to Treat</td>
</tr>
<tr>
<td>Non-experimental study</td>
<td>A study based on participants selected on the basis of their availability, with no attempt having been made to avoid problems of bias.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>NRT</td>
<td>Nicotine Replacement Therapy</td>
</tr>
<tr>
<td>NSF</td>
<td>National Service Framework</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Palliative care</td>
<td>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</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>Arterial Carbon Dioxide Tension</td>
</tr>
<tr>
<td>PEF</td>
<td>Peak Expiratory Flow</td>
</tr>
<tr>
<td>Pemax</td>
<td>Maximal Expiratory Pressure</td>
</tr>
<tr>
<td>PEP</td>
<td>Positive Expiratory Pressure</td>
</tr>
<tr>
<td>PIBW</td>
<td>Percent Ideal Body Weight</td>
</tr>
<tr>
<td>PICO</td>
<td>Population, intervention, comparison, outcome</td>
</tr>
<tr>
<td>Pimax</td>
<td>Maximum Inspiratory Pressure</td>
</tr>
<tr>
<td>Placebo</td>
<td>A pill, medicine, or other treatment that has no physiological effect and is used as a dummy treatment.</td>
</tr>
<tr>
<td>pMDI</td>
<td>Patient Administered Metered Dose Inhalers</td>
</tr>
<tr>
<td>Ppa</td>
<td>Pulmonary Artery Pressure</td>
</tr>
<tr>
<td>Prevalence</td>
<td>The proportion of a population of people who are experiencing a condition or disease at a given time.</td>
</tr>
<tr>
<td>Prospective study</td>
<td>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.</td>
</tr>
<tr>
<td>P-value</td>
<td>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.</td>
</tr>
<tr>
<td>Quality-Adjusted Life Year (QALY)</td>
<td>A measure of health outcome</td>
</tr>
<tr>
<td>Quasi experimental study</td>
<td>This is a study in which the treatment comparison groups are not assigned by</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>randomisation.</td>
<td></td>
</tr>
<tr>
<td>Randomised controlled trial (RCT)</td>
<td>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.</td>
</tr>
<tr>
<td>RCP</td>
<td>Royal College of Physicians</td>
</tr>
<tr>
<td>RD</td>
<td>Risk Difference</td>
</tr>
<tr>
<td>RR</td>
<td>Risk Ratio</td>
</tr>
<tr>
<td>RV</td>
<td>Residual Volume</td>
</tr>
<tr>
<td>SABA</td>
<td>Short-acting beta&lt;sub&gt;2&lt;/sub&gt; agonist</td>
</tr>
<tr>
<td>SAMA</td>
<td>Short-acting muscarinic antagonist</td>
</tr>
<tr>
<td>SaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Oxygen saturation – The % of oxygen present in the haemoglobin present in arterial blood</td>
</tr>
<tr>
<td>SEK</td>
<td>Swedish Krona unit of monetary currency</td>
</tr>
<tr>
<td>SGRQ</td>
<td>St George’s Respiratory Questionnaire</td>
</tr>
<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
</tr>
<tr>
<td>Six MD / 6MWT</td>
<td>Six minute distance or six minute walking test – 6MD / 6MWT</td>
</tr>
<tr>
<td>SMD</td>
<td>Standard Mean Difference</td>
</tr>
<tr>
<td>Stakeholder</td>
<td>Any national organisation, including patient and carers’ groups, healthcare professionals and commercial companies with an interest in the guideline under development.</td>
</tr>
<tr>
<td>Systematic review</td>
<td>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.</td>
</tr>
<tr>
<td>TAG</td>
<td>Technology Appraisal Guidance</td>
</tr>
<tr>
<td>TDI</td>
<td>Transition Dyspnoea Index</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------------------</td>
</tr>
<tr>
<td>TLC</td>
<td>Total Lung Capacity</td>
</tr>
<tr>
<td>T_{1}CO</td>
<td>Transfer Factor for Carbon Monoxide</td>
</tr>
<tr>
<td>TNF-(\alpha)</td>
<td>Tumour Necrosis Factor – alpha</td>
</tr>
<tr>
<td>Trial of treatment</td>
<td>A planned period during which a patient receives a treatment to find out if it will be of benefit to them as individuals.</td>
</tr>
<tr>
<td>TSF</td>
<td>Triceps Skin Fold</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>VC</td>
<td>Vital Capacity</td>
</tr>
<tr>
<td>VMT</td>
<td>Ventilatory Muscle Training</td>
</tr>
<tr>
<td>VO_{2}</td>
<td>Oxygen Uptake</td>
</tr>
<tr>
<td>WMD</td>
<td>Weight Mean Difference</td>
</tr>
</tbody>
</table>
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.
COPD (update)

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 FEV₁ ≥ 50% predicted: either long-acting beta₂ agonist (LABA) or long-acting muscarinic antagonist (LAMA)

- if FEV₁ < 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

Definition of chronic obstructive pulmonary disease (COPD)
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.

Algorithm 1:
Perform spirometry if COPD seems likely
Airflow obstruction is defined as post-bronchodilator:
- FEV₁/FVC < 0.7
Spirometric reversibility testing is not usually necessary as part of the diagnostic process or to plan initial therapy

Think of the diagnosis of COPD for patients who are
- over 35
- smokers or ex-smokers
- have any of these symptoms:
  - exertional breathlessness
  - chronic cough
  - regular sputum production
  - frequent winter 'bronchitis'
  - wheeze
- and have no clinical features of asthma (See box 'Clinical features differentiated COPD and asthma' below)

If still doubt about diagnosis consider the following pointers
- Asthma may be present if:
  - there is a > 400 ml response to bronchodilators
  - serial peak flow measurements show significant diurnal or day-to-day variability
  - there is a > 400 ml response to 30 mg prednisolone daily for 2 weeks
- Clinically significant COPD is not present if FEV₁ and FEV₁/FVC ratio return to normal with drug therapy
- Refer for more detailed investigations if needed (see section 6.6 of the full guideline)

If in no doubt diagnose COPD and start treatment

If still in doubt, make a provisional diagnosis and start empirical treatment

Reassess diagnosis in view of response to treatment

Clinical features differentiating COPD and asthma

<table>
<thead>
<tr>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker or ex-smoker</td>
<td>Nearly all</td>
</tr>
<tr>
<td>Symptoms under age 35</td>
<td>Rare</td>
</tr>
<tr>
<td>Chronic productive cough</td>
<td>Common</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>Persistent and progressive</td>
</tr>
<tr>
<td>Night-time waking with breathlessness and or wheeze</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Significant diurnal or day-to-day variability of symptoms</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
COPD (update)

**Algorithm 2: Management of stable COPD**

**Patient with COPD**

Assess symptoms/problems – Manage those that are present as below

Patients with COPD should have access to the wide range of skills available from a multidisciplinary team

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Breathlessness and exercise limitation</th>
<th>Frequent exacerbations</th>
<th>Respiratory failure</th>
<th>Cor pulmonale</th>
<th>Abnormal BMI</th>
<th>Chronic productive cough</th>
<th>Anxiety and depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer help to stop smoking at every opportunity</td>
<td>Offer annual influenza vaccination</td>
<td>Assess for appropriate oxygen: - LTOT - ambulatory - short burst</td>
<td>Optimise bronchodilator therapy using the algorithm (2a) below</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deleted</td>
<td>Offer pneumococcal vaccination</td>
<td>Use diuretics</td>
<td>Consider referral for assessment for long-term domiciliary NIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deleted in update</td>
<td>Give self-management advice</td>
<td></td>
<td>Deleted in update</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimise inhaled therapy using the algorithm (2a) below</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deleted in update</td>
<td>If still symptomatic consider adding theophylline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offer pulmonary rehabilitation to all patients who consider themselves functionally disabled (usual MRC grade 3 and above) including those who have had a recent hospitalisation for an exacerbation</td>
<td>Offer annual influenza vaccination</td>
<td>Assess need for oxygen</td>
<td>Refer for dietetic advice</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider referral for surgery: bullectomy, LVRS, transplantation</td>
<td>Offer pneumococcal vaccination</td>
<td>Use diuretics</td>
<td>Refer to ‘Nutrition support in adults’ (NICE clinical guideline 32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Give self-management advice</td>
<td></td>
<td>Give nutritional supplements if the BMI is low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consider trial of mucolytic therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continue if symptomatic improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Be aware of anxiety and depression and screen for them in those most physically disabled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Deleted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Refer to ‘Depression in Adults with a Chronic Physical Health Problem’ (NICE clinical guideline 91)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Palliative care**

Opiates should be used when appropriate for the palliation of breathlessness in patients with end-stage COPD unresponsive to other medical therapy

Use benzodiazepines, tricyclic antidepressants, major tranquillisers and oxygen when appropriate

Involve multidisciplinary palliative care teams
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.

Breathlessness and exercise limitation

SABA or SAMA as required*

Exacerbations or persistent breathlessness

FEV1 ≥ 50%

LABA

FEV1 < 50%

LAMA

LABA + ICS in a combination inhaler

Discontinue SAMA

Offer LAMA in preference to regular SAMA four times a day

Consider LABA + LAMA if ICS declined or not tolerated

LABA + ICS in a combination inhaler

LABA

Consider LABA + LAMA if ICS declined or not tolerated

LAMA + LABA + ICS in a combination inhaler

Abbreviations:
SABA – Short-acting beta agonist
SAMA – Short-acting muscarinic antagonist
LABA – Long-acting beta agonist
LAMA – Long-acting muscarinic antagonist
ICS – Inhaled corticosteroid

* SABA (as required) may continue at all stages

Offer therapy (strong evidence) • • • • • Consider therapy (less strong evidence)
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)

Factors to consider when deciding where to manage patient

<table>
<thead>
<tr>
<th>Factor</th>
<th>Favours treatment at home</th>
<th>Favours treatment in hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Able to cope at home</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>General condition</td>
<td>Good</td>
<td>Poor/deteriorating</td>
</tr>
<tr>
<td>Level of activity</td>
<td>Good</td>
<td>Poor/confined to bed</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Worsening peripheral oedema</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>Normal</td>
<td>Impaired</td>
</tr>
<tr>
<td>Already receiving LTOT</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Social circumstances</td>
<td>Good</td>
<td>Living alone/Not coping</td>
</tr>
<tr>
<td>Acute confusion</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Rapid rate of onset</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Significant comorbidity</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SaO2 &lt; 90%</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Changes on the chest radiograph</td>
<td>No</td>
<td>Present</td>
</tr>
<tr>
<td>Arterial pH level</td>
<td>≥ 7.35</td>
<td>&lt; 7.35</td>
</tr>
<tr>
<td>Arterial PaO2</td>
<td>≥ 7kPa</td>
<td>&lt; 7kPa</td>
</tr>
</tbody>
</table>

Abbreviations:
LTOT – long-term oxygen therapy
SaO2 – oxygen saturation of arterial blood
PaO2 – partial pressure of oxygen in arterial blood

Further management
- Deleted
- If necessary, oxygen should be given to keep the SaO2 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

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

*Readers should refer to local protocols for oxygen therapy
### 5.3 Suggested audit criteria for implementation

<table>
<thead>
<tr>
<th>Key Priority</th>
<th>Criterion</th>
<th>Exception</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Diagnose COPD</strong></td>
<td>a) percentage of smokers over the age of 35 consulting with a chronic cough and/or breathlessness who have had spirometry performed</td>
<td>Inability to perform spirometry, for example because of facial paralysis</td>
</tr>
<tr>
<td></td>
<td>b) percentage of patients with a diagnosis of COPD who have had spirometry performed</td>
<td></td>
</tr>
<tr>
<td><strong>2. Stop smoking</strong></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td><strong>3. Give effective inhaled therapy</strong></td>
<td>Appropriateness of inhaled steroid therapy</td>
<td>Patient choice</td>
</tr>
<tr>
<td></td>
<td>Either a long-acting beta-agonist and inhaled corticosteroid in a...</td>
<td></td>
</tr>
</tbody>
</table>
Combination inhaler, or a long-acting muscarinic antagonist should be used in patients with an FEV₁ < 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 FEV₁.

<table>
<thead>
<tr>
<th>4. Provide pulmonary rehabilitation for all who need it</th>
<th>Percentage of patients with COPD who have undergone pulmonary rehabilitation</th>
<th>Patient choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Use non-invasive ventilation</th>
<th>Percentage of patients presenting with acute hypercapnic ventilatory failure who have received non-invasive ventilation</th>
<th>Patient choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. Manage exacerbations</th>
<th>Frequency and appropriateness of oral steroid and antibiotic therapy</th>
<th>Patient choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>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:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- 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 and as the disease progresses the symptoms in individual patients vary.

Individual patients rank the importance of different symptoms differently; however, in general, breathlessness is the symptom which causes them most concern.

Individual symptoms in isolation are not useful in excluding or making the diagnosis of COPD.
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

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

Adapted from Fletcher CM et al (1959)\textsuperscript{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 FEV₁/FVC < 0.7 (i.e. 70%) and FEV₁ < 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 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 FEV₁ (forced expiratory volume in one second) compare with pre bronchodilator FEV₁ in terms of: a) sensitivity / specificity of FEV₁ 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) FEV₁ values to a clinical diagnosis of COPD (based on symptoms). Very few papers defined COPD in this way; i.e. without including FEV₁ as part of the definition of COPD. Several studies were excluded because pre and post BD FEV₁ values were compared to identify COPD defined according to GOLD criteria (post bronchodilator FEV₁/FVC < 0.70). By definition, post bronchodilator FEV₁ would correlate better with a definition of COPD that is based on post bronchodilator FEV₁.

Two studies were identified that addressed this issue.

The PLATINO study 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 FEV₁ to identify people with COPD defined as either an FEV₁/FVC < 0.70 or an FEV₁/FVC < 5th percentile. This study was included because it compared the FEV₁ measures in a high and low risk group. It should be noted that there is no accepted gold standard diagnostic test for COPD against which to compare the FEV₁ indices.

It was unclear if the assessors were blinded to whether the FEV₁ measurements were pre or post BD. The pre and post BD FEV₁ measurements were performed close together and all patients received both FEV₁ measurements (pre and post bronchodilator).
A case series study\textsuperscript{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\textsubscript{1} improved post BD by > ten percent of their predicted FEV\textsubscript{1} were excluded. This study was included because it measured FEV\textsubscript{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\textsubscript{1} to classify the severity of COPD.

**Evidence summary**

**Prevalence of COPD: Pre versus post bronchodilator FEV\textsubscript{1}**

In the PLATINO study\textsuperscript{43}, the prevalence of airway obstruction defined according to FEV\textsubscript{1}/FVC < 0.70 was less when FEV\textsubscript{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\textsubscript{1}/FVC < 0.70 was also less when FEV\textsubscript{1} was measured post BD than pre BD (8.2% versus 13.8%).

When airway obstruction was defined as FEV\textsubscript{1}/FVC < 5\textsuperscript{th} percentile, the prevalence of airway obstruction in the high risk group was lower when FEV\textsubscript{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\textsubscript{1}/FVC < 0.70 was 1.899. The likelihood ratio of post BD tests to detect FEV\textsubscript{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\textsubscript{1}/FVC < 5\textsuperscript{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\textsubscript{1}

Intraclass correlation coefficient

The mean post-bronchodilator FEV\textsubscript{1} was reproducible between visits (interclass correlation coefficient 0.93). The intraclass correlation coefficient for mean pre-BD FEV\textsubscript{1} was slightly less (interclass correlation coefficient 0.91) compared with post BD FEV\textsubscript{1}.\textsuperscript{44}

Health economic evidence

No relevant economic analyses were identified that compared COPD diagnosis or severity classification using post-bronchodilator FEV\textsubscript{1} with pre-bronchodilator FEV\textsubscript{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\textsubscript{1} to improve accuracy of diagnosis is offset by a small cost implication compared to using pre-bronchodilator FEV\textsubscript{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\textsubscript{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 FEV₁ 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 was from a non-UK population without robust predicted reference values. The data compared pre and post bronchodilator FEV₁ 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 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 FEV₁ and post FEV₁ 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 (FEV₁) 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).

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 FEV₁/FVC ratio < 0.70 or FEV₁ < 80, 50, or 30% predicted) are used for purposes of simplicity, but that these cut-points have not been clinically validated. The process of aging affects lung volumes, and the FEV₁/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. It has therefore been proposed that confirmation of obstructive lung disease should be based on an FEV₁/FVC ratio below the LLN, classifying the bottom 5% of the healthy population as abnormal. 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 FEV₁ and longitudinal studies to validate the use of the LLN are not available and urgently needed.

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 FEV₁/FVC compared with the lower limit of normal FEV₁/FVC ratio to diagnose COPD?
Methodological introduction

Four cross-sectional studies\textsuperscript{52,56,67,68} were found that compared FEV\textsubscript{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\textsubscript{1}/FVC < 70\%) and all measurements were post-bronchodilator (except for Celli et al\textsuperscript{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\textsubscript{1}/FVC ratio (fixed vs. LLN) vs. physician’s diagnosis

The two largest studies\textsuperscript{52,68} showed that FEV\textsubscript{1}/FVC (fixed ratio) was most similar to the physician’s diagnosis. The two smaller studies\textsuperscript{56,67} showed that the FEV\textsubscript{1}/FVC (LLN) was most similar to the physician’s diagnosis. (See summary table 6.2).

Celli et al\textsuperscript{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\textsubscript{1}/FVC < 0.70 and FEV\textsubscript{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 FEV₁/FVC ratio (fixed vs. LLN) vs. physician’s diagnosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients with diagnosis of COPD</th>
<th>FEV₁/FVC (fixed ratio)</th>
<th>FEV₁/FVC (LLN)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Physician diagnosis</td>
<td></td>
</tr>
<tr>
<td>Celli et al.</td>
<td>9838 cases/1000 population</td>
<td>77.3</td>
<td>167.8 (fixed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>142.1 cases per 1000 population</td>
</tr>
<tr>
<td>Ko et al.</td>
<td>1008 3.6%</td>
<td>25.9%</td>
<td>12.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor agreement with physician diagnosis</td>
<td>Poor agreement with physician diagnosis</td>
</tr>
<tr>
<td>Roche et al.</td>
<td>4764 8.4%</td>
<td>8.7%</td>
<td>6.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.96% (ERS definition using study population equations)</td>
</tr>
<tr>
<td>Shirtcliffe et al.</td>
<td>749 10.6%</td>
<td>15.5%</td>
<td>10.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poor agreement with physician diagnosis (K coefficient)</td>
</tr>
</tbody>
</table>

**Health economic evidence**

No relevant economic analyses were identified that compared COPD diagnosis using a fixed ratio FEV₁/FVC compared with the lower limit of normal FEV₁/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 showed that use of pre bronchodilator values of FEV₁/FVC ratio < 70% and FEV₁ < 80% predicted derived almost identical sensitivity to use of FEV₁/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 FEV₁/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 FEV₁ 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 FEV₁/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.

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 FEV₁/FVC ratio is < 0.7
   • younger people with symptoms of COPD where the FEV₁/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.

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.

R7  Spirometry services should be supported by quality control processes.

R8  It is recommended that ERS 1993 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.
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.

<table>
<thead>
<tr>
<th>Other conditions that may present with similar symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>• asthma</td>
</tr>
<tr>
<td>• bronchiectasis</td>
</tr>
<tr>
<td>• congestive cardiac failure</td>
</tr>
<tr>
<td>• carcinoma of the bronchus</td>
</tr>
<tr>
<td><strong>Less common</strong></td>
</tr>
<tr>
<td>• obliterative bronchiolitis</td>
</tr>
<tr>
<td>• bronchopulmonary dysplasia</td>
</tr>
</tbody>
</table>

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

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

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

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

Table 6.4 Additional investigations

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

To assess need for oxygen therapy
If cyanosis, or cor pulmonale present, or if FEV₁ < 50% predicted

### Sputum culture

To identify organisms if sputum is persistently present and purulent

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.

#### 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 FEV₁/FVC and FEV₁ measurements are recommended for the diagnosis and assessment of severity of COPD, the degree of reversibility of airflow limitation (e.g., change in FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ of more than 400 ml).

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

The BTS/SIGN 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 200 ml in FEV₁ after inhalation of short-acting beta₂ 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 FEV₁ following inhalation of a bronchodilator between individuals and within individuals tested on different days.²⁴,⁷⁴

A number of different methods for assessing the response to bronchodilators have been proposed.⁷⁵-⁷⁸

A change in FEV₁ of at least 160 ml is required to exclude changes within the natural variability in of FEV₁ in people with obstructive ventilatory defects.⁷⁹

A study of patients with fixed airflow obstruction diagnosed as having COPD or asthma on the basis of the clinical history 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.

Bronchodilator tests performed with different inspiratory manoeuvres before and after bronchodilator administration provide differing results.⁸¹

The response to a short course of oral steroids does not predict the response to long-term therapy.⁸²
### 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:

- repeated FEV\(_1\) measurements can show small spontaneous fluctuations
- the results of a reversibility test performed on different occasions can be inconsistent and not reproducible
- over-reliance on a single reversibility test may be misleading unless the change in FEV\(_1\) is greater than 400 ml
- the definition of the magnitude of a significant change is purely arbitrary
- response to long-term therapy is not predicted by acute reversibility testing.

**Grade D**

**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.

**Table 6.5 Clinical features differentiating COPD and asthma**

<table>
<thead>
<tr>
<th>Feature</th>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker or ex-smoker</td>
<td>Nearly all</td>
<td>Possibly</td>
</tr>
<tr>
<td>Symptoms under age 35</td>
<td>Rare</td>
<td>Often</td>
</tr>
<tr>
<td>Chronic productive cough</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>Persistent and progressive</td>
<td>Variable</td>
</tr>
</tbody>
</table>
### Night time waking with breathlessness and/or wheeze

<table>
<thead>
<tr>
<th></th>
<th>Uncommon</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant diurnal or day-to-day variability of symptoms</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
</tbody>
</table>

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

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:

- 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 FEV₁ and FEV₁/FVC ratio return to normal with drug therapy.

R16 If diagnostic uncertainty remains, referral for more detailed investigations, including imaging and measurement of T₁2CO₂, should be considered.

R17 If patients report a marked improvement in symptoms in response to inhaled therapy, the diagnosis of COPD should be reconsidered.
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 GOLD and the ATS/ERS guidelines. National Institutes of Health NHLBI. 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. 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.

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 (FEV₁ % 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 FEV₁ alone?**

**Methodological introduction**

Studies were included if they compared FEV₁ 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 study¹⁰¹ and three prospective case-series⁹⁸,¹⁰²,¹⁰³ were found that assessed the prognostic ability of FEV₁ vs. multidimensional indices to predict outcomes (mortality, hospitalisations and exacerbations) in stable COPD patients.

All of the studies⁹⁸,¹⁰¹-¹⁰³ compared FEV₁ with the BODE index in people with COPD.

**Evidence statements**

- 1 study¹⁰² found that the BODE index was a better predictor of the likelihood of COPD exacerbations at 5.1 years (mean follow-up) than FEV₁ and also predicted the time to first exacerbation.

- 1 study⁹⁸ found that the BODE index was a better predictor of hospitalisation (number of admissions) at 16.2 years (mean follow-up) than FEV₁.

- 3 studies⁹⁸,¹⁰¹,¹⁰³ found that the BODE index was a better predictor of mortality than FEV₁ (at 16.2 months⁹⁸, 28 months¹⁰³ and 36 months¹⁰¹ mean follow-up). Two studies¹⁰¹,¹⁰³
assessed risk of death and one study assessed time until death.

Table 6.6 Summary of studies assessing multidimensional indices vs. FEV₁ as predictors of COPD outcomes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Multidimensional index</th>
<th>FEV₁ (% predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome: number of hospital admissions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ong et al. 98</td>
<td>BODE index</td>
<td>FEV₁</td>
</tr>
<tr>
<td></td>
<td>IRR 1.20, 95% CI 1.15 to 1.25, p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FEV₁</td>
<td>IRR 0.08, 95% CI 0.04 to 0.16, p&lt;0.001</td>
</tr>
<tr>
<td><strong>Outcome: time to exacerbation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marin et al. 102</td>
<td>BODE index vs. FEV₁</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P&lt;0.01 (values not given); BODE predicts onset of exacerbations better than FEV₁ (values not given).</td>
<td></td>
</tr>
<tr>
<td><strong>Outcome: Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ong et al. 98</td>
<td>BODE index</td>
<td>FEV₁</td>
</tr>
<tr>
<td></td>
<td>Time until death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR 1.30, 95% CI 1.08 to 1.56, p=0.006</td>
<td>Time until death</td>
</tr>
<tr>
<td></td>
<td>HR 0.41, 95% CI 0.03 to 5.57, p=0.5</td>
<td></td>
</tr>
<tr>
<td>de Torres et al. 101</td>
<td>BODE index</td>
<td>FEV₁</td>
</tr>
<tr>
<td></td>
<td>Risk of death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR 1.41, 95% CI 01.22 to 1.61, p&lt;0.001</td>
<td>Risk of death</td>
</tr>
<tr>
<td></td>
<td>HR 0.96, 95% CI 0.94 to 0.98, p=0.001</td>
<td></td>
</tr>
<tr>
<td>Celli et al. 103</td>
<td>BODE index</td>
<td>FEV₁</td>
</tr>
<tr>
<td></td>
<td>Risk of death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-statistic 0.74</td>
<td>C-statistic 0.65</td>
</tr>
</tbody>
</table>

When BODE scores were divided into quartiles, the BODE index was a better predictor of hospital admissions than the GOLD Staging system (based on FEV₁). 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 FEV₁ (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.\textsuperscript{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\textsubscript{1} alone with regard to prognostic stratification. One study\textsuperscript{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

NEW 2010 UPDATE RECOMMENDATION 3 (U3)

Be aware that disability in COPD can be poorly reflected in the FEV₁. A more comprehensive assessment of severity includes the degree of airflow obstruction and disability, the frequency of exacerbations and the following known prognostic factors:

- FEV₁
- T₇CO
- Breathlessness (MRC scale)
- Health status
- Exercise capacity (for example, 6-minute walk test)
- BMI
- Partial pressure of oxygen in arterial blood (PaO₂)
- 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 (FEV₁ > 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 FEV₁, increased respiratory care utilisation and a lower quality of life compared with people with normal lung function\(^\text{104}\). This expands the NICE 2004 definition of airflow obstruction to include the group of people with an FEV₁ > 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 FEV₁ 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.
The severity of airflow obstruction should be assessed according to the reduction in FEV₁ as shown in table 6.7

### NEW 2010 UPDATE TABLE

**Gradation of severity of airflow obstruction**

<table>
<thead>
<tr>
<th>Post-bronchodilator FEV₁/FVC</th>
<th>FEV₁ % predicted</th>
<th>Severity of airflow obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post-bronchodilator</td>
<td>Post-bronchodilator</td>
</tr>
<tr>
<td>&lt; 0.7</td>
<td>≥ 80%</td>
<td>Mild</td>
</tr>
<tr>
<td>&lt; 0.7</td>
<td>50-79%</td>
<td>Mild</td>
</tr>
<tr>
<td>&lt; 0.7</td>
<td>30-49%</td>
<td>Moderate</td>
</tr>
<tr>
<td>&lt; 0.7</td>
<td>&lt; 30%</td>
<td>Severe</td>
</tr>
</tbody>
</table>

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

** or FEV₁ < 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.
COPD (update)

See section 2 for the methodology underpinning the evidence statements.

**Evidence statements**

COPD can be present in the absence of symptoms \(^{11}\).  

COPD can be detected by opportunistic case finding in primary care \(^{4,106}\) and in patients aged 65 and over discharged from hospital.

Opportunistic case finding has a high uptake, reaches most of the target group and has a high yield \(^4\).

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\(_1\) \(^{107}\).

Early diagnosis of abnormal lung function as part of a motivational package, significantly affects the success of smoking cessation therapy \(^{108,109}\).

**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.

**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.

R21  Spirometry should be considered in patients with chronic bronchitis. A significant proportion of these will go on to develop airflow limitation $^{110}$.

Grade D  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).

*Table 6.8 Reasons for referral include*

<table>
<thead>
<tr>
<th>Reason</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is diagnostic uncertainty</td>
<td>Confirm diagnosis and optimise therapy</td>
</tr>
<tr>
<td>Suspected severe COPD</td>
<td>Confirm diagnosis and optimise therapy</td>
</tr>
<tr>
<td>The patient requests a second opinion</td>
<td>Confirm diagnosis and optimise therapy</td>
</tr>
<tr>
<td>Onset of cor pulmonale</td>
<td>Confirm diagnosis and optimise therapy</td>
</tr>
<tr>
<td>Assessment for oxygen therapy</td>
<td>Optimise therapy and measure blood gases</td>
</tr>
<tr>
<td>Assessment for long-term nebuliser therapy</td>
<td>Optimise therapy and exclude inappropriate prescriptions</td>
</tr>
<tr>
<td>Assessment for oral corticosteroid therapy</td>
<td>Justify need for long-term treatment or supervise withdrawal</td>
</tr>
<tr>
<td>Bullous lung disease</td>
<td>Identify candidates for surgery</td>
</tr>
<tr>
<td>A rapid decline in FEV₁</td>
<td>Encourage early intervention</td>
</tr>
<tr>
<td>Assessment for pulmonary rehabilitation</td>
<td>Identify candidates for pulmonary rehabilitation</td>
</tr>
<tr>
<td>Assessment for lung volume reduction surgery</td>
<td>Identify candidates for surgery</td>
</tr>
<tr>
<td>Assessment for lung transplantation</td>
<td>Identify candidates for surgery</td>
</tr>
<tr>
<td>Dysfunctional breathing</td>
<td>Confirm diagnosis, optimise pharmacotherapy and access other therapists</td>
</tr>
</tbody>
</table>
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 FEV₁ 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 identified¹¹² which was specific to chronic obstructive pulmonary disease and contained five studies¹¹³⁻¹¹⁷. The review authors highlighted that only two of the five studies were of high quality and hence these were reviewed on an individual basis¹¹³,¹¹⁷. An additional two trials were identified¹¹⁸,¹¹⁹ 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 FEV₁ 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

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.

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.

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.

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 cost per life year saved.\(^{121}\)

**Recommendations**

<table>
<thead>
<tr>
<th>R24</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade D</td>
<td></td>
</tr>
<tr>
<td>R25</td>
<td>All COPD patients still smoking, regardless of age, should be encouraged to stop, and offered help to do so, at every opportunity.</td>
</tr>
<tr>
<td>Grade A</td>
<td></td>
</tr>
<tr>
<td>R26</td>
<td>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.</td>
</tr>
<tr>
<td>R27</td>
<td>Deleted and replaced by PH10</td>
</tr>
</tbody>
</table>

‘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).\(^{120}\)

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\(^{a}\) 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 Smoking cessation – varenicline

The following two recommendations are from ‘Varenicline for smoking cessation’ (NICE technology appraisal guidance 123)\textsuperscript{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 \textsuperscript{71,123}. The structural changes in the airways prevent bronchodilators returning airway calibre to normal. Clinically relevant improvements in FEV\textsubscript{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\textsubscript{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\textsubscript{1}.  

Page 97 of 673
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$^{127-129}$, 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)$^{57}$.

Evidence statements

SABA versus placebo

la

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)$^{126}$.

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\textsuperscript{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 \textit{FEV}_1 (WMD 0.140 L, 95\% CI 0.04 to 0.25, p=0.008)\textsuperscript{126}.

Short-acting \( \beta_2 \) agonists appear to be as effective when used on an \textit{as needed basis} as when used regularly on a background of other bronchodilators\textsuperscript{140}.

\textbf{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\textsuperscript{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.

\begin{quote}
Anticholinergic drugs are also referred to as muscarinic antagonists (e.g. short-acting muscarinic antagonist (SAMA)).
\end{quote}

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\textsuperscript{142-144} or short trial duration\textsuperscript{145}. Four trials\textsuperscript{146-149} had methodological limitations, which precluded making recommendations based upon the papers findings. Trials also used a variety of differing endpoint outcome measures.

\begin{quote}
The 2010 partial update did \textbf{not} update the section on short-acting anticholinergics compared with placebo.
\end{quote}
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.

One study\(^{152}\) found that dyspnoea measured by the Transition Dyspnoea Index (TDI) was significantly improved with short-acting anticholinergics compared to placebo.

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.

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).

Two studies\(^{150,151}\) found no significant differences between short-acting anticholinergics and placebo groups for quality of life.

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.

**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\textsubscript{2} agonists (LABA)

The bronchodilator effects of long-acting beta\textsubscript{2} agonists are similar to the short-acting agents but their duration of action is around 12 hours. There are two long-acting beta\textsubscript{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\textsuperscript{153} comparing long-acting beta\textsubscript{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\textsuperscript{152,154-160}, six were of a parallel group design of 12-16 weeks duration. Two were cross over studies\textsuperscript{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\textsuperscript{155} has only been published in abstract form and it includes data published by Mahler et al\textsuperscript{152}. Therefore this study is not included in the table below.

Shukla et al (2002)\textsuperscript{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\textsuperscript{153}.

In addition to the trials included in the systematic review, seven other trials were identified\textsuperscript{151,162-167}.

As well as this, Mahler et al\textsuperscript{165}, Calverley et al\textsuperscript{167} and Szanfranski et al\textsuperscript{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 beta₂ agonists

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sample size</th>
<th>Duration (weeks)</th>
<th>Drug</th>
<th>Dose (µg)</th>
<th>FEV₁</th>
<th>FVC</th>
<th>Diary symptoms</th>
<th>Night</th>
<th>Rescue</th>
<th>Dyspnoea</th>
<th>Ex test</th>
<th>HRQL</th>
<th>Exacerbations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rennard 2001 (a)</td>
<td>405</td>
<td>12</td>
<td>S</td>
<td>50</td>
<td>↑</td>
<td>↑</td>
<td>NS</td>
<td>NS</td>
<td>↑</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>150</td>
</tr>
<tr>
<td>Van Noord 2000</td>
<td>144</td>
<td>12</td>
<td>S</td>
<td>50</td>
<td>↑</td>
<td>↑</td>
<td>NS</td>
<td>↑</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>NS</td>
<td>NS</td>
<td>160</td>
</tr>
<tr>
<td>Mahler 1999</td>
<td>411</td>
<td>12</td>
<td>S</td>
<td>50</td>
<td>↑</td>
<td>↑</td>
<td>NS</td>
<td>NS</td>
<td>↑</td>
<td>-</td>
<td>↑</td>
<td>↑</td>
<td>NS</td>
<td>152</td>
</tr>
<tr>
<td>Boyd 1997 (b)</td>
<td>674</td>
<td>16</td>
<td>S</td>
<td>50</td>
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### v Ipratropium

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### v Tiotropium – this section has been updated

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<td>-</td>
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</table>

N.B. ↑ denotes statistically significant superiority versus comparator group (e.g. increased FEV₁, 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 FEV₁ 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 FEV₁ 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

(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.
Evidence statements

Long-acting beta\textsubscript{2} agonists compared to placebo in stable COPD

There was variation in the results within the systematic review \cite{84} for symptom scores across four studies \cite{152,154,159,160}. The largest of the trials \cite{154} demonstrated that long-acting beta\textsubscript{2} agonists reduce symptom scores. Day time (p=0.01). Night time (p=0.001).

There were three subsequent randomised controlled trials \cite{151,162,163}. Using standard therapeutic doses only one trial \cite{151} found that symptom scores were reduced (p<0.001).

With regard to the reduction of breathlessness, five trials within the systematic review \cite{84} found no significant differences between long-acting beta\textsubscript{2} agonist and placebo. One trial with the largest sample size (n=674) \cite{154} demonstrated that long-acting beta\textsubscript{2} agonist reduce the degree of breathlessness produced by exercise.

There were two subsequent randomised controlled trials \cite{162,164} with large sample sizes that demonstrated a statistically significant difference with the use of long-acting beta\textsubscript{2} agonists in reducing dyspnoea (p=0.002 and p<0.05 respectively).

In addition to this Brusasco\textsuperscript{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.

Mahler et al\textsuperscript{165} showed a significant reduction in overall use of supplemental albuterol after treatment with salmeterol compared with placebo (p \leq 0.045).
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$^{153}$. 

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.

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.

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$^{158}$.

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 $\geq 10$ 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\textsuperscript{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\textsuperscript{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 \textsuperscript{84} found that long-acting beta\textsubscript{2} agonists compared to placebo did not significantly affect the incidence of COPD exacerbations, however this meta-analysis was only based upon two RCTs \textsuperscript{154,160}.

One cross over study \textsuperscript{159} n = 63, not combined in the meta-analysis but also included in the systematic review \textsuperscript{84} found no significant difference in exacerbations.

Two subsequent trials by Dahl \textsuperscript{151} and Brusasco \textsuperscript{164} also found no significant difference in exacerbations.

However, two trials \textsuperscript{163,167} found significant differences favouring long-acting beta\textsubscript{2} agonists compared to placebo for exacerbations.

Rossi et al\textsuperscript{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 ≤ 0.008.

A large (n = 1465) multicentre RCT\textsuperscript{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.
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\textsubscript{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\textsubscript{2} agonists and placebo. One of these \textsuperscript{164} includes patients described in the earlier paper \textsuperscript{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**

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COPD (update)

**v Ipratropium**

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NB ↑ denotes statistically significant superiority versus comparator group (e.g. increased FEV₁, 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\textsuperscript{164,169-171} demonstrated a significant increase in FEV\textsubscript{1} and FVC in favour of long-acting anticholinergics compared to placebo. p<0.001 \textsuperscript{170}, p<0.01 \textsuperscript{171} and p=0.001 \textsuperscript{164}.

A one year clinical trial\textsuperscript{171} found that long-acting anticholinergic significantly improved morning and evening PEFR compared to placebo (p<0.005).

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

Two studies\textsuperscript{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\textsuperscript{164} and Casaburi et al\textsuperscript{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\textsuperscript{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.

Brusasco\textsuperscript{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.

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 \(<0.05\).

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 FEV₁, 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 study¹⁷² looked at the effects on **FEV₁ and FVC** and found that long-acting anticholinergic was superior to short-acting anticholinergic, p<0.05.

In a one year clinical trial¹⁷² long-acting anticholinergic significantly improved morning and evening **PEFR** compared to short-acting
anticholinergic, p<0.01.

Only one study\textsuperscript{172} measured \textit{dyspnoea}. TDI focal score for long-acting anticholinergic was superior to short-acting anticholinergic, p<0.05.

Only one study\textsuperscript{172} measured \textit{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.

One study\textsuperscript{172} looked at \textit{rescue medication} and found that it was used less often in the long compared to short-acting anticholinergic group, p<0.05.

Vincken\textsuperscript{172} found that the proportion of patients who experienced \textit{exacerbations} was significantly lower in the long (35%) compared to short (46%) acting anticholinergic group during the trial, p=0.014).

**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 comparison\textsuperscript{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\textsuperscript{175,176}.

No studies were identified in the original guideline search.
### Update 2010: Economic evidence profile

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations*</th>
<th>Applicability**</th>
<th>Other comments</th>
<th>Incremental† cost (£)</th>
<th>Incremental‡ effects</th>
<th>ICER‡</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oostenbrink et al (2005) 173</td>
<td>Potentially serious</td>
<td>Partially</td>
<td>Based on 1-year morbidity estimated by a Markov model of moderate, severe, and 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</td>
<td>-£118$^g$</td>
<td>0.026 QALYs</td>
<td>Dominant$^e$</td>
<td>Tiotropium was always the most cost-effective option (highest net benefit at a £20,000/QALY threshold) in base case PSA and sensitivity analyses.</td>
</tr>
<tr>
<td>Oostenbrink et al (2005) 173</td>
<td>Potentially serious</td>
<td>Partially</td>
<td></td>
<td>£2$^g$</td>
<td>0.026 QALYs</td>
<td>£77/QALY gained$^h$</td>
<td>None of the sensitivity analyses found SAMA to be the preferred option at a threshold of £20,000/QALY$^g$.</td>
</tr>
</tbody>
</table>

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$^b$ 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.


$^e$ 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$^e$ (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).
### COPD (update)

<table>
<thead>
<tr>
<th>Severe = FEV(_1) 30%-49% predicted</th>
<th>Very severe = FEV(_1) &lt;30% predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rutten et al (2007)</strong>(^{174})</td>
<td><strong>Potentially serious limitations(^i)</strong></td>
</tr>
<tr>
<td>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}).</td>
<td>£1,051(^m)</td>
</tr>
</tbody>
</table>

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

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\(^i\) 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.

\(^m\) 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\textsuperscript{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.
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 beta2 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 beta2 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)\textsuperscript{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).\textsuperscript{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\textsubscript{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<sub>2</sub> agonists be used for stable COPD?


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
</tr>
<tr>
<td>No</td>
<td>Randomised trial</td>
</tr>
<tr>
<td>No</td>
<td>Randomised trial</td>
</tr>
</tbody>
</table>

<sup>1</sup> Vogelmeier et al; Brusasco et al

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

<sup>3</sup> Very wide 95% CI that crosses the MID twice

<sup>4</sup> 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.

<sup>5</sup> Significant heterogeneity (I<sup>2</sup> = 69.6%)

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wide 95% CI that cross the MID twice; few events
Evidence statements

LAMA versus LABA

Brusasco\textsuperscript{164} compared long-acting anticholinergic to long-acting beta\textsubscript{2} agonist. The FEV\textsubscript{1} measures were statistically significant in favour of long-acting anticholinergic compared to long-acting beta\textsubscript{2} agonist (p < 0.05).

There was no significant difference in the TDI dyspnoea focal score\textsuperscript{164}.

There were no statistically significant outcomes for HRQL measured using the SGRQ when comparing long-acting anticholinergic to long-acting beta\textsubscript{2} agonist\textsuperscript{164}.

There were no statistically significant differences between the two groups for rescue medication use\textsuperscript{168}.

Evidence statements

There was no significant difference between tiotropium or long-acting beta\textsubscript{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\textsubscript{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\textsuperscript{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\textsuperscript{175}.

No studies were identified in the original guideline search.
## Update 2010: Economic evidence profile

### Economic evidence: LAMA vs LABA

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations*</th>
<th>Applicability*</th>
<th>Other comments</th>
<th>Incremental(†) cost (£)</th>
<th>Incremental(‡) effects</th>
<th>ICER(‡)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oostenbrink et al (2005)</td>
<td>Potentially serious limitations(^n)</td>
<td>Partially applicable(^e)</td>
<td>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%</td>
<td>£29(^q)</td>
<td>0.021 QALYs</td>
<td>LAMA dominant(^q)</td>
<td>Tiotropium was always the most cost-effective option (highest net benefit at a £20,000/QALY threshold) in base case PSA and sensitivity analyses.</td>
</tr>
<tr>
<td>Oostenbrink et al (2005) (^{173}) - Canada</td>
<td>Potentially serious limitations(^o)</td>
<td>Partially applicable(^e)</td>
<td></td>
<td>£3(^r)</td>
<td>0.021 QALYs</td>
<td>£134/QALY(^t)</td>
<td>Dominant to £36,403/QALY(^u) (ICER range in variety of sensitivity analyses).</td>
</tr>
</tbody>
</table>

* Key limitations: LAMA vs LABA treatment effect 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.

\(^n\) Some uncertainty over applicability of Netherlands resource use and unit costs to UK.

\(^o\) Some uncertainty over applicability of Canadian 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.

\(^r\) 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).

\(^s\) 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.

\(^t\) £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.
**Table: Tiotropium vs LABA/LAMA for COPD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations</th>
<th>Partially applicable</th>
<th>Treatment Effect</th>
<th>Cost (£)</th>
<th>QALYs</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutten et al (2007)</td>
<td>Potentially serious limitations</td>
<td>Partially applicable</td>
<td>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.</td>
<td>£469</td>
<td>0.14</td>
<td>£3,481/QALY</td>
</tr>
</tbody>
</table>

*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

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**Key limitations:**
- LAMA vs LABA treatment effects 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 FEV₁ 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.
- 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.
- 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 FEV₁ < 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 beta2-agonists is considered in section 7.3.6.
The GDG identified one systematic review; 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, duration 36 months, The Lung Health Study, duration 40 months, Vestbo 1999, duration 36 months and EUROSCOP, 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.

A systematic review (van Grunsven PM et al 1999) 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) 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, which was an analysis of the EUROSCOP 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 and a further post hoc analysis which looked at effects on exacerbation rates according to the severity of airflow obstruction.

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

The four identified RCTs were all placebo-controlled trials of inhaled steroids.

Vestbo 1999 (N=290) and Burge 2000 (N=751) included a systemic steroid run in phase. The Lung Health Study (N=1116) and EUROSCOP (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 \(^{185}\).

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 \(^{183}\).

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).

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, \(p=0.03\)).

Vestbo \(^{185}\), Pauwels \(^{186}\), Burge \(^{183}\) and the Lung Health Study \(^{184}\) found no significant differences in annual rate of FEV\(_1\) decline.
The systematic review found no significant differences between inhaled steroids and placebo on mortality rates.

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

**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 highlights that the definitions of adverse events were not uniform over the trials.

There were no significant differences for cataract or fracture rates 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 are quoted under issues for consideration in the introduction to inhaled corticosteroids.

The systematic review found the results of bone mineral density variable between studies.

The Lung Health Study, 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.

However the EUROSCOP study and a separate paper utilising the same study population was subsequently published exploring bone mineral density in N=192 patients with mild COPD (defined as FEV₁ > 50% and FEV₁/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.
Burge et al\textsuperscript{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).

Vestbo et al\textsuperscript{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.

The Lung Health Study\textsuperscript{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)”.

The response to inhaled steroids could not be predicted by the response to a short course of oral steroids\textsuperscript{82}.

\textbf{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.

The benefits of inhaled steroids have been shown in studies using a variety of doses of varying steroid molecules.
There is insufficient evidence to establish the minimum dose of inhaled steroid required to achieve the proven benefits.

There is limited experience of doses higher than 1000 μg fluticasone per day (or equivalent) and no evidence of superiority.

**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 beta₂-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 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 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 were added to the Naninni et al meta-analysis. One of these RCTs 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 compared budesonide/formoterol pMDI (320/9 microgram b.i.d.) with formoterol DPI (9 microgram b.i.d.) for either 6 months or 1 year. 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 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_≥ 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?


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
</tr>
<tr>
<td>No of patients</td>
<td></td>
</tr>
<tr>
<td>Change from baseline in post dose FEV₁ (follow-up 24-156 weeks; measured with: Litres; range of scores: ; Better indicated by more)</td>
<td>5</td>
</tr>
</tbody>
</table>

**Exacerbations (rate ratio) (follow-up 52 - 156 weeks)**

<table>
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<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
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</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
</tr>
<tr>
<td>No of patients</td>
<td></td>
</tr>
<tr>
<td>Mean rate of exacerbations per participant per year (follow-up 1 years; range of scores: ; Better indicated by less)</td>
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</tr>
</tbody>
</table>
## Number of participants with one or more exacerbation (follow-up 24-52 weeks)

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomised Trial</th>
<th>Serious Inconsistency</th>
<th>Serious Indirectness</th>
<th>Serious Imprecision</th>
<th>None</th>
<th>N</th>
<th>P</th>
<th>Rate Ratio</th>
<th>Absolute Difference</th>
<th>Very Low</th>
<th>Moderate</th>
<th>Very High</th>
</tr>
</thead>
<tbody>
<tr>
<td>4th</td>
<td>Randomised trial</td>
<td>serious</td>
<td>no serious</td>
<td>no serious</td>
<td>none</td>
<td>506/1245 (40.6%)</td>
<td>545/1213 (44.9%)</td>
<td>RR 0.91 (0.83 to 0.99)</td>
<td>506/1245 (40.6%)</td>
<td>4 fewer per 1,000</td>
<td>40 fewer per 1,000</td>
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</tbody>
</table>

## Exacerbations requiring hospitalisation (follow-up 52-156 weeks)

<table>
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<tr>
<th>Study</th>
<th>Randomised Trial</th>
<th>Serious Inconsistency</th>
<th>Serious Indirectness</th>
<th>Serious Indirectness</th>
<th>None</th>
<th>N</th>
<th>P</th>
<th>Rate Ratio</th>
<th>Absolute Difference</th>
<th>Very Low</th>
<th>Moderate</th>
<th>Very High</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd</td>
<td>Randomised trial</td>
<td>serious</td>
<td>no serious</td>
<td>no serious</td>
<td>none</td>
<td>2040</td>
<td>2008</td>
<td>rate ratio 0.86 (0.56 to 1.31)</td>
<td>2008</td>
<td>0 fewer per 1,000</td>
<td>0 fewer per 1,000</td>
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</tbody>
</table>

## Change from baseline in TDI (follow-up 24 weeks; measured with: TDI; range of scores: -; Better indicated by more)

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<thead>
<tr>
<th>Study</th>
<th>Randomised Trial</th>
<th>Very Serious Inconsistency</th>
<th>Very Serious Indirectness</th>
<th>Very Serious Imprecision</th>
<th>None</th>
<th>N</th>
<th>P</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd</td>
<td>Randomised trial</td>
<td>very serious</td>
<td>no serious</td>
<td>no serious</td>
<td>none</td>
<td>341</td>
<td>336</td>
<td>-</td>
<td>MD 0.47 (-0.02 to 0.96)</td>
</tr>
<tr>
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</tbody>
</table>

## Change from baseline in SGRQ (total score) (follow-up 24-156 weeks; measured with: SGRQ; range of scores: 0-100; Better indicated by less)

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomised Trial</th>
<th>Very Serious Inconsistency</th>
<th>Very Serious Indirectness</th>
<th>Very Serious Imprecision</th>
<th>None</th>
<th>N</th>
<th>P</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd</td>
<td>Randomised trial</td>
<td>very serious</td>
<td>no serious</td>
<td>no serious</td>
<td>none</td>
<td>3156</td>
<td>3094</td>
<td>-</td>
<td>MD -1.63 (-2.21 to -1.06)</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

## Mortality (follow-up 24-156 weeks)

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomised Trial</th>
<th>Very Serious Inconsistency</th>
<th>Very Serious Indirectness</th>
<th>Very Serious Imprecision</th>
<th>None</th>
<th>N</th>
<th>P</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>9th</td>
<td>Randomised trial</td>
<td>very serious</td>
<td>no serious</td>
<td>no serious</td>
<td>none</td>
<td>228/4557 (5%)</td>
<td>244/4522 (5.4%)</td>
<td>RR 0.93 (0.78 to 1.1)</td>
<td>228/4557 (5%)</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
### Pneumonia (follow-up 24-156 weeks)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Bias</th>
<th>Consistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Event Rate</th>
<th>RR</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>10(^{22})</td>
<td>Randomised trial</td>
<td>Very serious(^{22})</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>390/4691 (8.3%)</td>
<td>RR 1.46 (1.26 to 1.69)</td>
</tr>
</tbody>
</table>

### Cataracts (follow-up 156 weeks)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Bias</th>
<th>Consistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Event Rate</th>
<th>RR</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{24})</td>
<td>Randomised trial</td>
<td>Serious(^{24})</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Very serious(^{24})</td>
<td>None</td>
<td>14/52 (26.9%)</td>
<td>RR 1.84 (0.78 to 4.37)</td>
</tr>
</tbody>
</table>

### Fractures (follow-up 156 weeks)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Bias</th>
<th>Consistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Event Rate</th>
<th>RR</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{24})</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious(^{14})</td>
<td>None</td>
<td>78/1546 (5%)</td>
<td>RR 1.28 (0.92 to 1.77)</td>
</tr>
</tbody>
</table>

---

\(^{1}\) 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 (I\(^2\) = 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 (I\(^2\)=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

\(^{10}\) TORCH; Kardos et al

\(^{11}\) Both studies have adequate allocation concealment, are double blinded, and both conducted ITT. The larger study TORCH has dropout rates >20% over 3 years.

\(^{12}\) Significant heterogeneity (I\(^2\) = 70.8%)
wide 95% CI that crosses MID
Hanania et al; Mahler et al
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
Significant heterogeneity (I² = 76.6%)
TRISTAN; TORCH; Kardos et al; SCO100470; Tashkin et al; Rennard et al
3/6 RCTs had unclear allocation concealment, all double blind; all performed ITT; 4/6 studies had dropout rates > 20%.
TORCH; TRISTAN; SCD100470; Kardos et al; Calverley et al; Szafranski et al; Ferguson et al; Tashkin et al; Rennard et al
4/9 RCTs had unclear allocation concealment; all double blind; all performed ITT, 7/9 had dropout rates > 20%
TORCH; TRISTAN; Mahler et al; Hanania et al; SCO100470; Calverley et al; Kardos et al; Ferguson et al; Tashkin et al; Rennard et al
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.
TORCH
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$_1$

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>LABA + ICS</th>
<th>LABA</th>
<th>Litres (SE)</th>
<th>Litres (fixed) 95% CI</th>
<th>Weight</th>
<th>Litres (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 one year study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kendts 2007</td>
<td>597</td>
<td>487</td>
<td>0.0100 (0.0036)</td>
<td></td>
<td>4.94</td>
<td>0.01 (-0.05, 0.07)</td>
</tr>
<tr>
<td>Renard (320/8 ug)</td>
<td>494</td>
<td>495</td>
<td>0.0090 (0.0132)</td>
<td></td>
<td>25.50</td>
<td>0.05 (0.00, 0.06)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1091</td>
<td>982</td>
<td></td>
<td></td>
<td>40.44</td>
<td>0.03 (0.00, 0.05)</td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 0.37, df = 1 (P = 0.54), I^2 = 0%$</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: $Z = 2.21 (P = 0.03)$</td>
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<tr>
<td><strong>02 more than one year study</strong></td>
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<tr>
<td>TORCH 2007</td>
<td>1392</td>
<td>1394</td>
<td>0.0090 (0.0130)</td>
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<td>44.43</td>
<td>0.05 (0.03, 0.07)</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>1392</td>
<td>1394</td>
<td></td>
<td></td>
<td>44.43</td>
<td>0.05 (0.03, 0.07)</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
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<tr>
<td>Test for overall effect: $Z = 5.00 (P &lt; 0.00001)$</td>
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<tr>
<td>SOCIO010470 2008</td>
<td>510</td>
<td>502</td>
<td>0.0090 (0.0020)</td>
<td></td>
<td>11.11</td>
<td>0.05 (0.01, 0.09)</td>
</tr>
<tr>
<td>Tashkin (320/8 ug)</td>
<td>277</td>
<td>284</td>
<td>0.0460 (0.0178)</td>
<td></td>
<td>14.02</td>
<td>0.04 (0.01, 0.07)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>787</td>
<td>786</td>
<td></td>
<td></td>
<td>25.13</td>
<td>0.04 (0.02, 0.07)</td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 0.14, df = 1 (P = 0.71), I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 3.34 (P = 0.0009)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>3188</td>
<td>3132</td>
<td></td>
<td></td>
<td>100.00</td>
<td>0.04 (0.03, 0.05)</td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 2.77, df = 4 (P = 0.60), I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 8.23 (P = 0.00001)$</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LABA</th>
<th>Rate Ratio (fixed)</th>
<th>Weight</th>
<th>Rate Ratio (fixed)</th>
<th>Rate Ratio (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>log[Rate Ratio] (SE)</td>
<td>%</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>01 one year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calverley 2003</td>
<td>254</td>
<td>255</td>
<td>-0.2900 (0.1200)</td>
<td>5.10</td>
<td>0.75 [0.59, 0.95]</td>
<td></td>
</tr>
<tr>
<td>Szafranski 2003</td>
<td>208</td>
<td>201</td>
<td>-0.2600 (0.1300)</td>
<td>4.35</td>
<td>0.77 [0.60, 0.99]</td>
<td></td>
</tr>
<tr>
<td>TRISTAN 2003</td>
<td>358</td>
<td>372</td>
<td>-0.0700 (0.0700)</td>
<td>15.00</td>
<td>0.93 [0.81, 1.07]</td>
<td></td>
</tr>
<tr>
<td>Kardos 2007</td>
<td>507</td>
<td>487</td>
<td>-0.1300 (0.0700)</td>
<td>15.00</td>
<td>0.95 [0.83, 1.07]</td>
<td></td>
</tr>
<tr>
<td>Ferguson 2008</td>
<td>391</td>
<td>385</td>
<td>-0.1580 (0.0709)</td>
<td>14.62</td>
<td>0.95 [0.74, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1718</td>
<td>1700</td>
<td></td>
<td>54.07</td>
<td>0.79 [0.74, 0.85]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 14.72, \text{df} = 4 (P = 0.005), I^2 = 72.8\%$
Test for overall effect: $Z = 6.23 (P < 0.00001)$

<table>
<thead>
<tr>
<th>02 more than one year</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TORCH 2007</td>
<td>1533</td>
<td>1521</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1533</td>
<td>1521</td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: $Z = 3.25 (P = 0.001)$

| Total (95% CI)       | 3251             | 3221             |

Test for heterogeneity: $\chi^2 = 18.08, \text{df} = 5 (P = 0.003), I^2 = 72.3\%$
Test for overall effect: $Z = 6.78 (P < 0.00001)$

![Graph showing comparison between LABA + ICS and LABA]
Exacerbations (expressed as rate ratio)

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LABA</th>
<th>Rate Ratio (fixed)</th>
<th>Weight</th>
<th>Rate Ratio (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>log(Rate Ratio) (SE)</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>01 stabilising treatment given during run-in</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calverley 2003</td>
<td>254</td>
<td>255</td>
<td>-0.2900 (0.1200)</td>
<td>5.10</td>
<td>0.75 [0.59, 0.95]</td>
</tr>
<tr>
<td>Kardos 2007</td>
<td>507</td>
<td>487</td>
<td>-0.4300 (0.0700)</td>
<td>15.00</td>
<td>0.65 [0.57, 0.75]</td>
</tr>
<tr>
<td>Ferguson 2008</td>
<td>391</td>
<td>385</td>
<td>-0.1580 (0.0709)</td>
<td>14.62</td>
<td>0.85 [0.74, 0.98]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1152</td>
<td>1127</td>
<td></td>
<td>34.72</td>
<td>0.74 [0.68, 0.81]</td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 7.45, df = 2 (P = 0.02), I² = 73.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 6.41 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>02 All treatment removed during run-in</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Szafiranski 2003</td>
<td>208</td>
<td>201</td>
<td>-0.2600 (0.1300)</td>
<td>4.35</td>
<td>0.77 [0.60, 0.99]</td>
</tr>
<tr>
<td>TRISTAN 2003</td>
<td>358</td>
<td>372</td>
<td>-0.0700 (0.0700)</td>
<td>15.00</td>
<td>0.93 [0.81, 1.07]</td>
</tr>
<tr>
<td>TORCH 2007</td>
<td>1533</td>
<td>1521</td>
<td>-0.1300 (0.0400)</td>
<td>45.93</td>
<td>0.88 [0.81, 0.95]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2099</td>
<td>2094</td>
<td></td>
<td>65.28</td>
<td>0.88 [0.83, 0.94]</td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 1.71, df = 2 (P = 0.42), I² = 0%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 3.72 (P = 0.0002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>3251</td>
<td>3221</td>
<td></td>
<td>100.00</td>
<td>0.88 [0.79, 0.98]</td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 18.08, df = 5 (P = 0.003), I² = 72.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 6.78 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

0.5  0.7  1  1.5  2
Favours LABA +ICS  Favours LABA
### Mean number of exacerbations per person per year

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

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>LABA + ICS</th>
<th>LABA</th>
<th>WMD (fixed)</th>
<th>Weight</th>
<th>WMD (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
<td>Mean (SD)</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>01 All treatment removed during run in</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calverley 2003</td>
<td>254</td>
<td>1.38 (0.00)</td>
<td>255</td>
<td>1.85 (0.00)</td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>254</td>
<td>255</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>02 stabilising treatment given during run in</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Szaf ranski 2003</td>
<td>208</td>
<td>1.42 (1.49)</td>
<td>201</td>
<td>1.84 (1.38)</td>
<td>24.77</td>
</tr>
<tr>
<td>TRISTAN 2003</td>
<td>358</td>
<td>0.97 (1.10)</td>
<td>372</td>
<td>1.04 (1.10)</td>
<td>75.23</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>566</td>
<td>573</td>
<td></td>
<td>100.00</td>
<td>-0.16</td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 4.57, df = 1$ ($P = 0.03$), $\text{I}^2 = 78.1%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.22$ ($P = 0.03$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>820</td>
<td>828</td>
<td></td>
<td>100.00</td>
<td>-0.16</td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 4.57, df = 1$ ($P = 0.03$), $\text{I}^2 = 78.1%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.22$ ($P = 0.03$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-1  -0.5  0  0.5  1
Favours LABA + ICS  Favours LABA
**Number of participants with one or more exacerbation**

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

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>LABA + ICS n/N</th>
<th>LABA n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 Stabilising run in period and one year study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kardos 2007</td>
<td>210/507</td>
<td>241/487</td>
<td>0.84 [0.73, 0.96]</td>
<td>44.54</td>
<td></td>
</tr>
<tr>
<td>Ferguson 2008</td>
<td>211/391</td>
<td>230/385</td>
<td>0.90 [0.80, 1.02]</td>
<td>41.99</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>898</td>
<td>872</td>
<td>0.87 [0.79, 0.95]</td>
<td>86.54</td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>421 (LABA + ICS), 471 (LABA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong> Chi² = 0.67, df = 1 (P = 0.41), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong> Z = 2.98 (P = 0.003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>02 All drugs removed during run in period and six month study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mahler 2002</td>
<td>14/169</td>
<td>9/164</td>
<td>1.51 [0.67, 3.39]</td>
<td>1.66</td>
<td>1.51 [0.67, 3.39]</td>
</tr>
<tr>
<td>Hanania 2003</td>
<td>71/178</td>
<td>65/177</td>
<td>1.09 [0.83, 1.41]</td>
<td>11.81</td>
<td>1.09 [0.83, 1.41]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>347</td>
<td>341</td>
<td>1.14 [0.88, 1.47]</td>
<td>13.46</td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>85 (LABA + ICS), 74 (LABA)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong> Chi² = 0.59, df = 1 (P = 0.44), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong> Z = 1.00 (P = 0.32)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1245</td>
<td>1213</td>
<td>0.91 [0.83, 0.99]</td>
<td>100.00</td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>506 (LABA + ICS), 545 (LABA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong> Chi² = 4.62, df = 3 (P = 0.20), I² = 35.0%</td>
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<td></td>
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</tr>
<tr>
<td><strong>Test for overall effect:</strong> Z = 2.24 (P = 0.03)</td>
<td></td>
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</tr>
</tbody>
</table>
Change from baseline in health related quality of life (total SGRQ score)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>LABA + ICS N</th>
<th>LABA N</th>
<th>SGRQ units (SE)</th>
<th>95% CI</th>
<th>Weight %</th>
<th>SGRQ units (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 6 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCO100470 2000</td>
<td>518</td>
<td>532</td>
<td>-0.8000 (0.9000)</td>
<td></td>
<td>10.65</td>
<td>-0.80 [-2.56, 0.95]</td>
</tr>
<tr>
<td>Tashlin (320/5 ug)</td>
<td>277</td>
<td>294</td>
<td>-2.5600 (1.0690)</td>
<td></td>
<td>7.55</td>
<td>-2.56 [-4.65, -0.46]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>795</td>
<td>816</td>
<td></td>
<td></td>
<td>18.20</td>
<td>-1.53 [-2.88, -0.18]</td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 1.56, df = 1 (P = 0.21), I² = 37.0%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.22 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>02 one year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRISTAN 2003</td>
<td>558</td>
<td>372</td>
<td>-1.1000 (0.5900)</td>
<td></td>
<td>24.78</td>
<td>-1.10 [-2.28, 0.06]</td>
</tr>
<tr>
<td>Kardos 2007</td>
<td>507</td>
<td>407</td>
<td>-2.2400 (0.9000)</td>
<td></td>
<td>13.65</td>
<td>-2.24 [-4.00, -0.48]</td>
</tr>
<tr>
<td>Remillard (320/5 ug)</td>
<td>494</td>
<td>495</td>
<td>-1.0000 (0.8120)</td>
<td></td>
<td>11.88</td>
<td>-1.00 [-2.67, 0.67]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1353</td>
<td>1374</td>
<td></td>
<td></td>
<td>47.91</td>
<td>-1.03 [-2.17, -0.49]</td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 1.32, df = 2 (P = 0.52), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.12 (P = 0.002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>03 more than one year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TORCH 2007</td>
<td>1002</td>
<td>924</td>
<td>-2.1000 (0.5000)</td>
<td></td>
<td>34.50</td>
<td>-2.10 [-3.08, -1.12]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2156</td>
<td>2094</td>
<td></td>
<td></td>
<td>34.50</td>
<td>-2.10 [-3.08, -1.12]</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.20 (P &lt; 0.0001)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Favours LABA + ICS  Favours LABA
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 $\text{FEV}_1$ (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?


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Limitations</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Mortality - people with baseline post BD FEV₁ &lt; 30% (follow-up 3 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Randomised trial</td>
<td>very serious¹</td>
</tr>
<tr>
<td>Mortality - people with baseline post BD FEV₁ 30% to &lt; 50% (follow-up 3 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Randomised trial</td>
<td>very serious¹</td>
</tr>
</tbody>
</table>

¹ kicker for serious indirectness

<table>
<thead>
<tr>
<th>Quality</th>
<th>Importan ce</th>
</tr>
</thead>
<tbody>
<tr>
<td>VERY LOW</td>
<td>⁵.infinity</td>
</tr>
</tbody>
</table>

Page 149 of 673
### Mortality - People with Baseline Post BD FEV₁ Greater Than or Equal to 50% (Follow-Up 3 Years)

<table>
<thead>
<tr>
<th></th>
<th>Randomised Trial</th>
<th>Serious ¹</th>
<th>No Serious Inconsistency</th>
<th>No Serious Indirectness</th>
<th>Very Serious ²</th>
<th>None</th>
<th>44/562 (7.8%)</th>
<th>48/522 (9.2%)</th>
<th>RR 0.85 (0.58 to 1.26)</th>
<th>14 Fewer per 1000 (from 39 Fewer to 24 More)</th>
<th>Grade of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very Low</td>
</tr>
</tbody>
</table>

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\textsuperscript{207}, there was no significant difference between salmeterol plus fluticasone compared with salmeterol for:

- Death in people with baseline post-bronchodilator FEV\textsubscript{1} < 30\% (very low quality evidence)
- Death in people with baseline post-bronchodilator FEV\textsubscript{1} 30\% to < 50\% (very low quality evidence)
- Death in people with baseline post-bronchodilator FEV\textsubscript{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\textsubscript{2} agonists and ICS versus long-acting beta\textsubscript{2} agonists alone. This comparison was also subject to a call for unpublished evidence.

Four studies were included that included the relevant comparison\textsuperscript{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\textsuperscript{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\textsuperscript{214-217}.

No studies were identified in the original guideline search.
## Health economic evidence profile

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations*</th>
<th>Applicability*</th>
<th>Other comments</th>
<th>Incremental‡ cost (£)</th>
<th>Incremental‡ effects</th>
<th>ICER‡</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dal Negro et al (2007) – Italy SF vs. S</td>
<td>Potentially serious limitations(^2)</td>
<td>Partially applicable(^a)</td>
<td>Literature based lifetime Markov model of COPD natural history. Treatment effect on exacerbations applied in GOLD stage 3 and 4 (FEV(_1) &lt;50%) – data from Calverley 2003 (SF)(^1) and Szafranski (FB)(^1)</td>
<td>£496(^b)</td>
<td>0.98 exacerbations avoided</td>
<td>£505 per exacerbation avoided(^c)</td>
<td>Not reported(^d)</td>
</tr>
<tr>
<td>As above</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FB vs. S</td>
<td></td>
<td></td>
<td></td>
<td>£427(^d)</td>
<td>0.41 exacerbations avoided</td>
<td>£1033 per exacerbation avoided(^c)</td>
<td>Not reported(^d)</td>
</tr>
</tbody>
</table>

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\(^*\) 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).

\(^a\) Some uncertainty over the applicability of Italian resource use, costs and epidemiological data to UK. QALYs not used – inhibits interpretation of results.

\(^b\) Converted from 2005 Italian Euros using 2005 Purchasing Power Parities\(^77\).

\(^c\) Study included placebo and ICS alone as well as SF, FB and S. Placebo and ICS were both dominated by S.

\(^d\) Study undertook one way sensitivity but only reported SF vs placebo results.
<table>
<thead>
<tr>
<th>Study</th>
<th>Resource Use</th>
<th>Treatment Effect</th>
<th>QALYs</th>
<th>Cost/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lofdahl et al (2005)</td>
<td>1 year analysis of resource use and outcomes in Calverley 2003 RCT (GOLD stage 3 and 4 - FEV₁ &lt;50% predicted)</td>
<td>-£691&lt;sup&gt;ee&lt;/sup&gt;</td>
<td>0.01187</td>
<td>£4,497/QALY</td>
</tr>
<tr>
<td>Potentially serious limitations&lt;sup&gt;ee&lt;/sup&gt;</td>
<td>Partially applicable&lt;sup&gt;ff&lt;/sup&gt;</td>
<td>Reduction in exacerbations&lt;sup&gt;hh&lt;/sup&gt;</td>
<td>£53&lt;sup&gt;gg&lt;/sup&gt;</td>
<td>£4,497/QALY</td>
</tr>
<tr>
<td>LABA+ICS dominant&lt;sup&gt;ii&lt;/sup&gt;</td>
<td>LABA+ICS dominant in &gt;95% bootstrap replications</td>
<td>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.</td>
<td>£236&lt;sup&gt;ll&lt;/sup&gt;</td>
<td>£9833/QALY</td>
</tr>
</tbody>
</table>

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<sup>ee</sup> 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).

<sup>ff</sup> 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.

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

<sup>hh</sup> Improvements in FEV₁ and SGRQ also reported.

<sup>ii</sup> Study included placebo and ICS alone as well as LABA+ICS and LABA. LABA+ICS dominated all.

<sup>ll</sup> 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.

<sup>kk</sup> Some uncertainty over the applicability of Canadian resource use, costs and epidemiological data to UK.

<sup>177</sup> Converted from 2004 Canadian dollars using 2004 Purchasing Power Parities.
| LABA+ICS (mod&sev patients) vs. LABA | Moderate = FEV₁ 35-50% predicted | Severe = FEV₁ < 35% predicted | £1971
|-mm | 0.037 QALYs | £52,270/QALY
|nn | |
| As above LABA+ICS (all) patients vs. LABA | |
| |
| Briggs et al. (2009)†† 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 RCT (FEV₁ < 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

---

** 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).

*** 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).

OOSE 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.


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)

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations*</th>
<th>Applicability*</th>
<th>Other comments</th>
<th>Incremental cost (£)</th>
<th>Incremental effects</th>
<th>ICER†</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayers et al. (2007)210 – Canada</td>
<td>Potentially serious limitations²</td>
<td>Partially applicablekk</td>
<td>Literature based lifetime Markov model of COPD natural history. Treatment effect on exacerbations applied – data from Cal;verley 2003218, Szafranski166 and TRISTAN167. Mild = FEV₁ &gt;50% predicted Moderate = FEV₁ 35-50% predicted Severe = FEV₁ &lt; 35% predicted</td>
<td>£182²</td>
<td>0.01217 QALYs</td>
<td>£14,931 per QALY gained</td>
<td>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.</td>
</tr>
</tbody>
</table>

*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)

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations*</th>
<th>Applicability*</th>
<th>Other comments</th>
<th>Incremental(^\d) cost (£)</th>
<th>Incremental(^\d) effects</th>
<th>ICER(^\d)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayers et al. (2007)(^{210}) – Canada</td>
<td>Potentially serious limitations(^i)</td>
<td>Partially applicable(^{ik})</td>
<td>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) &gt;50% predicted Moderate = FEV(_1) 35-50% predicted Severe = FEV(_1) &lt; 35% predicted</td>
<td>£1735(^{k})</td>
<td>0.01323 QALYs</td>
<td>£131,165 per QALY gained</td>
<td>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.</td>
</tr>
</tbody>
</table>

*Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; \(^\d\) 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\textsubscript{1} < 50% predicted or < 60% predicted (depending on the analysis)\textsuperscript{209-211}. These were judged partially applicable due to their non-UK setting. Between them they used data from TRISTAN\textsuperscript{167}, Szafranski 2003\textsuperscript{166}, Calverley 2003\textsuperscript{218} and TORCH\textsuperscript{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 EQSD utility data collected prospectively within the trial\textsuperscript{197}.

One of the six studies only reported costs per exacerbation avoided and so was difficult to interpret\textsuperscript{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\textsubscript{1} < 50% predicted (those not receiving LABA+ICS received LABA alone)\textsuperscript{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) 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?


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>Effect</td>
</tr>
<tr>
<td>salmeterol/fluticasone propionate</td>
<td>tiotropium bromide</td>
</tr>
<tr>
<td>No of studies: 1</td>
<td>None: 0 fewer per 1000 (from 0 fewer to 0 more)</td>
</tr>
<tr>
<td>Design: randomised trial</td>
<td>Limitations: serious</td>
</tr>
<tr>
<td>Limitations: serious</td>
<td>Inconsistency: no serious inconsistency</td>
</tr>
<tr>
<td>Indirectness: no serious indirectness</td>
<td>Imprecision: none</td>
</tr>
<tr>
<td>Imprecision: none</td>
<td>Other considerations: none</td>
</tr>
</tbody>
</table>

**Mean exacerbations (rate ratio) requiring use of oral corticosteroids and/or antibiotics or hospitalisation (follow-up 2 years):**

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Rate ratio 0.97 (0.84 to 1.12)</th>
<th>Absolute 0 fewer per 1000 (from 0 fewer to 0 more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>salmeterol/fluticasone propionate</td>
<td>658 (1.28 mean exacerbations/year)</td>
<td>665 (1.32 mean exacerbations /year)</td>
</tr>
<tr>
<td>tiotropium bromide</td>
<td>Rate ratio 1.19 (1.02 to 1.38)</td>
<td>Absolute 0 more per 1000 (from 0 more to 0 more)</td>
</tr>
<tr>
<td>Relative (95% CI)</td>
<td>0 fewer per 1000 (from 0 fewer to 0 more)</td>
<td>0 more per 1000 (from 0 more to 0 more)</td>
</tr>
<tr>
<td>Absolute</td>
<td>0 fewer per 1000 (from 0 fewer to 0 more)</td>
<td>0 more per 1000 (from 0 more to 0 more)</td>
</tr>
</tbody>
</table>

**Mean exacerbations (rate ratio) requiring antibiotics (follow-up 2 years):**

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Rate ratio 1.19 (1.02 to 1.38)</th>
<th>Absolute 0 more per 1000 (from 0 more to 0 more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>salmeterol/fluticasone propionate</td>
<td>658 (0.97 mean exacerbations/year)</td>
<td>665 (0.82 mean exacerbations /year)</td>
</tr>
<tr>
<td>tiotropium bromide</td>
<td>Rate ratio 1.19 (1.02 to 1.38)</td>
<td>Absolute 0 more per 1000 (from 0 more to 0 more)</td>
</tr>
<tr>
<td>Relative (95% CI)</td>
<td>0 fewer per 1000 (from 0 fewer to 0 more)</td>
<td>0 more per 1000 (from 0 more to 0 more)</td>
</tr>
<tr>
<td>Absolute</td>
<td>0 fewer per 1000 (from 0 fewer to 0 more)</td>
<td>0 more per 1000 (from 0 more to 0 more)</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Serious?</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>----------</td>
</tr>
<tr>
<td>Mean exacerbations (rate ratio) requiring oral corticosteroids (follow-up 2 years)</td>
<td>1</td>
<td>randomised trial</td>
</tr>
<tr>
<td>Mean exacerbations (rate ratio) requiring hospitalisation (follow-up 2 years)</td>
<td>1</td>
<td>randomised trial</td>
</tr>
<tr>
<td>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)</td>
<td>1</td>
<td>randomised trial</td>
</tr>
<tr>
<td>Change from baseline in post bronchodilator FEV₁ (follow-up 2 years; range of scores: -; Better indicated by more)</td>
<td>1</td>
<td>randomised trial</td>
</tr>
<tr>
<td>All-cause mortality (follow-up 2 years)</td>
<td>1</td>
<td>randomised trial</td>
</tr>
</tbody>
</table>
### Pneumonia (follow-up 2 years)

<table>
<thead>
<tr>
<th>1</th>
<th>randomised trial</th>
<th>serious?</th>
<th>no serious inconsistency</th>
<th>no serious indirectness</th>
<th>no serious imprecision</th>
<th>none</th>
<th>50/658 (7.6%)</th>
<th>24/665 (3.6%)</th>
<th>RR 2.11 (1.31 to 3.38)</th>
<th>40 more per 1000 (from 11 more to 86 more)</th>
<th>MODERATE</th>
</tr>
</thead>
</table>

### Bone disorder (follow-up 2 years)

<table>
<thead>
<tr>
<th>1</th>
<th>randomised trial</th>
<th>serious?</th>
<th>no serious inconsistency</th>
<th>no serious indirectness</th>
<th>very serious</th>
<th>none</th>
<th>17/658 (2.6%)</th>
<th>12/665 (1.8%)</th>
<th>RR 1.43 (0.69 to 2.97)</th>
<th>8 more per 1000 (from 6 fewer to 35 more)</th>
<th>VERY LOW</th>
</tr>
</thead>
</table>

*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.*

*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 FEV₁ < 50% predicted value

*1.28 mean exacerbations/year in SFC group versus 1.32 mean exacerbations/year in tio group

*wide 95% CI that crosses MID

*0.97 mean exacerbations/year in SFC group versus 0.82 exacerbations/year in tio group

*0.69 mean exacerbation/year in SFC group versus 0.85 mean exacerbations/year in tio group

*wide 95% CI that crosses MID

*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).

*6 adjusted mean change at 2 years was -1.70 units in SFC and +0.37 units in tio group

*7 bone disorder not defined

*10 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 FEV₁ [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 beta₂ 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 FEV₁ <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 beta₂ 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 beta₂ agonists plus inhaled corticosteroids) with either:

a) long-acting beta₂ agonists plus inhaled corticosteroids

b) long-acting muscarinic antagonists alone

c) long-acting beta₂ agonists plus long-acting muscarinic antagonists
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 + ICS at baseline (N=2926). 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) be used in people with COPD?

**Bibliography:** Unpublished Data from UPLIFT RCT (Boehringer)

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies, Design, Limitations, Inconsistency, Indirectness, Imprecision, Other considerations</td>
<td>tiotropium + LABA (at baseline) + ICS (at baseline) vs. placebo + LABA (at baseline) + ICS (at baseline)</td>
<td>Relative (95% CI), Absolute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean post bronchodilator FEV₁ at 1 year (follow-up 1 years; range of scores: - ; Better indicated by more)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>very serious¹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td>Mean post bronchodilator FEV₁ at 4 years (follow-up 4 years; range of scores: - ; Better indicated by more)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>very serious¹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>very serious¹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>very serious¹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
</tbody>
</table>
### Number of patients with COPD exacerbations (follow-up 4 years)

| 1 | randomised trial | very serious¹ | 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)¹ | 54 fewer per 1000 (from 26 fewer to 85 fewer) | 💅มากๆ | LOW |

### Number of patients hospitalised for COPD exacerbations (follow-up 4 years)

| 1 | randomised trial | very serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 398/1464 (27.2%) | 442/1462 (30.2%) | HR 0.80 (0.7 to 0.92)² | 52 fewer per 1000 (from 20 fewer to 79 fewer) | 💅ๆๆ | VERY LOW |

### Mean COPD exacerbations per patient year (expressed as rate ratio) (follow-up 4 years)

| 1 | randomised trial | very serious¹ | 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)³ | 0 fewer per 1000 (from 0 fewer to 0 fewer) | 💅ๆๆ | LOW |

### Mean hospitalisations for COPD exacerbations per patient per year (expressed as rate ratio) (follow-up 4 years)

| 1 | randomised trial | very serious¹ | 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)⁴ | 0 fewer per 1000 (from 0 fewer to 0 more) | 💅ๆๆ | LOW |

### Mortality (adjudicated on treatment and vital status censoring at 1470 days) (follow-up 1470 days)

| 1 | randomised trial | very serious¹ | no serious inconsistency | no serious indirectness | serious² | none | 205/1464 (14%) | 220/1462 (15%) | HR 0.91 (0.76 to 1.15)⁵ | 13 fewer per 1000 (from 34 fewer to 20 more) | 💅ๆๆ | 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 FEV₁ 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 beta₂ 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 FEV₁ <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 is 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 beta₂ agonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists alone in the management of people with stable COPD?

In the double blind OPTIMAL RCT²⁰⁰ 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 RCT²⁰⁰ 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?


<table>
<thead>
<tr>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>tiotropium + salmeterol/fluticasone</td>
<td>tiotropium + placebo</td>
<td>Relative (95% CI)</td>
<td>Absolute</td>
</tr>
<tr>
<td>87/145 (60%)</td>
<td>98/156 (62.8%)</td>
<td>RR 0.96 (0.8 to 1.14)</td>
<td>25 fewer per 1000 (from 126 fewer to 88 more)</td>
</tr>
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<td></td>
<td></td>
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</tbody>
</table>

**Quality assessment**

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>tiotropium + salmeterol/fluticasone</th>
<th>tiotropium + placebo</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>serious</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>87/145 (60%)</td>
<td>98/156 (62.8%)</td>
<td>RR 0.96 (0.8 to 1.14)</td>
<td>25 fewer per 1000 (from 126 fewer to 88 more)</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>tiotropium + salmeterol/fluticasone</th>
<th>tiotropium + placebo</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>serious</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious</td>
<td>none</td>
<td>96/145 (66.2%)</td>
<td>117/156 (75%)</td>
<td>RR 0.88 (0.76 to 1.02)</td>
<td>90 fewer per 1000 (from 180 fewer to 15 more)</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th></th>
<th>randomised trial</th>
<th>serious¹</th>
<th>no serious inconsistency²</th>
<th>no serious indirectness¹</th>
<th>none</th>
<th>93/145 (64.1%)</th>
<th>112/156 (71.8%)</th>
<th>RR 0.89 (0.76 to 1.04)</th>
<th>79 fewer per 1000 (from 172 fewer to 29 more)</th>
<th></th>
</tr>
</thead>
</table>

Mean exacerbations/patient-year (expressed as rate ratio) (follow-up 1 years; blinded assessor)

<table>
<thead>
<tr>
<th></th>
<th>randomised trial</th>
<th>serious¹</th>
<th>no serious inconsistency²</th>
<th>no serious indirectness¹</th>
<th>none</th>
<th>145 (1.37 mean exacerbations/patient year)</th>
<th>156 (1.61 mean exacerbations/patient year)</th>
<th>rate ratio 0.85 (0.65 to 1.11)²</th>
<th>0 fewer per 1000</th>
<th></th>
</tr>
</thead>
</table>

Mean hospitalisation for acute exacerbation per patient year (expressed as rate ratio) (follow-up 1 years)

<table>
<thead>
<tr>
<th></th>
<th>randomised trial</th>
<th>serious¹</th>
<th>no serious inconsistency²</th>
<th>no serious indirectness¹</th>
<th>none</th>
<th>145 (0.19 mean hospitalisations/patient year)</th>
<th>156 (0.355 mean hospitalisations/patient year)</th>
<th>rate ratio 0.53 (0.33 to 0.86)²</th>
<th>0 fewer per 1000 (from 0 fewer to 0 fewer)</th>
<th></th>
</tr>
</thead>
</table>

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)

<table>
<thead>
<tr>
<th></th>
<th>randomised trial</th>
<th>serious¹</th>
<th>no serious inconsistency²</th>
<th>no serious indirectness¹</th>
<th>none</th>
<th>145</th>
<th>156</th>
<th>MD -4.1 (0 to 0)³</th>
<th></th>
</tr>
</thead>
</table>

Change from baseline in mean pre-bronchodilator FEV₁ (follow-up 1 years; range of scores: 0-; Better indicated by more)

<table>
<thead>
<tr>
<th></th>
<th>randomised trial</th>
<th>serious¹</th>
<th>no serious inconsistency²</th>
<th>no serious indirectness¹</th>
<th>none</th>
<th>145</th>
<th>156</th>
<th>MD 0.059 (0 to 0)³</th>
<th></th>
</tr>
</thead>
</table>
**COPD (update)**

**mean difference in breathlessness score (follow-up 1 years; measured with: Transitional Dyspnoea Index; range of scores: -9→9; Better indicated by less)**

<table>
<thead>
<tr>
<th></th>
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<th>no serious inconsistency</th>
<th>no serious indirectness?</th>
<th>serious?</th>
<th>none</th>
<th>145</th>
<th>156</th>
<th>-</th>
<th>MD 0.06 (-0.84 to 0.96)</th>
<th>📘🟢🟢🟢 LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 randomised trial</td>
<td>serious?</td>
<td>no serious inconsistency</td>
<td>no serious indirectness?</td>
<td>none</td>
<td>145</td>
<td>156</td>
<td>-</td>
<td>MD 0.06 (-0.84 to 0.96)</td>
<td>📘🟢🟢🟢 LOW</td>
<td></td>
</tr>
</tbody>
</table>

**All-cause mortality (follow-up 1 years)**

<table>
<thead>
<tr>
<th></th>
<th>randomised trial</th>
<th>serious?</th>
<th>no serious inconsistency</th>
<th>no serious indirectness?</th>
<th>very serious?</th>
<th>none</th>
<th>6/145 (4.1%)</th>
<th>4/156 (2.6%)</th>
<th>RR 1.61 (0.46 to 5.6)</th>
<th>16 more per 1000 (from 14 fewer to 120 more)</th>
<th>📘🟢🟢🟢 VERY LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 randomised trial</td>
<td>serious?</td>
<td>no serious inconsistency</td>
<td>no serious indirectness?</td>
<td>very serious?</td>
<td>none</td>
<td>1/145 (0.7%)</td>
<td>0/156 (0%)</td>
<td>RR 3.23 (0.13 to 78.56)</td>
<td>0 more per 1000 (from 0 fewer to 0 more)</td>
<td>📘🟢🟢🟢 VERY LOW</td>
</tr>
</tbody>
</table>

**Adverse event: Pneumonia leading to mechanical ventilation or death (follow-up 1 years)**

<table>
<thead>
<tr>
<th></th>
<th>randomised trial</th>
<th>serious?</th>
<th>no serious inconsistency</th>
<th>no serious indirectness?</th>
<th>very serious?</th>
<th>none</th>
<th>2/145 (1.4%)</th>
<th>2/156 (1.3%)</th>
<th>RR 1.08 (0.15 to 7.54)</th>
<th>1 more per 1000 (from 11 fewer to 85 more)</th>
<th>📘🟢🟢🟢 VERY LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 randomised trial</td>
<td>serious?</td>
<td>no serious inconsistency</td>
<td>no serious indirectness?</td>
<td>very serious?</td>
<td>none</td>
<td>2/145 (1.4%)</td>
<td>2/156 (1.3%)</td>
<td>RR 1.08 (0.15 to 7.54)</td>
<td>1 more per 1000 (from 11 fewer to 85 more)</td>
<td>📘🟢🟢🟢 VERY LOW</td>
</tr>
</tbody>
</table>

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 $\text{FEV}_1 < 65\%$; $\text{FEV}_1/\text{FVC} < 0.70$ and who had ≥ 1 exacerbation of COPD requiring antibiotic or systemic steroids within previous 12 mont hs.

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 FEV₁ [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 comparison²²⁰. 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 is included in appendix M.
### Health economic evidence profile

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations*</th>
<th>Applicability**</th>
<th>Other comments</th>
<th>Incremental cost (£)</th>
<th>Incremental effects</th>
<th>ICER‡</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Najafzadeh et al (2008)220 –</td>
<td>Potentially</td>
<td>Partially</td>
<td>1 year analysis of resource use and health outcomes (SGRQ – mapped</td>
<td>£731**</td>
<td>0.0056 QALYs**</td>
<td>£130,308/ QALY</td>
<td>LAMA cost-effective &gt;90% of bootstrapping/</td>
</tr>
<tr>
<td>Canada</td>
<td>serious</td>
<td>applicable†††</td>
<td>to EQ-5D utility) in Optimal RCT200 (FEV1&lt;65% predicted)</td>
<td></td>
<td></td>
<td></td>
<td>imputation simulations in base case, at threshold</td>
</tr>
<tr>
<td></td>
<td>limitations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>of £20,000/QALY.</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>One-way sensitivity analyses ICER range</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>£30,620 to £78,103/QALY.</td>
</tr>
</tbody>
</table>

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

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‡‡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.

††† Some uncertainty over the applicability of Canadian resource use and unit costs to UK.

** Converted from 2006 Canadian dollars using 2006 Purchasing Power Parities

† 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?


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>Effect</td>
<td>Quality</td>
</tr>
<tr>
<td>tiotropium +</td>
<td>Relative</td>
<td>Low</td>
</tr>
<tr>
<td>salmeterol/fluticasone</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>tiotropium +</td>
<td>Absolute</td>
<td></td>
</tr>
<tr>
<td>salmeterol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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)

<table>
<thead>
<tr>
<th>studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>tiotropium + salmeterol/fluticasone</th>
<th>tiotropium + salmeterol</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>serious⁴</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>none</td>
<td>87/145 (60%)</td>
<td>96/148 (64.9%)</td>
<td>RR 0.93 (0.77 to 1.11)</td>
<td>45 fewer per 1000 (from 149 fewer to 71 more)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

### 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)

<table>
<thead>
<tr>
<th>studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>tiotropium + salmeterol/fluticasone</th>
<th>tiotropium + salmeterol</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>serious⁴</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>none</td>
<td>96/145 (66.2%)</td>
<td>107/148 (72.3%)</td>
<td>RR 0.92 (0.79 to 1.07)</td>
<td>58 fewer per 1000 (from 152 fewer to 51 more)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

### 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)

<table>
<thead>
<tr>
<th>studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>tiotropium + salmeterol/fluticasone</th>
<th>tiotropium + salmeterol</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>serious⁴</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>none</td>
<td>93/145 (64.1%)</td>
<td>104/148 (70.3%)</td>
<td>RR 0.91 (0.78 to 1.07)</td>
<td>63 fewer per 1000 (from 155 fewer to 49 more)</td>
<td>LOW</td>
</tr>
</tbody>
</table>
### COPD (update)

#### All-cause mortality (follow-up 1 years)

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Randomised Trial</th>
<th>Serious Inconsistency</th>
<th>No Serious Indirectness</th>
<th>Very Serious Indirectness</th>
<th>None</th>
<th>MD</th>
<th>95% CI</th>
<th>RR</th>
<th>95% CI</th>
<th>Additional Notes</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>serious</td>
<td>no serious</td>
<td>none</td>
<td></td>
<td>145</td>
<td>156</td>
<td>-</td>
<td>0.44 (-0.46 to 1.34)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

#### Adverse event: Pneumonia leading to mechanical ventilation or death (follow-up 1 years)

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Randomised Trial</th>
<th>Serious Inconsistency</th>
<th>No Serious Indirectness</th>
<th>Very Serious Indirectness</th>
<th>None</th>
<th>6/145 (4.1%)</th>
<th>6/148 (4.1%)</th>
<th>RR 1.02 (0.34 to 3.09)</th>
<th>1 more per 1000 (from 27 fewer to 86 more)</th>
<th>VERY LOW</th>
</tr>
</thead>
</table>

#### Adverse event: MI or acute arrhythmia (follow-up 1 years)

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Randomised Trial</th>
<th>Serious Inconsistency</th>
<th>No Serious Indirectness</th>
<th>Very Serious Indirectness</th>
<th>None</th>
<th>1/145 (0.7%)</th>
<th>1/148 (0.7%)</th>
<th>RR 1.02 (0.06 to 16.16)</th>
<th>0 more per 1000 (from 7 fewer to 106 more)</th>
<th>VERY LOW</th>
</tr>
</thead>
</table>

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 wide 95% CI that crosses MID

3 wide 95% CI that crosses MID twice; study not powered for this outcome.

4 width: 95% CI that crosses MID twice; study not powered for this outcome.

**Strength of evidence:**
- LOW
- VERY LOW
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 beta2 agonists. This comparison was also subject to a call for unpublished evidence.

One study was identified in the update search that included this comparison\textsuperscript{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)

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations*</th>
<th>Applicability**</th>
<th>Other comments</th>
<th>Incremental(^\d) cost (£)</th>
<th>Incremental(^\d) effects</th>
<th>ICER(^\d)</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Najafzadeh et al (2008) – Canada</td>
<td>Potentially serious limitations(^{xx})</td>
<td>Partially applicable(^{yy})</td>
<td>1 year analysis of resource use and health outcomes (SGRQ – mapped to EQ-5D utility) in Optimal RCT(^{200}) (FEV(_1) &lt;65% predicted).</td>
<td>£665(^{xx})</td>
<td>0.0108 QALYs</td>
<td>£61,574/QALY(^{aaa})</td>
<td>Not reported for this comparison(^{bbb})</td>
</tr>
</tbody>
</table>

*Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable; ICER = incremental cost-effectiveness ratio; \(^{\d}\) 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.

\(^{aaa}\) 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\textsuperscript{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\textsuperscript{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\textsuperscript{221,222}.

7.3.6.3 Long-acting beta\textsubscript{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\textsubscript{2} agonists with monotherapy consisting of either long-acting beta\textsubscript{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\textsubscript{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\textsubscript{2} agonists compared to long-acting beta\textsubscript{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).\textsuperscript{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). 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.
COPD (update)
**Evidence Profile Drug 5a: LAMA + LABA vs. LABA alone**

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


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Limitations</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
</tr>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>serious</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious</td>
</tr>
</tbody>
</table>

**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. 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
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)

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<th>Summary of findings</th>
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</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
</tr>
<tr>
<td>No of patients</td>
<td>Effect</td>
</tr>
</tbody>
</table>

Mean post bronchodilator FEV1 at 1 year (follow-up 1 years; range of scores: -; Better indicated by more)

1 randomised trial very serious¹ no serious inconsistency no serious indirectness no serious imprecision none 276 278 - MD 0.033 (0 to 0.066)³ LOW

Mean post bronchodilator FEV1 at 4 years (follow-up 4 years; range of scores: -; Better indicated by more)

1 randomised trial very serious¹ no serious inconsistency no serious indirectness no serious imprecision none 212 180 - MD 0.020 (-0.025 to 0.066)³ 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 serious¹ no serious inconsistency no serious indirectness serious² none 268 264 - MD -1.899 (-4.046 to 0.247)³ 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)

<table>
<thead>
<tr>
<th></th>
<th>Randomised trial</th>
<th>Very serious</th>
<th>No serious inconsistency</th>
<th>No serious indirectness</th>
<th>No serious imprecision</th>
<th>None</th>
<th>206</th>
<th>172</th>
<th>-</th>
<th>MD -0.326 (-3.255 to 2.604)(^5)</th>
<th>Very Low</th>
</tr>
</thead>
</table>

Number of patients with COPD exacerbations (follow-up 4 years)

<table>
<thead>
<tr>
<th></th>
<th>Randomised trial</th>
<th>Very serious</th>
<th>No serious inconsistency</th>
<th>No serious indirectness</th>
<th>No serious imprecision</th>
<th>None</th>
<th>223/332 (67.2%)</th>
<th>236/346 (68.2%)</th>
<th>HR 0.82 (0.69 to 0.99)(^7)</th>
<th>73 fewer per 1000 (from 4 fewer to 136 fewer)</th>
<th>Very Low</th>
</tr>
</thead>
</table>

Number of patients hospitalised for COPD exacerbations (follow-up 4 years)

<table>
<thead>
<tr>
<th></th>
<th>Randomised trial</th>
<th>Very serious</th>
<th>No serious inconsistency</th>
<th>No serious indirectness</th>
<th>Serious 4</th>
<th>None</th>
<th>86/332 (25.9%)</th>
<th>87/346 (25.1%)</th>
<th>HR 0.95 (0.7 to 1.28)(^4)</th>
<th>11 fewer per 1000 (from 68 fewer to 58 more)</th>
<th>Very Low</th>
</tr>
</thead>
</table>

Mean COPD exacerbations per patient year (expressed as rate ratio) (follow-up 4 years)

<table>
<thead>
<tr>
<th></th>
<th>Randomised trial</th>
<th>Very serious</th>
<th>No serious inconsistency</th>
<th>No serious indirectness</th>
<th>No serious imprecision</th>
<th>None</th>
<th>332 (0.63 [SE 0.05] mean exacerbations/patient year)</th>
<th>346 (0.79 [SE 0.05] mean exacerbations/patient year)</th>
<th>Rate ratio 0.80 (0.66 to 0.97)(^5)</th>
<th>0 fewer per 1000 (from 0 fewer to 0 fewer)</th>
<th>Low</th>
</tr>
</thead>
</table>
### Mean hospitalisations for COPD exacerbations per patient per year (expressed as rate ratio) (follow-up 4 years)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Randomised trial</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>None</th>
<th>Mean hospitalisations/patient year</th>
<th>Rate ratio</th>
<th>10 fewer per 1000 (from 0 fewer to 0 more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Randomised trial</td>
<td>very serious¹</td>
<td>no serious</td>
<td>none</td>
<td>332 (0.14 [SE 0.02] mean hospitalisations/patient year)</td>
<td>0.89 (0.6 to 1.33)¹⁰</td>
<td>0 fewer per 1000 (from 0 fewer to 0 more)</td>
</tr>
</tbody>
</table>

### Mortality (adjudicated on treatment and vital status censoring at 1470 days) (follow-up 1470 days)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Randomised trial</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>None</th>
<th>Mean hospitalisations/patient year</th>
<th>Rate ratio</th>
<th>11 fewer per 1000 (from 58 fewer to 53 more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Randomised trial</td>
<td>very serious¹</td>
<td>no serious</td>
<td>none</td>
<td>53/332 (16%)</td>
<td>0.93 (0.64 to 1.35)¹²</td>
<td>11 fewer per 1000 (from 58 fewer to 53 more)</td>
</tr>
</tbody>
</table>

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 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.

⁹ HR based on Cox regression with treatment, baseline LABA use, and baseline LABA use by treatment interaction as covariates.

¹⁰ 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.

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 FEV₁ (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 FEV₁ 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 Sb) LAMA + LABA vs. LAMA alone

What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta₂ agonists compared to long-acting muscarinic antagonists in the management of people with stable COPD?

Two double blind RCTs\textsuperscript{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 plus placebo (b.i.d. via MDDPI) in adults with stable COPD (N=428; 6 months follow-up).\textsuperscript{178} In the OPTIMAL RCT\textsuperscript{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

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Limitations</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>2</td>
<td>randomised trial</td>
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<td>serious*</td>
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<td>very serious*</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>serious*</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
</tbody>
</table>

* Importance: LOW

**Number of people having exacerbation requiring further treatment**

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of people having exacerbation requiring further treatment</td>
<td>RR 0.95 (0.8 to 1.13)</td>
<td>LOW</td>
</tr>
<tr>
<td>Mean exacerbations per patient year (expressed as rate ratio) (follow-up 1 years)</td>
<td>rate ratio 1.09 (0.84 to 1.4)</td>
<td>LOW</td>
</tr>
<tr>
<td>Number of people Hospitalised for COPD exacerbations (follow-up 6 months)</td>
<td>RR 0.64 (0.16 to 2.65)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>
## Mean hospitalisations for acute exacerbations of COPD per patient year (expressed as rate ratio) (follow-up 1 years)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Randomisation</th>
<th>Blinding</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>N (treatment)</th>
<th>N (comparison)</th>
<th>Rate Ratio</th>
<th>95% CI</th>
<th>Number of Hospitalisations per Patient Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>randomised trial</td>
<td>very serious&lt;sup&gt;5&lt;/sup&gt;</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>None</td>
<td>148 (0.294 mean hospitalisations/patient year)</td>
<td>156 (0.355 mean hospitalisations/patient year)</td>
<td>0.83 (0.54 to 1.27)</td>
<td>0 fewer per 1000 (from 0 fewer to 0 more)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

## 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)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Randomisation</th>
<th>Blinding</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>N (treatment)</th>
<th>N (comparison)</th>
<th>MD</th>
<th>95% CI</th>
<th>Improvement in Health Related Quality of Life at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>randomised trial</td>
<td>very serious&lt;sup&gt;5&lt;/sup&gt;</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>None</td>
<td>148</td>
<td>156</td>
<td>-</td>
<td>MD -1.8 (0 to 0)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>LOW</td>
</tr>
</tbody>
</table>

## Mean difference in TDI score at 1 year (follow-up 1 years; measured with: TDI; range of scores: -; Better indicated by less)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Randomisation</th>
<th>Blinding</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>N (treatment)</th>
<th>N (comparison)</th>
<th>MD</th>
<th>95% CI</th>
<th>Improvement in TDI score at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>randomised trial</td>
<td>serious&lt;sup&gt;8&lt;/sup&gt;</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious&lt;sup&gt;12&lt;/sup&gt;</td>
<td>None</td>
<td>148</td>
<td>156</td>
<td>-</td>
<td>MD -0.38 (-1.28 to 0.52)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

## Difference in FEV1 after 24 weeks treatment (measured 2h post bronchodilator) (follow-up 6 months; range of scores: -; Better indicated by more)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Randomisation</th>
<th>Blinding</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>N (treatment)</th>
<th>N (comparison)</th>
<th>MD</th>
<th>95% CI</th>
<th>Improvement in FEV1 after 24 weeks treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>randomised trial</td>
<td>serious&lt;sup&gt;8&lt;/sup&gt;</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious&lt;sup&gt;12&lt;/sup&gt;</td>
<td>None</td>
<td>207</td>
<td>221</td>
<td>-</td>
<td>MD 0.06 (0 to 0.13)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>LOW</td>
</tr>
</tbody>
</table>

## All-cause mortality (follow-up 1 years)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Randomisation</th>
<th>Blinding</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>N (treatment)</th>
<th>N (comparison)</th>
<th>RR</th>
<th>95% CI</th>
<th>Difference in All-cause Mortality between Treatment and Comparison Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>randomised trial</td>
<td>very serious&lt;sup&gt;5&lt;/sup&gt;</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>very serious&lt;sup&gt;5&lt;/sup&gt;</td>
<td>None</td>
<td>6/148 (4.1%)</td>
<td>4/156 (2.6%)</td>
<td>1.58 (0.46 to 5.49)</td>
<td>15 more per 1000 (from 14 fewer to 117 more)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

## Number of people with pneumonia leading to mechanical ventilation or death (follow-up 1 years)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Randomisation</th>
<th>Blinding</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>N (treatment)</th>
<th>N (comparison)</th>
<th>RR</th>
<th>95% CI</th>
<th>Difference in Number of People with Pneumonia leading to Mechanical Ventilation or Death between Treatment and Comparison Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>randomised trial</td>
<td>very serious&lt;sup&gt;5&lt;/sup&gt;</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>very serious&lt;sup&gt;12&lt;/sup&gt;</td>
<td>None</td>
<td>1/148 (0.7%)</td>
<td>0/156 (0%)</td>
<td>3.16 (0.13 to 0.00)</td>
<td>0 more per 1000 (from 0 fewer to 0</td>
<td>VERY</td>
</tr>
<tr>
<td>Study</td>
<td>Randomised trial</td>
<td>Very serious</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Very serious</td>
<td>None</td>
<td>Number of MI or acute arrhythmia (follow-up 1 year)</td>
<td>RR</td>
<td>1 more per 1000 (from 11 fewer to 83 more)</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>-------</td>
<td>------------------</td>
<td>--------------</td>
<td>--------------------------</td>
<td>------------------------</td>
<td>--------------</td>
<td>------</td>
<td>-----------------------------------------------</td>
<td>-----</td>
<td>-----------------------------------------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>1</td>
<td>Aaron et al; Vogelmeier et al</td>
<td>100%</td>
<td>2/148 (1.4%)</td>
<td>2/156 (1.3%)</td>
<td>None</td>
<td>1 more per 1000 (from 11 fewer to 83 more)</td>
<td>1.05</td>
<td>(0.15 to 7.39)</td>
<td>LOW</td>
<td>76.99%</td>
<td>LOW</td>
</tr>
<tr>
<td>2</td>
<td>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</td>
<td>Very serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1 more per 1000 (from 11 fewer to 83 more)</td>
<td>1.05</td>
<td>(0.15 to 7.39)</td>
<td>LOW</td>
<td>76.99%</td>
<td>LOW</td>
</tr>
<tr>
<td>3</td>
<td>Significant heterogeneity I² = 68%</td>
<td>Very serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1 more per 1000 (from 11 fewer to 83 more)</td>
<td>1.05</td>
<td>(0.15 to 7.39)</td>
<td>LOW</td>
<td>76.99%</td>
<td>LOW</td>
</tr>
<tr>
<td>4</td>
<td>Aaron et al</td>
<td>Very serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1 more per 1000 (from 11 fewer to 83 more)</td>
<td>1.05</td>
<td>(0.15 to 7.39)</td>
<td>LOW</td>
<td>76.99%</td>
<td>LOW</td>
</tr>
<tr>
<td>5</td>
<td>Aaron et al</td>
<td>Very serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1 more per 1000 (from 11 fewer to 83 more)</td>
<td>1.05</td>
<td>(0.15 to 7.39)</td>
<td>LOW</td>
<td>76.99%</td>
<td>LOW</td>
</tr>
<tr>
<td>6</td>
<td>Mean exacerbation/patient year were 1.75 (LABA + tiotropium) versus 1.61 (tiotropium + placebo)</td>
<td>Very serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1 more per 1000 (from 11 fewer to 83 more)</td>
<td>1.05</td>
<td>(0.15 to 7.39)</td>
<td>LOW</td>
<td>76.99%</td>
<td>LOW</td>
</tr>
<tr>
<td>7</td>
<td>Vogelmeier et al</td>
<td>Very serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1 more per 1000 (from 11 fewer to 83 more)</td>
<td>1.05</td>
<td>(0.15 to 7.39)</td>
<td>LOW</td>
<td>76.99%</td>
<td>LOW</td>
</tr>
<tr>
<td>8</td>
<td>Mean hospitalisations for exacerbations per patient year were 0.294 (tiotropium + LABA) versus 0.355 (tiotropium + placebo)</td>
<td>Very serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1 more per 1000 (from 11 fewer to 83 more)</td>
<td>1.05</td>
<td>(0.15 to 7.39)</td>
<td>LOW</td>
<td>76.99%</td>
<td>LOW</td>
</tr>
<tr>
<td>9</td>
<td>Mean change from baseline in SGRQ score was -6.3 points (tiotropium + LABA) versus -4.5 points (tiotropium + placebo); p = 0.02</td>
<td>Very serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1 more per 1000 (from 11 fewer to 83 more)</td>
<td>1.05</td>
<td>(0.15 to 7.39)</td>
<td>LOW</td>
<td>76.99%</td>
<td>LOW</td>
</tr>
<tr>
<td>10</td>
<td>Wide 95% CI that crosses MID twice</td>
<td>Very serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1 more per 1000 (from 11 fewer to 83 more)</td>
<td>1.05</td>
<td>(0.15 to 7.39)</td>
<td>LOW</td>
<td>76.99%</td>
<td>LOW</td>
</tr>
<tr>
<td>11</td>
<td>Change from baseline in SGRQ score was -6.3 points (tiotropium + LABA) versus -4.5 points (tiotropium + placebo); p = 0.02</td>
<td>Very serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1 more per 1000 (from 11 fewer to 83 more)</td>
<td>1.05</td>
<td>(0.15 to 7.39)</td>
<td>LOW</td>
<td>76.99%</td>
<td>LOW</td>
</tr>
<tr>
<td>12</td>
<td>Wide 95% CI that crosses MID</td>
<td>Very serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1 more per 1000 (from 11 fewer to 83 more)</td>
<td>1.05</td>
<td>(0.15 to 7.39)</td>
<td>LOW</td>
<td>76.99%</td>
<td>LOW</td>
</tr>
<tr>
<td>13</td>
<td>p = 0.066; mean FEV; and SD not reported in each group</td>
<td>Very serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1 more per 1000 (from 11 fewer to 83 more)</td>
<td>1.05</td>
<td>(0.15 to 7.39)</td>
<td>LOW</td>
<td>76.99%</td>
<td>LOW</td>
</tr>
</tbody>
</table>
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 FEV₁ 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 beta₂ agonists. This comparison was also subject to a call for unpublished evidence.

One study was identified in the update search that included this comparison. 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)

<table>
<thead>
<tr>
<th>Study</th>
<th>Limitations*</th>
<th>Applicability*</th>
<th>Other comments</th>
<th>Incremental cost (£)</th>
<th>Incremental effects</th>
<th>ICER‡</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Najafzadeh et al (2008) – Canada</td>
<td>Potentially serious limitations†††</td>
<td>Partially applicableddd</td>
<td>1 year analysis of resource use and health outcomes (SGRQ – mapped to EQ-5D utility) in Optimal RCT (FEV$_1$ &lt; 65% predicted)</td>
<td>£66³³³</td>
<td>-0.0052 QALYs⁷⁷⁷⁷⁷</td>
<td>LAMA+LABA dominated by LAMA</td>
<td>One-way sensitivity analysis ICER range dominant to dominated⁸⁸⁸⁸⁸.</td>
</tr>
</tbody>
</table>

*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 Parities⁷⁷⁷.
fff Lower QALYs and increased exacerbations reported
⁸⁸⁸ 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 beta2 agonists compared to long-acting beta2 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 beta2 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\textsuperscript{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 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 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 beta₂ 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 FEV₁, 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 beta₂ 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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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 FEV1 < 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 FEV₁ < 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 FEV₁ < 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 FEV₁ below 60%. There is a greater body of evidence for patients with FEV₁ < 50%, and a suggestion from the post-hoc analysis of the Torch study207 that benefit is most marked in participants with a lower FEV₁ (although differences between severity groups were not significant in this analysis). One combination of LABA+ICS is licensed in people with an FEV₁ 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\textsuperscript{197}, Kardos et al \textsuperscript{223} and INSPIRE\textsuperscript{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\textsubscript{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\textsuperscript{201} from the published UPLIFT RCT\textsuperscript{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\textsuperscript{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\textsuperscript{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 FEV₁ < 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 FEV₁. 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 FEV₁ < 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 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\textsuperscript{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\textsuperscript{178} duration of follow-up was unlikely to highlight any difference in exacerbations. It also noted that although the OPTIMAL RCT\textsuperscript{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)

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.""

NEW 2010 UPDATE RECOMMENDATION 5 (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 FEV₁ ≥ 50% predicted: either long-acting beta₂ agonist (LABA) or LAMA
- if FEV₁ < 50% predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or LAMA.

"" The British National Formulary states that a SAMA should be discontinued when a LAMA is started.

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NEW 2010 UPDATE RECOMMENDATION 6 (U6)

In people with stable COPD and an FEV₁ ≥ 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.

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 FEV₁.

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 FEV₁.

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.

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\textsuperscript{225}, one systematic review\textsuperscript{226} two additional RCTs\textsuperscript{227,228} and one prospective study\textsuperscript{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.\textsuperscript{229} was excluded due to methodological limitations.

Factors for consideration within this topic included small sample sizes (range of N=7 to N=47)\textsuperscript{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)\textsuperscript{226}.

The recent BTS/SIGN guidelines for asthma\textsuperscript{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\textsuperscript{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. 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. 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.

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. The MDI is particularly difficult for those with impaired handgrip strength (common in those with arthritic conditions). The addition of a large-volume spacer improves both acquisition and retention of technique 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.

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, 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. pMDI 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 $\text{FEV}_1$ (difference in change from baseline 70ml, 95% CI; 10 to 130 ml). Respimat is unlicensed in the UK. The effect on change in $\text{FVC}$ was of similar size. There were no differences observed between these two devices for any other reported outcomes.
Using FEV1 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 COPD149.

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.

Handling of DPI was considered easier than the MDI (p=0.014) and the DPI was preferred to the MDI (p<0.001)227.

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 MDI227.

There were no significant differences in quality of life scores from the St George’s questionnaires and the HAD scores228.

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.

Cognitive function and praxis are more important than age in determining the ability of an older patient to use hand held inhalers or nebulisers.
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 FEV₁. IV

Acute changes in lung function are not the most appropriate means of assessing the benefits of nebulised therapy. IV
**Recommendations about Inhalers**

<table>
<thead>
<tr>
<th>R45</th>
<th>In most cases bronchodilator therapy is best administered using a hand-held inhaler device (including a spacer device if appropriate).</th>
<th>Grade D</th>
</tr>
</thead>
<tbody>
<tr>
<td>R46</td>
<td>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.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R47</td>
<td>Inhalers should be prescribed only after patients have received training in the use of the device and have demonstrated satisfactory technique.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R48</td>
<td>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.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R49</td>
<td>Deleted.</td>
<td></td>
</tr>
</tbody>
</table>

**Recommendations about spacers**

<table>
<thead>
<tr>
<th>R50</th>
<th>The spacer should be compatible with the patient’s metered-dose inhaler.</th>
<th>Grade D</th>
</tr>
</thead>
<tbody>
<tr>
<td>R51</td>
<td>It is recommended that spacers are used in the following way:</td>
<td>Grade D</td>
</tr>
<tr>
<td></td>
<td>• the drug is administered by repeated single actuations of the metered-dose inhaler into the spacer, with each followed by inhalation</td>
<td></td>
</tr>
</tbody>
</table>
• 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.

R55 Nebulised therapy should not be prescribed without an assessment of the patient’s and/or carer’s ability to use it. Grade D
A nebuliser system that is known to be efficient should be used. Once available, Comité Européen de Normalisation (European Committee for Standardisation, CEN) data should be used to assess efficiency.

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).

If nebuliser therapy is prescribed, the patient should be provided with equipment, servicing, advice and support.

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. Currently up to 70% of patients with COPD are prescribed an inhaled steroid and approximately 5% are prescribed oral steroids. 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. The primary outcome measure was FEV₁.
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.

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.

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.
**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\(^\text{251}\) but it is generally assumed that they relax airway smooth muscle. Theophylline may also increase diaphragmatic strength in patients with COPD\(^\text{252}\) and have effects on mucociliary clearance\(^\text{253}\). It also has extra pulmonary effects, particularly improvement in cardiac output\(^\text{254}\) that may also be beneficial in patients with COPD. Because of potential toxicity and significant interactions with other drugs\(^\text{255, 256}\) 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\(^\text{257}\), 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)\textsuperscript{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\textsuperscript{257} when the dates range from 1979 to 1995. Rossi et al.\textsuperscript{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 (12\textmu g) 25%, formoterol (24\textmu g) 19%, placebo 27% and theophylline 39\% \textsuperscript{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 FEV₁ and FVC in favour of the theophylline group compared to placebo. FEV₁ WMD 100ml; 95% CI; 40 to 160 ml. FVC WMD 210ml; 95% CI; 100 to 320 ml ²⁵⁷.

Theophylline was also significantly more effective at increasing FEV₁ 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.

There was a statistically significant improvement in oxygen uptake (VO₂ 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.

There was a statistically significant improvement in PaO₂ with treatment. WMD 3.18 mmHg; 95% CI; 1.23 to 5.13 mmHg ²⁵⁷.

There was a statistically significant decrease in PaCO₂ with theophylline compared to placebo. WMD –2.36 mmHg; 95% CI –3.52 to –1.21 mmHg ²⁵⁷.

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.

Nausea was experienced more often in the theophylline
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.

There were no statistically significant differences between the treatment groups for total diary symptom scores or use of rescue medication 163.

No data was available for health status or mortality 257.

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.

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.

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.

Although these drugs are effective, their usefulness is limited by the need to monitor plasma levels and their potential for
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.

**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.

**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.

**R36** The effectiveness of the treatment with theophylline should be assessed by improvements in symptoms, activities of daily living, exercise capacity and lung function.

**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.
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. Ages ranged from 40 to 80 years and with the exception of short-acting beta₂ 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. 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.

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:

**MUO:** 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), FEV1 (100 ml), and TDI (1 unit).

One systematic review was updated with three additional RCTs 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 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 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, beta2 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. 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?


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
</tr>
<tr>
<td>15</td>
<td>Randomised trial</td>
</tr>
<tr>
<td>11</td>
<td>Randomised trial</td>
</tr>
</tbody>
</table>

**Frequency of exacerbation (number of exacerbations per patient per month) (follow-up 0.5 to 3 years; range of scores: -; Better indicated by less)**

- People with no exacerbations in study period (follow-up 0.5 to 3 years)

<table>
<thead>
<tr>
<th>People with no exacerbations in study period (follow-up 0.5 to 3 years)</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of exacerbation (number of exacerbations per patient per month) (follow-up 0.5 to 3 years)</td>
<td>mucolytics</td>
<td>placebo</td>
<td>Relative (95% CI)</td>
</tr>
<tr>
<td>15</td>
<td>Randomised trial</td>
<td>very serious</td>
<td>serious</td>
</tr>
<tr>
<td>11</td>
<td>Randomised trial</td>
<td>very serious</td>
<td>serious</td>
</tr>
</tbody>
</table>
### Number of people hospitalised in the study period (follow-up .66 to 3 years)

<table>
<thead>
<tr>
<th></th>
<th>Randomised trial</th>
<th>Serious²</th>
<th>No serious inconsistency</th>
<th>No serious indirectness</th>
<th>Serious³</th>
<th>No serious imprecision</th>
<th>None</th>
<th>65/335 (19.4%)</th>
<th>88/343 (25.7%)</th>
<th>RR 0.76 (0.57 to 1.01)</th>
<th>62 fewer per 1000 (from 111 fewer to 3 more)</th>
<th>°°°° LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Randomised trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None</td>
<td>571</td>
<td>581</td>
<td>-</td>
<td>-0.57 (-2.1 to 0.95)</td>
<td>°°°° LOW</td>
</tr>
</tbody>
</table>

### 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)

<table>
<thead>
<tr>
<th></th>
<th>Randomised trial</th>
<th>Very serious¹</th>
<th>No serious inconsistency¹⁰</th>
<th>No serious indirectness</th>
<th>No serious imprecision¹¹</th>
<th>None</th>
<th>571</th>
<th>581</th>
<th>-</th>
<th>SMD 0.18 (0.06 to 0.3)</th>
<th>°°°° LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Randomised trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None</td>
<td>875</td>
<td>889</td>
<td>-</td>
<td></td>
<td>°°°° LOW</td>
</tr>
</tbody>
</table>

### FEV1 or % predicted FEV1 or PEFR at end of study (follow-up 0.5 to 3 years; range of scores: -; Better indicated by more)

<table>
<thead>
<tr>
<th></th>
<th>Randomised trial</th>
<th>Very serious¹²</th>
<th>No serious inconsistency</th>
<th>No serious indirectness</th>
<th>No serious imprecision</th>
<th>None</th>
<th>241/1525 (15.8%)</th>
<th>281/1522 (18.5%)</th>
<th>RR 0.86 (0.74 to 1)</th>
<th>26 fewer per 1000 (from 48 fewer to 0 more)</th>
<th>°°°° LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Randomised trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None</td>
<td>11/490 (2.2%)</td>
<td>14/503 (2.8%)</td>
<td>RR 0.82 (0.38 to 1.75)</td>
<td>5 fewer per 1000 (from 17 fewer to 21 more)</td>
<td>°°°° VERY LOW</td>
</tr>
</tbody>
</table>

### Adverse events (follow-up 0.5 to 1 years)

- 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.

### Death (follow-up 0.5 to 3 years)

<table>
<thead>
<tr>
<th></th>
<th>Randomised trial</th>
<th>Very serious¹³</th>
<th>No serious inconsistency</th>
<th>No serious indirectness</th>
<th>Very serious¹⁴</th>
<th>None</th>
<th>11/490 (2.2%)</th>
<th>14/503 (2.8%)</th>
<th>RR 0.82 (0.38 to 1.75)</th>
<th>5 fewer per 1000 (from 17 fewer to 21 more)</th>
<th>°°°° VERY LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Randomised trial</td>
<td></td>
<td></td>
<td></td>
<td>Very serious¹⁴</td>
<td>None</td>
<td>11/490 (2.2%)</td>
<td>14/503 (2.8%)</td>
<td>RR 0.82 (0.38 to 1.75)</td>
<td>5 fewer per 1000 (from 17 fewer to 21 more)</td>
<td>°°°° VERY LOW</td>
</tr>
</tbody>
</table>

² High heterogeneity (I² = 87.7% p <0.00001) that could not be explained.
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.

3 High heterogeneity ($I^2 = 68.3\%$, $p=0.0005$)

4 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.

5 wide 95% CI that crosses MID

6 the larger RCT (Decramer) had dropout rates > 20% and unequal between arms

7 High heterogeneity ($I^2 = 90\%$, $p=0.002$)

8 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.

9 high levels of heterogeneity ($I^2 = 81.5\%$, $p<0.0001$) overall, however, this is explained by stratifying by drug type

10 difficult to assess precision as the outcome is a combination of many different measures of lung function

11 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.

12 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

13 wide 95% CI that crosses MID twice.
Forest Plots:

Mucolytics versus Placebo

Frequency of exacerbations

<table>
<thead>
<tr>
<th>Study or Sub-category</th>
<th>Mucolytic Mean (SD)</th>
<th>Placebo Mean (SD)</th>
<th>WMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>WMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 Non-acetylcysteine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grass 1978</td>
<td>0.14 (0.15)</td>
<td>0.27 (0.21)</td>
<td>0.84 (0.13)</td>
<td>95.4%</td>
<td>-0.12 (-0.22, -0.04)</td>
</tr>
<tr>
<td>Debbie 1986</td>
<td>0.13 (0.14)</td>
<td>0.30 (0.26)</td>
<td>3.79 (0.20)</td>
<td>90.0%</td>
<td>-0.24 (-0.34, -0.14)</td>
</tr>
<tr>
<td>Borgie 1988</td>
<td>0.13 (0.13)</td>
<td>0.26 (0.17)</td>
<td>0.42 (0.10)</td>
<td>88.8%</td>
<td>-0.22 (0.02, 0.24)</td>
</tr>
<tr>
<td>Ronco 1983</td>
<td>0.25 (0.27)</td>
<td>0.36 (0.25)</td>
<td>1.62 (0.15)</td>
<td>85.5%</td>
<td>-0.12 (-0.25, -0.00)</td>
</tr>
<tr>
<td>Medit 1986</td>
<td>0.15 (0.13)</td>
<td>0.20 (0.19)</td>
<td>2.56 (0.05)</td>
<td>81.4%</td>
<td>-0.10 (-0.20, -0.00)</td>
</tr>
<tr>
<td>Bink 1987</td>
<td>0.21 (0.13)</td>
<td>0.21 (0.21)</td>
<td>4.17 (0.03)</td>
<td>76.9%</td>
<td>-0.07 (0.00, 0.02)</td>
</tr>
<tr>
<td>Retzmann 1988</td>
<td>0.13 (0.21)</td>
<td>0.26 (0.04)</td>
<td>0.92 (0.02)</td>
<td>75.9%</td>
<td>0.03 (0.07, 0.00)</td>
</tr>
<tr>
<td>Nowak 1989</td>
<td>0.03 (0.16)</td>
<td>0.02 (0.16)</td>
<td>13.40 (0.03)</td>
<td>69.8%</td>
<td>-0.05 (-0.10, -0.00)</td>
</tr>
<tr>
<td>Pea 1991</td>
<td>0.17 (0.18)</td>
<td>0.29 (0.11)</td>
<td>0.98 (0.12)</td>
<td>62.1%</td>
<td>-0.25 (-0.35, -0.15)</td>
</tr>
<tr>
<td>Dommesen 2005</td>
<td>0.25 (0.44)</td>
<td>0.27 (0.56)</td>
<td>11.40 (0.01)</td>
<td>56.7%</td>
<td>-0.03 (-0.05, 0.01)</td>
</tr>
<tr>
<td>Steimer 2006</td>
<td>0.09 (0.10)</td>
<td>0.09 (0.10)</td>
<td>11.52 (0.02)</td>
<td>50.8%</td>
<td>-0.04 (0.00, 0.00)</td>
</tr>
<tr>
<td>Summary (Q5 CI)</td>
<td>0.86 (0.10)</td>
<td>0.63 (0.05)</td>
<td>50.99 (0.03)</td>
<td>90.4%</td>
<td>-0.04 (0.00, 0.00)</td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 14.69, df = 10 (P = 0.00001), P = 90.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.69 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Q2 Carbocysteine

<table>
<thead>
<tr>
<th>Study or Sub-category</th>
<th>Mucolytic Mean (SD)</th>
<th>Placebo Mean (SD)</th>
<th>WMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>WMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 Carbocysteine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Griffith 1995</td>
<td>0.10 (0.20)</td>
<td>0.12 (0.03)</td>
<td>0.15 (0.03)</td>
<td>95.5%</td>
<td>-0.06 (-0.16, 0.00)</td>
</tr>
<tr>
<td>Diggle 1996</td>
<td>0.07 (0.11)</td>
<td>0.11 (0.14)</td>
<td>11.42 (0.04)</td>
<td>97.7%</td>
<td>-0.06 (-0.16, -0.02)</td>
</tr>
<tr>
<td>Zheng 2008</td>
<td>0.09 (0.09)</td>
<td>0.11 (0.09)</td>
<td>55.61 (0.03)</td>
<td>97.7%</td>
<td>-0.04 (-0.06, -0.02)</td>
</tr>
<tr>
<td>Summary (Q5 CI)</td>
<td>0.10 (0.20)</td>
<td>0.11 (0.09)</td>
<td>46.93 (0.03)</td>
<td>97.7%</td>
<td>-0.04 (-0.06, -0.02)</td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 0.53, df = 1 (P = 0.47), P = 9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.50 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Q3 Endotisine

<table>
<thead>
<tr>
<th>Study or Sub-category</th>
<th>Mucolytic Mean (SD)</th>
<th>Placebo Mean (SD)</th>
<th>WMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>WMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 Endotisine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kornett 2009</td>
<td>0.12 (0.14)</td>
<td>0.17 (0.17)</td>
<td>2.08 (0.05)</td>
<td>99.4%</td>
<td>-0.10 (0.00, 0.00)</td>
</tr>
<tr>
<td>Summary (Q5 CI)</td>
<td>0.12 (0.14)</td>
<td>0.17 (0.17)</td>
<td>2.08 (0.05)</td>
<td>99.4%</td>
<td>-0.10 (0.00, 0.00)</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.78 (P = 0.07)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (Q5 CI) 2016

<table>
<thead>
<tr>
<th>Study or Sub-category</th>
<th>Mucolytic Mean (SD)</th>
<th>Placebo Mean (SD)</th>
<th>WMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>WMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 Mucolytics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.25 (0.09)</td>
<td>0.26 (0.09)</td>
<td>100.00 (0.00)</td>
<td>100.0%</td>
<td>-0.04 (-0.06, -0.02)</td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 105.09, df = 12 (P = 0.00001), P = 100.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.25 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Number of people with no exacerbations

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Mucolyc</th>
<th>Placebo</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 N-acetylcycteine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grassi 1978</td>
<td>10/35</td>
<td>11/34</td>
<td></td>
<td>2.25</td>
<td>1.69 [0.99, 2.88]</td>
</tr>
<tr>
<td>Elgina 1980</td>
<td>134/254</td>
<td>153/241</td>
<td></td>
<td>14.66</td>
<td>2.19 [1.70, 2.82]</td>
</tr>
<tr>
<td>Ippolito 1983</td>
<td>7/10</td>
<td>4/7</td>
<td></td>
<td>1.04</td>
<td>1.58 [0.66, 3.63]</td>
</tr>
<tr>
<td>Domini 1983</td>
<td>45/58</td>
<td>29/105</td>
<td></td>
<td>6.69</td>
<td>1.70 [1.17, 2.47]</td>
</tr>
<tr>
<td>Meader 1988</td>
<td>37/90</td>
<td>34/91</td>
<td></td>
<td>0.82</td>
<td>1.10 [0.77, 1.56]</td>
</tr>
<tr>
<td>Rannitski 1989</td>
<td>29/44</td>
<td>24/47</td>
<td></td>
<td>5.71</td>
<td>1.25 [0.97, 1.64]</td>
</tr>
<tr>
<td>Norwak 1995</td>
<td>114/147</td>
<td>101/148</td>
<td></td>
<td>24.77</td>
<td>1.14 [0.98, 1.31]</td>
</tr>
<tr>
<td>Peda 1999</td>
<td>37/83</td>
<td>17/80</td>
<td></td>
<td>4.28</td>
<td>2.18 [1.25, 3.41]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>341</td>
<td>286</td>
<td></td>
<td>68.98</td>
<td>1.61 [1.38, 1.88]</td>
</tr>
<tr>
<td><strong>Total events</strong>: 421 (Mucolyc), 270 (Placebo)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 31.61$, df = 7 ($P = 0.0001$), $I^2 = 76.3%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 7.37$ ($P &lt; 0.00001$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **02 Carboxylate** |         |         |                   |          |                   |
| Corliss 1986         | 36/55   | 28/56   |                   | 7.07     | 1.23 [0.99, 1.56] |
| Jilnson 1998         | 0.01/0.02 | 39/101  |                   | 21.20    | 1.32 [1.10, 1.59] |
| Subtotal (95% CI)    | 225     | 236     |                   | 28.05    | 1.30 [1.11, 1.52] |
| **Total events**: 146 (Mucolyc), 118 (Placebo)** |
| Test for heterogeneity: $\chi^2 = 0.01$, df = 1 ($P = 0.72$), $I^2 = 0\%$ |
| Test for overall effect: $Z = 3.20$ ($P = 0.001$) |

| **03 Endosolene** |         |         |                   |          |                   |
| Moretti 2004         | 26/63   | 13/61   |                   | 3.25     | 1.94 [1.10, 3.41] |
| Subtotal (95% CI)    | 63      | 61      |                   | 3.25     | 1.94 [1.10, 3.41] |
| **Total events**: 23 (Mucolyc), 13 (Placebo)** |
| Test for heterogeneity: not applicable |
| Test for overall effect: $Z = 2.29$ ($P = 0.02$) |

**Total (95% CI)**

| Total events: 583 (Mucolyc), 400 (Placebo)** |
| Test for heterogeneity: $\chi^2 = 31.57$, df = 10 ($P = 0.0006$), $I^2 = 68.3\%$ |
| Test for overall effect: $Z = 8.31$ ($P < 0.00001$) |
### FEV₁ or % predicted FEV₁ or PEFR at study end

**Review:** Mucolytics 070809 (Version 02)
**Comparison:** 01 mucolytic vs. placebo
**Outcome:** 01 FEV₁ or % predicted FEV₁ or PEFR at end of study

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mucolytic Mean (SD)</th>
<th>N</th>
<th>Placebo Mean (SD)</th>
<th>SMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>SMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 N-acetylcysteine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boccon 1980</td>
<td>224</td>
<td>2.25 (1.00)</td>
<td>224</td>
<td>2.23 (0.60)</td>
<td>-0.02 (0.44)</td>
<td>1.78</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Bongio 1991</td>
<td>10</td>
<td>3.54 (0.50)</td>
<td>9</td>
<td>3.05 (1.14)</td>
<td>-0.19 (0.37)</td>
<td>77.56</td>
<td>0.52 [-0.40, 1.44]</td>
</tr>
<tr>
<td>Bower 1983</td>
<td>52</td>
<td>77.60 (0.50)</td>
<td>52</td>
<td>77.50 (0.50)</td>
<td>-0.00 (0.44)</td>
<td>1.78</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Novell 1992</td>
<td>33</td>
<td>56.30 (1.00)</td>
<td>37</td>
<td>56.10 (0.60)</td>
<td>-0.07 (0.31)</td>
<td>77.56</td>
<td>0.52 [-0.40, 1.44]</td>
</tr>
<tr>
<td>Peix 1992</td>
<td>92</td>
<td>1.82 (0.29)</td>
<td>80</td>
<td>1.50 (0.55)</td>
<td>0.20 (0.37)</td>
<td>15.15</td>
<td>0.10 [-0.17, 0.44]</td>
</tr>
<tr>
<td>Drescher 2005</td>
<td>267</td>
<td>1.60 (0.48)</td>
<td>257</td>
<td>1.60 (0.39)</td>
<td>0.00 (0.17)</td>
<td>51.29</td>
<td>0.00 [-0.17, 0.17]</td>
</tr>
<tr>
<td>Buchon 2007</td>
<td>96</td>
<td>56.40 (1.40)</td>
<td>88</td>
<td>55.20 (7.80)</td>
<td>0.73 (0.31)</td>
<td>76.40</td>
<td>0.36 [-0.05, 0.20]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>77.56</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 3.98, df = 3 (P = 0.68), P = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.85 (P = 0.39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 02 Carbocysteine       |     |                     |     |                   |                     |          |                   |
| On Beige 1985          | 54  | 272.00 (127.00)     | 54  | 252.00 (82.00)    | 0.75 (0.43)         | 16.65    | 0.17 [-0.21, 0.55]|
| Subtotal (95% CI)      | 84  | 84                  | 84  |                   |                     | 16.65    | 0.17 [-0.21, 0.55]|
| Test for heterogeneity: not applicable |
| Test for overall effect: Z = 0.89 (P = 0.37) |

| 03 Bromhexine          |     |                     |     |                   |                     |          |                   |
| Meroni 2004            | 63  | 1.84 (0.32)         | 61  | 1.51 (0.28)       | 0.33 (0.47)         | 10.55    | 1.09 [0.71, 1.47] |
| Subtotal (95% CI)      | 63  | 63                  | 63  |                   |                     | 10.55    | 1.09 [0.71, 1.47] |
| Test for heterogeneity: not applicable |
| Test for overall effect: Z = 6.66 (P = 0.00001) |

| Total (95% CI)         | 872 | 872                 | 872 |                   |                     | 106.60   | 0.10 [0.06, 0.20] |
| Test for heterogeneity: Chi² = 27.69, df = 6 (P = 0.00001), P = 01.0% |
| Test for overall effect: Z = 2.00 (P = 0.04) |
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\textsubscript{1}, % predicted FEV\textsubscript{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.\textsuperscript{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\textsuperscript{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.

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

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>R94</td>
<td>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).</td>
<td>B</td>
</tr>
<tr>
<td>R95</td>
<td>Mucolytic therapy should be continued if there is symptomatic improvement (for example, reduction in frequency of cough and sputum production).</td>
<td>D</td>
</tr>
<tr>
<td>U10</td>
<td><strong>NEW 2010 UPDATE RECOMMENDATION 10 (U10)</strong>  Do not routinely use mucolytic drugs to prevent exacerbations in people with stable COPD.</td>
<td></td>
</tr>
</tbody>
</table>

### 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.
COPD (update)

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 beta2 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.

Neither of the antioxidant supplements had a statistically significant effect on the risk of being admitted to hospital due to a COPD diagnosis 276.
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 and 1 Polish observational study.

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, Moguisteine vs. codeine, Moguisteine vs. Dextromethorphan and Moguisteine vs. placebo.

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\(^{284,298-305}\).
COPD (update)

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)$^{306}$. 
Patients in the salmeterol/theophylline combination group experienced significantly more symptom-free days ($p = 0.023$) compared with the theophylline group $^{306}$.

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 $^{306}$.

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 $^{306}$.

Salmeterol/theophylline combination group experienced significantly greater improvements in dyspnoea (TDI) scores) compared with either the salmeterol alone group or theophylline alone group $^{306}$.

During the study by Zu Wallack et al. $^{306}$, each treatment group experienced significant improvements compared with baseline in overall CRDQ scores.

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).

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 gastrointestinal (GI) events (p<0.042).

7.5.2 Anticholinergics and theophylline

One randomised, double-blind, placebo-controlled parallel trial; Bellia 2002 (n = 236) and 1 randomised, double-blind crossover trial; Nishimura 1995 (n = 24).

Evidence statements on combinations of anticholinergics and theophylline

Although FEV₁ 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.

Without inhalation of bronchodilators, FEV₁ was significantly lower.
During ipratropium/salbutamol combination compared with ipratropium/salbutamol/theophylline combination (p<0.01) \(^{308}\).

At 15 and 60 minutes after inhalation of salbutamol, 400 ug the FEV\(_1\) was significantly lower during ipratropium/salbutamol combination compared with ipratropium/salbutamol/theophylline combination (p<0.01) \(^{308}\).

At 15 and 60 minutes after inhalation of ipratropium 80 ug, 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 \(^{308}\).

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 \(^{307}\).

No significant alteration of cough, sputum, wheezing, and shortness of breath was observed throughout the different phases of treatment \(^{308}\).

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 \(^{307}\).

Both pre-inhalation and post-inhalation values of daily PEFR were
significantly higher during the ipratropium/salbutamol/theophylline combination period than during the ipratropium/salbutamol period (p<0.01).\textsuperscript{308}

Total \textit{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.\textsuperscript{307}

The proportion of patients reporting treatment-related \textit{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.\textsuperscript{307}

Sixteen patients (67%) complained of gastrointestinal side effects while receiving ipratropium/salbutamol/theophylline and 10 patients (42%) reported similar effects during ipratropium/salbutamol administration.\textsuperscript{308} 

\textbf{GDG consensus statements}

\begin{itemize}
  \item 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. \textsuperscript{IV}
  \item 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. \textsuperscript{IV}
\end{itemize}
COPD (update)

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*
- beta₂ 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 PaO₂ 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. 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.

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.”

“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.”

“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.”
“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. Data from the NOTT trial also showed that the benefits of LTOT were present in relatively normocapnic patients. 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.”

“In COPD patients considered for LTOT, the FEV₁ should normally be less than 1.5 litres, or less than 40% of predicted normal values. The presence of arterial hypoxaemia with a higher FEV₁ 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 PaO₂ above 8 kPa.”

**Evidence statements on provision of LTOT**

Oxygen concentrators are currently the most convenient and economical method of providing domiciliary long term oxygen therapy.

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.
Health economic evidence

One study was found which was a cost minimization analysis of providing oxygen by concentrator or cylinder in the home\textsuperscript{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 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

R\textsuperscript{59} Clinicians should be aware that inappropriate oxygen therapy in people with COPD may cause respiratory depression. Grade C

R\textsuperscript{60} LTOT is indicated in patients with COPD who have a PaO\textsubscript{2} less than 7.3 kPa when stable or a PaO\textsubscript{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\textsubscript{2}] less than 90\% for more than 30\% of the time), peripheral oedema or pulmonary hypertension. Grade A

R\textsuperscript{61} 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
The need for oxygen therapy should be assessed in:

- all patients with **very severe** airflow obstruction (FEV₁ < 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 (FEV₁ 30-49% predicted).

To ensure all patients eligible for LTOT are identified, pulse oximetry should be available in all healthcare settings.

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.

Patients receiving LTOT should be reviewed at least once per year by practitioners familiar with LTOT and this review should include pulse oximetry.

Oxygen concentrators should be used to provide the fixed supply at home for long-term oxygen therapy.

Patients should be warned about the risks of fire and explosion if they continue to smoke when prescribed oxygen.
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).

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\textsuperscript{309}.

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.

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\textsuperscript{318} (N=41) suggested benefits in health status.

In a small number of appropriately assessed patients who show desaturation on exercise, ambulatory oxygen therapy improves exercise capacity in patients with COPD.

Overall, in patients who have not undergone such an assessment, evidence available to date\textsuperscript{171, 319} does not allow any firm conclusions to be drawn concerning the effectiveness of ambulatory oxygen therapy in patients with COPD.

Most of the devices for the provision of ambulatory oxygen therapy are not currently available on prescription.

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.

The technology for the provision of ambulatory oxygen is developing rapidly.

**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\textsuperscript{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.  

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.

R70 Ambulatory oxygen therapy is not recommended in COPD if \( \text{PaO}_2 \) is greater than 7.3 kPa and there is no exercise desaturation.

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.

R72 Small light-weight cylinders, oxygen-conserving devices and portable liquid oxygen systems should be available for the treatment of patients with COPD.

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
7.6.3 Short-burst oxygen therapy

Short-burst oxygen therapy is widely prescribed 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 than 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.

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.

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.

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.
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. NIV may also improve sleep time and efficiency 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.

One systematic review was found 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 (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 PaCO₂ during oxygen breathing.

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).
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.

Hospital admissions were not significantly different between groups during follow-up.

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.
COPD (update)

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, but could not predict the degree of hypertension and considerable inter observer variation in its measurement has been reported.

Detection of right ventricular hypertrophy on ECG is specific but not sensitive.
Echocardiography can be used to assess Ppa non-invasively\textsuperscript{333}. IV

Examinations are technically inadequate because of hyperinflation in up to 35% of patients\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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).

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.

MRI scanning and radionuclide ventriculography are the most accurate ways of measuring right ventricular function in patients with COPD.

Chest radiography cannot be relied upon to identify pulmonary hypertension in COPD.

**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.

**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.
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\textsuperscript{310}. \(\text{Ib}\)

Oxygen reduces the abnormal rise in Ppa seen during exercise\textsuperscript{312} and prevents the fall in right ventricular ejection fraction\textsuperscript{339}. \(\text{IIa}\)

ACE Inhibitors

One study was found on the use of an ACE inhibitor\textsuperscript{340} and one study on the use of an angiotensin receptor antagonist\textsuperscript{341} in pulmonary hypertension but there were methodological limitations with these studies such that it was not possible to formulate any evidence statements. \(\text{N/A}\)
Calcium channel blockers

Two studies, one of 18 months duration\textsuperscript{342} and one of 3 months duration\textsuperscript{342} failed to show benefits of nifedipine.

Alpha-blockers

Alpha-blockers reduce pain in patients with COPD but their use is limited by their side-effects\textsuperscript{344-346}.

Digoxin

Studies of the effects of digoxin have failed to show any benefit in cor pulmonale unless there was co-existent left ventricular failure\textsuperscript{347-349}.

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.
**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.  

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, ACCP Evidence-Based Guidelines, BTS Statement and a meta-analysis 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 FEV₁ 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)\(^\text{351}\).

Pulmonary rehabilitation reduces dyspnoea\(^\text{350,351}\).\(^{\text{IV & ia}}\)

A single study (n=119) using the Centres for Epidemiologic Studies Depression Scale (CES-D) showed that there was no effect on depression\(^\text{353}\).\(^{\text{lb}}\)

The ACCP evidence-based guideline\(^\text{351}\) 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.\(^{\text{Ia}}\)

The GDG was aware of one RCT\(^\text{354}\) (n=200) contained within the Lacasse systematic review\(^\text{355}\), which found no difference between the rehabilitation and control groups in the number of hospitalisations.\(^{\text{lb}}\)

There was conflicting evidence regarding the number of days spent in hospital.\(^{\text{Ib}}\)

Griffiths et al.\(^\text{354}\) 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.\(^{\text{lb}}\)
However Ries et al.\textsuperscript{356} in a smaller RCT (n=119) found that duration of hospital stay was non significant.

In relation to the outcome of primary care consultations, Griffiths et al.\textsuperscript{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).

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\textsuperscript{357}.

**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\textsuperscript{358}. Griffiths et al\textsuperscript{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\textsuperscript{359}.

There is good evidence that pulmonary rehabilitation is cost effective in the outpatient setting compared to usual care\textsuperscript{359}. 

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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.

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. 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.

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.

Two meta analyses were found of respiratory muscle training, which demonstrate conflicting findings.
The Smith\textsuperscript{360} meta-analysis of 17 RCTs demonstrated no significant findings for FEV\textsubscript{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.

Lotters\textsuperscript{361} updated the work in this area and includes five of the studies that had previously been included in the Smith\textsuperscript{360} meta-analysis.

Lotters\textsuperscript{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.

A single centre study\textsuperscript{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.

The BTS statement on pulmonary rehabilitation\textsuperscript{350} provides an evidence update to the ACCP guidelines\textsuperscript{351} and concludes that pulmonary rehabilitation is effective in all settings including hospital inpatient, hospital outpatient, the community, and possibly the home.
Puente-Maestu \textsuperscript{363} undertook a small (n=41) RCT comparing the effects of \textit{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.

A single centre study\textsuperscript{364} compared \textit{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).

**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.

The GDG concluded that the evidence regarding prolonged supervised outpatient programmes showed very modest benefits and that such programmes were unrealistic.

The COPD GDG augmented the BTS statement with the following italicised consensus addition:

In relation to \textit{duration of the initial programme}, and taking in to account current evidence (cited in\textsuperscript{350}) the GDG believe that outpatient programmes should contain a minimum of 6 weeks \textit{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.

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\(^{350}\).

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\(^{350}\).

The only issues material to selection are poor motivation and the logistical factors of **geography**, **transport**, **equipment usage**, and the **group composition**\(^{350}\).
GDG consensus statements

The COPD GDG augmented the BTS statement\textsuperscript{350} with the following italicised consensus addition:

Rehabilitation should be considered at all stages of disease progression when symptoms \textit{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).

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\textsuperscript{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.
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), FEV₁ (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

<table>
<thead>
<tr>
<th>Included trials</th>
<th>Follow up</th>
<th>N</th>
<th>Rehabilitation details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behnke 2000</td>
<td>18 months</td>
<td>26</td>
<td>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</td>
</tr>
<tr>
<td>Kirsten 1998</td>
<td>11 days</td>
<td>29</td>
<td>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</td>
</tr>
<tr>
<td>Nava 1998</td>
<td>6 weeks</td>
<td>80</td>
<td>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</td>
</tr>
<tr>
<td>Eaton 2009</td>
<td>3 months</td>
<td>97</td>
<td>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</td>
</tr>
<tr>
<td>Study</td>
<td>Duration</td>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Mann 2004</td>
<td>3 months</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Murphy 2005</td>
<td>6 months</td>
<td>Outpatient rehab initiated immediately after discharge from hospital consisting of twice weekly supervised exercise sessions in their homes for 6 weeks</td>
<td></td>
</tr>
</tbody>
</table>
**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:**


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Limitations</td>
</tr>
<tr>
<td>No of patients</td>
<td>Effect</td>
<td>Quality</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>randomised trial</td>
<td>very serious⁴</td>
</tr>
<tr>
<td>Mortality (follow-up 6 weeks -18 months)</td>
<td>3</td>
<td>randomised trial</td>
</tr>
<tr>
<td>Exacerbations (follow-up 6-18 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2  randomised trial</td>
<td>very serious</td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td>Health-related quality of life (follow-up 3-6 months; measured with: SGRQ; range of scores: ; Better indicated by less)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2  randomised trial</td>
<td>very serious</td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3  randomised trial</td>
<td>very serious</td>
<td>serious</td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4  randomised trial</td>
<td>very serious</td>
<td>serious</td>
</tr>
<tr>
<td>Change from baseline in shuttle walk test (follow-up 3-6 months; range of scores: ; Better indicated by more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2  randomised trial</td>
<td>very serious</td>
<td>no serious inconsistency</td>
</tr>
</tbody>
</table>

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

1 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

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

5 high heterogeneity (I² = 97%) that cannot be explained

10 wide 95% CI that crosses MID
Forest Plots

Readmission

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>early pulmonary rehab</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.1.1 Rehab initiated in-hospital (inpatient)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behnke 2000</td>
<td>3</td>
<td>14</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Eaton 2009</td>
<td>11</td>
<td>47</td>
<td>16</td>
<td>50</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>61</td>
<td>62</td>
<td>60.1%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>14</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: (\chi^2 = 2.20, \text{df} = 1 \ (P = 0.14); I^2 = 55%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: (Z = 2.09 \ (P = 0.04))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.2 Rehab initiated after discharge (outpatient)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Man 2004</td>
<td>2</td>
<td>20</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Murphy 2005</td>
<td>2</td>
<td>13</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>33</td>
<td>34</td>
<td>39.9%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>4</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: (\chi^2 = 0.68, \text{df} = 1 \ (P = 0.41); I^2 = 0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: (Z = 2.82 \ (P = 0.005))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>94</td>
<td>96</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>18</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: (\chi^2 = 4.75, \text{df} = 3 \ (P = 0.19); I^2 = 37%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: (Z = 3.45 \ (P = 0.0006))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Change in SGRQ

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man 2004</td>
<td>-12.70</td>
<td>3.93</td>
<td>60.1%</td>
<td>[-20.40, -5.00]</td>
</tr>
<tr>
<td>Murphy 2005</td>
<td>-8.80</td>
<td>4.82</td>
<td>39.9%</td>
<td>[-18.25, 0.65]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>-11.14</td>
<td>100.0%</td>
<td></td>
<td>[-17.11, -5.17]</td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 0.39, \text{ df} = 1 (P = 0.53); I^2 = 0\%

Test for overall effect: \( Z = 3.66 \) (\( P = 0.0003 \))
Change from baseline in 6 minute walk test

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>SE</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Fixed, 95% CI</td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>1.5.1 Rehab initiated in hospital (inpatient)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behnke 2000</td>
<td>215</td>
<td>28</td>
<td>24.0%</td>
<td>215.00 [160.12, 269.88]</td>
<td></td>
</tr>
<tr>
<td>Kirsten 1998</td>
<td>158</td>
<td>28</td>
<td>24.0%</td>
<td>158.00 [103.12, 212.88]</td>
<td></td>
</tr>
<tr>
<td>Nava 1998</td>
<td>68</td>
<td>19</td>
<td>52.1%</td>
<td>68.00 [30.76, 105.24]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>124.81 [97.94, 151.68]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 20.72, df = 2 (P &lt; 0.0001); I² = 90%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 9.10 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5.2 Inpatient rehab only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kirsten 1998</td>
<td>158</td>
<td>28</td>
<td>31.5%</td>
<td>158.00 [103.12, 212.88]</td>
<td></td>
</tr>
<tr>
<td>Nava 1998</td>
<td>68</td>
<td>19</td>
<td>68.5%</td>
<td>68.00 [30.76, 105.24]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>96.38 [65.56, 127.19]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 7.07, df = 1 (P = 0.008); I² = 86%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 6.13 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5.3 Inpatient rehab followed by outpatient rehab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behnke 2000</td>
<td>215</td>
<td>28</td>
<td>100.0%</td>
<td>215.00 [160.12, 269.88]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>215.00 [160.12, 269.88]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 7.68 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 13.65, df = 2 (P = 0.001), I² = 85.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Mean difference between groups in six minute walk test at end of follow-up

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>early pulmonary rehab</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>1.6.1 Rehab initiated in hospital (inpatient)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behnke 2000</td>
<td>480</td>
<td>40</td>
<td>15</td>
<td>230</td>
</tr>
<tr>
<td>Eaton 2009</td>
<td>334</td>
<td>119</td>
<td>47</td>
<td>313</td>
</tr>
<tr>
<td>Kirsten 1998</td>
<td>420</td>
<td>42</td>
<td>14</td>
<td>255</td>
</tr>
<tr>
<td>Nava 1998</td>
<td>220</td>
<td>110</td>
<td>60</td>
<td>140</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>136</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 87.84, \text{df} = 3 \) (\( P < 0.00001 \)); \( I^2 = 97\%

Test for overall effect: \( Z = 21.35 \) (\( P < 0.00001 \))

1.6.2 inpatient rehab only

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirsten 1998</td>
<td>420</td>
<td>42</td>
<td>14</td>
<td>255</td>
<td>27</td>
<td>15</td>
<td>74.9%</td>
<td>165.00 [139.10, 190.90]</td>
</tr>
<tr>
<td>Nava 1998</td>
<td>220</td>
<td>110</td>
<td>60</td>
<td>140</td>
<td>80</td>
<td>20</td>
<td>25.1%</td>
<td>80.00 [35.23, 124.77]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>74</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 10.38, \text{df} = 1 \) (\( P = 0.001 \)); \( I^2 = 90\%

Test for overall effect: \( Z = 12.56 \) (\( P < 0.00001 \))

1.6.3 inpatient rehab followed by outpatient rehab

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behnke 2000</td>
<td>480</td>
<td>40</td>
<td>15</td>
<td>230</td>
<td>30</td>
<td>15</td>
<td>79.7%</td>
<td>250.00 [224.70, 275.30]</td>
</tr>
<tr>
<td>Eaton 2009</td>
<td>334</td>
<td>119</td>
<td>47</td>
<td>313</td>
<td>126</td>
<td>45</td>
<td>20.3%</td>
<td>21.00 [-29.13, 71.13]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>62</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 63.89, \text{df} = 1 \) (\( P < 0.00001 \)); \( I^2 = 98\%

Test for overall effect: \( Z = 17.66 \) (\( P < 0.00001 \))
## Change from baseline in shuttle walk test

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>SE</th>
<th>Weight</th>
<th>95% CI</th>
<th>Mean Difference</th>
<th>SE</th>
<th>Weight</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8.1 Rehab initiated after hospital discharge (outpatient)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Man 2004</td>
<td>74</td>
<td>21</td>
<td>67.1%</td>
<td>74.00 [32.84, 115.16]</td>
<td>96</td>
<td>30</td>
<td>32.9%</td>
<td>96.00 [37.20, 154.80]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>81.23 [47.52, 114.95]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>81.23 [47.52, 114.95]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 4.72 (P < 0.00001)

Test for subgroup differences: Not applicable
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 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 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 in the Eaton et al RCT, 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 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 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

<table>
<thead>
<tr>
<th>R83</th>
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<tbody>
<tr>
<td><strong>NEW 2010 UPDATE RECOMMENDATION 11 (U11)</strong></td>
<td>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.</td>
</tr>
<tr>
<td>R84</td>
<td>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</td>
</tr>
<tr>
<td>R85</td>
<td>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</td>
</tr>
<tr>
<td>R86</td>
<td>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</td>
</tr>
<tr>
<td>R87</td>
<td>Patients should be made aware of the benefits of pulmonary rehabilitation and the commitment required to gain these. Grade D</td>
</tr>
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</table>
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\textsuperscript{376} but clinical experience with these drugs is limited.

Since publication of the 2004 COPD guideline NICE have replaced:

TA67 Flu prevention – amantadine and oseltamivir with TA158

TA58 Flu treatment – zanamivir (review) amantadine and oseltamivir with TA168

Influenza

One systematic review was identified\textsuperscript{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\textsuperscript{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


A systematic review and economic decision modelling for the prevention and treatment of influenza A and B\textsuperscript{380} underpins the NICE TAG, No 58\textsuperscript{376}.
COPD (update)

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 176.

Pneumococcal vaccination

Two retrospective cohort studies were found381,382, 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 identified384 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. 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).

There was no difference in the number of hospitalisations for all respiratory conditions between the two groups.

There was a 70% reduction in risk for death (Adjusted odds ratio, 0.30; p<0.001) in the vaccinated patients.

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.

Treatment of influenza

Italics represent direct quotes from the Technology Appraisal Guidance No. 58:

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: -0.97 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.”
subgroup."

“There is some evidence that treatment with oseltamivir treatment for influenza reduces complications. In an overlapping set of trials 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:

- 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. 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:

- 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. 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 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.

**R89** Deleted.

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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. 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\textsuperscript{387}. This identified 2 RCTs and two additional RCTs were found\textsuperscript{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 \textsuperscript{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 \textsuperscript{390}. There are other case series comparing LVRS with transplantation \textsuperscript{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 \textsuperscript{393}. Outcomes from individual transplant centres have been reported as case series \textsuperscript{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 \textsuperscript{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.

Study of serial CXR is helpful in judging whether the collapse of normal lung surrounding bullae is responsible for the patient’s functional state.

The size of bullae, the presence of emphysema in the non-bullous lung and the amount of collapse are best assessed by CT.

Pulmonary function (FEV₁, 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.

Other predictors of a successful outcome are a large volume of sequestered gas, a reasonably preserved TlCO and a normal PaCO₂.

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%.
One third to one half of the patients appeared to maintain improvement in pulmonary function for about 5 years.

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 $82 \text{ ml/yr}$; 5 of the 9 still maintained some of their postoperative improvement.

Among 11 patients operated on for bullous disease 4 to 20 years earlier, $FEV_1$ (prebronchodilator) and $TlCO$ declined more rapidly in 6 smokers than in 5 ex-smokers ($p<0.05$), suggesting the great importance of smoking cessation after surgery.

In general, resection of giant bullae does not seem to affect the size of other bullae.

Lung volume reduction surgery (LVRS)

LVRS improves $FEV_1^{389,396}$. 

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$^{389,396}$. 

LVRS improves quality of life$^{389,396}$. 

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Overall, LVRS does not appear to have any effect on long term survival (but see subgroup results below)\(^{389,396}\).

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).

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)\(^{389}\).

Among patients with predominantly upper-lobe emphysema and low exercise capacity (40 W in men and < 25 W 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)\(^{389}\).

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 (<40 W in men and < 25 W 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.\(^{389}\).
COPD patients are considered potentially to be in the transplant window if they meet the following criteria:\footnote{395}:

- \( FEV_1 < 25\% \text{ of predicted (without reversibility)} \)
- and/or \( PaCO_2 \geq 55\text{mmHg (7.3kPa)} \) 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:\footnote{395}:

- single lung transplants \( \sim 65 \) years
- bilateral lung transplants \( \sim 60 \) 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%) \(^{194}\).

Lung transplantation leads to improvements in FEV\(_1\), exercise capacity and quality of life \(^{398}\).

Bilateral lung transplantation results in a greater improvement in FEV\(_1\), but improvements in exercise capacity are not always significantly greater \(^{398}\).

**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: Grade A

- FEV$_1$ more than 20% predicted
- PaCO$_2$ less than 7.3 kPa
- upper lobe predominant emphysema
- T$_1$CO more than 20% predicted.

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: Grade C

- age
- FEV$_1$
- PaCO$_2$
- homogeneously distributed emphysema on CT scan
- elevated pulmonary artery pressures with progressive deterioration.
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. 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 was the only RCT. This was powered to detect a 50% difference in decline in FEV1 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 (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 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 and the Registry study found no significant effect of alpha-1 antitrypsin replacement therapy on the rate of decline in FEV1.
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.  

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.

Health economics evidence statements

Only one economic study was found. 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).
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.

COPD care should be delivered by a multidisciplinary team.

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
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, 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 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 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.

Their role within the multi-disciplinary team will vary depending on local circumstances and individual competencies.

**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. 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. A cohort study by Kolaczkowski et al. was also excluded due to limited methodological details being available.

One randomised controlled trial was identified and one quasi-experimental study that met quality appraisal criteria.

Christensen et al. 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. 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**

Casciari et al. 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).

During exercise, PaO\textsubscript{2} increased between exercising and breathing retraining (p<0.01).

After 9 weeks, PaO\textsubscript{2} and base excess differed significantly between the two groups in favour of the breathing retraining group; PaO\textsubscript{2} breathing retraining 77.5 compared to the control group 60.0 (mmHg).

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.

“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 (update)

COPD participants who received breathing retraining compared to those who received exercise only. \(^4\)  

Christensen et al. \(^4\) 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).

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 (\(p<0.05\))\(^4\).  

There was a statistically significant difference in the \(\text{FEV}_1\) at one year in favour of the PEP group (\(p=0.039\))\(^4\).

**Recommendations**

R102 If patients have excessive sputum, they should be taught:

- the use of positive expiratory pressure masks
- active cycle of breathing techniques.
7.13.3 Identifying and managing anxiety and depression

COPD leads to disabling and distressing symptoms. Patients 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. One examined the prevalence of depression in COPD, the other examined psychologically-based interventions to reduce anxiety and panic in patients with COPD. 2 additional RCTs were critically appraised one with n = 36 and the other with n = 56 but this was rejected because of methodological limitations. One randomised self-controlled crossover trial was critically appraised and 3 case-controlled studies, 2 uncontrolled cross-sectional cohort studies and 4 uncontrolled longitudinal cohort studies were critically appraised. One of the case controlled studies and two of the cohort studies 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 FEV₁ 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 the methodologically best-rated studies did not find a statistically significant difference in the prevalence of depression between patients with COPD and controls.

A striking difference in prevalence of depression was seen between studies (between 6% and 42%).

Van Manen et al. (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.

Results were adjusted to account for demographic variables and comorbidity. 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 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).

In addition, 20 patients (18%; 95% CI: 12 to 27) were severely depressed (GDS > 20/30).
Yohannes (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).

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).

The most powerful predictor of severity of anxiety was MADRS (the more depressed patients being more likely to suffer anxiety).

**Relationship of depression to severity of COPD**

Van Manen (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.

Results were adjusted to account for demographic variables and comorbidity. 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).
The risk of depression was significantly increased in patients with a reversibility FEV₁ 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.

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).

Depressed COPD patients (identified by GMS) had poorer quality of life scores compared with non-depressed patients (54 ± 1.8 vs. 36 ± 1.2, p = 0.04).\(^{423}\)

Depressed COPD patients (identified by GMS) had lower mean MRADL scores compared with non-depressed patients (9.9 ± 0.7 vs. 14.4 ± 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).

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).
Mean inpatient days of hospitalisation for depressed was 9.8 ± 1.7 and non-depressed was 2.3 ± 0.6 days (p<0.0001)\textsuperscript{423}.

Yohannes\textsuperscript{87} (uncontrolled longitudinal cohort study (n = 137)) \textsuperscript{IIb} found that depression scores and QOL scores do not predict mortality.

Identification of depression and anxiety in COPD patients

The Brief Assessment Schedule Depression Cards (BASDEC) has \textsuperscript{IIa} been validated in patients with COPD including those over 60 years of age\textsuperscript{87,422,423}.

Other scales that have been used are: \textsuperscript{III}

- Hospital Anxiety and Depression Scale (HADS)\textsuperscript{428}
- Geriatric Depression Scale\textsuperscript{424}
- Geriatric Mental State Schedule\textsuperscript{423}
- Montgomery Asberg Depression Rating Scale\textsuperscript{423}
- Centre for Epidemiological Studies Depression Scale (CES-D)\textsuperscript{421}
- Clinical Global Improvement Scale\textsuperscript{417}
- Hamilton Depression Rating Scale (HAM-D)\textsuperscript{417}
- Patient Related Anxiety Scale\textsuperscript{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 \(^{416}\). 

Borson et al. \(^{417}\) (RCT (n = 36)) found that **Nortriptyline** treatment was superior to placebo for treatment of depression. 

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 ± 7.6 to 12.6 ± 6.9) compared with 17% (29.5 ± 6.4 to 22.8 ± 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 ± 17 to 29.9 ± 11.4) compared with only 4% improvement (47.4 ± 21.5 to 45.3 ± 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 \(^{429}\). 

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.
**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.

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.

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.

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.
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 (SaO₂, reference value deleted)
- who have severe dyspnoea
- who have been seen at or admitted to a hospital with an exacerbation of COPD.

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. The mechanisms of this remain unclear but probably relate to systemic effects of cytokines, particularly TNF-α.

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 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 and 14 cohort studies were critically appraised, all but two of these 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 (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.

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 (FEV₁ %pred <50) in whom mortality was lowest in the obese and increased with decreasing BMI (p<0.001).

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.

Schols (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).

Marquis (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). Compared with patients with an FEV >50% predicted and a MTCSAct > 70 cm², those with an FEV < 50% predicted and a MTCSAct > 70cm² 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).
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).

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.

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 (FEV₁ % predicted ≥ 70) or moderate (FEV₁ % 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 (FEV₁ % 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\textsuperscript{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\textsuperscript{442}.

Sahebjami \textsuperscript{443} (uncontrolled cohort study n = 126) found that:

BMI is significantly correlated with diffusing capacity for carbon monoxide (DLCO), FEV\textsubscript{1} and the FEV\textsubscript{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\textsubscript{1} and FEV\textsubscript{1}/FVC compared with normal weight (BMI = 20-27) and overweight patients (BMI>27) (p<0.001).

Underweight (BMI < 21 kg/m\textsuperscript{2}) patients with COPD are more dyspnoeic than normal weight (BMI 21-28 kg/m\textsuperscript{2}) (p = 0.03) - Dyspnoea scale normal weight 2.5 ± 1.2 vs. underweight 3.1 ± 0.9.

Carbon monoxide diffusing capacity (DLCO) was significantly lower in underweight compared with normal weight patients – DLCO % predicted normal weight 57 ± 17 vs. underweight 36 ± 11 (p<0.001).

Maximum inspiratory pressure (Pimax) was significantly lower in underweight patients compared with normal weight patients. Pimax cmH\textsubscript{2}O normal weight 66 ± 19 vs. underweight 55 ± 18 (p = 0.02). Pimax % predicted normal weight 62 ± 17 vs. underweight 52 ± 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.

**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).

Baarends \(^{438}\) (uncontrolled cohort study \(n = 62\)) found that peak VO\(_2\) correlated significantly with the FFM index (kg/m\(^2\); \(r = 0.57\), \(p<0.001\)) BMI (kg/m\(^2\); \(r = 0.56\), \(p<0.001\)) and intracellular water (kg/m\(^2\); \(r = 0.54\), \(p<0.001\)).

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\(_L\)CO) 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 cm\(^2\) was associated with a fourfold increase (95% CI, 1.52 to 8.09) in mortality rate, independently of any other variables (\(p = 0.004\)).
Engelen \textsuperscript{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.

Measures of muscle strength were lower in the depleted group, but only the difference in handgrip strength reached statistical significance (p<0.01)\textsuperscript{439}.

Sahebjami \textsuperscript{443} (uncontrolled cohort study n = 126) found that 46.8% of COPD patients (n =126) had nutritional abnormalities (i.e. underweight BMI <20kg/m\textsuperscript{2} = 23% and overweight BMI >27 kg/m\textsuperscript{2} = 23.8%).

Schols \textsuperscript{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.

Prescott \textsuperscript{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.

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)\textsuperscript{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)\textsuperscript{442}.

Gray-Donald \textsuperscript{445} (uncontrolled cohort study n = 135) found that 24.4% of COPD participants had % IBW of <90%.
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).

Among underweight participants (IBW <90% predicted), 32% reported weight loss of > 5% in the last year.

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%.

The mean weight loss from usual weight in the underweight group was 17% (± 13%).

The systematic review / meta-analysis (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.

Otte (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.

Schols (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.
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.\(^{\text{IV}}\)

Exercise may augment the effects of nutritional supplementation on weight gain.\(^{\text{IV}}\)
**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 clinical 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.

**R108** In older patients attention should also be paid to changes in weight, particularly if the change is more than 3 kg.

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**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\(^{457}\).

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) \(p=0.0042\)\(^{457}\).
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.
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 discussions 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 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.
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.
COPD (update)

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 identified the following themes; quality of life, services in the community, adaptations and equipment, informal care, after death support and meeting needs.

Relatives reported that quality of life in the year before death was often very low.

Regarding services in the community, there 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 highlighted descriptive percentages from 214 UK GPs relating to discussions of prognosis in severe COPD. 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.
Oxygen may also be used to palliate breathlessness not relieved by other therapies (see section 7.6).

Patients dying with COPD can benefit from the services of multidisciplinary palliative care teams, including admission to hospices.

### Recommendations

<table>
<thead>
<tr>
<th>R109</th>
<th>Opioids should be used when appropriate to palliate breathlessness in patients with end-stage COPD which is unresponsive to other medical therapy.</th>
<th>Grade D</th>
</tr>
</thead>
<tbody>
<tr>
<td>R110</td>
<td>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.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R111</td>
<td>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.</td>
<td>Grade D</td>
</tr>
</tbody>
</table>
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, 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. 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 and can be used for the global assessment of patients. An assessment tool has been developed to assess patients needs for occupational therapy 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, the London Chest Activity of Daily Living scale (LCADL) or the Canadian Occupational Performance Measure (COPM), can be used to formally assess patients need for occupational therapy.

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.

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.

The processing time for many applications for financial and social assistance reduces the potential benefits for many patients.
COPD (update)

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. 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 (Paco2) 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 FEV1 <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.”
level to 2438 m (8000 ft). There is one case report of fatal air embolism in a patient with a giant intrapulmonary bronchogenic cyst. 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:

- 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.

Depending on the results of the initial assessment a hypoxic challenge test may be necessary (see Table 7.6).
### Table 7.6 Results of initial assessment

<table>
<thead>
<tr>
<th>Screening result</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sea level SaO(_2) &gt;95%</td>
<td>Oxygen not required [B]</td>
</tr>
<tr>
<td>Sea level SaO(_2) 92-95% and no risk factor*</td>
<td>Oxygen not required [C]</td>
</tr>
<tr>
<td>Sea level SaO(_2) 92-95% and additional risk factor*</td>
<td>Perform hypoxic challenge test with arterial or capillary measurements [B]</td>
</tr>
<tr>
<td>Sea level SaO(_2) &lt;92%</td>
<td>In-flight oxygen [B]</td>
</tr>
<tr>
<td>Receiving supplemental oxygen at sea level</td>
<td>Increase the flow while at cruising altitude [B]</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>R115</td>
<td>All patients on LTOT planning air travel should be assessed in line with the BTS recommendations(^\text{467}).</td>
</tr>
<tr>
<td>R116</td>
<td>All patients with an FEV(_1) &lt; 50% predicted who are planning air travel should be assessed in line with the BTS recommendations.</td>
</tr>
<tr>
<td>R117</td>
<td>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.</td>
</tr>
<tr>
<td>R118</td>
<td>Scuba diving is not generally recommended for patients with COPD. Advise people with queries to seek specialist advice.</td>
</tr>
</tbody>
</table>
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.

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.
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\textsubscript{1} results in the educated patient with COPD compared with the control group. (Patient education did increase the HRQL and FEV\textsubscript{1} among asthmatics but not among patients with COPD).

Howland\textsuperscript{470} compared education to a control group in a quasi-experimental design. In patients with mild to severe COPD (defined respectively as FEV\textsubscript{1}/FVC 70 to 60 per cent and FEV\textsubscript{1}/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.

**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.

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.

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).

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\textsuperscript{474} and one additional RCT (N=191)\textsuperscript{475}. 
The main aim of self-management is to prevent exacerbations by lifestyle adaptation and to allow patients to acquire the skills to treat their exacerbation at an early stage. 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 cites seven studies with self-management education components. Two additional studies have a self-management education component augmented with a self-management action plan, 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 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 the Bourbeau study was excluded.

There were varying degrees of detail when operationally defining COPD and importantly Monninkhof et al. 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 in a meta-analysis of Gallefoss and Littlejohns 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).
Within the Monninkhof systematic review, two studies, Watson and Littlejohns 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.

Use of rescue medication (short-acting beta₂ agonist) was assessed by Gallefoss as cited in the systematic review. The original paper by Gallefoss 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.

Monninkhof reported four studies (overall sample size n=417) that looked at COPD related hospitalisations and found no statistically significant overall differences.

Monninkhof highlights that meta-analysis of two studies 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).

There were no statistically significant differences between the groups for emergency room visits, use of other health care facilities, days lost from work.

Gallefoss and Watson (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
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<0.05.¹⁷⁴

There were no statistically significant differences between the groups for lung function.¹⁷⁴

There were no statistically significant differences between the groups for symptom scores.¹⁷⁴

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.

There is no evidence that self management plans similar to those used in asthma are of value in COPD.

Self management plans need to be refined and the key components identified.
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. \(\text{IV}\)

FEV\(_1\) on its own has little clinical usefulness in predicting post-operative pulmonary complications \(\text{III}\).\(^{486-488}\)

Composite assessment tools such as the widely used ASA scoring system \(\text{IV}\) can be used to assess operative risk and plan patients' management.
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.

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.

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.

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).

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.

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.

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.

R134 Patients with severe disease requiring interventions such as long-term non-invasive ventilation should be reviewed regularly by specialists.
Table 7.7 Summary of follow-up of patients with COPD in primary care

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mild/moderate/severe (stages 1 to 3)</th>
<th>Very severe (stage 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment</td>
<td>● smoking status and desire to quit</td>
<td>● smoking status and desire to quit</td>
</tr>
<tr>
<td></td>
<td>● adequacy of symptom control:</td>
<td>● adequacy of symptom control:</td>
</tr>
<tr>
<td></td>
<td>- breathlessness</td>
<td>- breathlessness</td>
</tr>
<tr>
<td></td>
<td>- exercise tolerance</td>
<td>- exercise tolerance</td>
</tr>
<tr>
<td></td>
<td>- estimated exacerbation frequency</td>
<td>- estimated exacerbation frequency</td>
</tr>
<tr>
<td></td>
<td>● presence of complications</td>
<td>● presence of cor pulmonale</td>
</tr>
<tr>
<td></td>
<td>● effects of each drug treatment</td>
<td>● need for long-term oxygen therapy</td>
</tr>
<tr>
<td></td>
<td>● inhaler technique</td>
<td>● patient’s nutritional state</td>
</tr>
<tr>
<td></td>
<td>● need for referral to specialist and therapy services</td>
<td>● presence of depression</td>
</tr>
<tr>
<td></td>
<td>● need for pulmonary rehabilitation</td>
<td>● effects of each drug treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● inhaler technique</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● need for social services and occupational therapy input</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● need for referral to specialist and therapy services</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● need for pulmonary rehabilitation</td>
</tr>
<tr>
<td>Measurements to make</td>
<td>● FEV&lt;sub&gt;1&lt;/sub&gt; and FVC</td>
<td>● FEV&lt;sub&gt;1&lt;/sub&gt; and FVC</td>
</tr>
<tr>
<td></td>
<td>● calculate BMI</td>
<td>● calculate BMI</td>
</tr>
<tr>
<td></td>
<td>● MRC dyspnoea score</td>
<td>● MRC dyspnoea score</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● SaO&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
</tbody>
</table>
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. 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.
In a Spanish study of patients admitted to hospital with an exacerbation of COPD 63% were readmitted within 1 year\(^4\). 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)\(^4\).

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\(^4\).

Studies of a cohort of patients observed in the community have shown that symptoms and peak expiratory flow rates recover slowly after an exacerbation.

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\(^4\).

Studies in the same cohort have shown that patients experiencing frequent exacerbations (more than 2.92 per year) have more rapid
l 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)\(^4\). 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)\(^4\).

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)\(^4\) and Price et al (1999)\(^4\) 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)\(^4\).

Costs given in SEK, converted to GBP by using purchasing power parities for 2002 from the OECD (www.oecd.org).

<table>
<thead>
<tr>
<th>Severity</th>
<th>Cost (GBP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>£7.94</td>
</tr>
<tr>
<td>Mild/moderate</td>
<td>£23.43</td>
</tr>
<tr>
<td>Moderate</td>
<td>£139.74</td>
</tr>
<tr>
<td>Severe</td>
<td>£1,446.48</td>
</tr>
</tbody>
</table>

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.

### 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 COPD⁴⁹⁸.

<table>
<thead>
<tr>
<th>Infections</th>
<th>Rhinoviruses (common cold)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>Parainfluenza</td>
</tr>
<tr>
<td></td>
<td>Coronavirus</td>
</tr>
<tr>
<td></td>
<td>Adenovirus</td>
</tr>
<tr>
<td></td>
<td>Respiratory Syncytial Virus</td>
</tr>
<tr>
<td></td>
<td>C pneumoniae</td>
</tr>
<tr>
<td></td>
<td><em>H influenzae</em></td>
</tr>
<tr>
<td></td>
<td><em>S pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td><em>M catarrhalis</em></td>
</tr>
<tr>
<td></td>
<td><em>Staph aureus</em></td>
</tr>
<tr>
<td></td>
<td><em>P aeruginosa</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common pollutants</th>
<th>Nitrogen dioxide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Particulates</td>
</tr>
<tr>
<td></td>
<td>Sulphur dioxide</td>
</tr>
<tr>
<td></td>
<td>Ozone</td>
</tr>
</tbody>
</table>

The cause of the exacerbation may be unidentifiable in up to 30% of exacerbations.
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:

- 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.
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:

- 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:

- 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**

Factors that should be used to assess the need to treat patients in hospital are listed in table 8.1:

**Table 8.1 Factors to consider when deciding where to treat the patient**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Treat at home</th>
<th>Treat in hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Able to cope at home</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>General condition</td>
<td>Good</td>
<td>Poor/deteriorating</td>
</tr>
<tr>
<td>Level of activity</td>
<td>Good</td>
<td>Poor/confined to bed</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Worsening peripheral oedema</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>Normal</td>
<td>Impaired</td>
</tr>
<tr>
<td>Already receiving LTOT</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Social circumstances</td>
<td>Good</td>
<td>Living alone/not coping</td>
</tr>
<tr>
<td>Acute confusion</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Rapid rate of onset</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Significant comorbidity</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>(particularly cardiac and insulin-dependent diabetes)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SaO₂ &lt; 90%</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Changes on chest radiograph</td>
<td>No</td>
<td>Present</td>
</tr>
<tr>
<td>Arterial pH level</td>
<td>≥ 7.35</td>
<td>&lt; 7.35</td>
</tr>
<tr>
<td>Arterial PaO₂</td>
<td>≥ 7 kPa</td>
<td>&lt; 7 kPa</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>R136</th>
<th>In patients who have their exacerbation managed in primary care:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• sending sputum samples for culture is not recommended in routine practice</td>
</tr>
<tr>
<td></td>
<td>• pulse oximetry is of value if there are clinical features of a severe exacerbation.</td>
</tr>
</tbody>
</table>
Recommendations for patients referred to hospital

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.

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. Early discharge schemes aim to facilitate the early discharge of patients admitted with an exacerbation of COPD. 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\textsuperscript{501-504}, one qualitative study\textsuperscript{505}, one survey\textsuperscript{506} and one service evaluation\textsuperscript{499} which were applicable to hospital-at-home care. One RCT\textsuperscript{507} relates to early discharge. All but the qualitative research\textsuperscript{505} and the survey\textsuperscript{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\textsubscript{1}\textsuperscript{501-503} or readmission rates\textsuperscript{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\textsuperscript{503}.

There were no significant differences in mortality rates between those patients cared for as part of a hospital-at-home scheme and in-patients\textsuperscript{502,504}.

Two studies showed no significant differences between the groups for HRQL (SGRQ) (subgroup analysis)\textsuperscript{502}, chronic respiratory questionnaire (CRQ)\textsuperscript{501}. One Spanish study showed significant improvement in SGRQ\textsuperscript{504}. 

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There were no significant differences between the groups for symptom scores\textsuperscript{503}.

In relation to additional support services Skwarska et al\textsuperscript{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.

There were no significant differences in the satisfaction scores with the care package for either patient or carers between the two groups\textsuperscript{503}.

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\textsuperscript{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.

Cotton et al\textsuperscript{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.

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\textsuperscript{507}.
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\textsuperscript{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\textsuperscript{508}. In a Spanish study based around tertiary referral hospitals, hospital-at-home was cheaper in the short term than conventional care\textsuperscript{504}.

There is limited evidence that a supported discharge scheme may be cheaper than usual inpatient care\textsuperscript{501}.
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.

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.

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.

Patients’ preferences about treatment at home or in hospital should be considered.
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 of bronchodilator delivery in acute airflow obstruction.\(^{509}\)  

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\textsuperscript{241}.

For low dose bronchodilator therapy - for example, 100-400 mcg salbutamol or terbutaline - treatment with a metered dose inhaler is more convenient whilst a nebuliser can deliver higher doses more easily\textsuperscript{240}.

Breathless patients are less likely to be able to inspire slowly or breath hold for optimum lung deposition from a metered dose inhaler\textsuperscript{240}.

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\textsuperscript{241}.

This usage does not imply that nebulized therapy is superior and this should be made clear to patients and their relatives\textsuperscript{241}.

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\textsuperscript{240}.
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.\(^{240}\)

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.

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 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 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 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 data only contributed 7.7%. The other two systematic reviews 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 (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\textsuperscript{510-512} all reviewed virtually the same RCTs. The reviews demonstrated a significant effect in favour of steroids over placebo for FEV\textsubscript{1} for at least 72 hours. In the meta-analysis by Wood Baker et al\textsuperscript{511} of 6 RCTs, the WMD was 120 ml (95% CI; 5 ml to 190 ml).

One additional RCT was found\textsuperscript{514}. This trial also demonstrated significant improvements in FEV\textsubscript{1} up to 36 hours with a mean difference of 160 ml (95% CI; 9 ml to 240 ml) in favour of the intervention compared to placebo.

Davies et al\textsuperscript{515}, Niewoehner et al\textsuperscript{516} and Thompson et al\textsuperscript{517} (all trials included in the systematic reviews) measured FEV\textsubscript{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.\textsuperscript{510}

Maltais et al\textsuperscript{514} and Thompson\textsuperscript{517} demonstrated a statistically significant improvement in arterial PaO\textsubscript{2} in the first 72 hours in favour of the steroid group compared to placebo <0.05.

Significantly shorter duration of hospitalisation was demonstrated by Niewoehner et al\textsuperscript{516} (p=0.03) and Davies et al\textsuperscript{515} (p=0.027) in favour of the steroids compared to placebo.

In one further study with no objective assessment of fitness for discharge, Maltais\textsuperscript{514} found no significant differences in the mean duration of hospitalisation between steroid and placebo groups.

A meta-analysis of 5 RCTs found no statistically significant differences between the steroid and control groups for mortality\textsuperscript{511}.
The systematic review by McCrory et al\textsuperscript{516} highlighted the current debate around \textbf{duration} of steroid treatment and \textbf{dose} during COPD exacerbations\textsuperscript{515,516,518}. Niewoehner et al\textsuperscript{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\textsuperscript{515} and even shorter courses of treatment\textsuperscript{518} may be effective”.

Meta-analysis by Wood Baker et al\textsuperscript{511} of 5 RCTs showed a significantly beneficial effect of steroids compared to placebo at reducing \textbf{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.

Three RCTs\textsuperscript{515,516,518} were combined in a meta-analysis by Wood Baker et al\textsuperscript{511} for \textbf{adverse events}. “Overall, patients receiving corticosteroid treatment were 2.7 times more likely to have an adverse drug reaction than those receiving placebo”.

Niewoehner et al\textsuperscript{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\textsuperscript{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.
### Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Text</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>R147</td>
<td>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.</td>
<td>Grade A</td>
</tr>
<tr>
<td>R148</td>
<td>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.</td>
<td>Grade B</td>
</tr>
<tr>
<td>R149</td>
<td>Patients requiring corticosteroid therapy should be encouraged to present early to get maximum benefits (see recommendations 122-126).</td>
<td>Grade D</td>
</tr>
<tr>
<td>R150</td>
<td>Prednisolone 30 mg orally should be prescribed for 7 to 14 days.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R151</td>
<td>It is recommended that a course of corticosteroid treatment should not be longer than 14 days as there is no advantage in prolonged therapy.</td>
<td>Grade A</td>
</tr>
<tr>
<td>R152</td>
<td>For guidance on stopping oral corticosteroid therapy it is recommended that clinicians refer to the British National Formulary section 6.3.2.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R153</td>
<td>Osteoporosis prophylaxis should be considered in patients requiring frequent courses of oral corticosteroids.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R154</td>
<td>Patients should be made aware of the optimum duration of treatment and the adverse effects of prolonged therapy.</td>
<td>Grade D</td>
</tr>
</tbody>
</table>
Patients, particularly those discharged from hospital, should be given clear instructions about why, when and how to stop their corticosteroid treatment.

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\textsuperscript{519}.

There have been two recent publications\textsuperscript{510,520} that have assimilated the evidence base (including the meta-analysis by Saint et al\textsuperscript{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\textsuperscript{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\textsuperscript{521} cited in\textsuperscript{510} found a small but statistically significant effect favouring antibiotics over placebo in patients with \textit{exacerbations of COPD}. Effect size 0.22 (95% CI, 0.1 to 0.34).

Four studies\textsuperscript{525-527} all cited by AHRQ\textsuperscript{510} and Allegra et al\textsuperscript{524} assessed whether there was a relationship between severity of exacerbation and the effectiveness of antibiotic use.

Three of these studies suggest that the worse the COPD severity of exacerbation (lung function impairment (FEV\textsubscript{1}, PEFR), purulence of sputum) then the greater the degree of benefit from antibiotics.

Anthonisen et al\textsuperscript{525} showed a relationship of better outcomes with antibiotic versus placebo treatment based upon the severity of exacerbations. \textit{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.

Berry et al\textsuperscript{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 \textit{moderate or severe exacerbations}, the antibiotic group had significantly less severe symptoms on days 2 and 7 (but were not significant at two weeks).

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 amoxicillin-clavulanic acid to placebo in patients with exacerbations of chronic bronchitis. The improvement or success rate vs. the failure rate was significantly different in \textit{severe exacerbation} patients compared to those with exacerbations of a less severity.
In relation to the use of quinolones, the SIGN publication on Community Management of Lower Respiratory Tract Infection\textsuperscript{520} cites Davies et al\textsuperscript{528}. Although quinolones have performed equally well in clinical trials, no clinical superiority over other antibiotics has yet been shown\textsuperscript{528}.

Nouira et al\textsuperscript{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.

Sin et al\textsuperscript{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).
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 amoxicillin 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\textsuperscript{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**

<table>
<thead>
<tr>
<th>R156</th>
<th>Antibiotics should be used to treat exacerbations of COPD associated with a history of more purulent sputum.</th>
<th>Grade A</th>
</tr>
</thead>
<tbody>
<tr>
<td>R157</td>
<td>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.</td>
<td>Grade B</td>
</tr>
<tr>
<td>R158</td>
<td>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.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R159</td>
<td>When sputum has been sent for culture, the appropriateness of antibiotic treatment should be checked against laboratory culture and sensitivities when they become available.</td>
<td>Grade D</td>
</tr>
</tbody>
</table>
8.11.5 Theophylline and other methylxanthines

As well as their apparent actions as bronchodilators, theophylline also appears to increase respiratory drive\textsuperscript{532,533} and this appears capable of overcoming some of the respiratory depression present during exacerbations\textsuperscript{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\textsuperscript{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\textsuperscript{535} or were excluded due to use in stable COPD patients\textsuperscript{137,163,306,536,537} or small sample size\textsuperscript{538}.

Evidence statements

The systematic review\textsuperscript{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\textsubscript{1} were used, and only three trials\textsuperscript{539-541} plus one abstract\textsuperscript{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.

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.
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\(^491\) compared doxapram with other stimulants not currently used. The fourth study contains data from an
unpublished study\textsuperscript{548} comparing doxapram with non-invasive ventilation. No numerical data is available for inclusion into the analyses.

An additional RCT\textsuperscript{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.

There is insufficient evidence to recommend a change from current clinical practice of using doxapram to treat respiratory failure during exacerbations of COPD.

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 and developed guidelines on the use of emergency oxygen therapy for breathless patients. 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 have shown that the PaO₂ falls from 55-60mmHg to 25-50mmHg during an exacerbation.

There are marked variations in the response of individual patients to oxygen. King et al gave 24% oxygen to patients with exacerbations of chronic respiratory failure. They recorded a mean PO₂ of 40.4 mm Hg in these patients on room air and a mean PO₂ of 57.3 mm Hg after 30 to 60 minutes of 24% oxygen but 15 out of 40 patients did not
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.

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 acidic and 4.6% of patients had a pH less than 7.25. More than 50% of hypercapnic patients were acidic if the PaO\(_2\) was greater than 75 mm Hg\(^{555}\).

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.

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.
Eldridge et al\textsuperscript{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\textsubscript{2} with increasing PaO\textsubscript{2} and the PaCO\textsubscript{2} fell when the arterial PaO\textsubscript{2} changed from a higher to a lower value. Again, there was great variability in the increases in PaCO\textsubscript{2} for a given increase in PaO\textsubscript{2} between patients.

Prime and Wenstlake\textsuperscript{559} gave 100\% oxygen to 35 patients with stable COPD for 30 to 40 minutes. Thirty-three had increases in PaCO\textsubscript{2} ranging from 1.2 to 25.4 mm Hg.

Aubier et al\textsuperscript{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\textsubscript{2} of 23 +/- 5 mm Hg and there was an average drop in pH from 7.34 +/- 0.01 to 7.25 +/- 0.02.

Radial stabs to obtain blood for arterial blood gas analysis are not more painful than arterialised ear lobe gases\textsuperscript{561}.

Arterialised ear lobe gases may not accurately reflect PaO\textsubscript{2} but are acceptable for PaCO\textsubscript{2}\textsuperscript{561-564}.

\textbf{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.
## 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.

<table>
<thead>
<tr>
<th>R164</th>
<th>The oxygen saturation should be measured in patients with an exacerbation of COPD, if there are no facilities to measure arterial blood gases.</th>
<th>Grade D</th>
</tr>
</thead>
<tbody>
<tr>
<td>R165</td>
<td>If necessary, oxygen should be given to keep the SaO\textsubscript{2} within the individualised target range.\textsuperscript{iii}</td>
<td>Grade C</td>
</tr>
<tr>
<td>R166</td>
<td>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\textsubscript{2} or pH.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R167</td>
<td>Deleted.</td>
<td></td>
</tr>
<tr>
<td>R168</td>
<td>Deleted.</td>
<td></td>
</tr>
<tr>
<td>R169</td>
<td>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.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R170</td>
<td>Deleted.</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{iii} 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)\(^{565}\).

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)\(^{565}\).

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), 
\(\text{PaCO}_2\) WMD –0.40kPa, (95% CI; -0.78 to –0.03), and respiratory rate WMD –3.08 rpm, (95% CI; -4.26 to –1.89)\(^{567}\).

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)\(^{567}\).

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)\(^{565}\).

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...
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)\textsuperscript{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.

Heath economics

Five papers were found. There were some methodological limitations in the papers. Keenan et al\textsuperscript{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\textsuperscript{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\textsuperscript{570}, Plant et al 2003\textsuperscript{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\textsuperscript{572-575}. Esteban et al\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{574} looked at a population of patients with severe COPD and acute respiratory failure and examined correlates for survival at the time of intubation.

\textbf{Evidence statements}

The mean \textit{duration of mechanical ventilation} for COPD patients compared to acute respiratory distress syndrome (ARDS) patients was 5.1 vs. 8.8 respectively $p<0.001$\textsuperscript{573}. However Nevins et al 2001\textsuperscript{575} identified a mean duration of ventilation was 9 days (median 4 days).

\textit{Duration of weaning} was non significant between the two groups\textsuperscript{573}.

\textbf{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 \textbf{length of stay in hospital} was 21.2 days in the COPD group versus 24.5 days in the ARDS group $p=0.07$\textsuperscript{573}. Nevins et al\textsuperscript{575} identified a mean duration of hospital stay of 22 days in COPD patients requiring ventilation.
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\textsuperscript{573}.

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)\textsuperscript{575}.

NIV can be successfully used to shorten duration of mechanical ventilation (p=0.002)\textsuperscript{576}.

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.
**Recommendations**

R174 Patients with exacerbations of COPD should receive treatment on intensive care units, including invasive ventilation when this is thought to be necessary.  

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 FEV1, when assessing suitability for intubation and ventilation. Neither age nor FEV1 should be used in isolation when assessing suitability.  

R176 NIV should be considered for patients who are slow to wean from invasive ventilation.

**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 identified520, two RCTs577,578 and two quasi-experimental studies579,580.
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\textsuperscript{475} (COPD stable and exacerbations, asthmatics, cystic fibrosis) and McCrory 2001\textsuperscript{510} (stable, exacerbations and post exacerbation population), small sample sizes Bellone et al 2000\textsuperscript{577} (N=10, Wollmer et al 1985\textsuperscript{580} N=10) and hence potentially significant under powering, short-term interventions, short term outcome assessments or did not report suitable outcome data\textsuperscript{475}. Many of the trials precluded meta-analysis due to the diversity of patient groups and outcomes\textsuperscript{475}. One RCT by Bellone 2000\textsuperscript{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\textsuperscript{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\textsuperscript{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.

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)\textsuperscript{579}.

Weaning time from NIV was found to be significantly lower in the intervention group (5 days v 7 days) p<0.01\textsuperscript{579}. 

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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\textsuperscript{581}. 

**Recommendations**

<table>
<thead>
<tr>
<th>R177</th>
<th>Physiotherapy using positive expiratory pressure masks should be considered for selected patients with exacerbations of COPD, to help with clearing sputum.</th>
</tr>
</thead>
</table>

**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.

R179 Pulse oximetry should be used to monitor the recovery of patients with non-hypercapnic, non-acidotic respiratory failure.

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.

R181 Daily monitoring of PEF or FEV₁ 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.

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

<table>
<thead>
<tr>
<th>R182</th>
<th>Spirometry should be measured in all patients before discharge.</th>
<th>Grade D</th>
</tr>
</thead>
<tbody>
<tr>
<td>R183</td>
<td>Patients should be re-established on their optimal maintenance bronchodilator therapy before discharge.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R184</td>
<td>Patients who have had an episode of respiratory failure should have satisfactory oximetry or arterial blood gas results before discharge.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R185</td>
<td>All aspects of the routine care that patients receive (including appropriateness and risk of side effects) should be assessed before discharge.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R186</td>
<td>Patients (or home carers) should be given appropriate information to enable them to fully understand the correct use of medications, including oxygen, before discharge.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R187</td>
<td>Arrangements for follow-up and home care (such as visiting nurse, oxygen delivery, referral for other support) should be made before discharge.</td>
<td>Grade D</td>
</tr>
<tr>
<td>R188</td>
<td>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.</td>
<td>Grade D</td>
</tr>
</tbody>
</table>
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\textsuperscript{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.
COPD (update)

**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

#### 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.

- **Criterion**
  - 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

- **Exception**
  - 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.

- **Criterion**
  - 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

### 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

- **Criterion**
  - Appropriateness of inhaled steroid therapy

- **Exception**
  - Patient choice
drugs. Either a long-acting beta₂ agonist and inhaled corticosteroid in a combination inhaler, or a long-acting muscarinic antagonist should be used in patients with an FEV₁ < 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 FEV₁.

<table>
<thead>
<tr>
<th>4. Pulmonary rehabilitation for all who need it</th>
<th>Percentage of patients with COPD who have undergone pulmonary rehabilitation</th>
<th>Patient choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Use non-invasive ventilation</th>
<th>Percentage of patients presenting with acute hypercapnic respiratory failure who have received non-invasive ventilation</th>
<th>Patient choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
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</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Frequency and appropriateness of oral steroid and antibiotic therapy</th>
<th>Patient choice</th>
</tr>
</thead>
</table>


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)
COPD (update)

- 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
### 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?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>In people with COPD</td>
<td>Early pulmonary rehabilitation programme:</td>
<td>Later pulmonary rehabilitation programme (after one month)</td>
<td>• Hospitalisations</td>
</tr>
<tr>
<td></td>
<td>• during hospital admission</td>
<td></td>
<td>• Exacerbations</td>
</tr>
<tr>
<td></td>
<td>• during hospital admission and in the early recovery period (within one month of admission)</td>
<td></td>
<td>• QoL</td>
</tr>
<tr>
<td></td>
<td>• during the early recovery period (within one month of admission)</td>
<td></td>
<td>• Cost effectiveness</td>
</tr>
</tbody>
</table>

**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 FEV₁ or other components measured alone in a wide range of COPD patients, and applicable in a primary care setting?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>In people with COPD</td>
<td>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)</td>
<td>FEV₁ or other component measures alone</td>
<td>Prognosis and response to treatment:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Hospitalisations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Exacerbations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- QoL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Cost effectiveness</td>
</tr>
</tbody>
</table>

**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?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>In people with COPD</td>
<td>LAMA+LABA+ICS</td>
<td>LAMA or LABA or LABA+ICS</td>
<td>Prognosis and response to treatment:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hospitalisations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Exacerbations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• QoL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Cost effectiveness</td>
</tr>
</tbody>
</table>

**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?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>In people with COPD</td>
<td>Mucolytic drugs</td>
<td>Placebo or other effective therapies (e.g. inhaled LABA, LAMA and LABA+ICS)</td>
<td>Prognosis and response to treatment:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hospitalisations</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Exacerbations</td>
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<td></td>
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<td>• QoL</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Cost effectiveness</td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>Question</th>
<th>Population</th>
<th>Study Type</th>
<th>Database and Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 What is a useful, robust definition of COPD?</td>
<td></td>
<td></td>
<td>Expert Review</td>
</tr>
<tr>
<td>Q2 Must the definition of COPD include the presence of airflow obstruction?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3 Must the definition of COPD include reversibility criteria?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 Must the definition of COPD discuss causation and pathophysiology?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Q5 What is the current and future burden of COPD in England &amp; Wales?</td>
<td>Expert Review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q6 Can COPD be detected before the onset of symptoms?</td>
<td>Expert Review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q7 What factors can be used to identify patients opportunistically as being at risk of having COPD?</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Q8 What methods can be used to confirm the diagnosis in patients identified opportunistically as being at risk of having COPD?</td>
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</tr>
<tr>
<td>Q9 Question removed.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q10 Does early diagnosis of COPD affect the success of smoking cessation therapy?</td>
<td>Expert Review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q11 What are the aims of COPD management?</td>
<td>Expert Review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q12 What symptoms are suggestive of a diagnosis of COPD?</td>
<td>Expert Review</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Q13 What other conditions may present with similar symptoms/signs/results?

Q14 In patients with suspected COPD, what are the most effective diagnostic criteria?

Q15 What clinical signs are useful (confirm or refute the diagnosis) in stable COPD?

Q16 What are the most appropriate tests in a patient with suspected COPD to confirm the diagnosis?

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?

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?

Q21 What is the role of other lung function tests in the diagnosis of COPD? (IRC, T1,CO,KCO, Lung Volumes)
### 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

<table>
<thead>
<tr>
<th>Q24 Which patients with stable COPD should be referred for specialist advice?</th>
<th>Stable COPD</th>
<th>Systematic Reviews</th>
<th>Cochrane Library</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exclude asthma</td>
<td>RCT</td>
<td>Medline 1966-2003</td>
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<td></td>
<td></td>
<td>Cohort</td>
<td>Embase 1980-2003</td>
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<td></td>
<td>CINAHL 1982-2003</td>
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<td></td>
<td></td>
<td></td>
<td>AMED 1985-2003</td>
</tr>
</tbody>
</table>

### 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?  
Expert Review

<table>
<thead>
<tr>
<th>Q26 What is the most appropriate smoking cessation strategy in patients with stable COPD?</th>
<th>COPD</th>
<th>Systematic Reviews</th>
<th>Cochrane Library</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exclude asthma</td>
<td>RCTs</td>
<td>Medline 1966-2003</td>
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<td></td>
<td>Cohorts</td>
<td>Embase 1980-2003</td>
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<td>CINAHL 1982-2003</td>
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<td>PsycINFO 1887-2003</td>
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<td></td>
<td></td>
<td></td>
<td>AMED 1985-2003</td>
</tr>
<tr>
<td>Q27 What drug therapy is effective (reduces morbidity or mortality in) for patients with stable COPD?</td>
<td>This is not a question in its own right but merely a heading for questions 28-57.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q28 Which patients with stable COPD should be treated with short-acting inhaled bronchodilators?</td>
<td>This is not a question in its own right but merely a heading for questions 29 and 30.</td>
<td></td>
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</tr>
<tr>
<td>Q31 How should the effects of this treatment be assessed?</td>
<td>Exclude asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q31 How should the effects of this treatment be assessed?</td>
<td>Exclude asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q32 Which patients with stable COPD should be treated with long-acting inhaled bronchodilators?</td>
<td>This is not a question in its own right but merely a heading for questions 33 and 34.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q33 Which patients with stable COPD should be treated with long-acting beta₂-agonists?</td>
<td>COPD Systematic Reviews RCTs Cochrane Library Medline 1966-2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q34</td>
<td>Which patients with stable COPD should be treated with long-acting anticholinergics?</td>
<td>COPD Exclude asthma</td>
<td>Systematic Reviews</td>
</tr>
<tr>
<td>Q35</td>
<td>How should the effects of this treatment be assessed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q36</td>
<td>Which patients with stable COPD should be treated with methylxanthines / PDE4 inhibitors?</td>
<td>Stable COPD Exclude asthma</td>
<td>Systematic Reviews</td>
</tr>
<tr>
<td>Q37</td>
<td>How should the effects of this treatment be assessed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q40</td>
<td>Which patients with stable COPD should be treated with inhaled steroids?</td>
<td>COPD Exclude asthma</td>
<td>Systematic Reviews</td>
</tr>
<tr>
<td>Q41</td>
<td>How should the effects of this treatment be assessed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q42</td>
<td>Which patients with stable COPD should be treated with oral steroids?</td>
<td>COPD Exclude asthma</td>
<td>Systematic Reviews</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RCTs</td>
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<td></td>
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<td>RCTs</td>
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<td>Systematic Reviews</td>
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<td>RCTs</td>
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<td></td>
<td></td>
<td></td>
<td>RCTs</td>
</tr>
<tr>
<td>Q43 How should the effects of this treatment be assessed?</td>
<td>Stabil COPD</td>
<td>Systematic Reviews</td>
<td>Embase 1980-2003</td>
</tr>
<tr>
<td>Q44 What is the role of combination therapy in patients with stable COPD?</td>
<td>Stable COPD</td>
<td>Systematic Reviews</td>
<td>Cochrane Library</td>
</tr>
<tr>
<td>Exclude asthma</td>
<td>RCTs</td>
<td></td>
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</tr>
<tr>
<td>Q45 How should the effects of this treatment be assessed?</td>
<td>Systematic Reviews</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q46 What are the most appropriate delivery systems for giving inhaled therapy to patients with stable COPD?</td>
<td>RCTs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable COPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclude asthma except in elderly patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q47 Which patients with stable COPD benefit from nebulised therapy compared to other delivery mechanisms?</td>
<td>Systematic Reviews</td>
<td>Cochrane Library 1980-2003</td>
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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?
<table>
<thead>
<tr>
<th>Q63</th>
<th>In patients with stable COPD how can right heart failure / chronic salt and water retention be identified?</th>
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<tbody>
<tr>
<td>Q64</td>
<td>In patients with stable COPD what therapies can be used to manage right heart failure / chronic salt and water retention?</td>
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<tr>
<td>Q65</td>
<td>In patients with stable COPD how can pulmonary hypertension be identified?</td>
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<tr>
<td>Q66</td>
<td>In patients with stable COPD what therapies can be used to manage pulmonary hypertension?</td>
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</table>

**Q67 Main Stem Question**  How are patients with stable COPD affected by anxiety and / or depression?  

<table>
<thead>
<tr>
<th>Q68</th>
<th>In patients with stable COPD, how can anxiety and depression be identified?</th>
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<tbody>
<tr>
<td>Q69</td>
<td>How can anxiety and depression in stable COPD patients be managed? (Pharmacological &amp; non-pharmacological)</td>
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<thead>
<tr>
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**COPD Include asthma**

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<td>PsycINFO</td>
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</table>
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?

Q73 Do self-management plans & patient education affect concordance with treatment and improve outcomes in patients with stable COPD?

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?
| Q76 In patients with stable COPD, what are the benefits of short burst oxygen? | COPD | Systematic Reviews | Cochrane Library |
| Q77 In patients with stable COPD, what are the benefits of portable oxygen? | Exclude asthma | RCTs | Medline 1966-2003 |
| Q78 In patients with stable COPD, what are the criteria for continuous oxygen therapy? | | | Embase 1980-2003 |
| Q79 What is the role of immunisation in patients with stable COPD? | Stable COPD | Systematic Reviews | Cochrane Library 1980-2003 |
| | Exclude asthma | RCTs | Medline 1980-2003 |
| | | | Embase 1980-2003 |
Q81 What management strategies can be used to provide palliative care in the end stages of COPD?

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<tr>
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</table>

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?

Q85 In patients with stable COPD, what is the role of respiratory nurse specialists?

<table>
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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?

Q90 What is a robust and useful definition of an exacerbation of COPD?

Q91 What symptoms are suggestive of an exacerbation of COPD?

Q92 What other conditions present with similar symptoms?
Q93 What are the factors known to cause exacerbations of COPD?  

Q94 What is known about the consequences (short & long term outcome impact) of having an exacerbation (chest episodes, infective episodes) of COPD?  

Q95 What clinical signs are useful (confirm or refute) in making a diagnosis and assessing the severity of an exacerbation of COPD?  

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?
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?

Q102 What is the role (reduction of morbidity or mortality and comparative efficacy) of pharmacotherapy in patients with an exacerbation of COPD?

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?

Q105 Are oral steroids useful / effective in the treatment of patients with an exacerbation of COPD?
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<td>Q108 Which delivery systems should be used for giving inhaled therapy to patients with an exacerbation of COPD?</td>
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<td>Q110 Which patients with an exacerbation of COPD should be treated with antibiotics?</td>
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<td>Q111 Which patients with an exacerbation of COPD should be treated with oxygen (how much and how monitored, including use during transfer to hospital)?</td>
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<td>Q114 What is the role of therapies for managing right heart failure / chronic salt and water retention in patients with exacerbations of COPD?</td>
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<td>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?</td>
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<td>Q118 Which patients with exacerbations of COPD require IPPV / ITU care?</td>
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<td>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.</td>
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<td>Q120 What multi professional team membership is effective in providing hospital-at-home / assisted discharge schemes for patients with exacerbations of COPD?</td>
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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, 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. Smoking cessation can alter length of life and quality of life and the earlier smoking cessation is achieved, the greater the effect. 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 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.

\[
\text{Incremental cost per life year gained} = \frac{(C_1 - C_2)}{(Y_1 - Y_2)}
\]

\[
\text{Incremental cost per QALY} = \frac{(C_1 - C_2)}{(Q_1 - Q_2)}
\]

Where

- \( C_1 = \) Expected cost of opportunistically case finding
- \( C_2 = \) Expected cost of not opportunistically 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.

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<td>D</td>
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</tr>
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<td>E</td>
<td>73.1</td>
<td>Fletcher C (1977) and HTA (2002)</td>
</tr>
<tr>
<td>F</td>
<td>71</td>
<td>Fletcher C (1977) and HTA (2002)</td>
</tr>
<tr>
<td>G</td>
<td>71</td>
<td>Fletcher C (1977) and HTA (2002)</td>
</tr>
<tr>
<td>H</td>
<td>79.73</td>
<td>Life tables</td>
</tr>
</tbody>
</table>
### Probabilities

<table>
<thead>
<tr>
<th></th>
<th>Baseline value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>0.27</td>
<td>van Schayck (2002)</td>
</tr>
<tr>
<td>no COPD</td>
<td>0.73</td>
<td>van Schayck (2002)</td>
</tr>
<tr>
<td>success of smoking if early</td>
<td>0.1305</td>
<td>HTA (2002)</td>
</tr>
<tr>
<td>Failure of smoking if early</td>
<td>0.8695</td>
<td>HTA (2002)</td>
</tr>
<tr>
<td>success of smoking if late</td>
<td>0.1305</td>
<td>HTA (2002)</td>
</tr>
<tr>
<td>Failure of smoking if late</td>
<td>0.8695</td>
<td>HTA (2002)</td>
</tr>
<tr>
<td>Compliance if early</td>
<td>0.9</td>
<td>Assumption</td>
</tr>
<tr>
<td>Non concordance if early</td>
<td>0.1</td>
<td>Assumption</td>
</tr>
<tr>
<td>Compliance if late</td>
<td>0.5</td>
<td>Assumption</td>
</tr>
<tr>
<td>Non concordance if late</td>
<td>0.5</td>
<td>Assumption</td>
</tr>
</tbody>
</table>

### Cost

<table>
<thead>
<tr>
<th>Incremental cost p.a. for mild COPD</th>
<th>£159.63</th>
<th>Britton et al 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental cost p.a. for moderate COPD</td>
<td>£328.21</td>
<td>Britton et al 2003</td>
</tr>
<tr>
<td>Incremental cost p.a. for severe COPD</td>
<td>£1,394</td>
<td>Britton et al 2003</td>
</tr>
</tbody>
</table>
### Cost

<table>
<thead>
<tr>
<th>Cost</th>
<th>Baseline value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of spirometry test in GP practice</td>
<td>£9.91</td>
<td>From estimates provided by GDG</td>
</tr>
<tr>
<td>Cost of intensive smoking cessation programme</td>
<td>£171.49</td>
<td>HTA (2002)</td>
</tr>
<tr>
<td>Other diagnosis costs</td>
<td>£50</td>
<td>Assumption</td>
</tr>
</tbody>
</table>

### Utility

<table>
<thead>
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<th>Utility</th>
<th>Baseline value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>0.6102</td>
<td>Data from Harper et al (1997)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.5659</td>
<td>Data from Harper et al (1997)</td>
</tr>
<tr>
<td>Severe</td>
<td>0.5428</td>
<td>Data from Harper et al (1997)</td>
</tr>
<tr>
<td>Non COPD</td>
<td>1</td>
<td>Assumption</td>
</tr>
</tbody>
</table>
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\textsuperscript{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\textsuperscript{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\textsubscript{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\textsubscript{1}
Moderate 50-80 % predicted FEV\textsubscript{1}
Severe <30% predicted FEV\textsubscript{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. 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) 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\textsuperscript{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\textsuperscript{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\textsuperscript{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. 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 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 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. 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 FEV1. 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.

<table>
<thead>
<tr>
<th>Opportunistically case finding</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Life expectancy</td>
<td>25.25</td>
</tr>
<tr>
<td>QALYS</td>
<td>19.36</td>
</tr>
<tr>
<td>Cost</td>
<td>£1,731.83</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not opportunistically case finding</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Life expectancy</td>
<td>25.20</td>
</tr>
<tr>
<td>QALYS</td>
<td>19.32</td>
</tr>
<tr>
<td>Cost</td>
<td>£1,696.33</td>
</tr>
</tbody>
</table>

| 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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discount rate of costs and benefits</td>
<td>Both 0%</td>
</tr>
<tr>
<td>Prevalence of COPD</td>
<td>5%</td>
</tr>
<tr>
<td>Smoking cessation success rate</td>
<td>3%</td>
</tr>
<tr>
<td>Compliance for early diagnosis</td>
<td>50%</td>
</tr>
<tr>
<td>Cost of diagnosis</td>
<td>Base+low spirometry</td>
</tr>
<tr>
<td>Cost of the intervention</td>
<td>£300</td>
</tr>
</tbody>
</table>

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% 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. 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.
COPD (update)

Appendix B.1

One-way sensitivity analysis

![Graph showing varying the discount rate](image1)

![Graph showing varying the prevalence](image2)
Varying the smoking cessation rate

Cost per LYG/QALY

Varying early compliance rate

Cost per LYG/QALY
Varying the cost of intervention

![Graph showing varying costs of intervention](image)

Varying cost of diagnosis

![Graph showing varying costs of diagnosis](image)
Appendix B.2

Varying the smoking cessation rate when the prevalence is 10%

![Graph showing the cost per LYG/QALY for different effectiveness of smoking cessation rates. The graph plots cost per LYG/QALY on the y-axis and effectiveness of smoking cessation on the x-axis. The y-axis ranges from £0.00 to £18,000.00 in increments of £2,000.00. The x-axis ranges from 10% to 3% in decrements of 7%. There are two lines on the graph: one for Cost/LYG and one for Cost/QALY, both showing an increase in cost as the effectiveness of smoking cessation decreases.]
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.
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.

<table>
<thead>
<tr>
<th>Author Category</th>
<th>Calverley (^{588})</th>
<th>Guest 1999 (^{586})</th>
<th>Sullivan 2000 (^{587})</th>
<th>Britton 2003 (^{33})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year for cost data</td>
<td>1995/6</td>
<td>1996/7</td>
<td>1996</td>
<td>2000/01</td>
</tr>
<tr>
<td>Sources</td>
<td>Used data from the 4(^{th}) GP National Morbidity Study, Hospital Episode Statistics, Scottish NHS, Welsh Office, Mortality Statistics and DSS.</td>
<td>Based on a subgroup analysis of a previously published prevalence-based burden of illness analysis</td>
<td>NHS Burdens of disease: a discussion document 1996</td>
<td>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</td>
</tr>
</tbody>
</table>
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)  

- 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)  

COPD (update)

Costs given in SEK, converted to £ 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)\textsuperscript{597}

Mild £14.81
Moderate £95.20
Severe £1,658.59

Gibson et al (1998)\textsuperscript{590} This identifies resource by COPD patients with an exacerbation but does not cost it.

McGuire et al (2001)\textsuperscript{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
COPD (update)

- (cost or costs or costed or costly or costing$).tw
- (economic$ or pharmacoeconomic$ or price$ or pricing).tw
- or/1-13

Searches were restricted to 1995 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.
COPD (update)

**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.

<table>
<thead>
<tr>
<th>Area</th>
<th>Number of papers reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial cost of COPD to the NHS</td>
<td>5</td>
</tr>
<tr>
<td>Cost of an exacerbation</td>
<td>4</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>10</td>
</tr>
<tr>
<td>Pulmonary rehabilitation</td>
<td>15</td>
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<tr>
<td>Smoking cessation</td>
<td>4</td>
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<tr>
<td>Education</td>
<td>3</td>
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<tr>
<td>Oxygen-stable COPD: Long term oxygen therapy</td>
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<tr>
<td>Oxygen – stable COPD: Ambulatory oxygen therapy</td>
<td>1</td>
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<tr>
<td>Antibiotics</td>
<td>3</td>
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<tr>
<td>Hospital-at-home</td>
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<tr>
<td>Antitrypsin</td>
<td>1</td>
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<tr>
<td>Non invasive ventilation</td>
<td>5</td>
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### COPD (update)

<table>
<thead>
<tr>
<th>Area</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucolytics</td>
<td>1</td>
</tr>
<tr>
<td>Immunisation</td>
<td>3</td>
</tr>
<tr>
<td>Lung volume reduction surgery</td>
<td>1</td>
</tr>
<tr>
<td>Corticosteroids for stable COPD</td>
<td>4</td>
</tr>
</tbody>
</table>

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](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](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.


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

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


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 beta₂ agonists compared to long-acting beta₂ 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 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 muscarinic antagonists 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 muscarinic antagonists plus long-acting beta₂ agonists plus inhaled corticosteroids compared to long-acting beta₂ 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 FEV₁ (forced expiratory volume in one second) compare with pre bronchodilator FEV₁ in terms of: a) sensitivity / specificity of FEV₁ for diagnosis; b) classification of severity of disease?

DIAG 2: In individuals where the diagnosis of COPD is considered and spirometry is conducted, what is the sensitivity and specificity of a fixed ratio FEV₁ / FVC compared with lower limit of normal FEV₁ / FVC ratio to diagnose COPD?

MU CO: 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 FEV₁ alone?
### 20 Appendix I NEW 2010 update research protocols

<table>
<thead>
<tr>
<th>Question</th>
<th>How does post bronchodilator FEV₁ (forced expiratory volume in one second) compare with pre bronchodilator FEV₁ in terms of: a) sensitivity / specificity of FEV₁ for diagnosis; b) classification of severity of disease?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To determine if spirometry should be performed pre or post bronchodilator in order to accurately diagnose COPD</td>
</tr>
<tr>
<td>Criteria</td>
<td>Observational studies that compare pre and post bronchodilator (BD) FEV₁ values to a clinical diagnosis of COPD (based on symptoms). Exclude studies if pre and post BD FEV₁ values were compared to identify COPD defined according to GOLD criteria (post bronchodilator FEV₁/FVC &lt; 0.70). By definition, post bronchodilator FEV₁ would correlate better with a definition of COPD that is based on post bronchodilator FEV₁. Outcomes: sensitivity, specificity; % people identified with COPD; correlation coefficient</td>
</tr>
<tr>
<td>Search Strategy</td>
<td>Literature Search Strategy: Stable COPD AND FEV₁ AND Bronchodilators. Sources: MED, EMB, CIN, COCH.</td>
</tr>
<tr>
<td>Review Strategy</td>
<td>No RCTs; no GRADE performed; summary of study quality provided</td>
</tr>
<tr>
<td>Research protocol</td>
<td></td>
</tr>
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<td>-------------------</td>
<td></td>
</tr>
<tr>
<td><strong>DIAG 2</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Question</strong></td>
<td>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 the lower limit of normal $FEV_1 / FVC$ ratio to diagnose COPD?</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To determine if fixed $FEV_1 / FVC$ or lower limit of normal [LLN] $FEV_1 / FVC$ is a more accurate way to diagnose COPD (especially in younger and older people).</td>
</tr>
<tr>
<td><strong>Criteria</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Search Strategy</strong></td>
<td>Literature Search Strategy: Fixed Ratio $FEV_1$ AND Lower Limit $FEV_1$. Sources: MED, EMB, CIN, COCH. Limits: Study Types: RCTs, SRs</td>
</tr>
<tr>
<td><strong>Review Strategy</strong></td>
<td>No RCTs; no GRADE performed; summary of study quality provided</td>
</tr>
<tr>
<td>Research protocol</td>
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<tr>
<td><strong>Mucolytics</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Question</strong></td>
<td>What is the clinical and cost effectiveness of mucolytic agents vs. placebo in people with stable COPD?</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To determine if mucolytic agents improve outcomes (specifically decrease exacerbations) in people with COPD</td>
</tr>
<tr>
<td><strong>Criteria</strong></td>
<td>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 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), FEV₁ (100 ml), and TDI (1 unit).</td>
</tr>
<tr>
<td><strong>Search Strategy</strong></td>
<td>Literature Search Strategy: Stable COPD AND Mucolytics. Sources: MED, EMB, CIN, COCH. Limits: Study Types: RCTs, SRs, Years: 2003-20/8/09</td>
</tr>
<tr>
<td><strong>Review Strategy</strong></td>
<td>Meta-analysis where appropriate; important subgroups are type of mucolytic agent and study duration</td>
</tr>
</tbody>
</table>
Research protocol

DRUG 1: LABA vs. LAMA

<table>
<thead>
<tr>
<th>Question</th>
<th>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?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To compare the 2 classes of long-acting bronchodilators</td>
</tr>
</tbody>
</table>
| 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 FEV₁ (at ≥1year)  
• SGRQ 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), FEV₁ (100 ml), and TDI (1 unit). adverse events (15%) |
<p>| Search Strategy | Literature Search Strategy: <strong>DRUG1,3,4,5,6 were run as one search</strong>: 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 |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Research protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUG 3a:</strong> LABA + ICS vs. LABA</td>
<td>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?</td>
</tr>
<tr>
<td><strong>DRUG 3b:</strong> LABA + ICS vs. LAMA alone</td>
<td>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?</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To determine if addition of ICS to long-acting bronchodilators is clinically and economically beneficial compared with monotherapy with long-acting bronchodilators</td>
</tr>
</tbody>
</table>
| **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 FEV₁ (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), FEV₁ (100 ml), and TDI (1 unit); adverse events (15%)

<table>
<thead>
<tr>
<th>Literature Search Strategy: <strong>DRUG1,3,4,5,6 were run as one search</strong>: Stable COPD <strong>AND</strong> (LABA OR LAMA OR ICS). Sources: MED, EMB, CIN, COCH. Limits: Study Types: RCTs, SRs, Years: 2003-20/8/09</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Original MA may be required or updating published MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important subgroup analyses: study duration; type of run-in (either not stated; drug withdrawal; or drug optimisation)</td>
</tr>
<tr>
<td>- lung function level: separate by FEV₁ &lt; 50, &lt;60, &lt; 70</td>
</tr>
<tr>
<td>- 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)</td>
</tr>
</tbody>
</table>
### 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? |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To determine if addition of ICS to long-acting antimuscarinic agents is clinically and economically beneficial compared with monotherapy with long-acting bronchodilators</td>
</tr>
</tbody>
</table>
| 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 FEV₁ (at ≥1year)  
- SGRQ 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), FEV₁ (100 ml), and TDI (1 unit); adverse events (15%) |
### 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 FEV₁ < 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

<table>
<thead>
<tr>
<th>DRUG 5a: LAMA + LABA vs LABA / DRUG 5b) LAMA + LABA vs. LAMA / DRUG 5c) LAMA + LABA vs LABA + ICS</th>
</tr>
</thead>
</table>

### 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\textsubscript{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\textsubscript{1} (100 ml), and TDI (1 unit); adverse events (15%)
<table>
<thead>
<tr>
<th>Research protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRUG 6a: LAMA + LABA + ICS vs LABA + ICS / DRUG 6b) LAMA + LABA + ICS vs. LAMA alone / DRUG 6c) LAMA + LABA + ICS vs LABA + LAMA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRUG 6a: LAMA + LABA + ICS vs. LABA + ICS</td>
</tr>
<tr>
<td>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?</td>
</tr>
<tr>
<td>DRUG 6b) LAMA + LABA + ICS vs. LAMA alone</td>
</tr>
<tr>
<td>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?</td>
</tr>
<tr>
<td>DRUG 6c) LAMA + LABA + ICS vs. LABA + LAMA</td>
</tr>
<tr>
<td>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?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>To determine if triple therapy is clinically and economically beneficial compared with long-acting bronchodilators or dual therapy with LABA + ICS</td>
</tr>
</tbody>
</table>
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 ≥1 year)
- Mean rate of exacerbation (at ≥1 year)
- Hospitalisation (at ≥1 year)
- Rate of decline of FEV₁ (at ≥1 year)
- SGROQ 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), FEV₁ (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 FEV₁ < 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)
<table>
<thead>
<tr>
<th><strong>Research protocol</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug 8 LAMA vs SAMA</strong></td>
</tr>
</tbody>
</table>

### 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
<table>
<thead>
<tr>
<th>Research protocol</th>
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</thead>
<tbody>
<tr>
<td><strong>REHAB</strong></td>
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</table>

**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 FEV₁ (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), FEV₁ (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 FEV₁ alone?

### Objective
To determine the prognostic ability of FEV₁ vs. multidimensional indices to predict outcomes in stable COPD patients

### Criteria
Observational studies comparing FEV₁ 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 FEV₁. 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 ≥1 year),
- Mean rate of exacerbation (at ≥1 year),
- Hospitalisation (at ≥1 year),
- Rate of decline of FEV₁ (at ≥1 year),
- SRGQ QoL (6-12 months),
- TDI score (≥ 6 month follow up)
- Adverse events (specifically MI, arrhythmia, CHF, pneumonia, osteoporosis)
<table>
<thead>
<tr>
<th><strong>Search Strategy</strong></th>
<th><strong>Letter to stakeholders - no search required</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review Strategy</strong></td>
<td><strong>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</strong></td>
</tr>
</tbody>
</table>
### Overall protocol

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Types of Studies</td>
<td>Meta analyses / RCTs (parallel and crossover)</td>
</tr>
<tr>
<td>Types of participants</td>
<td>Adults with stable COPD (without asthma) characterised by no recent infections, exacerbations or hospitalisations in the previous month. Minimum of 10 smoking pack years</td>
</tr>
<tr>
<td>Types of intervention</td>
<td>LAMA vs SAMA</td>
</tr>
<tr>
<td></td>
<td>LAMA vs LABA</td>
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<tr>
<td></td>
<td>LABA + LAMA vs LAMA</td>
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<tr>
<td></td>
<td>LABA+LAMA vs. LABA</td>
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<td>LAMA + ICS vs LAMA</td>
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<tr>
<td></td>
<td>LAMA + ICS vs LABA</td>
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<td>LABA+ICS vs LABA</td>
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<tr>
<td></td>
<td>LABA + ICS vs LAMA</td>
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<td>LABA+LAMA+ICS vs. LABA + LAMA</td>
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<tr>
<td></td>
<td>LABA+LAMA+ICS vs. LABA + ICS</td>
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<tr>
<td></td>
<td>LABA + LAMA + ICS vs LAMA</td>
</tr>
<tr>
<td></td>
<td>Nebulised route of delivery</td>
</tr>
<tr>
<td></td>
<td>Short-acting LAMA or LABA</td>
</tr>
<tr>
<td></td>
<td>Specific populations that are not relevant e.g. Japanese and African American</td>
</tr>
</tbody>
</table>
### Types of Outcome measures

- All cause mortality (at ≥1year),
- Mean rate of exacerbation (at ≥1year),
- Hospitalisation (at ≥1year),
- Rate of decline of FEV₁ (at ≥1year)
- SRGQ QoL (6-12 months),
- TDI score (≥ 6 month follow up)
- Adverse events (cardiac, osteoporosis and pneumonia)

### Follow up

≥ 6 months

<p>| End exercise isotime Transdiaphragmatic pressure |
| Dynamic hyperinflation |
| Trough FEV₁/FVC |
| Inspired capacity |
| FEV₁ AUC 0-12 |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>All clinical questions for guideline as specified in clinical review protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To identify economic evaluations that address the clinical questions as specified above</td>
</tr>
</tbody>
</table>

**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

|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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


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$).ti.
17. sleep apnea.ti.
18. (bronchiolitis or bronchiectasis).ti.
19. interstitial.ti.
20. (interstitial adj2 (lung or pulmonary or airway$ 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.
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.
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 23

**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 5c) 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 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 muscarinic antagonists 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 muscarinic antagonists plus long-acting beta2 agonists plus inhaled corticosteroids compared to long-acting beta2 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

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Filters used</th>
<th>Date parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable COPD</td>
<td>LABA or LAMA or ICS</td>
<td></td>
<td>SRs, RCTs, (Medline and Embase only)</td>
<td>2003-20/8/09</td>
</tr>
</tbody>
</table>

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 Evoxhaler or Diskhaler).ti,ab.
12. Bronchodilator Agents/
13. or/1-12
14. Cholinergic Antagonists/
15. Muscarinic Antagonists/
16. (anti?muscacinic$ 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 adrenogenic) 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 Evoxhaler 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. (Flixtotide 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 Cyclohaler or TX Fostair  
S4  TX Respules or TX Symbicort or TX fluticasone or TX Flixtotide 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
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?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Filters used</th>
<th>Date parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable COPD</td>
<td>LAMA</td>
<td>SAMA</td>
<td>SRs RCTs (Medline and Embase only)</td>
<td>2003-20/8/09</td>
</tr>
</tbody>
</table>
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. (Bronchodilatat$ 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. (Bronchodilatat$ 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?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Filters used</th>
<th>Date parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>bronchodilators</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

**Literature search strategy**

**Medline search terms**

1. *Respiratory Function Tests/
2. *Lung function Test/
3. exp Spirometry/
4. Bronchspirometry/
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/
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. Bronchspirometry/
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/
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 Bronchspirometry 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?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Filters used</th>
<th>Date parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed ratio FEV(_1)</td>
<td>Lower limit FEV(_1)</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

**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. FEV\(_1\).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. Bronchspirometry/
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
21. letter/
22. editorial.pt.
23. note.pt.
24. case report/
25. case study/
26. animal/ not (animal/ and human/)
27. nonhuman/
COPD (update)

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)

**MUCCO:** What is the clinical and cost effectiveness of mucolytic agents vs. placebo in people with stable COPD?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Filters used</th>
<th>Date parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable COPD</td>
<td>Mucolytics</td>
<td></td>
<td>SRs RCTs</td>
<td>2003-20/8/09</td>
</tr>
</tbody>
</table>

**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 Dithioisteine 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.
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?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Filters used</th>
<th>Date parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable COPD</td>
<td>Pulmonary rehabilitation</td>
<td></td>
<td>SRs RCTs</td>
<td>2003-20/8/09</td>
</tr>
</tbody>
</table>

Literature search strategy

Medline search terms

1. *Rehabilitation/
2. (Pulmonary adj2 rehabilitation).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 FEV₁ alone?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Filters used</th>
<th>Date parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable COPD</td>
<td>Assessment indices</td>
<td>FEV1</td>
<td>SRs RCTs, Observational studies</td>
<td>2003-20/8/09</td>
</tr>
</tbody>
</table>
**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.
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 Dyspnea
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)
Economics Search

Economic searches were conducted in Medline, Embase and CRD for EED and HTA

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Filters used</th>
<th>Date parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable COPD</td>
<td></td>
<td></td>
<td>Economic (Medline and Embase only)</td>
<td>Medline and Embase 2007-24/7/09</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>CRD EED and HTA 2003-24/7/09</td>
</tr>
</tbody>
</table>

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 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. 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\textsuperscript{594}, and practical experience. It approximates to a modification of the RAND Nominal Group process (as cited in the Health Technology Appraisal\textsuperscript{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\textsuperscript{18} prior to publication.
6.4 Spirometry

GDG consensus statements

A diagnosis of airflow obstruction can be made if the FEV₁/FVC < 0.7 (i.e. 70%) and FEV₁ < 80% predicted.

6.8 Assessment of severity

GDG consensus statements

Currently there are no validated severity assessment tools that incorporate the variables quoted above.

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:

- FEV₁
- T₇CO
- breathlessness (MRC scale)
- health status
- exercise capacity
- body mass index (BMI)
- partial pressure of oxygen in arterial blood (PaO₂)
- cor pulmonale.

Grade D
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 FEV1 as a percentage of the predicted value**

<table>
<thead>
<tr>
<th>Severity</th>
<th>FEV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild airflow obstruction</td>
<td>50-79% predicted</td>
</tr>
<tr>
<td>Moderate airflow obstruction</td>
<td>30-49% predicted</td>
</tr>
<tr>
<td>Severe airflow obstruction</td>
<td>&lt;30% predicted</td>
</tr>
</tbody>
</table>

### 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.

**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.’
7.3 Inhaled bronchodilator therapy

Although COPD is characterised by substantially irreversible airflow obstruction, bronchodilators have been the mainstay of pharmacotherapy. 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 FEV₁ 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 FEV₁.

**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)$^{160}$.

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)$^{595}$.

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)$^{596}$.

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$^{597}$.

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)$^{598}$. 
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)$^{599}$.

During 12 weeks of treatment, FVC responses to ipratropium and salmeterol combination were significantly increased compared with salmeterol alone and placebo (p<0.01)$^{160}$. 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$^{160}$. 

COPD symptom scores did not change and did not differ between ipratropium + albuterol combination and individual component groups$^{596, 597}$. Mean total symptom score was 0.6 points lower during 6 weeks treatment with formoterol/ipratropium than with salbutamol/ipratropium (p = 0.0042)$^{599}$. 

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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. 

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.

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.

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).

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.
No significant difference between ipratropium and albuterol group and individual component groups in **use of concomitant respiratory medication** \(^{596}\).

After 12 weeks treatment there were no significant differences between ipratropium/albuterol combination and either component alone in **distance walked** in 6 minutes \(^{598}\).

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 \(^{595}\).

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) \(^{160}\).

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) \(^{595}\).

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%) \(^{599}\).
During 12 weeks of treatment, no significant difference in adverse events was seen in salmeterol alone, placebo and ipratropium/salmeterol combination groups\textsuperscript{160}.

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\textsuperscript{595}.

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\textsuperscript{595}.

No significant differences were found in adverse events over 12 weeks in 863 patients treated with ipratropium/albuterol combination and either component alone\textsuperscript{598}.

Beta\textsubscript{2}-agonists and inhaled steroids

Three randomised, double-blind, placebo-controlled parallel trials; Calverley 2003\textsuperscript{167} (n = 1465), Szanfranski 2003\textsuperscript{166} (n = 812), Mahler 2002\textsuperscript{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.\textsuperscript{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.

In the study by Szanfranski et al.\textsuperscript{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).

In the study by Mahler et al.\textsuperscript{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.

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)\textsuperscript{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
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.

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.

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.

Budesonide/formoterol improved and maintained morning and evening PEFR compared with placebo, budesonide and formoterol alone (p<0.001).

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).

Greater increases in morning PEF were observed throughout the 24 week treatment period with salmeterol/fluticasone combination treatment compared with fluticasone, salmeterol and placebo.

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
(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)\textsuperscript{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)\textsuperscript{166}.

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\textsuperscript{165}. There was no difference between the combination and salmeterol groups.

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)\textsuperscript{165}.

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\textsuperscript{165}.

Calverley et al\textsuperscript{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.
In the study by Szanfranski et al.\textsuperscript{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.

In the study by Mahler et al.\textsuperscript{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).

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).\textsuperscript{165}

In the study by Calverley et al.\textsuperscript{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.

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.\textsuperscript{167}

The treatment effect in relation to the number of exacerbations was more pronounced in patients with a baseline FEV\textsubscript{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\textsubscript{1} that was greater than 50% of that predicted.\textsuperscript{167}

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.\textsuperscript{167}
Szafranski et al\textsuperscript{166} showed that compared with placebo, budesonide/formoterol combination significantly reduced the number of severe exacerbations.

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.\textsuperscript{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.

In the study by Calverley et al\textsuperscript{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%).

In the study by Mahler et al\textsuperscript{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.
If patients remain symptomatic on monotherapy, their treatment should be intensified by combining therapies from different drug classes. Effective combinations include:

- beta₂-agonist and anticholinergic*
- long-acting beta₂ agonist and inhaled corticosteroid.*

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.

### 7.3.7 Delivery systems used to treat patients with stable COPD

To ensure optimum efficacy for each patient with COPD, the dose of medication should be titrated according to individual clinical response.

### 7.5.4 Oral mucolytics

Many patients with COPD cough up sputum. 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. The studies included in these systematic reviews tended to be the same trials although the systematic review by Poole did include additional papers. In addition to the trials included in the systematic reviews there were two other papers, an RCT that compared mucolytic agents to placebo and a retrospective cohort study that looked at the risk of re-hospitalisation among COPD patients using N-acetylcysteine compared to non-users.
Stey et al. 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. 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. 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 had mild COPD, only McGavin 1995 and Petty 1990 included patients with an FEV₁ 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 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. 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.

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)\(^{604}\).

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\(^{265}\)).

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)\(^{602}\).

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.
Petty et al.\textsuperscript{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.

There were no significant serious adverse events reported\textsuperscript{265,601,602}.

7.6.1 Inhaled corticosteroids

**Recommendations**

\textbf{R39} Inhaled corticosteroids should be prescribed for patients with FEV\textsubscript{1} \leq 50\% predicted, who are having 2 or more exacerbations requiring treatment with antibiotics or oral corticosteroids in a 12-month period. The aim of treatment is to reduce exacerbation rates and slow the decline in health status and not to improve lung function per se.

\textbf{R40} Clinicians should be aware of the potential risk of developing osteoporosis and other side effects in patients treated with high-dose inhaled corticosteroids (especially in the presence of other 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\textsuperscript{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

<table>
<thead>
<tr>
<th>Used at a flow rate of</th>
<th>A portable cylinder without an oxygen conserving device will last</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 l/min</td>
<td>7 hours 40 minutes</td>
</tr>
<tr>
<td>2 l/min</td>
<td>3 hours 50 minutes</td>
</tr>
<tr>
<td>4 l/min</td>
<td>1 hour 55 minutes</td>
</tr>
<tr>
<td>6 l/min</td>
<td>57 minutes</td>
</tr>
</tbody>
</table>

(N.B. The usual regulator only delivers at 2 l/min and 4 l/min)

Table 7.4 Appropriate equipment for ambulatory oxygen therapy

<table>
<thead>
<tr>
<th>Usage</th>
<th>Equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>For a duration of use of less than 90 minutes</td>
<td>Small cylinder</td>
</tr>
<tr>
<td>For a duration of use of less than 4 hours but more than 90 min</td>
<td>Small cylinder with oxygen conserving device</td>
</tr>
<tr>
<td>For duration of use of more than 4 hours</td>
<td>Liquid oxygen</td>
</tr>
<tr>
<td>For flow rates greater than 2 l/min and duration of use of more than 30 min</td>
<td>Liquid oxygen</td>
</tr>
</tbody>
</table>
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:

- beta₂-agonist and anticholinergic
- beta₂-agonist and theophylline
- anticholinergic and theophylline
- long-acting beta₂ 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

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.  

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”. This publication includes a new (draft) pneumococcal replacement chapter (November 2003).
NICE Technology Appraisal Guidance No. 58 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.

7.13.3 Identifying and managing anxiety and depression

The presence of anxiety and depression in patients with COPD can be identified using validated assessment tools.

Patients found to be depressed or anxious should be treated with conventional pharmacotherapy.

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.
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 prolonged period before the ambulance arrives.

Grade D
The aim of supplemental oxygen therapy in exacerbations of COPD is to maintain adequate levels of oxygenation ($\text{SaO}_2 > 90\%$), without precipitating respiratory acidosis or worsening hypercapnia. Patients with $\text{pH} < 7.35$ should be considered for ventilatory support.
## Appendix L NEW 2010 update criteria for selecting high-priority research recommendations

<table>
<thead>
<tr>
<th>Criterion</th>
<th>FRR1 – Timing of pulmonary rehabilitation</th>
<th>FRR2 – Multi dimensional assessment</th>
<th>FRR3 – Triple therapy</th>
<th>FRR4 – Mucolytics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Importance to the patients of the population</td>
<td>Impacts upon patient quality of life</td>
<td>Impacts upon assessment of disease severity</td>
<td>Impacts upon severity of disease and quality of life</td>
<td>Impacts upon quality of life</td>
</tr>
<tr>
<td>Relevance to NICE guidance</td>
<td>Medium, the research is relevant to the recommendations in the guideline</td>
<td>Medium, the research is relevant to the recommendations in the guideline</td>
<td>High, the research is essential to inform future updates of key recommendations in the guideline</td>
<td>Low, the research is of interest and will fill exiting evidence gaps</td>
</tr>
<tr>
<td>Relevance to NHS</td>
<td>Facilities already exist therefore benefits are to people with COPD</td>
<td>Would impact upon both primary and secondary care</td>
<td>Clinical and cost effectiveness issues of relevance to NHS</td>
<td>Clinical and cost effectiveness issues of relevance to NHS</td>
</tr>
<tr>
<td>National priorities</td>
<td>National Strategy for COPD yet to be published</td>
<td>National Strategy for COPD yet to be published</td>
<td>National Strategy for COPD yet to be published</td>
<td>National Strategy for COPD yet to be published</td>
</tr>
<tr>
<td>Current evidence base</td>
<td>Nil found on timing</td>
<td>BODE index felt by the GDG to be time-consuming and impractical for use in a primary care setting</td>
<td>Limited evidence base. Needs adequate powering and study duration</td>
<td>Limited evidence base. Requires trial design stratification re concomitant therapies</td>
</tr>
<tr>
<td>Equality</td>
<td>No special considerations – applies to all with</td>
<td>No special considerations – applies to all with</td>
<td>No special considerations – applies to all with</td>
<td>No special considerations</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>COPD</td>
<td>COPD</td>
<td>COPD</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Feasibility</td>
<td>No identified ethical or technical issues</td>
<td>No identified ethical or technical issues</td>
<td>No identified ethical (equipoise demonstrable) or technical issues</td>
<td>No identified ethical or technical issues</td>
</tr>
<tr>
<td>Other comments</td>
<td>Would benefit from cluster randomised design</td>
<td>Important to both primary and secondary care settings</td>
<td>Focus on differential dropout rates would be prudent</td>
<td>Baseline severity needs well defining out the outset</td>
</tr>
</tbody>
</table>
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 FEV₁ <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 FEV₁ <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 (FEV₁ ≥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 (FEV₁ 30 to <50% predicted), very severe COPD (FEV₁ <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*

<table>
<thead>
<tr>
<th>Input</th>
<th>Data</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparators</td>
<td>LAMA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LABA+ICS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triple therapy (LAMA+LABA+ICS)</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>COPD, FEV\textsubscript{1} &lt;50% predicted, requiring initial maintenance therapy</td>
<td></td>
</tr>
<tr>
<td>Initial cohort</td>
<td>Age (a)</td>
<td>66 years</td>
</tr>
<tr>
<td>Severity:</td>
<td>Female (b)</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td>Severe (c)</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>Very severe (c)</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>(a) Mean across RCTs used to inform treatment effects\textsuperscript{200,201,219}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(b) Analysis of UK GP records\textsuperscript{15}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(c) DH analysis\textsuperscript{609}</td>
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</tr>
<tr>
<td>Progression</td>
<td>Severe to very severe</td>
<td>0.064 (0.053-0.076)</td>
</tr>
<tr>
<td>Annual probability</td>
<td>Derived from mean decline in FEV\textsubscript{1} of 39ml/year\textsuperscript{610}</td>
<td></td>
</tr>
<tr>
<td>Baseline event rates (LABA+ICS)</td>
<td>Severe</td>
<td>0.91 (0.87-0.96)</td>
</tr>
<tr>
<td>Exacerbation/ year</td>
<td>Very severe</td>
<td>1.54 (1.44-1.64)</td>
</tr>
<tr>
<td></td>
<td>Based on 19% of exacerbations requiring hospitalisation with LABA+ICS\textsuperscript{197}</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation/ year</td>
<td>Severe</td>
<td>0.17 (0.16-0.18)</td>
</tr>
<tr>
<td></td>
<td>Very severe</td>
<td>0.29 (0.27-0.31)</td>
</tr>
<tr>
<td>Mortality RR vs. gen pop</td>
<td>Severe</td>
<td>3.1 (2.6-4.1)</td>
</tr>
<tr>
<td></td>
<td>Very severe</td>
<td>5.0 (3.5-11.8)</td>
</tr>
<tr>
<td></td>
<td>Mortality risk by GOLD stage vs. non-COPD population\textsuperscript{611} (applied to age dependent mortality rates for the UK general population\textsuperscript{612})</td>
<td></td>
</tr>
<tr>
<td>Utilities</td>
<td>COPD utility</td>
<td>0.750 (0.731-0.768)</td>
</tr>
<tr>
<td></td>
<td>Very severe</td>
<td>0.647 (0.598-0.695)</td>
</tr>
<tr>
<td></td>
<td>EQ-5D utilities reported by Rutten van Molken\textsuperscript{613}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QALY loss per exacerbation</td>
<td>0.011 (0.006-0.018)</td>
</tr>
<tr>
<td></td>
<td>Non-hospitalised</td>
<td>0.020 (0.015-0.027)</td>
</tr>
<tr>
<td></td>
<td>Hospitalised</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Derived from O’Reilly\textsuperscript{614}, Paterson\textsuperscript{615}, Spencer\textsuperscript{616}, Starkie\textsuperscript{617}</td>
<td></td>
</tr>
</tbody>
</table>
COPD (update)

<table>
<thead>
<tr>
<th>Costs</th>
<th>LAMA</th>
<th>LABA+ICS</th>
<th>Triple therapy</th>
<th>Based on recommended dosing(^{221,618-621}), UK prices(^{522}), and the Prescription Cost Analysis 2007(^{623})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug costs</td>
<td>£395.18</td>
<td>£488.76</td>
<td>£883.94</td>
<td></td>
</tr>
<tr>
<td>Costs per exacerbation</td>
<td>Non-hospitalised</td>
<td>£34 (22-48)</td>
<td>£2403 (2063-2771)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospitalised</td>
<td>£2403 (2063-2771)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance costs/year (excl. exacerbations)</td>
<td>Severe</td>
<td>£273 (208-347)</td>
<td></td>
<td>Derived from Britton et al. 2003(^{143})</td>
</tr>
<tr>
<td></td>
<td>Very severe</td>
<td>£896 (735-1079)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative treatment effects</td>
<td>LABA+ICS vs. LAMA</td>
<td>0.97 (0.84-1.12)</td>
<td>0.85 (0.79-0.92)</td>
<td>0.85 (0.65-1.11)</td>
</tr>
<tr>
<td>Exacerbations</td>
<td>Triple vs. LABA+ICS</td>
<td>0.85 (0.79-0.92)</td>
<td>0.85 (0.65-1.11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triple vs. LAMA</td>
<td>0.85 (0.65-1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalisations</td>
<td>1.08 (0.73-1.59)</td>
<td>0.89 (0.75-1.07)</td>
<td>0.53 (0.33-0.86)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0.56 (0.33-0.94)</td>
<td>0.91 (0.76-1.15)</td>
<td>1.61 (0.46-5.60)</td>
<td></td>
</tr>
<tr>
<td>Stable utility</td>
<td>+0.023 (0.001-0.046)</td>
<td>+0.021 (0.006-0.036)</td>
<td>+0.040 (0.007-0.075)</td>
<td>Derived from above RCTs mapped to EQ-5D(^{617})</td>
</tr>
</tbody>
</table>

*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 FEV1 with pharmacological treatment compared to no treatment (notably in the TORCH study)\textsuperscript{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

<table>
<thead>
<tr>
<th>COPD populations</th>
<th>Annual FEV\textsubscript{1} decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Health Study 5-year FU (Scanlon 2000)\textsuperscript{118}</td>
<td>52ml/year (SD 55)</td>
</tr>
<tr>
<td>East London Cohort (Donaldson 2003)\textsuperscript{629}</td>
<td>34.5ml/year</td>
</tr>
<tr>
<td>Anthonisen (Anthonisen 1986)\textsuperscript{41}</td>
<td>44ml/year (SD 129)</td>
</tr>
<tr>
<td>Fletcher and Peto (1977)\textsuperscript{583}</td>
<td>48 (SE 2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment specific</th>
<th>Annual FEV\textsubscript{1} decline (post-bronchodilator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TORCH RCT (3-year follow-up; n = 5343)\textsuperscript{610}</td>
<td>LABA+ICS 39.0ml/year (SE 3.0)</td>
</tr>
<tr>
<td></td>
<td>LABA 42.3ml/year (SE 3.1)</td>
</tr>
<tr>
<td></td>
<td>ICS 42.3ml/year (SE 3.1)</td>
</tr>
<tr>
<td></td>
<td>Placebo 55.3ml/year (SE 3.2)</td>
</tr>
<tr>
<td>UPLIFT RCT (4-year follow-up n = 4993)\textsuperscript{124}</td>
<td>Current treatment +placebo 42ml/year (SE 1)</td>
</tr>
<tr>
<td></td>
<td>Current treatment +LAMA 40ml/year (SE 1)</td>
</tr>
</tbody>
</table>

The probability of transitioning from severe (FEV\textsubscript{1} 30 to <50% predicted) to very severe (FEV\textsubscript{1} <30% predicted) was calculated as follows.

A typical patient in the severe (FEV\textsubscript{1} 30 to <50% predicted) was attributed the following characteristics:

- male – based on UK GP records\textsuperscript{15}
- aged 66 years – the average in the trials used in this analysis for treatment effects\textsuperscript{197,200,219}
- 1.75m tall – the average male height in the UK\textsuperscript{630}
- an FEV\textsubscript{1} 40% of predicted – the midpoint of the range in this group and the mean in this group in the TORCH study\textsuperscript{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:

\[
\text{Annual rate} = -\frac{\ln(1 - p)}{t} = -\frac{\ln(1 - 0.5)}{10.4} = 0.0664
\]

Where: \(p = \text{the proportion of patients that progress over time period } t\).

This was then converted from an annual rate to an annual transition probability using the standard formula:

\[
\text{Probability of progressing (moderate to severe)} = 1 - e^{-rt} \\
= 1 - e^{-0.0664 \times 1} \\
= 0.0642
\]

Where: \(r = \text{rate}; t = \text{time period}\)
Table 4: Modelled FEV\textsubscript{1} decline for male aged 66, height 1.76m, FEV\textsubscript{1} 40\% predicted and a decline of 39ml/year

<table>
<thead>
<tr>
<th>Age</th>
<th>FEV\textsubscript{1}</th>
<th>Predicted FEV\textsubscript{1}</th>
<th>FEV\textsubscript{1} % predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td>1.27</td>
<td>3.16</td>
<td>40.0%</td>
</tr>
<tr>
<td>67</td>
<td>1.23</td>
<td>3.14</td>
<td>39.1%</td>
</tr>
<tr>
<td>68</td>
<td>1.19</td>
<td>3.11</td>
<td>38.2%</td>
</tr>
<tr>
<td>69</td>
<td>1.15</td>
<td>3.08</td>
<td>37.3%</td>
</tr>
<tr>
<td>70</td>
<td>1.11</td>
<td>3.05</td>
<td>36.4%</td>
</tr>
<tr>
<td>71</td>
<td>1.07</td>
<td>3.02</td>
<td>35.5%</td>
</tr>
<tr>
<td>72</td>
<td>1.03</td>
<td>2.99</td>
<td>34.5%</td>
</tr>
<tr>
<td>73</td>
<td>0.99</td>
<td>2.96</td>
<td>33.5%</td>
</tr>
<tr>
<td>74</td>
<td>0.95</td>
<td>2.93</td>
<td>32.5%</td>
</tr>
<tr>
<td>75</td>
<td>0.91</td>
<td>2.90</td>
<td>31.5%</td>
</tr>
<tr>
<td>76</td>
<td>0.88</td>
<td>2.87</td>
<td>30.5%</td>
</tr>
<tr>
<td>77</td>
<td>0.84</td>
<td>2.85</td>
<td>29.4%</td>
</tr>
<tr>
<td>78</td>
<td>0.80</td>
<td>2.82</td>
<td>28.3%</td>
</tr>
<tr>
<td>79</td>
<td>0.76</td>
<td>2.79</td>
<td>27.2%</td>
</tr>
<tr>
<td>80</td>
<td>0.72</td>
<td>2.76</td>
<td>26.1%</td>
</tr>
<tr>
<td>81</td>
<td>0.68</td>
<td>2.73</td>
<td>24.9%</td>
</tr>
<tr>
<td>82</td>
<td>0.64</td>
<td>2.70</td>
<td>23.8%</td>
</tr>
<tr>
<td>83</td>
<td>0.60</td>
<td>2.67</td>
<td>22.6%</td>
</tr>
<tr>
<td>84</td>
<td>0.56</td>
<td>2.64</td>
<td>21.3%</td>
</tr>
<tr>
<td>85</td>
<td>0.52</td>
<td>2.61</td>
<td>20.1%</td>
</tr>
<tr>
<td>86</td>
<td>0.49</td>
<td>2.58</td>
<td>18.8%</td>
</tr>
</tbody>
</table>

**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\textsubscript{1} 30 to <50\% predicted) and 1.54 (SE 0.051) per person per year for very severe (FEV\textsubscript{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\textsubscript{1} groups and imputed error estimates (see below)\textsuperscript{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\textsuperscript{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\textsubscript{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\textsubscript{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\textsuperscript{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\textsubscript{1} 30-49% predicted and 243 FEV\textsubscript{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\textsuperscript{631}. A Spanish and a Swedish cohort study were also identified\textsuperscript{496,632}.

**Mortality**

Age-dependant mortality was incorporated into the model using life tables for England and Wales and severity specific COPD mortality data\textsuperscript{611,612}. A relative risk for mortality with COPD was applied of 3.1 and 5.0 for severe (FEV\textsubscript{1} 30 to <50% predicted) and very severe (FEV\textsubscript{1} <30%) stage respectively\textsuperscript{611}.

COPD severity specific mortality data was reported by Ekberg et al. based on a Swedish population study with 22,044 people\textsuperscript{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\textsubscript{1} 30 to <50% predicted) and GOLD stage 4 (FEV\textsubscript{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

<table>
<thead>
<tr>
<th></th>
<th>GOLD 3 (FEV\textsubscript{1} 30 to &lt;50%)</th>
<th>GOLD 4 (FEV\textsubscript{1} &lt;30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>LCI</td>
</tr>
<tr>
<td>Male smoker</td>
<td>2.42</td>
<td>1.84</td>
</tr>
<tr>
<td>Male former smoker</td>
<td>2.42</td>
<td>1.44</td>
</tr>
<tr>
<td>Male never smoker</td>
<td>3.93</td>
<td>1.86</td>
</tr>
<tr>
<td>Female smoker</td>
<td>5.11</td>
<td>3.09</td>
</tr>
<tr>
<td>Female former smoker</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female never smoker</td>
<td>3.91</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Weighted average</strong></td>
<td><strong>3.1</strong></td>
<td><strong>192</strong></td>
</tr>
</tbody>
</table>

Source: Ekberg et al. 2005\textsuperscript{611}
COPD mortality rates stratified by FEV₁ 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 FEV₁ group compared with a general population. Soriano et al. also reported stratified COPD mortality rates compared to a matched control group from a UK cohort. COPD severity was however classified as mild, severe and very severe by prescribed drugs and the Ekberg FEV₁ 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.

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. 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. 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. The UK tariff for the EQ-5D was used. Patients were assessed at admission, then every other day.
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. 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. For hospitalised exacerbations the figure reported by O'Reilly and colleagues is used (0.653) for the corresponding period. 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. SGRQ values at week 4 and 12 (42.5 and 37.8 – mean difference 4.7) were mapped to EQ-5D using a published algorithm. 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**

<table>
<thead>
<tr>
<th>Non-hospitalised exacerbation:</th>
<th>Hospitalised exacerbation:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key:</strong></td>
<td></td>
</tr>
<tr>
<td>Blue line = person’s utility</td>
<td></td>
</tr>
<tr>
<td>Blue fill (area under blue line) = person’s QALYs</td>
<td></td>
</tr>
<tr>
<td>Orange fill = QALY loss during exacerbation</td>
<td></td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Approach to exacerbations</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Utility during exacerbation</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Spencer et al. 2005</strong></td>
<td>ATS 1/2/3: Minor = 0.72/0.658/0.475 Major = 0.519/0.447/0.408</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Borg et al. 2004</strong></td>
<td>Mild = -5% Moderate = -15% Severe = -70%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oostenbrink et al. 2005</strong> Rutten-van Molken et al. 2007**</td>
<td>Non-severe = -15% Severe = -50%</td>
</tr>
</tbody>
</table>

**mmmm** 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
<table>
<thead>
<tr>
<th>Study</th>
<th>Utility Weight</th>
<th>Duration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maniadakis et al. 2006</td>
<td>-0.32</td>
<td></td>
<td>Mild = 1 week Moderate = 2 weeks Severe = 4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Utility weight for ‘cough, wheeze or trouble breathing’ from US stated preference experiment</td>
</tr>
<tr>
<td>Sin et al. 2004</td>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Brady et al. 2007</td>
<td>Mild = -0.17</td>
<td>3 months</td>
<td>Mild – estimate reported by Paterson et al. 2000</td>
</tr>
<tr>
<td></td>
<td>Moderate = -0.47</td>
<td></td>
<td>Moderate and severe – derivation unclear, reference to Spencer et al. 2001</td>
</tr>
</tbody>
</table>

\[999\] 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

<table>
<thead>
<tr>
<th>Studies</th>
<th>Population</th>
<th>EQ-5D tariff</th>
<th>Stratification</th>
<th>N</th>
<th>EQ-5D index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall COPD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rutten-van Molken</td>
<td>Multinational</td>
<td>UK</td>
<td>n/a</td>
<td>1235</td>
<td>0.76 (SD 0.21)</td>
</tr>
<tr>
<td>Punekar</td>
<td>Multinational</td>
<td>UK</td>
<td>n/a</td>
<td>2703</td>
<td>0.62-0.71 (range across countries)</td>
</tr>
<tr>
<td>Sullivan</td>
<td>USA</td>
<td>US</td>
<td>n/a</td>
<td>1609</td>
<td>0.797 (IQR 0.76-0.83)</td>
</tr>
<tr>
<td>Harper</td>
<td>UK</td>
<td>NR</td>
<td>n/a</td>
<td>125</td>
<td>0.524 (SD 0.157)</td>
</tr>
<tr>
<td>Hazell</td>
<td>UK</td>
<td>UK</td>
<td>n/a</td>
<td>1054</td>
<td>0.63</td>
</tr>
<tr>
<td>Stavem</td>
<td>Norway</td>
<td>UK</td>
<td>n/a</td>
<td>59</td>
<td>0.73 (IQR 0.62-0.81)</td>
</tr>
<tr>
<td>Polley</td>
<td>UK</td>
<td>NR</td>
<td>n/a</td>
<td>18</td>
<td>0.45 (SD 0.31)</td>
</tr>
<tr>
<td>Szende</td>
<td>Sweden</td>
<td>European</td>
<td>n/a</td>
<td>176</td>
<td>0.76 (SD 0.22)</td>
</tr>
<tr>
<td>Johansson</td>
<td>Sweden</td>
<td>NR</td>
<td>n/a</td>
<td>21</td>
<td>0.52 (SD 0.30)</td>
</tr>
<tr>
<td><strong>By severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rutten-van Molken</td>
<td>Multinational</td>
<td>UK</td>
<td>GOLD 2</td>
<td>622</td>
<td>0.787 (CI: 0.771-0.802)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GOLD 3</td>
<td>513</td>
<td>0.750 (CI: 0.731-0.768)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GOLD 4</td>
<td>91</td>
<td>0.647 (CI: 0.598-0.695)</td>
</tr>
<tr>
<td>Stahl</td>
<td>Sweden</td>
<td>UK</td>
<td>GOLD 1</td>
<td>26</td>
<td>0.84 (SD 0.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GOLD 2</td>
<td>91</td>
<td>0.73 (SD 0.23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GOLD 3</td>
<td>33</td>
<td>0.74 (SD 0.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GOLD 4</td>
<td>9</td>
<td>0.52 (SD 0.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BTS 0</td>
<td>26</td>
<td>0.84 (SD 0.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BTS 1</td>
<td>63</td>
<td>0.74 (SD 0.21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BTS 2</td>
<td>47</td>
<td>0.72 (SD 0.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BTS 3</td>
<td>23</td>
<td>0.63 (SD 0.25)</td>
</tr>
<tr>
<td>Punekar</td>
<td>Multinational</td>
<td>UK</td>
<td>GOLD 1</td>
<td>92/218</td>
<td>PCP 0.77 (CI: 0.73-0.81) / RS 0.68 (CI: 0.64-0.72)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GOLD 2</td>
<td>77/314</td>
<td>0.68 (CI:0.62-0.74) / 0.72 (CI:0.69-0.75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GOLD 3/4</td>
<td>79/340</td>
<td>0.62 (CI:0.56-0.68) / 0.64 (CI:0.61-0.67)</td>
</tr>
<tr>
<td>Spencer</td>
<td>UK</td>
<td>UK</td>
<td>ATS 1</td>
<td>283</td>
<td>0.81 (SE 0.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ATS 2</td>
<td></td>
<td>0.72 (SE 0.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ATS 3</td>
<td></td>
<td>0.67 (SE 0.05)</td>
</tr>
</tbody>
</table>

*Brazier et al. also reports on the same dataset and is not included above. **Szende also reports on the same dataset and is not included above.

† FEV₁ % 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. ² 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. 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.

- 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Within class use*</th>
<th>Formulation</th>
<th>Preparation</th>
<th>Units/pack</th>
<th>Cost/pack†</th>
<th>Cost/unit</th>
<th>Units/dose‡</th>
<th>Doses/day‡</th>
<th>Cost/day</th>
<th>Cost/year</th>
<th>Preparation use %**</th>
<th>Av. cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LAMA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiotropium</td>
<td>100%</td>
<td>Spiriva®</td>
<td>(Boehringer Ingelheim)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HandiHaler® (inhalation powder), device + capsules, 18 micrograms</td>
<td>30</td>
<td>£34.87</td>
<td>£1.16</td>
<td>1</td>
<td>1</td>
<td>£1.16</td>
<td>£424.25</td>
<td>20%</td>
<td></td>
<td>£395.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HandiHaler® (inhalation powder), capsules, 18 micrograms</td>
<td>30</td>
<td>£31.89</td>
<td>£1.06</td>
<td>1</td>
<td>1</td>
<td>£1.06</td>
<td>£388.00</td>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LABA+ICS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide/formoterol</td>
<td>26%</td>
<td>Symbicort®</td>
<td>(AstraZeneca)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>200/6 Turbohaler® (dry powder inhaler), metered dose, 200/6 micrograms</td>
<td>120</td>
<td>£38.00</td>
<td>£0.32</td>
<td>2</td>
<td>2</td>
<td>£1.27</td>
<td>£462.33</td>
<td>72%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>400/12 Turbohaler® (dry powder inhaler), metered dose, 400/12 micrograms</td>
<td>60</td>
<td>£38.00</td>
<td>£0.63</td>
<td>1</td>
<td>2</td>
<td>£1.27</td>
<td>£462.33</td>
<td>28%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone/salmeterol</td>
<td>74%</td>
<td>Seretide®</td>
<td>(A&amp;H)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 Accuhaler® (dry powder for inhalation), device + blisters, 500/50 micrograms</td>
<td>60</td>
<td>£40.92</td>
<td>£0.68</td>
<td>2</td>
<td>1</td>
<td>£1.36</td>
<td>£497.86</td>
<td>100%</td>
<td></td>
<td>£488.76</td>
</tr>
</tbody>
</table>

*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. budesonide/formoterol) sums to 100%. Sources: †NHS Drug Tariff February 2010622, ‡product licences221,628,629,631, */** Prescription Cost Analysis 2007623

580
**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. 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). 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.

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. 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. 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 steam 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.

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.

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. 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.
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\textsuperscript{626}. The cost of a GP visit was based on the 2008 average UK cost (latest available at time of analysis)\textsuperscript{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)\textsuperscript{624,627} (before inflated £30.69, SD 111.4)\textsuperscript{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\textsuperscript{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

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Setting and study design</th>
<th>Exacerbation definitions</th>
<th>Cost/exacerbation (2007/8 £)***</th>
<th>Resource use reported?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lucioni et al 2005</td>
<td>Italy (resource use and unit costs)</td>
<td>Not reported (includes exacerbations requiring hospitalisation and not)</td>
<td>£1085***</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>People diagnosed with COPD hospitalised for an exacerbation; followed-up prospectively for 6 months post-discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Data collection via patient questionnaires</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N = 570 (282 with ≥1 exacerbation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbations = 282</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersson et al 2002</td>
<td>Sweden (resource use and unit costs)</td>
<td>Mild = self-managed by increasing dose of current medication (including adding OTC medication)</td>
<td>Mild = £11</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>People diagnosed with COPD who had experienced an exacerbation the previous winter</td>
<td>Mild-moderate = telephone contact and/or antibiotics/systemic corticosteroids</td>
<td>Mild/moderate = £34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Data collection via patient questionnaires; visits and hospitalisations verified via medical records</td>
<td>Moderate = requiring GP/outpatient visit</td>
<td>Moderate = £202</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N = 61</td>
<td>Severe = requiring A&amp;E visit or hospitalisation</td>
<td>Severe = £2092</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbations = 75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miravitlles et al. 2002</td>
<td>Spain (resource use and unit costs)</td>
<td>Exacerbation = presence of increased dyspnoea, and/or increased production and/or purulence that led to a change or increase in treatment</td>
<td>£144</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>People diagnosed with COPD who presented to GP with exacerbation; followed-up at 1 month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Data collection by GP at planned follow-up visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N = 2414</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*** 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. Reported to nearest whole £.

*** Direct cost only presented here; calculated by dividing exacerbation costs/year by exacerbations/year.
<table>
<thead>
<tr>
<th>Study</th>
<th>Resource Use/Unit Costs</th>
<th>Exacerbation Definition</th>
<th>Non-Severe Cost (£)</th>
<th>Severe Cost (£)</th>
<th>Resource Use Included</th>
<th>Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutten-van Molken 2007</td>
<td>Spain (resource use and unit costs)</td>
<td>Exacerbation = as per Miravitlles et al. 2002 above</td>
<td>Non-severe = £75³</td>
<td>Severe = £1940³</td>
<td>Reanalysis of data from Miravitlles et al. 2002 above. Resource use included: healthcare contacts, A&amp;E visits, hospitalisation</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Reanalysis of data from Miravitlles et al 2002 above</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O'Reilly et al. 2006</td>
<td>UK (resource use and unit costs)</td>
<td>Symptom-defined = increased symptoms for ≥2 days</td>
<td>Symptom-defined = £18</td>
<td>Healthcare-defined = £34</td>
<td>Symptom-defined = requiring antibiotics and/or oral corticosteroids for chest problems</td>
<td>Partly</td>
</tr>
<tr>
<td></td>
<td>People diagnosed with COPD registered in a PCT; followed-up prospectively for 1 year</td>
<td>Healthcare-defined = requiring A&amp;E visit or hospitalisation</td>
<td></td>
<td></td>
<td>Resource use included: drugs, healthcare contacts, A&amp;E visits, hospitalisation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Data collection by daily diary cards</td>
<td></td>
<td></td>
<td></td>
<td>Note: no patients were hospitalised during study</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N = 848</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbations: symptom-defined = 296; healthcare defined = 351</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptomatic COPD patients enrolled in fluticasone propionate RCT; resource use collected prospectively</td>
<td>Moderate = physician-treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbations: mild = 64; moderate = 112; severe = 18</td>
<td>Severe = hospitalised</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oostenbrink et al. 2004</td>
<td>Netherlands/Belgium (86%/14%) (Netherlands unit costs)</td>
<td>Mild = awareness of a sign or symptom which is easily tolerated³⁴</td>
<td>Mild = £74</td>
<td>Moderate = £498³⁵</td>
<td>Resource use included: hospitalisation, A&amp;E visits, healthcare contacts, tests, drugs</td>
<td>Partly</td>
</tr>
<tr>
<td></td>
<td>People with stable COPD enrolled in 2 tiotropium vs. ipratropium RCTs; prospective follow-up for 1 year</td>
<td>Moderate = causing discomfort enough to cause interference with usual activity³⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N = 519 (207 with ≥1 exacerbation)</td>
<td>Severe = incapacitating or causing inability to do work or usual activity³⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbations = 364</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

³ Direct medical costs only included here; NHS sick leave benefit and other excluded.
⁻⁻⁻⁻ 52% of severe exacerbations required hospital admission.
⁻⁻⁻⁻ Classification of exacerbations based on ratings by the physician-investigator.
⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻~-~-~

584
<table>
<thead>
<tr>
<th>Study</th>
<th>Country and Exacerbation Details</th>
<th>Resource Use Included</th>
<th>Original Resource Use Data Reported</th>
<th>CEA Analysis</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oostenbrink et al. 2005</td>
<td>Canada (resource use and unit costs)</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Original resource use data reported as part of CEA. People with COPD; prospective follow-up for 1 year</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>N = 598</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbations = NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maniadakis et al. 2006</td>
<td>Greece (resource use and unit costs)</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Original resource use data reported as part of CEA. Analysis of medical records at the University General Hospital of Heraklion in Greece.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N = NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbations = NR</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

The 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\textsubscript{1} 30 to <50% predicted) and very severe (FEV\textsubscript{1} <30% predicted) stages respectively were applied in the model. Mean estimates were derived from a UK COPD costing study\textsuperscript{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\textsuperscript{33}. Severity classification was by self-designation or dyspnoea scale (into mild, moderate and severe) rather than FEV\textsubscript{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\textsubscript{1} based severity groups and excluded exacerbation costs but from non-UK settings\textsuperscript{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 incorporated 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 estimates 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>
<thead>
<tr>
<th>Study design</th>
<th>Maintenance cost/year (2007/8 £)</th>
<th>Resource use reported?</th>
</tr>
</thead>
</table>
| Lucioni et al 2005 | ● 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  
● 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 | ● 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 | ● 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 | ● 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 | ● GOLD 2 = £352  
● GOLD 3 = £617  
● GOLD 4 = £1363  
Resource use included: medical visits, hospital admission, tests, drugs, oxygen. | Yes |

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. Reported to nearest whole £. FEV₁ % predicted: GOLD 1/2/3/4 = ≥80/79-50/49-30/<30; ATS 1/2/4 = 80-50/50-35/<35.

Direct cost only presented here; calculated by dividing exacerbation costs/year by exacerbations/year.
<table>
<thead>
<tr>
<th>Country</th>
<th>Resource Use and Unit Costs</th>
<th>Resource Use Included</th>
<th>Excludes Exacerbation Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>- Canada (resource use and unit costs)</td>
<td>- Canada</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Original resource use data reported as part of CEA. People with COPD; prospective follow-up for 1 year</td>
<td>- Gold 2 = £330</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- N = 598</td>
<td>- Gold 3 = £797</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Gold 4 = £1194</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resource use included: healthcare contacts, tests, drugs, oxygen.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excludes exacerbation costs.</td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>- Greece (resource use and unit costs)</td>
<td>- Greece</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Original resource use data reported as part of CEA. Analysis of medical records at the University General Hospital of Heraklion in Greece.</td>
<td>- Gold 2 = £355</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>- N = NR</td>
<td>- Gold 3 = £431</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Gold 4 = £562</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resource use included: healthcare contacts, spirometry, drugs.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excludes exacerbation costs.</td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>- Ireland</td>
<td>- Ireland</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- People with COPD diagnosis attending an outpatients clinic</td>
<td>- Gold 0 = £1637</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Data collected by patient interview for previous 6 months and annualised</td>
<td>- Gold 1 = £2000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- N = 150 (GOLD 0/1/2/3/4 = 20/14/46/38/24)</td>
<td>- Gold 2 = £2753</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Gold 3 = £4004</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Gold 4 = £6703</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resource use included: healthcare contacts, hospitalisation, drugs, tests. Includes exacerbation costs</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>- UK</td>
<td>- UK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- N = 400</td>
<td>- Mild = £171 / £291bbb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Data from telephone interviews</td>
<td>- Moderate = £352 / £683</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Recorded info about the past year</td>
<td>- Severe = £1494 / £2239</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- People with COPD</td>
<td>Mild, moderate, severe = Self reported severity / MRC dyspnoea 0-2, 3-4, 5.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resource use included: healthcare contacts, tests, drugs, oxygen.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Includes exacerbation costs; in whole population costs not related to unscheduled care = 40%.</td>
<td></td>
</tr>
</tbody>
</table>

**bbb** Other country reports of same study available but not reported as same format as for UK.

**bbb** Direct costs only presented here
| Jansson 2002<sup>655</sup> | Sweden (resource use and costs) | FEV<sub>1</sub> >80% predicted = £173  
FEV<sub>1</sub> 60-79% predicted = £384  
FEV<sub>1</sub> 40-59% predicted = £1297  
FEV<sub>1</sub> <40% predicted = £4258  
Resource use included: drugs, healthcare contacts, hospitalisation, oxygen. Includes exacerbation costs. | Partly |
| --- | --- | --- | --- |
| People with COPD; followed-up over 1 year  
Data collected via telephone interviews every 3 months  
N = 212 | | | |
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\textsuperscript{219}: LAMA vs LABA+ICS
- UPLIFT subgroup analysis\textsuperscript{201}: triple therapy vs LABA+ICS
- OPTIMAL study\textsuperscript{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

<table>
<thead>
<tr>
<th>1. INSPIRE, UPLIFT</th>
<th>2. INSPIRE, OPTIMAL</th>
<th>3. UPLIFT, OPTIMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LABA+ICS</td>
<td>LABA+ICS</td>
<td>LABA+ICS</td>
</tr>
<tr>
<td>LAMA ↔ Triple</td>
<td>LAMA ↔ Triple</td>
<td>LAMA ↔ Triple</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>LABA+ICS vs. LAMA</th>
<th>Triple vs. LABA+ICS</th>
<th>Triple vs. LAMA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exacerbations: rate ratio (95% confidence interval); grey/italic = implicit value</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. INSPIRE, UPLIFT</td>
<td>0.97 (0.84-1.12)</td>
<td>0.85 (0.78-0.92)</td>
<td>0.82</td>
</tr>
<tr>
<td>2. INSPIRE, OPTIMAL</td>
<td>0.97 (0.84-1.12)</td>
<td>0.88</td>
<td>0.85 (0.65-1.11)</td>
</tr>
<tr>
<td>3. UPLIFT, OPTIMAL</td>
<td>1.00</td>
<td>0.85 (0.78-0.92)</td>
<td>0.85 (0.65-1.11)</td>
</tr>
<tr>
<td><strong>Hospitalisations: rate ratio (95% confidence interval); grey/italic = implicit value</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. INSPIRE, UPLIFT</td>
<td>1.08 (0.73-1.59)</td>
<td>0.89 (0.75-1.07)</td>
<td>0.96</td>
</tr>
<tr>
<td>2. INSPIRE, OPTIMAL</td>
<td>1.08 (0.73-1.59)</td>
<td>0.49</td>
<td>0.53 (0.33-0.86)</td>
</tr>
<tr>
<td>3. UPLIFT, OPTIMAL</td>
<td>0.60</td>
<td>0.89 (0.75-1.07)</td>
<td>0.53 (0.33-0.86)</td>
</tr>
<tr>
<td><em><em>Stable utility (EQ-5D): mean difference mapped from SGRQ</em>; grey/italic = implicit value</em>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. INSPIRE, UPLIFT</td>
<td>0.023 (0.001-0.046)</td>
<td>0.021 (0.006-0.036)</td>
<td>0.044</td>
</tr>
<tr>
<td>2. INSPIRE, OPTIMAL</td>
<td>0.023 (0.001-0.046)</td>
<td>0.017</td>
<td>0.040 (0.007-0.075)</td>
</tr>
<tr>
<td>3. UPLIFT, OPTIMAL</td>
<td>0.019</td>
<td>0.021 (0.006-0.036)</td>
<td>0.040 (0.007-0.075)</td>
</tr>
<tr>
<td><strong>Mortality: risk ratio (95% confidence interval); grey box = implicit value</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. INSPIRE, UPLIFT</td>
<td>0.56 (0.33-0.94)</td>
<td>0.91 (0.76-1.11)</td>
<td>0.51</td>
</tr>
<tr>
<td>2. INSPIRE, OPTIMAL</td>
<td>0.56 (0.33-0.94)</td>
<td>2.88</td>
<td>1.61 (0.46-0.56)</td>
</tr>
<tr>
<td>3. UPLIFT, OPTIMAL</td>
<td>1.72</td>
<td>0.91 (0.76-1.11)</td>
<td>1.61 (0.46-0.56)</td>
</tr>
</tbody>
</table>

*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: INSPIRE219, UPLIFT subgroup201, OPTIMAL200

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\textsuperscript{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\textsuperscript{175,617}. However, it is noted that both approaches yielded similar values in the middle. The Starkie formula is displayed below.

$$\text{Predicted utility score} = 1 - 0.0335 \cdot T + 0.0017 \cdot T^2 + 0.0001 \cdot T^3 - 0.0279 \cdot G$$

*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.

$$\text{Total discounted QALYs} = \sum_{i=1}^{i} \frac{Q(t)}{(1 + r)^{i-1}}$$

Where: $t = \text{cycle number}; i = \text{maximum cycle number}; Q(t) = \text{QALYs in cycle } t; r = \text{discount rate}$

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.

$$\text{Total discounted costs} = \sum_{i=1}^{i} \frac{C(t)}{(1 + r)^{i-1}}$$

Where: $t = \text{cycle number}; i = \text{maximum cycle number}; C(t) = \text{Costs in cycle } t; r = \text{discount rate}$

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.

$$\text{ICER} = \frac{\text{Costs (B)} - \text{Costs (A)}}{\text{QALYs (B)} - \text{QALYs (A)}}$$

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 terms 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.

\[
Net\ Benefit\ (X) = \text{QALYs} (X) \times D \Rightarrow Costs (X)
\]

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)

<table>
<thead>
<tr>
<th></th>
<th>Mean Cost</th>
<th>Mean QALYs</th>
<th>Net benefit* (threshold=£20,000 per QALY)</th>
<th>Probability that strategy is most cost-effective (threshold=£20,000 per QALY)</th>
<th>Net benefit* (threshold=£30,000 per QALY)</th>
<th>Probability that strategy is most cost-effective (threshold=£30,000 per QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. INSPIRE, UPLIFT data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>£5296</td>
<td>2.350</td>
<td>£41,709</td>
<td>16%</td>
<td>£65,211</td>
<td>17%</td>
</tr>
<tr>
<td>LAMA</td>
<td>£4896</td>
<td>2.349</td>
<td>£42,087</td>
<td>84%</td>
<td>£65,579</td>
<td>83%</td>
</tr>
<tr>
<td>Triple</td>
<td>£6426</td>
<td>2.357</td>
<td>£40,721</td>
<td>0%</td>
<td>£64,294</td>
<td>0%</td>
</tr>
<tr>
<td><strong>2. INSPIRE, OPTIMAL data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>£5296</td>
<td>2.350</td>
<td>£41,709</td>
<td>15%</td>
<td>£65,211</td>
<td>16%</td>
</tr>
<tr>
<td>LAMA</td>
<td>£4896</td>
<td>2.349</td>
<td>£42,087</td>
<td>84%</td>
<td>£65,579</td>
<td>81%</td>
</tr>
<tr>
<td>Triple</td>
<td>£5764</td>
<td>2.358</td>
<td>£41,405</td>
<td>1%</td>
<td>£64,989</td>
<td>3%</td>
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<tr>
<td><strong>3. UPLIFT, OPTIMAL data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>£5296</td>
<td>2.350</td>
<td>£41,709</td>
<td>92%</td>
<td>£65,211</td>
<td>92%</td>
</tr>
<tr>
<td>LAMA</td>
<td>£6260</td>
<td>2.345</td>
<td>£40,643</td>
<td>8%</td>
<td>£64,094</td>
<td>8%</td>
</tr>
<tr>
<td>Triple</td>
<td>£6426</td>
<td>2.357</td>
<td>£40,721</td>
<td>0%</td>
<td>£64,294</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Highest net benefit = most cost effective option at stated threshold
Figure 4: Basecase results on the cost-effectiveness plane (exacerbation effect only; 4 years)

<table>
<thead>
<tr>
<th></th>
<th>LABA+ICS</th>
<th>LAMA</th>
<th>Triple therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>£187,697/QALY</td>
<td>£93,737/QALY</td>
<td>£159,353/QALY</td>
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</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th></th>
<th>Exacerbations</th>
<th>Cost of treating exacerbations</th>
<th>COPD maintenance</th>
<th>Total cost</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Total</td>
<td>Non-hospitalised</td>
<td>Hospitalised</td>
<td>Total</td>
</tr>
<tr>
<td><strong>1. INSPIRE, UPLIFT data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>4161</td>
<td>3370</td>
<td>791</td>
<td>£1,753,181</td>
</tr>
<tr>
<td>LAMA</td>
<td>4286</td>
<td>3551</td>
<td>735</td>
<td>£1,417,488</td>
</tr>
<tr>
<td>Triple</td>
<td>3537</td>
<td>2833</td>
<td>704</td>
<td>£3,170,669</td>
</tr>
<tr>
<td><strong>2. INSPIRE, OPTIMAL data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>4161</td>
<td>3370</td>
<td>791</td>
<td>£1,753,181</td>
</tr>
<tr>
<td>LAMA</td>
<td>4286</td>
<td>3551</td>
<td>735</td>
<td>£1,417,488</td>
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<tr>
<td>Triple</td>
<td>3643</td>
<td>3253</td>
<td>390</td>
<td>£3,170,669</td>
</tr>
<tr>
<td><strong>3. UPLIFT, OPTIMAL data</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>4161</td>
<td>3370</td>
<td>791</td>
<td>£1,753,181</td>
</tr>
<tr>
<td>LAMA</td>
<td>4149</td>
<td>2832</td>
<td>1317</td>
<td>£1,417,488</td>
</tr>
<tr>
<td>Triple</td>
<td>3537</td>
<td>2833</td>
<td>704</td>
<td>£3,170,669</td>
</tr>
</tbody>
</table>
**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)

<table>
<thead>
<tr>
<th></th>
<th>Mean Cost</th>
<th>Mean QALYs</th>
<th>Net benefit* (threshold= £20,000 per QALY)</th>
<th>Probability that strategy is most cost-effective (threshold= £20,000 per QALY)</th>
<th>Net benefit* (threshold= £30,000 per QALY)</th>
<th>Probability that strategy is most cost-effective (threshold= £30,000 per QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. INSPIRE, UPLIFT data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>£5298</td>
<td>2.349</td>
<td>£41,688</td>
<td>21%</td>
<td>£65,180</td>
<td>6%</td>
</tr>
<tr>
<td>LAMA</td>
<td>£4895</td>
<td>2.268</td>
<td>£40,475</td>
<td>4%</td>
<td>£63,160</td>
<td>1%</td>
</tr>
<tr>
<td>Triple</td>
<td>£6429</td>
<td>2.427</td>
<td>£42,105</td>
<td>76%</td>
<td>£66,373</td>
<td>93%</td>
</tr>
<tr>
<td><strong>2. INSPIRE, OPTIMAL data</strong></td>
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<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>£5298</td>
<td>2.349</td>
<td>£41,688</td>
<td>29%</td>
<td>£65,180</td>
<td>25%</td>
</tr>
<tr>
<td>LAMA</td>
<td>£4895</td>
<td>2.268</td>
<td>£40,475</td>
<td>0%</td>
<td>£63,160</td>
<td>0%</td>
</tr>
<tr>
<td>Triple</td>
<td>£5766</td>
<td>2.413</td>
<td>£42,496</td>
<td>71%</td>
<td>£66,628</td>
<td>75%</td>
</tr>
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<td><strong>3. UPLIFT, OPTIMAL data</strong></td>
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<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>£5298</td>
<td>2.349</td>
<td>£41,688</td>
<td>22%</td>
<td>£65,180</td>
<td>6%</td>
</tr>
<tr>
<td>LAMA</td>
<td>£6244</td>
<td>2.279</td>
<td>£39,340</td>
<td>2%</td>
<td>£62,131</td>
<td>1%</td>
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<tr>
<td>Triple</td>
<td>£6429</td>
<td>2.427</td>
<td>£42,105</td>
<td>76%</td>
<td>£66,373</td>
<td>93%</td>
</tr>
</tbody>
</table>

*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)

1 (inspire, uplift)

2 (inspire, optimal)

3 (uplift, optimal)
**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)

<table>
<thead>
<tr>
<th></th>
<th>Mean Cost</th>
<th>Mean QALYs</th>
<th>Net benefit* (threshold=£20,000 per QALY)</th>
<th>Probability that strategy is most cost-effective (threshold=£20,000 per QALY)</th>
<th>Net benefit* (threshold=£30,000 per QALY)</th>
<th>Probability that strategy is most cost-effective (threshold=£30,000 per QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. INSPIRE, UPLIFT data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>£5293</td>
<td>2.350</td>
<td>£41,714</td>
<td>89%</td>
<td>£65,218</td>
<td>66%</td>
</tr>
<tr>
<td>LAMA</td>
<td>£4443</td>
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<td>£38,614</td>
<td>4%</td>
<td>£60,142</td>
<td>2%</td>
</tr>
<tr>
<td>Triple</td>
<td>£6491</td>
<td>2.380</td>
<td>£41,104</td>
<td>7%</td>
<td>£64,902</td>
<td>31%</td>
</tr>
<tr>
<td><strong>2. INSPIRE, OPTIMAL data</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>£5293</td>
<td>2.350</td>
<td>£41,714</td>
<td>92%</td>
<td>£65,218</td>
<td>93%</td>
</tr>
<tr>
<td>LAMA</td>
<td>£4443</td>
<td>2.153</td>
<td>£38,614</td>
<td>3%</td>
<td>£60,142</td>
<td>2%</td>
</tr>
<tr>
<td>Triple</td>
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<td>1.885</td>
<td>£33,166</td>
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<td>£52,014</td>
<td>5%</td>
</tr>
<tr>
<td><strong>3. UPLIFT, OPTIMAL data</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>£5293</td>
<td>2.350</td>
<td>£41,714</td>
<td>34%</td>
<td>£65,218</td>
<td>22%</td>
</tr>
<tr>
<td>LAMA</td>
<td>£6519</td>
<td>2.429</td>
<td>£42,064</td>
<td>64%</td>
<td>£66,355</td>
<td>69%</td>
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<tr>
<td>Triple</td>
<td>£6491</td>
<td>2.380</td>
<td>£41,104</td>
<td>2%</td>
<td>£64,902</td>
<td>8%</td>
</tr>
</tbody>
</table>

*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)

1 (inspire, uplift)

2 (inspire, optimal)

3 (uplift, optimal)
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 (highest 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)

<table>
<thead>
<tr>
<th></th>
<th>1 (inspire, uplift):</th>
<th></th>
<th>2 (inspire, optimal):</th>
<th></th>
<th>3 (uplift, optimal):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost</td>
<td>QALYs</td>
<td>Probability that strategy is most cost-effective (threshold= £20,000 per QALY)</td>
<td>Cost</td>
<td>QALYs</td>
</tr>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>£1,483</td>
<td>0.681</td>
<td>79%</td>
<td>£1,483</td>
<td>0.681</td>
</tr>
<tr>
<td>LAMA</td>
<td>£1,337</td>
<td>0.666</td>
<td>21%</td>
<td>£1,337</td>
<td>0.666</td>
</tr>
<tr>
<td>Triple</td>
<td>£1,815</td>
<td>0.684</td>
<td>0%</td>
<td>£1,520</td>
<td>0.642</td>
</tr>
<tr>
<td>4 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>£5,293</td>
<td>2.350</td>
<td>89%</td>
<td>£5,293</td>
<td>2.350</td>
</tr>
<tr>
<td>LAMA</td>
<td>£4,443</td>
<td>2.153</td>
<td>4%</td>
<td>£4,443</td>
<td>2.153</td>
</tr>
<tr>
<td>Triple</td>
<td>£6,491</td>
<td>2.380</td>
<td>7%</td>
<td>£4,531</td>
<td>1.885</td>
</tr>
<tr>
<td>Lifetime (4-years differential treatment period with lifetime extrapolation)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>£11,788</td>
<td>4.972</td>
<td>38%</td>
<td>£11,788</td>
<td>4.972</td>
</tr>
<tr>
<td>LAMA</td>
<td>£9,729</td>
<td>4.311</td>
<td>1%</td>
<td>£9,729</td>
<td>4.311</td>
</tr>
<tr>
<td>Triple</td>
<td>£13,133</td>
<td>5.057</td>
<td>61%</td>
<td>£8,470</td>
<td>3.509</td>
</tr>
<tr>
<td>Lifetime (lifetime differential treatment period)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>£11,772</td>
<td>4.965</td>
<td>34%</td>
<td>£11,772</td>
<td>4.965</td>
</tr>
<tr>
<td>LAMA</td>
<td>£7,976</td>
<td>3.751</td>
<td>1%</td>
<td>£7,976</td>
<td>3.751</td>
</tr>
<tr>
<td>Triple</td>
<td>£14,845</td>
<td>5.197</td>
<td>65%</td>
<td>£7,449</td>
<td>3.026</td>
</tr>
</tbody>
</table>

*Minor discrepancies in LABA+ICS figures between the two lifetime analyses are due to them being generated by different runs of the probabilistic 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 simulations where triple therapy was optimal increased.

Table 17: Exacerbation rates used in sensitivity analysis

<table>
<thead>
<tr>
<th>Change from baseline exacerbation rate</th>
<th>COPD stage</th>
<th>Exacerbations/ year</th>
<th>Hospitalisations/ year</th>
</tr>
</thead>
<tbody>
<tr>
<td>-50%</td>
<td>Severe</td>
<td>0.46</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Very severe</td>
<td>0.77</td>
<td>0.15</td>
</tr>
<tr>
<td>0% (baseline)</td>
<td>Severe</td>
<td>0.91</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Very severe</td>
<td>1.54</td>
<td>0.29</td>
</tr>
<tr>
<td>100%</td>
<td>Severe</td>
<td>1.82</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>Very severe</td>
<td>3.08</td>
<td>0.59</td>
</tr>
<tr>
<td>200%</td>
<td>Severe</td>
<td>2.73</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>Very severe</td>
<td>4.62</td>
<td>0.88</td>
</tr>
<tr>
<td>300%</td>
<td>Severe</td>
<td>3.64</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>Very severe</td>
<td>6.16</td>
<td>1.17</td>
</tr>
</tbody>
</table>

Severe = FEV1 30% to <50% predicted; Very severe = FEV1 <30% predicted
Figure 7: Exacerbation rate sensitivity analysis: basecase analysis (exacerbation effect only; 4 years)

1 (inspire, uplift)

% simulations each treatment was the most cost-effective option at a £20,000/QALY threshold

Change in baseline exacerbation rate

2 (inspire, optimal)

% simulations each treatment was the most cost-effective option at a £20,000/QALY threshold

Change in baseline exacerbation rate

3 (uplift, optimal)

% simulations each treatment was the most cost-effective option at a £20,000/QALY threshold

Change in baseline exacerbation rate
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 threshold 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 FEV₁ <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

<table>
<thead>
<tr>
<th>GDG MEMBER</th>
<th>Declarations of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margaret Barnard</td>
<td>24/08/2008 I have COPD</td>
</tr>
<tr>
<td>Graham Burns</td>
<td>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.</td>
</tr>
<tr>
<td>Peter Calverley</td>
<td>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.</td>
</tr>
<tr>
<td>Barbara Foggo</td>
<td>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.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th><strong>Kevin Gruffydd Jones</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>25.07.08</td>
<td>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, Trinti Chiesi. My practice has carried out commercial 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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Erica Haines</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>12.1.09 x1GDG deputy</td>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>David Halpin (Invited expert)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>23.7.08</td>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Karen Heslop</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Date? 2008</td>
<td>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.</td>
</tr>
<tr>
<td>24.06.09</td>
<td>Boehringer Ingelheim - consultancy work for workshop on CBT in COPD; Astra Zeneca - consultancy fee for workshop on CBT.</td>
</tr>
<tr>
<td>16.9.09</td>
<td>Presentation on CBT in COPD for GSK on 11.9.09. Presentation on oxygen guidelines and inhaler workshop on 23.9.09 for AZ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Kevin Holton</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>07.01.09 x1 GDG</td>
<td>NONE</td>
</tr>
<tr>
<td>Name</td>
<td>Date</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Melvyn Jones</td>
<td>22.05.09</td>
</tr>
<tr>
<td>Katherine Leach</td>
<td>10.12.08</td>
</tr>
<tr>
<td>Christine Loveridge</td>
<td>8.10.08</td>
</tr>
<tr>
<td>Phyo Kyan Myint</td>
<td>24.10.08</td>
</tr>
<tr>
<td>Fiona Phillips</td>
<td>12.07.09</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Date</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Michael Rudolf</td>
<td>31.07.08</td>
</tr>
<tr>
<td>Sally Singh</td>
<td>07.08.08</td>
</tr>
<tr>
<td>Jadwiga Wedzicha</td>
<td>9.08.08</td>
</tr>
</tbody>
</table>
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**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Tiotropium n/N</th>
<th>LABA n/N</th>
<th>RR (fixed)</th>
<th>Weight</th>
<th>RR (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brusasco 2003</td>
<td>46/402</td>
<td>56/405</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vogelmeier 2006</td>
<td>23/221</td>
<td>17/210</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>623</td>
<td>618</td>
<td>76.19</td>
<td>0.81 [0.56, 1.17]</td>
<td>23.81 [1.19, 2.34]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chisq = 1.67, df = 1 (P = 0.20), I² = 40.1%
Test for overall effect: Z = 0.51 (P = 0.61)
Number of people with COPD exacerbations requiring hospitalisation

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Tiotropium nN</th>
<th>LABA nN</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brusasco 2003</td>
<td>12/402</td>
<td>20/406</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vogelmeier 2008</td>
<td>6/221</td>
<td>1/216</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>623</td>
<td>615</td>
<td></td>
<td>100.00</td>
<td>0.01 (0.43, 1.62)</td>
</tr>
</tbody>
</table>

Total events: 17 (Tiotropium), 21 (LABA)
Test for heterogeneity: Chi² = 3.29, df = 1 (P = 0.07), I² = 69.6%
Test for overall effect: Z = 0.66 (P = 0.51)

From section 7.3.6.1 Long-acting beta₂ 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

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>LABA + ICS</th>
<th>LABA</th>
<th>Rate Ratio (random)</th>
<th>Weight</th>
<th>Rate Ratio (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>log(Rate Ratio) (SE)</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>All treatment withdrawn during run in and more than one year study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TORCH 2007</td>
<td>1533</td>
<td>1521</td>
<td>0.0200 (0.0900)</td>
<td>60.41</td>
<td>1.02 [0.86, 1.22]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1533</td>
<td>1521</td>
<td></td>
<td>60.41</td>
<td>1.02 [0.86, 1.22]</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.22 (P = 0.82)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Stabilising treatment given during run in and one year study |            |      |                     |        |                    |
| Kardos 2007         | 507        | 487  | -0.4200 (0.2200)    | 39.59  | 0.66 [0.43, 1.01]   |
| Subtotal (95% CI)    | 507        | 487  |                      | 39.59  | 0.66 [0.43, 1.01]   |
| Test for heterogeneity: not applicable |        |      |                     |        |                    |
| Test for overall effect: Z = 1.91 (P = 0.06) |        |      |                     |        |                    |

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Total (95% CI)</th>
<th>2040</th>
<th>2008</th>
<th>100.00</th>
<th>0.86 [0.56, 1.31]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test for heterogeneity: Ch² = 3.43, df = 1 (P = 0.06), I² = 70.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.72 (P = 0.47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.1  0.2  0.5  1  2  5  10

Favours LABA + ICS  Favours LABA
## Change from baseline in breathlessness score (TDI)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>LAEA + ICS Mean (SD)</th>
<th>N</th>
<th>LABA Mean (SD)</th>
<th>WMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>WMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahler 2002</td>
<td>163</td>
<td>2.10 (4.34)</td>
<td>159</td>
<td>0.90 (3.40)</td>
<td>3.36</td>
<td>33.64</td>
<td>1.20 [0.35, 2.05]</td>
</tr>
<tr>
<td>Harania 2003</td>
<td>178</td>
<td>1.70 (2.91)</td>
<td>177</td>
<td>1.60 (2.91)</td>
<td>3.66</td>
<td>66.36</td>
<td>0.10 [-0.51, 0.71]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>341</td>
<td>2.10 (4.34)</td>
<td>336</td>
<td>1.60 (2.91)</td>
<td>100.00</td>
<td>4.07</td>
<td>0.47 [-0.02, 0.96]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: CH² = 4.27, df = 1 (P = 0.04), I² = 75.6%
Test for overall effect: Z = 1.87 (P = 0.03)
Mortality

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>LABA + ICS n/N</th>
<th>LABA n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC0100470 2006</td>
<td>3/532</td>
<td>3/518</td>
<td>1.24 [0.20, 4.80]</td>
<td>0.40</td>
<td>3.08 [0.32, 29.39]</td>
</tr>
<tr>
<td>Trnvlkin (3209 μg)</td>
<td>3/277</td>
<td>1/284</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (65%) CI</td>
<td>609</td>
<td>602</td>
<td></td>
<td>1.64</td>
<td>1.49 [0.46, 5.24]</td>
</tr>
<tr>
<td>Total events: 5 (LABA + ICS), 4 (LABA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: CHI² = 0.57, df = 1 (P = 0.41), χ² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.52 (P = 0.53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 one year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calverley 2003</td>
<td>5/254</td>
<td>13/265</td>
<td>5.29 [0.14, 1.07]</td>
<td>0.82</td>
<td>1.50 [0.75, 2.96]</td>
</tr>
<tr>
<td>Szefran 2003</td>
<td>6/298</td>
<td>6/201</td>
<td>2.49 [0.32, 2.95]</td>
<td>0.80</td>
<td>1.87 [0.75, 2.29]</td>
</tr>
<tr>
<td>TRISTAN 2003</td>
<td>2/358</td>
<td>2/373</td>
<td>0.89 [0.15, 7.96]</td>
<td>0.80</td>
<td>1.40 [0.28, 1.99]</td>
</tr>
<tr>
<td>Kardos 2007</td>
<td>7/507</td>
<td>9/487</td>
<td>3.71 [0.80, 8.62]</td>
<td>1.25</td>
<td>1.55 [0.50, 4.82]</td>
</tr>
<tr>
<td>Ferguson 2008</td>
<td>6/394</td>
<td>3/385</td>
<td>1.50 [0.50, 4.82]</td>
<td>0.80</td>
<td>1.50 [0.50, 4.82]</td>
</tr>
<tr>
<td>Rennard (2009 μg)</td>
<td>3/494</td>
<td>2/495</td>
<td>0.82 [0.50, 1.33]</td>
<td>1.25</td>
<td>1.55 [0.50, 4.82]</td>
</tr>
<tr>
<td>Subtotal (65%) CI</td>
<td>2215</td>
<td>2199</td>
<td></td>
<td>1.43</td>
<td>0.82 [0.50, 1.33]</td>
</tr>
<tr>
<td>Total events: 20 (LABA + ICS), 36 (LABA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: CHI² = 4.99, df = 5 (P = 0.51), χ² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.82 (P = 0.41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>03 more than one year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TORCH 2007</td>
<td>193/1533</td>
<td>205/1621</td>
<td>93.98 [0.78, 1.12]</td>
<td>0.99</td>
<td>1.12 [0.78, 1.12]</td>
</tr>
<tr>
<td>Subtotal (65%) CI</td>
<td>1533</td>
<td>1621</td>
<td></td>
<td>83.98</td>
<td>0.93 [0.78, 1.12]</td>
</tr>
<tr>
<td>Total events: 193 (LABA + ICS), 205 (LABA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.73 (P = 0.47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (65%) CI</td>
<td>4657</td>
<td>4622</td>
<td></td>
<td>100.00</td>
<td>0.99 [0.78, 1.10]</td>
</tr>
<tr>
<td>Total events: 226 (LABA + ICS), 244 (LABA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: CHI² = 5.58, df = 6 (P = 0.69), χ² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.36 (P = 0.36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Cataracts

**Review:** Drug 3a: LABA + ICS vs. LABA (Cochrane) (latest 300309)

**Comparison:** 01 LABA + ICS vs. LABA

**Outcome:** 18 Cataracts

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>LABA+ICS n/N</th>
<th>LABA n/N</th>
<th>RR (fixed)</th>
<th>Weight %</th>
<th>95% CI</th>
<th>RR (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TORCH 2007</td>
<td>14/52</td>
<td>6/41</td>
<td></td>
<td>100.00</td>
<td>1.84 [0.78, 4.37]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>52</td>
<td>41</td>
<td></td>
<td>100.00</td>
<td>1.84 [0.78, 4.37]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 14 (LABA+ICS), 6 (LABA)

Test for heterogeneity: not applicable

Test for overall effect: Z = 1.38 (P = 0.17)
Fractures

Review: Drug 3a: LABA + ICS vs. LABA (Cochrane) (130609)
Comparison: 01 LABA + ICS vs. LABA
Outcome: 19 Fractures (total)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>LABA + ICS n/N</th>
<th>LABA n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferguson 2009</td>
<td>79/1546</td>
<td>61/1542</td>
<td></td>
<td>100.00</td>
<td>1.28 [0.92, 1.77]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1546</td>
<td>1542</td>
<td></td>
<td>100.00</td>
<td>1.28 [0.92, 1.77]</td>
</tr>
</tbody>
</table>

Total events: 79 (LABA + ICS), 61 (LABA)
Test for heterogeneity: not applicable
Test for overall effect: $z = 1.46$ ($P = 0.15$)
From section 7.4.4 Oral mucolytics

**Mucolytics versus Placebo**

**Number of people hospitalised**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Mucolytic</th>
<th>Placebo</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moretti 2004</td>
<td>16/75</td>
<td>19/76</td>
<td>0.51 [0.25, 1.02]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doermer 2005</td>
<td>55/256</td>
<td>69/267</td>
<td>0.63 [0.61, 1.13]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>335</td>
<td>343</td>
<td>0.75 [0.67, 1.01]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 65 (mucolytic), 66 (placebo)
Test for heterogeneity: CH² = 1.82, df = 1 (P = 0.20), P = 36.4%
Test for overall effect: Z = 1.91 (P = 0.05)
### Change from baseline in health related quality of life (total SGRQ score)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>Mucolytic Mean (SD)</th>
<th>Placebo Mean (SD)</th>
<th>WMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>WMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decramer 2005</td>
<td>218</td>
<td>-3.76 (13.40)</td>
<td>227</td>
<td>-4.96 (4.61)</td>
<td>66.06</td>
<td>1.19 [-0.69, 3.07]</td>
</tr>
<tr>
<td>Zheng 2006</td>
<td>354</td>
<td>-4.06 (16.43)</td>
<td>354</td>
<td>-0.08 (19.01)</td>
<td>39.74</td>
<td>-4.01 [-6.63, -1.39]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>572</td>
<td></td>
<td>581</td>
<td></td>
<td>100.00</td>
<td>-0.57 [-2.16, 0.95]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Q=10.00, df=1 (P = 0.003), I² = 90.0%
Test for overall effect: Z = 0.74 (P = 0.46)

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

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>mucolytic</th>
<th>placebo</th>
<th>RR (fixed)</th>
<th>VWeight</th>
<th>RR (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mN</td>
<td>mN</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 N-acetylcysteine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ebbadini 1990</td>
<td>23/371</td>
<td>41/373</td>
<td>1.46</td>
<td>0.55</td>
<td>0.92</td>
</tr>
<tr>
<td>Donnan 1993</td>
<td>44/127</td>
<td>45/132</td>
<td>1.02</td>
<td>1.06</td>
<td>1.50</td>
</tr>
<tr>
<td>Mesler 1996</td>
<td>44/90</td>
<td>46/91</td>
<td>1.29</td>
<td>0.97</td>
<td>1.30</td>
</tr>
<tr>
<td>Nornal 1999</td>
<td>22/159</td>
<td>30/184</td>
<td>1.08</td>
<td>0.71</td>
<td>1.18</td>
</tr>
<tr>
<td>Pola 1999</td>
<td>6/85</td>
<td>3/86</td>
<td>1.09</td>
<td>1.97</td>
<td>7.64</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>172</td>
<td>97</td>
<td>1.08</td>
<td>0.56</td>
<td>1.04</td>
</tr>
<tr>
<td>Total events: 139 (mucolytic), 163 (placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 6.6, df = 4 (P = 0.14), I² = 42.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.54 (P = 0.12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 02 Corbicoverine      |           |         |            |         |            |
|                       |           |         |            |         |            |
| Grillo 1992           | 16/32     | 12/26   | 0.34       | 1.27    | 0.44       |
| Allegro 1998          | 16/32     | 11/26   | 0.46       | 0.20    | 0.26       |
| Zheng 2008            | 52/353    | 56/351  | 0.92       | 1.01    | 1.13       |
| Subtotal (95% CI)     | 530       | 527     | 0.86       | 0.49    | 1.16       |
| Total events: 89 (mucolytic), 95 (placebo) | | | | | |
| Test for heterogeneity: Chi² = 6.53, df = 2 (P = 0.06), I² = 63.8% |
| Test for overall effect: Z = 0.88 (P = 0.38) |

| 03 Enalostatone       |           |         |            |         |            |
|                       |           |         |            |         |            |
| Moretti 2004          | 14/63     | 19/61   | 0.89       | 0.71    | 1.29       |
| Subtotal (95% CI)     | 53        | 61      | 0.88       | 0.71    | 1.29       |
| Total events: 14 (mucolytic), 18 (placebo) | | | | | |
| Test for heterogeneity: not applicable |
| Test for overall effect: Z = 1.14 (P = 0.27) |
| Total (95% CI)        | 1525      | 1522    | 1.00       | 0.86    | 1.00       |
| Total events: 241 (mucolytic), 281 (placebo) | | | | | |
| Test for heterogeneity: Chi² = 12.59, df = 8 (P = 0.01), I² = 36.4% |
| Test for overall effect: Z = 1.97 (P = 0.05) |

0 to 100%: Favour mucolytic; 50%: equal; 100%: favour placebo.
## Mortality

**Review:** Mucolytics (Version 2)

**Comparison:** 01 mucolytic vs. placebo

**Outcome:** 00 Death during study period

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>01 more than one year follow up</th>
<th>02 6 months follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mucolytic, nN</td>
<td>placebo, nN</td>
</tr>
<tr>
<td>Soehner</td>
<td>1/96</td>
<td>3/96</td>
</tr>
<tr>
<td>Subtotal (55%) C1</td>
<td>352</td>
<td>363</td>
</tr>
<tr>
<td>Total events (mucolytic), 12 (placebo)</td>
<td>10/1020</td>
<td>14/1020</td>
</tr>
<tr>
<td>Test for heterogeneity: Ch² = 0.86, df = 1 (P = 0.35), I² = 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.36 (P = 0.72)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>01 more than one year follow up</th>
<th>02 6 months follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mucolytic, nN</td>
<td>placebo, nN</td>
</tr>
<tr>
<td>Cotton 1985</td>
<td>1/154</td>
<td>1/155</td>
</tr>
<tr>
<td>Peit 1999</td>
<td>1/64</td>
<td>1/65</td>
</tr>
<tr>
<td>Subtotal (95%) C1</td>
<td>138</td>
<td>140</td>
</tr>
<tr>
<td>Total events (mucolytic), 2 (placebo)</td>
<td>12/360</td>
<td>14/360</td>
</tr>
<tr>
<td>Test for heterogeneity: Ch² = 0.27, df = 1 (P = 0.61), I² = 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.48 (P = 0.63)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>01 more than one year follow up</th>
<th>02 6 months follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mucolytic, nN</td>
<td>placebo, nN</td>
</tr>
<tr>
<td>Total events (mucolytic), 14 (placebo)</td>
<td>490</td>
<td>503</td>
</tr>
<tr>
<td>Test for heterogeneity: Ch² = 1.21, df = 3 (P = 0.76), I² = 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.51 (P = 0.61)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
From section 7.9.5 Timing of rehabilitation programmes

Early pulmonary rehabilitation post exacerbation compared with usual care/control

Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>early pulmonary rehab</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early pulmonary rehab (inpatient)</td>
<td></td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
<td></td>
</tr>
<tr>
<td>Behnke 2000</td>
<td>1</td>
<td>14</td>
<td>12</td>
<td>11.9%</td>
</tr>
<tr>
<td>Nava 1998</td>
<td>12</td>
<td>60</td>
<td>4</td>
<td>66.5%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>74</td>
<td>32</td>
<td>78.4%</td>
<td>0.98 [0.38, 2.52]</td>
</tr>
<tr>
<td>Total events</td>
<td>13</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.05 (P = 0.96)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Early pulmonary rehab (outpatient) | 1 | 2 | 2 | 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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>early pulmonary rehab</th>
<th>Control</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3.1 Rehab initiated in hospital (inpatient)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behnke 2000</td>
<td>1</td>
<td>3</td>
<td>0.33 [0.04, 2.97]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>23</td>
<td>23</td>
<td>37.5%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.98 (P = 0.33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 1.3.2 rehab initiated after hospital discharge (outpatient) | | | | |
| Murphy 2005       | 2                      | 5       | 0.40 [0.09, 1.70]             |                               |
| Subtotal (95% CI) | 13                     | 13      | 62.5%                         |                               |
| Total events      | 2                      | 5       |                               |                               |
| Heterogeneity: Not applicable | | | | |
| Test for overall effect: Z = 1.24 (P = 0.22) | | | | |
| Total (95% CI)    | 36                     | 36      | 100.0%                        | 0.38 [0.11, 1.26]             |
| Total events      | 3                      | 8       |                               |                               |
| Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0% | | | | |
| Test for overall effect: Z = 1.58 (P = 0.11) | | | | |
| Test for subgroup differences: Not applicable | | | | |
27 Reference List


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