6-year surveillance 2015 – Chronic obstructive pulmonary disease in over 16s: diagnosis and management

Appendix A: Decision matrix

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
Working definition of COPD			
101 – 01 What is a useful, robust definition of COPD? (2004; not linked to a specific guideline recommendation)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 02 Must the definition of COPD include the presence of airflow obstruction? (2004; not linked to a specific guideline recommendation)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 03 Must the definition of COPD include reversibility criteria? (2004; not linked to a specific guideline recommendation)			
Surveillance decision			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 04 Must the definition of COPD discuss causation and pathophysiology? (2004; not linked to a specific guideline recommendation)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 05 What is the current and future burden of COPD in England & Wales? (2004; not linked to a specific guideline recommendation)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	A systematic review[1] which assessed the excess costs of comorbidities in COPD indicated that pneumonia, cardiovascular disease and diabetes were associated with the highest excess costs. On average, the factors constituted a doubling of respective costs in	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. The new evidence does not give a direct indication of the current and future burden of COPD in England and Wales. As a result, it is unlikely to impact on recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	patients with comorbidities. The main cost driver, among all studies, was inpatient cost.		
Diagnosing COPD			
101 – 06 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? (2010; 1.1.2.2, 1.1.6.1)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 07 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? (2010; 1.1.2, 1.1.6.1)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) A systematic review[2] was identified which reported that the prevalence of spirometry-based COPD was greater when using the fixed value of FEV1/FVC in comparison to using the lower limit of normal (LLN). As such, the review concluded that using the LLN of FEV1/FVC may	No relevant evidence identified.	Topic experts felt that discussions are needed about whether the diagnostic criterion of using FEV1/FVC <70% to detect airway obstruction should be changed to use LLN: observational studies suggest different outcomes if the LLN of the FEV1/FVC ratio is used	No new evidence was identified that would affect recommendations. At the previous review there was a lack of predictive equations and reference values for post bronchodilator FEV1 and FVC values. As a result, it was considered that more research was needed to confirm the

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
underestimate COPD. One GDG member suggested the need to consider the importance of using LLN rather than a fixed FEV1/FVC ratio to define obstructive spirometry. Due to lack of predictive equations and reference values for post bronchodilator FEV1 and FVC values, it was considered that more research was needed to confirm the role of LNN in COPD diagnosis. **Evidence Update (2012)** No relevant evidence identified		to diagnose COPD.	role of LNN in COPD diagnosis
101 – 08 Is routine assessment using multidimensional severity assessment indices (e.g. BODE) more predictive of outcomes compared with FEV1 alone? (2010; 1.1.5.1)			
Surveillance decision This review question should be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	One systematic review[3] assessed the reliability, validity, responsiveness and minimum clinically important difference (MCID) of the self-administered COPD assessment test (CAT). Included studies indicated that the CAT had high internal consistency (range, 0.85 to 0.98) and test-retest reliability (range, 0.80 to 0.96). Scores differed with GOLD stages, as	Topic experts stated that there is a need to review the role of multidimensional assessments of COPD severity. They highlighted various multidimensional severity assessment tools, such as GOLD, DECAF, CAT, BODE and DOSE. The respiratory lead at the Royal College of General Practitioners	New evidence identified that may change current recommendations. The guideline does not mention or make recommendations on the use of multidimensional severity assessment indices. Although, it is unclear whether these indices will supersede spirometry, an update of the guideline may be needed to outline when and how they should be used.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	well as exacerbation and modified Medical Research Council (mMRC) dyspnoea grades. Furthermore, mean scores decreased with pulmonary rehabilitation and increased at exacerbation onset. A meta-analysis[4] compared the diagnostic accuracy of the COPD Diagnostic Questionnaire (CDQ) with that of handheld flow meters. Among 'ever smokers', the CDQ had a pooled sensitivity of 64.5% and specificity of 65.2% whereas handheld flow meters had a sensitivity of 79.9% and specificity of 84.4%. A network analysis[5] which compared the predictive capacity of the 2011 GOLD staging system with the GOLD 2007, reported that the 2011 system shifted the overall COPD severity distribution to more severe categories. There were nearly 3 times more COPD patients in stage D than in former stage IV (statistically significant). The predictive capacity for survival up to 10 years was significant for both systems; however, there was no significant difference	highlighted concerns about the lack of a forthcoming update of the COPD guideline. They highlighted that considerable changes have been made to assessment and management recommendations in the international GOLD Guidelines. This was supported by NICE's Medicines and Prescribing Programme (MPP) which suggested that it is a significant issue in practice. Feedback from their clinical networks revealed that CG101 is considered outdated, especially in relation many new inhalers that have become available over the last few years, and is largely ignored in favour of the GOLD guideline.	

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	between groups. One systematic review[6] reported that case finding approaches including pre-screening with questionnaires (not specified), handheld flow meters, and direct invitation to diagnostic spirometry were more effective strategies of identifying undiagnosed COPD than usual care.		
101 – 09 Can COPD be detected before the onset of symptoms? (2004; 1.1.7.1-1.1.7.2)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 10 What factors can be used to identify patients opportunistically as being at risk of having COPD? (2004; 1.1.1.1, 1.1.7.1-1.1.7.2)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) An RCT[7] compared the effectiveness of 2 strategies for early detection of COPD. In the 'practice-managed' strategy, the clinical practice was responsible for the whole procedure,	Three systematic reviews[10-12] indicated that workplace exposure to vapours, gases, dusts or fumes significantly increased the risk of COPD. One review highlighted that	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. The new evidence suggests additional risk factors for COPD; however, the identified

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
whereas in the 'patient-managed' strategy, patients were responsible for calculating their Respiratory Health Screening Questionnaire (RHSQ) risk score and applying for a spirometry test. Authors reported higher COPD detection rates in the practice-managed strategy (36%) than in the patient-managed strategy (18%). Another study[8] reported that the COPD Assessment Test (CAT) aided physician assessments of COPD in primary care consultations. It was considered that additional research was needed to support results of identified studies before considering whether the CAT and other strategies for detection of COPD should be included in the guideline. **Evidence Update (2012)** A meta-analysis[9] highlighted that the presence of residential dampness and mould may be linked with both bronchitis and respiratory tract infections. Several limitations were identified with the study design however, the EUAG felt that the evidence suggested that residential dampness and mould may be associated with lung health problems, and these data may be relevant to the aetiology of COPD, particularly in the context of the potential links between COPD and poverty.	both organic and inorganic workplace exposures increased the risk of COPD[11]. Another review[12] reported that exposure to respirable quartz reduced the mean ratio of FEV1 to FVC. Furthermore, the FEV1 of workers exposed to respirable quartz dust was 4.6% less than predicted compared with workers with no/low exposure. Another systematic review[13] reported a significant association between a history of tuberculosis and the presence of COPD in adults aged over 40 years. Two systematic reviews[14,15] of observational studies indicated a significant association between Helicobacter pylori infections and COPD.		systematic reviews are small and assess different risk factors in different populations. Further research is needed to confirm apparent associations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 11 What methods can be used to confirm the diagnosis in patients identified opportunistically as being at risk of having COPD? (2004; 1.1.2.1 – 1.1.7.2)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 12 Does early diagnosis of COPD affect the success of smoking cessation therapy? (2004; not linked to a specific guideline recommendation)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 13 What symptoms are suggestive of a diagnosis of COPD? (2004; 1.1.1.1-1.1.1.3)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 14 What other conditions may present with similar symptoms/signs/results? (2004; 1.1.1.2)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 15 In patients with suspected COPD, what are the most effective diagnostic criteria? (2004; 1.1.2.1–1.1.2.7)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 16 What clinical signs are useful (confirm or refute the diagnosis) in stable COPD? (2004; 1.1.1.2)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 17 What are the most appropriate tests in a patient with suspected COPD to confirm the diagnosis? (2004; 1.1.3)			
Surveillance decision This review question should be updated.			
4-year surveillance (2014) A meta-analysis[16] performed in 1 systematic review indicated that computed tomography (CT) improved the accuracy of COPD diagnosis. Another systematic reported that (18)F-fluorodeoxyglucose positron emission tomography ((18)F-FDG-PET) may be useful in differentiating COPD from other diseases. Clinical feedback highlighted the potential use of biomarkers, multi-dimensional assessments (COPD Assessment Test - CAT) and cardio-metabolic co-morbidities as a guide to severity and prognosis. CT scanning was already recommended as a tool to aid investigations in some circumstances. The identified new evidence supported that recommendation. In terms of (18)F-FDG-PET), it was considered that further research was needed before recommendations were included in the guideline. **Evidence Update (2012)**	A systematic review[17] of observational studies reported that patients with stable COPD had higher sputum myeloperoxidase levels than healthy controls. Furthermore, authors reported that theophylline treatment was able to reduce myeloperoxidase levels in COPD patients. One systematic review[18] explored the association between serum interleukin-6 (IL-6) concentrations and COPD. Authors reported that serum IL-6 concentrations were higher in patients with stable COPD than healthy controls. Furthermore, patients who had COPD without major comorbidities had higher IL-6 concentrations than healthy controls. No significant differences in IL-6 concentrations were observed between patients with mild to moderate COPD and those with severe to very severe COPD.	Topic experts highlighted that recent evidence suggests that systemic inflammatory markers and biomarkers, including eosinophils, may have a role in predicting COPD phenotypes, exacerbation risk and related outcomes. One expert added that there may be a need to consider positioning of drug therapies in the context of COPD phenotypes rather than FEV1 and presence or persistence of breathlessness and/or exacerbations. Topic experts also highlighted that a number of observational studies show that diagnostic precision improves with the aid of Computed Tomography scanning.	New evidence identified that may change current recommendations A CT scan is already recommended as a tool to aid investigations in some circumstances and the identified new evidence during the 4-year review supported the recommendation. The guideline makes no references to the use of inflammatory markers and biomarkers for diagnosing COPD. The identified new evidence, in combination with topic expert opinions, suggests that these tests that could aid with the diagnosis of COPD.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
No relevant evidence identified			
101 – 18 What is the role of spirometry in the diagnosis of COPD? (2004; 1.1.2.1–1.1.2.7)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) One clinical trial[19] reported that the quality and reproducibility of spirometry in people with COPD was acceptable and improved over time. The results of a trial indicated that spirometry was found to be acceptable and improved over time which is supportive of the recommendation which states that spiromtery should be performed at the time of diagnosis. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. During the previous review, only 1 study was identified. The results of this study were in favour of guideline recommendations.
101 – 19 Where and by whom should spirometry be performed in order to maximise reliable and valid test result outcomes? (2004; 1.1.2.4–1.1.2.6)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 20 What is the role of reversibility testing in the diagnosis of COPD? (2004; 1.1.4.1–1.1.4.6)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 21 What is the role of reversibility testing in the prediction of response to COPD drugs? (2004; 1.1.4.4)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 22 How should the severity of stable COPD be assessed? (2004; 1.1.6.1)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No new evidence identified. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 23 Which patients with stable COPD should be referred for specialist advice? (2004; 1.1.8.1)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
Managing stable COPD			
101 – 24 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? (2010; 1.2.2.6)			
Surveillance decision Although the new evidence does not indicate a need to update this review question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.			
4-year surveillance (2014) An RCT[20] compared the effects of salmeterol with that of tiotropium on muscular efficiency in people with COPD. Treatment with tiotropium resulted in significantly greater endurance times than treatment with placebo. Conversely, there was no significant difference between endurance times of patients who received salmeterol and those who received placebo.	In a systematic review[30] comparing indacaterol against tiotropium in patients with moderate to severe COPD, no significant differences in FEV1 measurements and St. George's Respiratory Questionnaire scores were observed between groups at 12 and 26 weeks. Furthermore, the incidence rates of nasopharyngitis, serious cardiovascular events, and serious adverse events were not different between indacaterol and	Topic experts suggested that the algorithm for inhaled therapy needs to be amended. One expert suggested that the guideline needs to be changed in order to promote usage of LAMAs as first line treatment rather than LABAs: they suggested that the evidence in 2010 was pointing in that direction but wasn't strong enough to suggest a LAMA. One topic expert highlighted that some LAMAs (such	New evidence is unlikely to impact on guideline recommendations. The guideline currently recommends that people with FEV1 ≥ 50% predicted should be offered either a LAMA or LABA whilst those with FEV1 ≤ 50% should receive a LABA plus inhaled corticosteroid or a LAMA. The identified systematic review, comparing indacaterol and tiotropium, reports no significant differences in outcome measures

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
A meta-analysis[21] revealed that indacaterol had a superior safety and efficacy profile than tiotropium, and placebo at 12, 26 and 52 week follow-up. Similarly, a systematic review[22] which compared indarcaterol and tiotropium reported significantly greater reductions in dyspnoea and usage of rescue medications. An RCT reported that treatment with indacaterol or tiotropium resulted in significantly greater improvements in FEV1 and FVC values when compared with placebo: results indicated that both treatments had a similar bronchodilator effect. This observation was supported by a post-hoc analysis[23] of clinical studies which indicated that both medications had similar effects in people with less severe dyspnoea. In people with more severe dyspnoea, both treatments improved trough FEV1 and dyspnoea scores but only tiotropium decreased the risk of COPD exacerbations when compared against placebo. The results of an individual patient data network meta-analysis[24] indicated that indacaterol was at least as efficacious as formoterol and comparable to tiotropium and salmeterol regarding FEV1. A systematic review[25] reported that	tiotropium. Authors stated that the incidence of coughing and COPD worsening were higher in patients who were treated by indacaterol.	as tiotropium) are coming to the end of their patents and generic versions should become commercially available. The expert felt that this could have considerable impact on the cost effectiveness of this class of bronchodilator. Further investigations by NICE's Medicines and Prescribing Programme (MPP) revealed that the patent for tiotropium expired in October 2015; however, there appeared to be additional protection until March 2016 under paediatric extension. The MPP could not identify any generic products on the European Medicines Agency website but suggested that applications may appear shortly after March 2016. The patents for aclidinium bromide, glycopyrronium bromide, and umeclidinium bromide are due to expire in 2025, 2027 and 2029, respectively. The MPP and the respiratory lead at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy	between groups. Furthermore, the abstract does not specify the FEV1% values of the included populations. As a result, there is no evidence indicating superiority of one treatment over another in any particular group of people with COPD. Although the new evidence does not indicate a need to update this review question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
tiotropium was more effective than LABAs in preventing COPD exacerbations and disease-related hospitalisations, although there were no statistical differences between groups in overall hospitalisation rates or mortality during the study periods. The results of a meta-analysis[26] suggested that a tiotropium Soft Mist Inhaler was associated with a universally increased risk of overall death (particularly in people with more severe COPD) compared with placebo, a tiotropium HandiHaler, LABA-alone and LABA-ICS combinations. LABA-ICS was associated with the lowest risk of death among all treatments no excess risk was noted for tiotropium HandiHaler or LABA. In 2014, Feedback from the GDG highlighted that there was more data available on the choice between LABA and LAMA as first line therapy and also about the safety of ICSs. It was considered, that there was insufficient evidence that conclusively indicated superiority of one treatment over the other. Assessment of the abstracts gave no clear indication of the FEV1% values of study populations. The guideline currently recommends that people with FEV1 ≥ 50% predicted should be offered either a LAMA		using newer bronchodilator medications.	

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
or LABA whilst those with FEV1 ≤ 50% should receive a LABA plus inhaled corticosteroid or a LAMA and it is unlikely that the new evidence would change this recommendation. **<u>Evidence Update (2012)</u>** An RCT of patients treated by tiotropium or salmeterol reported the duration of time until first exacerbation was greater in the tiotropium group. Patients were allowed to use ICS medications during the study period. As a result, interpretation of the impact on this evidence on the guideline was complicated. The INTENSITY non-inferiority RCT[27] compared (Transition Dyspnea Index) TDI scores of patients treated by indacaterol 150 micrograms or tiotropium 18 micrograms for 12 weeks. The mean difference in scores between the 2 groups was less than the MCID (1 point) outlined in CG101. The INHANCE RCT[28] assessed patients who received indacaterol 150 or 300 micrograms, tiotropium 18 micrograms or placebo once a day for 26 weeks. Both doses of indacaterol had greater improvements in trough FEV than placebo at 12 week follow-up. Furthermore, both			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
indacaterol doses were reported to be statistically significant for non-inferiority to tiotropium for trough FEV at 12 weeks follow-up. The INSIST trial[29] reported that treatment with indacaterol, 150 micrograms once a day, resulted in greater improvements in trough FEV than salmeterol, 50 micrograms twice daily. Furthermore, the mean difference in TDI scores between groups was less than the MCID (1 point) outlined in CG101.			
101 – 25 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? (2010; 1.2.2.6–1.2.2.10)			
Surveillance decision Although the new evidence does not indicate a need to update this review question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.			
4-year surveillance (2014) The results of 2 Cochrane systematic reviews[31,32] revealed that treatment with LABA plus ICS combinations lead to lower COPD exacerbation rates compared to treatment with LABA alone. Furthermore, there was no significant difference in mortality rates between groups but the incidence of pneumonia was higher in the	One network meta-analysis[54] assessed trough FEV1 and St George's Respiratory Questionnaire (SGRQ) scores of patients treated by LAMA, LABA, LABA plus ICS or ICS alone and ranked interventions. In relation to trough FEV1, LABA plus ICS was the highest ranked intervention; yielding the greatest mean improvement over placebo at 6 and 12 month follow-up assessments.	One topic expert highlighted that some LABA plus ICS combinations (such as seretide) are coming to the end of their patents and generic versions should become commercially available. The expert felt that this could have considerable impact on the cost effectiveness of this class of bronchodilator. The	New evidence is unlikely to impact on guideline recommendations The identified new evidence on clinical effectiveness is broadly in line with the studies currently included in the guideline; particularly in relation to improved FEV1, reduction in exacerbations and increased risk of pneumonia. No studies on cost

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
LABA plus ICS group. An RCT[33] reported that 2 bronchodilators significantly decreased hyperinflation more than 1 bronchodilator and an inhaled corticosteroid. A Cochrane systematic review[34] and a small RCT[35] indicated that the LABA plus ICS therapy improved total lung capacity and dyspnoea in people with COPD: however, there was significantly higher rate of exacerbations leading to hospitalisation[34]. In an RCT[36] of patients with mild to moderate COPD treated by inhaled salmeterol plus fluticasone propionate or placebo, inspiratory capacity improved in the FSC group but no changes in dyspnoea intensity were observed. Additionally, the results of a post-hoc cluster analysis[37] indicated that salmeterol plus fluticasone propionate significantly reduced the annual rate of moderate/severe exacerbations in comparison to salmeterol alone. Three RCTs reported that treatment with mometasone furoate plus formoterol fumarate resulted in significantly greater improvements in lung function and COPD	LAMA, LABA and ICS monotherapy were ranked second, third and fourth, respectively, at 6 months. Class differences between LABA, LAMA and ICS were less prominent at 12 months. As for SGRQ, combination LABA plus ICS was the highest ranked intervention; yielding the greatest mean improvement over placebo at 6 and 12 month follow-up. LAMA and LABA monotherapy showed roughly equivalent results and ICS therapy was ranked fourth at 6 months. Class differences between LABA, LAMA and ICS were less prominent at 12 months. One network meta-analysis[55] evaluated data from RCTs of patients treated by LABA plus ICS, LABA alone or placebo over a 12 week follow-up period. Compared with placebo or LABA alone, most LABA plus ICS combinations reduced the incidence of moderate-to-severe exacerbations, but none of them reduced severe exacerbations. No further details were provided. One RCT[56] explored the effect of switching patients at low risk of COPD exacerbations from salmeterol plus fluticasone to indacaterol monotherapy. The primary objective was to demonstrate non-inferiority of indacaterol to salmeterol plus fluticasone	Medicines and Prescribing Programme (MPP) confirmed that the patent for seretide expired in 2010 and 2 generic variants (AirFluSal and Sirdupla) are commercially available. One generic product (AirFluSal) is reported to be equivalent to seretide 50 (25 micrograms of salmeterol and 50 micrograms of fluticasone propionate) but cheaper; £32.74 compared with £40.92. The second generic product (Sirdupla) is also cheaper; £44.61 compared with £70.00 for 120 doses of the 250 microgram strength metered-dose inhaler. The MPP and the respiratory lead at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	effectiveness were identified but the impending expiration of patents for some LABA plus ICS combination inhalers may have considerable impact on their cost effectiveness. Although the new evidence does not indicate a need to update this review question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
exacerbation rates compared with mometasone furoate alone or placebo[38-40]. The results of 4 RCTs and 1 systematic review highlighted that formoterol plus budesonide therapy improved lung function and COPD symptoms and reduced exacerbation rates[41-45] although pneumonia rates increased[43,46]. Conversely, a network meta-analysis[47] which compared the efficacy of indacaterol alone with formoterol plus budesonide or salmeterol plus fluticasone, reported significantly greater improvements from baseline in FEV1 in the indacaterol group. Four RCTs evaluating vilanterol plus fluticasone furoate indicated that treatment improved FEV1 measurements and reduced COPD exacerbation rates[48-51]. Feedback stated that data suggested a continuing widespread inappropriate use of LABA+ICS combination therapy in patients with mild obstruction, and inappropriate use as a first line therapy in all severities. Furthermore, the GDG made reference to new LABAs, LAMAs, LAMA plus LABA and LABA plus ICS treatments, indicating there may be a requirement to review stratification of therapies and health	using trough FEV1 measurements. The objective was met, with a mean treatment difference of 9 millimetres. No significant differences in Transition Dyspnoea Index scores and SGRQ scores were observed between groups at 12 week and 26 week follow-up assessments. Furthermore, no significant difference in rescue medication use or COPD exacerbation rates were observed between groups at 26 week follow-up.		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
economics. Finally, the GDG highlighted that a very large which evaluates the safety (notably mortality) of LABA plus ICS combination drugs should report by 2016. It was considered that the new evidence was broadly in line with the evidence included in the guideline; particularly in relation to improved FEV1, reduction in exacerbations and increased risk of pneumonia. **Evidence Update (2012)** A meta-analysis[52] assessed the safety and efficacy of combined LABA plus ICS therapy versus LABA monotherapy in patients with stable COPD. Compared with LABA monotherapy, LABA plus ICS did not significantly reduce severe exacerbations or all-cause mortality. The TORCH study[53] also reported that treatment with combination therapy did not result in greater reductions in mortality rates than LABA monotherapy; however, results indicated that exacerbation rates were lower in the combination therapy group. The Evidence Update concluded that the evidence suggests that LABA plus ICS reduce moderate exacerbations, in line			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
with the intent of this regimen in CG101, and are associated with a known risk of pneumonia as already stated in current guidance.			
101 – 26 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? (2010; 1.2.2.6–1.2.2.10)			
Surveillance decision Although the new evidence does not indicate a need to update this review question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	One network meta-analysis[54] assessed trough FEV1 and St George's Respiratory Questionnaire (SGRQ) scores of patients treated by LAMA, LABA, LABA plus ICS or ICS alone and ranked interventions. In relation to trough FEV1, LABA plus ICS was the highest ranked intervention; yielding the greatest mean improvement over placebo at 6 and 12 month follow-up. LAMA, LABA and ICS monotherapy were ranked second, third and fourth, respectively, at 6 months. Class differences between LABA, LAMA and ICS were less prominent at 12 months. As for SGRQ, combination	One expert stated that some LAMAs (such as tiotropium) and LABA plus ICS combinations (such as seretide: salmeterol xinafoate plus fluticasone proprionate) are coming to the end of their patents and generic versions are due to become commercially available. The expert felt that this could have considerable impact on the cost effectiveness of these 2 classes of bronchodilators. Further investigations by NICE's Medicines and Prescribing Programme (MPP) revealed that the patent for tiotropium expired in October 2015; however, there appeared to be additional protection until March 2016 under	New evidence is unlikely to impact on guideline recommendations. The guideline currently recommends that people with FEV1 ≥ 50% predicted should be offered either a LAMA or LABA whilst those with FEV1 ≤ 50% should receive a LABA plus inhaled corticosteroid or a LAMA. The identified new evidence on clinical effectiveness is broadly in line with the studies currently included in the guideline; particularly in relation to improved SGRQ scores. Although the new evidence does not indicate a need to update this review question, the decision to update other related clinical questions (101-29 to 101-31)

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	LABA plus ICS was the highest ranked intervention; yielding the greatest mean improvement over placebo at 6 and 12 month follow-up. LAMA and LABA monotherapy showed roughly equivalent results and ICS therapy was ranked fourth at 6 months. Class differences between LABA, LAMA and ICS were less prominent at 12 months.	paediatric protection. The MPP could not identify any generic products on the European Medicines Agency website but suggested that applications may appear shortly after March 2016. The Medicines and Prescribing Programme (MPP) confirmed that the patent for seretide expired in 2010 and 2 generic variants (AirFluSal and Sirdupla) are commercially available. One generic product (AirFluSal) is reported to be equivalent to seretide 50 (25 micrograms of salmeterol and 50 micrograms of fluticasone propionate) but cheaper; £32.74 compared with £40.92. The second generic product (Sirdupla) is also cheaper; £44.61 compared with £70.00 for 120 doses of the 250 microgram strength metered-dose inhaler. The MPP and the respiratory lead at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 27 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? (2010; 1.2.2.6–1.2.2.10)			
Surveillance decision Although no new evidence was identified related to this clinical question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	The Medicines and Prescribing Programme and the respiratory lead at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	No new evidence was identified that would affect recommendations.
101 – 28 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? (2010; 1.2.2.6–1.2.2.10)			
Surveillance decision Although no new evidence was identified related to this clinical question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.			
4-year surveillance (2014)	No relevant evidence identified.	The Medicines and Prescribing	No new evidence was identified that would

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
One RCT[57] comparing a single-dose of salbutamol/ipratropium plus flunisolide added to regular treatment found no improvement in endurance time in people with COPD. The study did not compare the intervention with an active treatment, such as a LAMA or a LABA and therefore was unlikely to impact the recommendations. **Evidence Update (2012)** No relevant evidence identified		Programme and the respiratory lead at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	affect recommendations.
101 – 29 What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta2 agonists compared to long-acting beta2 agonists in the management of people with stable COPD? (2010; 1.2.2.6–1.2.2.10)			
Surveillance decision This review question should be updated.			
4-year surveillance (2014) Two RCTs[58,59] and 1 Cochrane systematic review[60] compared the safety and efficacy tiotropium plus LABA against LABA or LAMA alone. The systematic review found no significant differences in symptom scores, exacerbation rates, serious adverse events rates, and withdrawal rates between groups[60]. One RCT[59] reported greater inspiratory muscle strength compared with LABA alone, while the second RCT[58] indicated that dual therapy improved walking distance more than LAMA monotherapy but there was no significant difference in FEV1	One systematic review[64] compared the efficacy of a fixed-dose combination of umeclidinium plus vilanterol with its monocomponents, tiotropium alone or salmeterol plus fluticasone. Authors reported that umeclidinium plus vilanterol provided significantly superior improvements in trough FEV1 and COPD exacerbation rates compared with vilanterol alone. Furthermore, umeclidinium plus vilanterol had a greater likelihood of demonstrating a minimal clinically	In an RCT[67] of patients with COPD treated by glycopyrronium plus indacaterol or indacaterol alone, significantly greater improvements in trough FEV1, peak FEV1, and trough FVC in the glycopyrronium plus indacaterol group. Furthermore, significantly greater improvements in TDI focal scores were reported in the glycopyrronium plus indacaterol group. The incidence of adverse events was similar in the two	New evidence identified that may change current recommendations The guideline currently states: "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

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
between the 2 groups. Two RCTs reported that glycopyrronium plus indacaterol therapy induced sustained bronchodilation compared with placebo[61] and reduced the rate of moderate to severe exacerbations compared with glycopyrronium[62]. In an RCT[63] of patients with COPD treated by umeclidinium plus vilanterol, umeclidinium alone, vilanterol alone or placebo, all active treatments significantly improved FEV1 measurements. The greatest improvements were reported in the umeclidinium plus vilanterol group. Generally, the new evidence indicated treatment with combination therapy produced benefits in some outcomes. However, it was considered that there was insufficient consistent evidence available to determine whether there is an added benefit of dual therapy over LABA monotherapy **Evidence Update (2012)** No relevant evidence identified	important difference in Transition Dyspnoea Index scores compared with vilanterol alone. A systematic review[65] pooled data from RCTs which compared tiotropium plus LABA against tiotropium or LABA alone. Compared to LABA alone, treatment with tiotropium plus LABA resulted in a small but significant improvement in mean HRQOL. Furthermore, greater improvements in FEV1 measurements and exacerbation rates were attributable to treatment with tiotropium plus LABA. A network meta-analysis[66] compared outcomes of patients treated by LAMA plus LABA with those treated by LAMA or LABA alone. LAMA plus LABA combinations were associated with greater improvements in Transition Dyspnea Index (TDI) scores and St. George's Respiratory Questionnaire (SGRQ) than monotherapies. LAMA plus LABA combinations were associated with fewer moderate to severe COPD exacerbations compared with LABAs but not when compared with LAMAs.	treatment groups. One RCT[68] compared outcomes of patients who received tiotropium plus olodaterol, tiotropium alone, olodaterol alone or placebo. After 6 weeks of treatment, significantly greater improvements in FEV1 measurements were observed in the tiotropium plus indacaterol group versus placebo and monotherapies. One RCT[69] compared the efficacy of a fixed-dose combination of aclidinium bromide and formoterol fumerate with its individual components and placebo. Treatment with aclidinium bromide plus formoterol fumerate produced significantly greater improvements in trough FEV1 measurements than treatment with aclidinium bromide or formoterol fumerate alone. Compared with placebo, aclidinium bromide plus formoterol fumerate significantly improved TDI focal scores. One RCT[70] compared the efficacy of a fixed-dose combination of umeclidinium and vilanterol with its individual components and placebo.	with an inhaled corticosteroid (ICS) in a combination inhaler, or LAMA. [new 2010]" The guideline then recommends the use of LAMA plus LABA where use of ICSs is declined or not tolerated The identified new studies are in agreement studies identified during the 4-year review and add further evidence of benefits of dual bronchodilation over LABA monotherapy.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	There were no significant differences in adverse events and severe exacerbations rates between groups.	Treatment with umeclidinium plus vilanterol produced significantly greater improvements in trough FEV1 measurements than treatment with umeclidinium or vilanterol alone. Compared with placebo, umeclidinium plus vilanterol significantly reduced salbutamol use and improved both TDI scores and SGRQ scores. Topic experts suggested that the algorithm for inhaled therapy needs to be amended. Three experts felt that new studies highlight advantages of using dual bronchodilation (LAMA plus LABA) over monotherapy alone in patients with moderate to severe COPD. One expert stated that clinical guidance must address the issues of whether to start at different points in the algorithm; for example, with dual bronchodilation rather than monotherapy in those presenting with breathlessness (especially if severe) or exacerbation phenotype (especially if frequent or severe), or with severe airflow obstruction. The Medicines and Prescribing Programme and the respiratory lead	

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
		at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	
101 – 30 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? (2010; 1.2.2.6–1.2.2.10)			
Surveillance decision This review question should be updated.			
4-year surveillance (2014) A post-hoc analysis[71] and 4 RCTs indicated improvements in dysponea[72], FEV1[73,74] and exercise capacity[75] in patients with COPD treated by LAMA plus LABA therapy. It was considered that the new evidence supported the guideline recommendation which states that a LAMA plus a LABA should be offered to people with stable COPD and an FEV1 ≥ 50% who remain breathless or have exacerbations despite maintenance therapy with a LABA. **Evidence Update (2012)** A meta-analysis[76] compared a combined regimen of tiotropium plus formoterol with	A systematic review[77] compared the efficacy of a fixed dose combination of glycopyrronium and indacaterol (QVA149) with that of tiotropium, glycopyrronium alone. Compared with either LAMA, QVA149 showed a significant increase in trough FEV1 and a decrease in the use of rescue medication. Compared with tiotropium, patients who received QVA149 had a 19% greater likelihood of experiencing a minimal clinical important difference (MCID) in the number needed to treat for benefit and a 16% greater likelihood of achieving an MCID in the St. George's Respiratory Questionnaire (SGRQ).	Topic experts recommended the following studies: One RCT[68] compared outcomes of patients with COPD treated by tiotropium plus olodaterol, tiotropium alone, olodaterol alone or placebo. After 6 weeks of treatment, significantly greater improvements in FEV1 measurements were observed in the tiotropium plus indacaterol group versus placebo and monotherapies. One RCT[69] compared the efficacy of a fixed-dose combination of aclidinium bromide and formoterol	New evidence identified that may change current recommendations The guideline currently states: "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. [new 2010]"

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
tiotropium alone in stable COPD. The results suggested that lung function and symptoms (based on data for transitional dyspnoea index only) may be improved with a combined regimen of tiotropium plus formoterol over tiotropium alone, but there was not enough evidence to suggest a reduction in mortality or exacerbations.	Compared with glycopyrronium alone, treatment with QVA149 produced a significant increase in the rate of patients achieving an MCID in the SGRQ. QVA149 showed similar levels of safety and tolerability to both comparators. One systematic review[64] compared the efficacy of a fixed-dose combination of umeclidinium plus vilanterol against its monocomponents, tiotropium alone or salmeterol plus fluticasone. Authors reported that umeclidinium plus vilanterol provided significantly superior improvements in trough FEV1 and COPD exacerbation rates compared with tiotropium or umeclidinium alone. Furthermore, umeclidinium plus vilanterol had a greater likelihood of demonstrating a minimal clinically important difference in Transition Dyspnoea Index scores compared with umeclidinium alone. No significant differences in dyspnea scores, health status (not defined) and COPD exacerbation rates were observed between umeclidinium plus vilanterol and tiotropium alone. A systematic review[65] pooled data from	fumerate with its individual components and placebo. Treatment with aclidinium bromide plus formoterol fumerate produced significantly greater improvements in trough FEV1 measurements than treatment with aclidinium bromide or formoterol fumerate alone. Compared with placebo, aclidinium bromide plus formoterol fumerate significantly improved TDI focal scores. One RCT[70] compared the efficacy of a fixed-dose combination of umeclidinium and vilanterol with its individual components and placebo. Treatment with umeclidinium plus vilanterol produced significantly greater improvements in trough FEV1 measurements than treatment with umeclidinium or vilanterol alone. Compared with placebo, umeclidinium plus vilanterol significantly reduced salbutamol use and improved both TDI scores and St. George's Respiratory Questionnaire scores. In an RCT[78] of patients with COPD treated by umeclidinium plus vilanterol, umeclidinium alone or	The guideline then recommends the use of LAMA plus LABA where use of ICSs is declined or not tolerated The identified new studies are in agreement studies identified during the 4-year review and add further evidence of benefits of dual bronchodilation over LAMA monotherapy.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	RCTs which compared tiotropium plus LABA against tiotropium or LABA alone. Compared to tiotropium alone, treatment with tiotropium plus LABA resulted in a significantly larger improvement in mean HRQOL: the mean difference was larger than the minimal clinically important difference. Furthermore, improvements in FEV1 were observed in the tiotropium plus LABA group. No significant differences in exacerbation, adverse event, hospital admission, withdrawal, and mortality rates were observed between the tiotropium plus LABA group and the tiotropium alone group. A network meta-analysis[66] compared outcomes of patients treated by LAMA plus LABA with those treated by LAMA or LABA alone. LAMA plus LABA combinations were associated with greater improvements in Transition Dyspnea Index (TDI) scores and St. George's Respiratory Questionnaire (SGRQ) than monotherapies. LAMA plus LABA combinations were associated with fewer moderate to severe COPD exacerbations compared with LABAs but not when compared with LAMAs. There were no significant	placebo significant improvements in lung function were observed in active treatment groups. Furthermore, patients who received active treatments used fewer exacerbations and used rescue medications less often than patients who received placebo. The overall incidence of adverse events was similar between treatment groups. Headache was the most common adverse event in each treatment group. The incidences of atrial arrhythmias were similar in the umeclidinium plus vilanterol group and the placebo group. The incidences of ectopic supraventricular beats, sustained supraventricular tachycardia, and ectopic supraventricular rhythm were higher in the umeclidinium alone group than the placebo group. An RCT[79] compared the efficacy and safety of umeclidinium plus vilanterol with tiotropium in COPD. Significantly greater improvements in HRQoL scores and trough FEV1 measurements were reported in the umeclidinium plus vilanterol group. Additionally, patients who received	

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	differences in adverse events and severe exacerbations rates between groups.	umeclidinium plus vilanterol used fewer rescue medications than those who received tiotropium at 24 week follow-up. In 1 RCT[80] patients were randomised to receive glycoyrronium plus indacaterol, tiotropium alone or placebo. Compared with placebo or tiotropium alone, treatment with glycoyrronium plus indacaterol resulted in significant improvements in lung function with a higher FEV1 area under the curve from 0 to 4 hours post-dose. The glycoyrronium plus indacaterol group had significantly greater improvements in dyspnoea and greater reductions in the number of patients who were using recue medications than the placebo group and the tiotropium group. Another RCT[81] compared patients treated by glycoyrronium plus indacaterol with patients who received tiotropium alone or placebo. At 21 days, glycoyrronium plus indacaterol significantly improved exercise endurance times compared with placebo; however no significant	

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
		difference was observed when a comparison was made with tiotropium alone. Authors state that glycoyrronium plus indacaterol produced significant improvements in dynamic inspiratory capacity at exercise isotime, trough FEV1, residual volume and functional residual capacity measurements from the first day of treatment: improvements were maintained throughout the study. The safety profiles were similar across groups. Topic experts suggested that the algorithm for inhaled therapy needs to be amended. Three experts felt that new studies highlight advantages of using dual bronchodilation (LAMA plus LABA) over monotherapy alone in patients with moderate to severe COPD. One expert stated that clinical guidance must address the issues of whether to start at different points in the algorithm; for example, with dual bronchodilation rather than monotherapy in those presenting with breathlessness (especially if severe) or exacerbation phenotype (especially if frequent or severe), or	

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
		with severe airflow obstruction. The Medicines and Prescribing Programme and the respiratory lead at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	
101 – 31 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? (2010; 1.2.2.6–1.2.2.10)			
Surveillance decision This review question should be updated.			
4-year surveillance (2014) In an RCT[82] of patients with moderate to severe COPD treated by salmeterol plus fluticasone or indacaterol plus glycopyrronium, significantly higher FEV1 measurements were reported in the indacaterol plus glycopyrronium group. NICE published an Evidence Summary (ESNM33 Chronic obstructive pulmonary disease: indacaterol/glycopyrronium (Ultibro Breezhaler)) on the first LABA/LAMA (indacaterol plus glycopyrronium) combination inhaler approved for treating COPD. It is licensed as a	One systematic review[64] compared the efficacy of a fixed-dose combination of umeclidinium plus vilanterol with its monocomponents, tiotropium alone or salmeterol plus fluticasone. Authors reported that umeclidinium plus vilanterol provided significantly superior improvements in trough FEV1 compared with salmeterol plus fluticasone. In a systematic review[83] which compared LAMA plus LABA and	Topic experts highlighted the following studies: One RCT[85] compared the outcomes of patients treated by umeclidinium plus vilanterol with patients treated by salmeterol plus fluticasone proprionate. Greater improvements in trough FEV1 were observed in the umeclidinium plus vilanterol group. Furthermore, significantly greater improvements in Transition Dyspnoea Index (TDI) scores and SGRQ scores	New evidence identified that may change current recommendations. The guideline currently states: "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

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
maintenance bronchodilator treatment to relieve symptoms in adults with COPD and was expected to be launched in the UK in the second quarter of 2014. Although some small statistically significant improvements in lung function, dyspnoea, health status and use of rescue medication were seen with indacaterol/glycopyrronium compared with placebo and active comparators, the clinical importance of these differences was unclear. The Evidence Summary concluded that indacaterol/glycopyrronium's place in therapy is difficult to assess. The summary highlighted an ongoing trial comparing the effects of indacaterol/glycopyrronium and fluticasone/salmeterol on exacerbations in people with moderate to very severe COPD (NCT01782326: QVA vs. Salmeterol/Fluticasone, 52-week Exacerbation Study). This study is likely to provide better long-term comparative safety data for the 2 treatments. Although 1 RCT was identified in the surveillance review comparing LAMA plus LABA against LABA plus ICS, it was considered that further research, conducted over longer periods of time, was needed to confirm the results. **Evidence Update (2012)** No relevant evidence identified	LABA plus ICS, significantly greater improvements in trough FEV1 measurements, transition index scores, exacerbation rates, and pneumonia rates were reported in the LAMA plus LABA group. No significant differences in St George Respiratory Questionnaire (SGRQ) scores, adverse event rates and discontinuation rates were reported between groups. A network meta-analysis[84] pooled data from RCTs which assessed the efficacy of LABA, LAMA and ICS, alone or in combination, versus each other or placebo. The combination of tiotropium, formoterol and budesonide was found to be the most effective intervention in reducing exacerbations of COPD according to the Surface Under the Cumulative Ranking (SUCRA) curve. The second most effective intervention in reducing COPD exacerbations was glycopyrronium plus indacaterol. Salmeterol plus fluticasone was more effective in reducing mortality than placebo, formoterol and fluticasone alone. In the same study, analysis of	were observed in the umeclidinium plus vilanterol group at 12 week follow-up. The incidence of adverse events was 28% in the umeclidinium plus vilanterol group and 29% in the salmeterol plus fluticasone proprionate; nasopharyngitis and headache were most common. In an RCT[86] of patients with moderate to severe COPD treated by glycopyrronium plus indacaterol or salmeterol plus fluticasone significantly greater improvements in trough FEV1 measurements were reported in the glycopyrronium plus indacaterol group at 26 week follow-up. Similar improvements in TDI scores and SGRQ scores were reported in each group. Additionally, the proportion of patients who used rescue medications was significantly lower in the glycopyrronium plus indacaterol group. Compared with salmeterol plus fluticasone, glycopyrronium plus indacaterol significantly reduced the rate of moderate to severe COPD exacerbations. Authors state that the adverse event rates in each group	with an inhaled corticosteroid (ICS) in a combination inhaler, or LAMA. [new 2010]" The guideline then recommends the use of LAMA plus LABA where use of ICSs is declined or not tolerated The identified studies add further evidence indicating that dual bronchodilation results in better outcomes compared to LABA plus ICS combinations. Conversely, new intelligence suggests that LABA plus ICS combinations are becoming more cost-effective. A thorough examination of the clinical and cost effectiveness of both treatment approaches is needed to ascertain whether recommendations in the guideline should remain.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	cardiovascular-related mortality revealed that Triamcinolone acetonide was the most harmful medication. Analysis also revealed that salmeterol plus fluticasone and fluticasone were likely to increase the risk of pneumonia in comparison to placebo.	were similar; however, the incidence of pneumonia was threefold lower in the glycopyrronium plus indacaterol group. One topic expert suggested equivalence between LAMA plus LABA and LABA plus ICS in patients with mild to moderate COPD. Thus, it was suggested that the treatment algorithm needs to recommend dual bronchodilation for patients with mild to moderate COPD and persistent breathlessness whose symptoms are not controlled with monotherapy using LABA or LAMA alone. Additionally, 2 experts stated that recent evidence indicates that dual bronchodilation results in greater improvements in FEV1 and dyspnoea than LABA plus ICS combinations in patients with severe COPD. One topic expert highlighted that some LABA plus ICS combinations (such as seretide) are coming to the end of their patents and generic versions should become commercially available. The expert felt that this could have considerable impact on the cost effectiveness of this class of	

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
		bronchodilator. The Medicines and Prescribing Programme (MPP) confirmed that the patent for seretide expired in 2010 and 2 generic variants (AirFluSal and Sirdupla) are commercially available. One generic product (AirFluSal) is reported to be equivalent to seretide 50 (25 micrograms of salmeterol and 50 micrograms of fluticasone propionate) but cheaper; £32.74 compared with £40.92. The second generic product (Sirdupla) is also cheaper; £44.61 compared with £70.00 for 120 doses of the 250 microgram strength metered-dose inhaler. The MPP and the respiratory lead at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	
101 – 32 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? (2010; 1.2.2.6–1.2.2.10)			
Surveillance decision Although the new evidence does not indicate a need to update this review question, the decision to update other related clinical questions (101-29 to 101-31) means that this			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	A network meta-analysis[84] pooled data from RCTs which assessed the efficacy of LABA, LAMA and ICS, alone or in combination, versus each other or placebo. The combination of tiotropium, formoterol and budesonide was found to be the most effective intervention according to the Surface Under the Cumulative Ranking (SUCRA) curve. Salmeterol plus fluticasone was more effective in reducing mortality than placebo, formoterol and fluticasone alone. In the same study, analysis of cardiovascular-related mortality revealed that Triamcinolone acetonide was the most harmful medication. Analysis also revealed that salmeterol plus fluticasone and fluticasone were likely to increase the risk of pneumonia in comparison to placebo.	Topic experts highlighted 1 RCT[87]. In the RCT patients were randomised to receive once-daily glycopyrronium (50 micrograms), once-daily tiotropium (18 micrograms) or placebo combined with salmeterol plus fluticasone propionate (50/500 micrograms) twice daily. At 12 weeks, glycopyrronium plus salmeterol/fluticasone propionate demonstrated non-inferiority to tiotropium plus salmeterol/fluticasone propionate for trough FEV1. Glycopyrronium plus salmeterol/fluticasone propionate produced significantly better improvements in total St George's Respiratory Questionnaire total scores than placebo plus salmeterol/fluticasone propionate. Furthermore, the glycopyrronium plus salmeterol/fluticasone propionate group had significantly greater reductions in rescue medication use than the placebo plus salmeterol/fluticasone propionate	New evidence is unlikely to impact on guideline recommendations The guideline recommends that triple therapy should be offered as step-up treatment if symptoms or exacerbations persist on current therapy, irrespective of the patient's FEV1. No new evidence was identified which would change the direction of recommendations. Although the new evidence does not indicate a need to update this review question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
		group. The Medicines and Prescribing Programme and the respiratory lead at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	
101 – 33 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? (2010; 1.2.2.6–1.2.2.10)			
Surveillance decision Although the new evidence does not indicate a need to update this review question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.			
4-year surveillance (2014) Four RCTs and 2 systematic reviews reported greater improvements in lung function and QoL in people with COPD treated with tiotropium and fluticasone propionate/salmeterol compared with tiotropium alone or placebo[88-93]. Conversely, a Cochrane systematic review[94] assessing the relative effects of inhaled corticosteroid plus LABA or tiotropium alone identified only limited data and concluded that there was uncertainty regarding the long-term benefits and risks of	In a systematic review[95] which compared tiotropium plus fluticasone propionate/salmeterol (triple therapy) with tiotropium alone, significantly better FEV1 measurements, exacerbation rates and HRQoL scores were reported in the triple therapy group. A network meta-analysis[84] pooled data from RCTS which assessed the	The Medicines and Prescribing Programme and the respiratory lead at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	New evidence is unlikely to impact on guideline recommendations The guideline recommends that triple therapy should be offered as step-up treatment if symptoms or exacerbations persist on current therapy, irrespective of the patient's FEV1. No new evidence was identified which would change the direction of recommendations. Although the new evidence does not

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
triple therapy. It was considered that the new evidence was unlikely to change guideline recommendations which state that triple therapy should be offered as step-up treatment if symptoms or exacerbations persist on current therapy. **Evidence Update (2012)** No relevant evidence identified	efficacy of LABA, LAMA and ICS, alone or in combination, versus each other or placebo. The combination of tiotropium, formoterol and budesonide was found to be the most effective intervention according to the Surface Under the Cumulative Ranking (SUCRA) curve.		indicate a need to update this review question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components
101 – 34 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? (2010; 1.2.2.6–1.2.2.10)			
Surveillance decision Although the new evidence does not indicate a need to update this review question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	Topic experts proffered 1 RCT[96]. In the RCT patients with moderate to severe COPD received triple therapy (tiotropium plus salmeterol plus fluticasone) over a 6 week period. Subsequently, patients were randomly assigned to continue triple therapy or to discontinue ICS (fluticasone) treatment in 3 steps, over 12 weeks. No significant difference in the period of time to first moderate to severe COPD	New evidence is unlikely to impact on guideline recommendations The guideline recommends that triple therapy should be offered as step-up treatment if symptoms or exacerbations persist on current therapy, irrespective of the patient's FEV1. No new evidence was identified which would change the direction of recommendations. Although the new evidence does not indicate a need to update this review

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
		exacerbation was observed between groups; demonstrating non-inferiority. At 18 week follow-up, patients who discontinued ICS treatment had significantly greater reductions in trough FEV1 measurements than those who continued triple therapy. A similar difference was observed at 52 week follow-up. No change in dyspnoea and minor changes in health status (not specified) occurred in the ICS discontinuation group. The Medicines and Prescribing Programme and the respiratory lead at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components
101 – 35 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? (2010; 1.2.2.5)			
Surveillance decision Although no new evidence was identified related to this clinical question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	The Medicines and Prescribing Programme and the respiratory lead at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	No new evidence was identified that would affect recommendations.
101 – 36 What is the clinical and cost effectiveness of long-acting beta2 agonists compared to short-acting beta2 agonists in the management of people with stable COPD? (2010; 1.2.2.1)			
Surveillance decision Although no new evidence was identified related to this clinical question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	The Medicines and Prescribing Programme and the respiratory lead at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 37 What is the clinical and cost effectiveness of mucolytic agents vs. placebo in people with stable COPD? (2010; 1.2.3.7–1.2.3.9)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	A systematic review[97] of RCTs which compared oral mucolytic therapy versus placebo reported a reduction in the number of exacerbations in patients treated by mucolytic therapy. Compared with placebo, mucolytic therapy was associated with improved quality of life, a reduction in the number of hospitalisations, and a reduction in the days of disability per participant per month.	Topic experts suggested 1 RCT[98] of patients with moderate to severe COPD treated by N-acetylcysteine or placebo. The exacerbation rate was 1·16 exacerbations per patient-year in the N-acetylcysteine group and 1·49 exacerbations per patient-year in the placebo group at 1 year follow-up ($p<0.05$). The occurrence of adverse events was similar in both treatment arms, with acute COPD exacerbation being the most common serious adverse event.	New evidence is unlikely to impact on guideline recommendations. The guideline recommends: "1.2.3.7 Mucolytic drug therapy should be considered in patients with a chronic cough productive of sputum. [2004] 1.2.3.8 Mucolytic therapy should be continued if there is symptomatic improvement (for example, reduction in frequency of cough and sputum production). [2004] 1.2.3.9 Do not routinely use mucolytic drugs to prevent exacerbations in people with stable COPD. [new 2010]" The identified new evidence is in agreement with previous literature reviewed in the 2010 update of the guideline.
101 – 38 What are the aims of COPD management? (2004; not linked to a specific guideline recommendation)			
Surveillance decision			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 39 In patients with stable COPD, how should the (initial) management plan be determined? (2004; not linked to a specific guideline recommendation)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 40 Which patients with stable COPD should be referred for an oxygen assessment? (2004; 1.2.5.4)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	The Medicines and Prescribing Programme highlighted that the British Thoracic society's guidelines on oxygen were updated in April 2015 and appear to be consistent with the NICE 2010 guidance.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 41 What is the most appropriate smoking cessation strategy in patients with stable COPD? (2004; 1.2.1.1–1.2.1.5)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) Two RCTs[99,100] and a systematic review[101] reported that varenicline was an efficacious smoking cessation strategy although it was associated with an increased risk of psychiatric side effects. Furthermore, a probabilistic sensitivity analysis[102] from the perspective of European healthcare systems suggested varenicline had a high probability (>95%) of being cost-effective at a threshold of 30,000/QALY. Two systematic reviews[103,104] reported that the combination of pharmacotherapy and psychosocial interventions may be effective in smoking cessation although the effect was not statistically significant in 1 systematic review[104]. A cost-effectiveness analysis[105] based on RCT data, reported that high-intensity 'SmokeStop Therapy' was more cost-effective than versus a medium-intensity 'Minimal Intervention Strategy' for COPD. The components of the programmes were not reported in the abstract. Consequently, any impact on the guideline was unclear. The new evidence supported the guideline	One systematic[108] review attempted to identify which behaviour change techniques (BCTs) were associated with greater effectiveness in smoking cessation interventions for people with COPD. The following techniques were associated with significantly large effect sizes: facilitating action planning (developing treatment plans), prompt self-recording, advising on weight control methods, and facilitating or advising on use of social support. No further details were provided in the abstract. A systematic review[109] of 10 studies which evaluated the cost-effectiveness of smoking cessation interventions(not specified in the abstract) in people with COPD reported inconsistent results; ranging from cost savings to additional costs of 17,004 per quality adjusted life. Year.	None identified relevant to this question.	New evidence is consistent with guideline recommendations. No new studies which evaluated the effectiveness of pharmacological interventions for smoking cessation were identified from the 6-year surveillance searches. The identified new evidence outlines which BCTs were associated with an increased likelihood of smoking cessation. This supports guideline recommendations which state that NRT, varenicline or bupropion can be offered in combination with an appropriate support programme in order to optimise smoking quit rates for people with COPD who are planning to stop smoking.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
recommendation: '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'. **<u>Evidence Update (2012)</u>** A meta-analysis[106] examined the decline in FEV1 measurements among non-smokers, continued smokers, ex-smokers and quitters (those who stopped smoking during follow-up). The study was unable to confirm relative benefits of smoking cessation at different stages of COPD severity. Conversely, an observational study reported that people with any severity of COPD who continued smoking were at greater risk of deterioration of their condition. The Evidence Update concluded that the studies strengthened messages on smoking cessation in the guideline and indicate that even in severe COPD, stopping smoking may be of benefit. A network meta-analysis[107] found that smoking cessation counselling (SCC) plus nicotine replacement therapy (NRT) was deemed most effective. SCC plus antidepressant was second place. The Evidence Update concluded that SCC plus either NRT or antidepressant were equally effective smoking cessation interventions and there was little evidence for the superiority of			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
high-intensity over low-intensity counselling.			
101 – 42 Which patients with stable COPD should be treated with short-acting beta2-agonists? How should the effects of this treatment be assessed? (2004; 1.2.2.1)			
Surveillance decision Although no new evidence was identified related to this clinical question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	The Medicines and Prescribing Programme and the respiratory lead at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	No new evidence was identified that would affect recommendations.
101 – 43 Which patients with stable COPD should be treated with short-acting anticholinergics? How should the effects of this treatment be assessed? (2004l; 1.2.2.5)			
Surveillance decision Although no new evidence was identified related to this clinical question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.			
4-year surveillance (2014) An RCT[110] assessed the effectiveness of nurse-initiated use of a metered-dose salbutamol	No relevant evidence identified.	The Medicines and Prescribing Programme and the respiratory lead at the Royal College of General	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
inhaler for relieving the signs and symptoms of acute exacerbations of COPD. Oxygen saturation and dyspnoea improved in the salbutamol group but not in the control group. Recommendations state that short-acting bronchodilators, as necessary, should be the initial empirical treatment for the relief of breathlessness and exercise limitation. It was considered that the identified evidence was unlikely to change the direction of the recommendation. **Evidence Update (2012)** No relevant evidence identified		Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	During the 4-year review, only 1 study was identified that was related to the clinical question but it was considered that the identified evidence was unlikely to change the direction of the recommendation. Although no new evidence was identified related to this clinical question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.
101 – 44 Which patients with stable COPD should be treated with long-acting beta2-agonists? How should the effects of this treatment be assessed? (2004; 1.2.2.6)			
Surveillance decision Although no new evidence was identified related to this clinical question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.			
4-year surveillance (2014) Eighteen RCTs[111-128] two post-hoc analyses[129,130,130] and three systematic reviews[131-133] were identified which indicated that LABAs are effective in people with COPD. Studies that compared different LABAs generally	No relevant evidence identified.	The Medicines and Prescribing Programme and the respiratory lead at the Royal College of General Practitioners highlighted that the guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy	No new evidence was identified that would affect recommendations. Since the guideline was published additional LABAs (including indacaterol) have been licensed for use in the UK. The studies identified during the previous review

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
indicated that indacaterol was the most effective[134-136] although 2 systematic reviews indicated that the efficacy of indacaterol was similar to other LABAs including formoterol and salmeterol[137,138]. The identified studies reported inconsistent results. Therefore, it was considered that currently insufficient consistent evidence to include details on the use of specific LABAs in the guideline. **Evidence Update (2012)** The INVOLVE RCT[139] compared patients with COPD treated by indacaterol (300 or 600 micrograms) once daily, formoterol 12 micrograms twice daily or placebo over 52 weeks. All active treatments produced greater improvements in FEV1 than placebo. Both doses of indacaterol produced greater improvements (100 ml) than formoterol. The clinical relevance of this difference was questioned by the European Medicines Agency. The INSIST trial[140] compared Indacaterol 150 micrograms once daily against salmeterol 50 micrograms twice daily over 12 weeks. Significantly greater trough FEV measurements were observed in the indacaterol group at 12-week follow-up. Indacaterol also produced a statistically superior improvement in TDI but this		using newer bronchodilator medications.	reported inconsistent results. Therefore, it was considered that currently insufficient consistent evidence to include details on the use of specific LABAs in the guideline. Although no new evidence was identified related to this clinical question, the decision to update other related clinical questions (101-29 to 101-31) means that this question may be updated. The pathway for inhaled therapy needs to be considered as a whole. If an individual component of the pathway is amended, it is likely that this will impact on other related components.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
was less than the MCID of 1 point indicated by CG101. In the INLIGHT-2 RCT[141], Indacaterol 150 micrograms daily was compared against salmeterol 50 micrograms twice daily or placebo. The indacaterol had significantly greater improvements in FEV trough values than placebo at 12-week follow-up. Indacaterol produced statistically superior improvements in TDI cores at 4 weeks and 12 weeks, but not at 26 weeks. This is less than the MCID of 1 point indicated in CG101. A meta-analysis[142] that evaluated the safety of indacaterol in people with COPD, pooled data from published and unpublished studies which followed-up participants for at least 12 weeks. No significant differences in the risks of acute respiratory serious adverse events (leading to hospitalisation, intubation, or death), and major adverse cardiovascular events were observed between indacaterol and placebo. The Evidence Update concluded that indacaterol therapy may be a potential consideration for future reviews of CG101.			
101 – 45 Which patients with stable COPD should be treated with long-acting anticholinergics? How should the effects of this treatment be assessed? (2004; 1.2.2.6)			
Surveillance decision			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
This review question should be updated.			
4-year surveillance (2014) Twenty one RCTs[142-162] and five systematic reviews[163-165,165,166] were identified which indicated that LAMAs are effective in people with COPD. Furthermore, a cost-utility analysis[167] of adding tiotropium to usual care versus usual care alone for patients with moderate to very severe COPD in the UK and Belgium indicated that the probability of tiotropium being cost-effective at 30,000 per QALY gained was greater than 60%. Studies which compared various LAMAs suggested that tiotropium may be more effective[168] while others reported that tiotropium and aclidinium were comparable[169,170]. In other studies there was an indication that concomitant treatment of two LAMAs[171] or a SAMA/LAMA[172] was efficacious although the risk of adverse events was greater[171]. Since the guideline was updated NICE published 2 Evidence Summaries on LAMAs for COPD: **ESNM8 Chronic obstructive pulmonary disease: aclidinium bromide** and **ESNM9 Chronic obstructive pulmonary disease: glycopyrronium bromide** (both published January 2013). Both summaries concluded that the publication of longer term studies comparing patient-orientated outcomes for aclidinium	A systematic review[176] compared the outcomes of patients with moderate to severe COPD treated by aclidinium bromide (a LAMA), a LABA or placebo. When aclidinium bromide was compared against placebo, significantly greater improvements in FEV1 values and St George's Respiratory Questionnaire (SGRQ) scores were observed in the intervention arm. Aclidinium produced significantly greater reductions in the number of patients with exacerbations that needed hospitalisation; however, no significant difference in the number of patients with exacerbations that needed a short course of oral steroids or antibiotics was observed between the 2 groups. Compared to tiotropium, aclidinium did not demonstrate significant differences for exacerbations requiring oral steroids or antibiotics, exacerbation-related hospitalisations and non-fatal serious adverse events. Authors state that the evidence was 'very low' in quality. Inadequate data prevented the comparison of aclidinium to	One topic expert highlighted that some LAMAs (such as tiotropium) are coming to the end of their patents and generic versions should become commercially available. The expert felt that this could have considerable impact on the cost effectiveness of this class of bronchodilator. Further investigations by NICE's Medicines and Prescribing Programme (MPP) revealed that the patent for tiotropium expired in October 2015; however, there appeared to be additional protection until March 2016 under paediatric extension. The MPP could not identify any generic products on the European Medicines Agency website but suggested that applications may appear shortly after March 2016. The patents for aclidinium bromide, glycopyrronium bromide, and umeclidinium bromide are due to expire in 2025, 2027 and 2029, respectively. The MPP and the respiratory lead at the Royal College of General Practitioners highlighted that the	New evidence identified that may change current recommendations The guideline currently recommends that LAMAs should be offered 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. Evidence summaries on aclidinium bromide and glycopyrronium bromide suggested that publication of longer term studies comparing patient-orientated outcomes for aclidinium bromide and glycopyrronium bromide with other active treatments for COPD would enable their place in therapy to be more clearly established. The identified new evidence indicates that aclidinium bromide produces greater improvements in subjective and objective outcome measures than tiotropium whereas glycopyrronium was found to be non-inferior to tiotropium. This may be sufficient to include details on the use of specific LAMAs

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
bromide and glycopyrronium bromide with other active treatments for COPD would enable their place in therapy to be more clearly established. It was considered that there was insufficient consistent evidence to include details on the use of specific LAMAs in the guideline. **<u>Evidence Update (2012)</u>** A meta-analysis[173] and an RCT[174] found no increased risk of cardiovascular events or mortality when tiotropium was delivered via a dry-powder inhaler compared with placebo. One meta-analysis[175] highlighted safety issues associated with a tiotropium mist inhaler; Spiriva Respimat. The Evidence Update concluded that the potential safety issues may be a consideration in future reviews of CG101, particularly for patients with cardiovascular disease. The Medicines and Prescribing Programme considered the safety issues and advised that health professionals looking after people with COPD should continue to follow NICE guidance: long-acting bronchodilator (either a long-acting anticholinergic [tiotropium] or a long-acting beta agonist [LABA]) should be offered for people who experience exacerbations or persistent breathlessness despite use of a short-acting bronchodilator. The guidance does	formoterol or other LABAs. A network meta-analysis[177] which compared the effectiveness of various LAMAs for treating moderate to severe COPD exacerbations reported that glycopyrronium was associated with the least-effective treatment strategy whereas aclidinium was associated with the greatest probability of being the best therapy in preventing severe exacerbations. One systematic review[178] of 2 large RCTs compared the efficacy of tiotropium with ipratropium bromide in patients with stable COPD. Significantly better improvements in FEV1 measurements and SGRQ scores were reported in the tiotropium group. Exacerbations, withdrawals, disease specific serious adverse events and hospital admissions were less common in the tiotropium group. Additionally, there were fewer people experiencing one or more non-fatal serious adverse events in the tiotropium group. There was no significant difference in mortality between the treatments.	guideline is widely considered out of date because it offers little or no useful guidance on inhaled therapy using newer bronchodilator medications.	in the guideline.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
not give preference to either tiotropium or LABA. The MPP also advised health professionals to follow MHRA advice on tiotropium Respimat which reminds prescribers to use tiotropium Respimat with caution in patients with known cardiac rhythm disorders. At the time of publication of the Evidence Update a safety trial was underway[144]. Upon publication, the study reported that tiotropium Respimat at a dose of 5 µg or 2.5 µg had a similar safety profile to that of a tiotropium HandiHaler at a dose of 18 µg in patients with COPD.	One systematic review[179] explored the risk of myocardial infarction in patients with COPD treated by LAMAs. Meta-analysis comparing tiotropium against placebo showed a decreased risk of MI in patients treated by tiotropium. One non-inferiority RCT[180] compared patients with moderate to severe COPD treated by glycopyrronium or tiotropium. Least squares mean trough FEV1 values for glycopyrronium were non inferior to tiotropium at 12 week follow-up. The FEV1 area under the curve from 0 to 4 hours post-treatment with glycopyrronium was significantly superior to tiotropium on Day 1 and was comparable to tiotropium at 12 week follow-up. No significant differences in Transition Dyspnea Index focal scores, SGRQ total scores, proportions of patients using rescue medication and COPD exacerbation rates were observed between groups. Patients treated by glycopyrronium had a significantly lower total COPD symptom score than patients treated by tiotropium.		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	Adverse events were reported by a similar percentage of patients receiving glycopyrronium (40.4%) and tiotropium (40.6%).		
101 – 46 Which patients with stable COPD should be treated with methylxanthines / PDE4 inhibitors? How should the effects of this treatment be assessed? (2004; 1.2.2.1)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) The new evidence on PDE4 inhibitors was mixed. Studies included people with different disease severities, and compared roflumilast with placebo rather than making comparisons with other active treatments. Some systematic reviews and RCTs reported a modest benefit or insufficient evidence of benefit[181-186] whereas other studies indicated roflumilast was efficacious and safe[187-191]. A network meta-analysis[192] suggested that the combination of a LAMA plus roflumilast produced the largest treatment effects, and had the highest probability of being the best first-line treatment. The guideline was unable to make recommendations on the use of PDE4 inhibitors for COPD as insufficient evidence was identified. Since the guideline was published, a Technology Appraisal on roflumilast had been developed	A systematic review of RCTs[193] which evaluated the efficacy of roflumilast, reported that roflumilast significantly improved mean exacerbation rates, trough FEV1 measurements and other post-bronchodilator spirometric paramaters (comparator groups were not specified). Treatment with roflumilast did not improve St George's Respiratory Questionnaire scores or decrease the overall mortality rate. Roflumilast increased some adverse events; including diarrhoea, headache, nausea, weight loss, and insomnia.	Topic experts suggested the following studies: An RCT[194] of patients with severe COPD treated by roflumilast or placebo reported significantly lower exacerbation rates in the roflumilast group. Adverse events were reported in 67% of patients in the roflumilast 59% of patients in the placebo group. Serious adverse events (COPD exacerbations, pneumonia, and death) occurred 1.8% of patients in the roflumilast group and 1.9% of patients in the placebo group. Finally, the percentage of patients who withdrew from the study was 11% in the roflumilast group and 5% of patients in the placebo group.	New evidence is unlikely to impact on guideline recommendations The guideline was unable to make recommendations on the use of PDE4 inhibitors for COPD as insufficient evidence was identified. Since the guideline was published, a Technology Appraisal on roflumilast had been developed (TA244 Roflumilast for the management of severe chronic obstructive pulmonary disease, 2012). The appraisal recommends that roflumilast should be used only in the context of research as part of a clinical trial for adults with severe COPD associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment. Furthermore, the appraisal recommends that research should be designed to generate robust evidence

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
(TA244 Roflumilast for the management of severe chronic obstructive pulmonary disease, 2012). The appraisal recommends that roflumilast should be used only in the context of research as part of a clinical trial for adults with severe COPD (for the purposes of the technology appraisal guidance defined as forced expiratory volume in 1 second [FEV] post-bronchodilator less than 50% predicted) associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment. Furthermore, the appraisal recommends that research should be designed to generate robust evidence about the benefits of roflumilast as an add-on to long-acting muscarinic antagonists (LAMA) plus long-acting beta2 agonists (LABA) plus inhaled corticosteroids (ICS), or LAMA plus LABA for people who are intolerant to ICS. It was considered that the new evidence was unlikely to impact on guideline recommendations. Clinical feedback indicated that studies on PDE4 inhibitors, particularly roflumilast, were ongoing and it was pertinent to wait until they were published before considering an update. **Evidence Update (2012)** The Evidence Update noted recommendations in NICE technology appraisal 244 mentioned		A post-hoc analysis[195] pooled data from 2 RCTs of patients treated by roflumilast plus LABA, roflumilast plus LABA plus ICS, or placebo. In patients who discontinued ICS prior to study entry, addition of roflumilast to LABAs resulted in significantly greater reductions in the risk of COPD exacerbations and greater improvements pre-and post-bronchodilator FEV1 measurements compared to placebo. Similar improvements were reported in patients treated by roflumilast plus LABA plus ICS. The significant reduction in COPD exacerbation risk with roflumilast vs. placebo was observed regardless of age or smoking status, in patients who had severe or very severe COPD. Significantly improved lung function was observed with roflumilast in all the subgroups, apart from patients with moderate COPD. Topic experts stated that there is new evidence on the efficacy of roflumilast, used with or without LABA plus ICS therapy. Evidence suggests that treatment can reduce the	about the benefits of roflumilast as an add-on to long-acting muscarinic antagonists (LAMA) plus long-acting beta2 agonists (LABA) plus inhaled corticosteroids (ICS), or LAMA plus LABA for people who are intolerant to ICS. The majority of evidence identified during this 6-year review compared roflumilast with placebo rather than making comparisons with other active treatments. Only 1 of the studies identified at this review time-point (the post-hoc analysis of 2 RCTs) made assessments in line with recommendations with TA244. Results indicate some additional benefit of adding roflumilast to LABAs. Larger studies with longer follow-up periods are needed to add recommendations on PDE4 inhibitors to the guideline

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
above.		frequency of exacerbations and prevent subsequent hospital admissions. Investigations by the MPP revealed that the patent for roflumilast is due to expire in July 2019.	
101 – 47 Which patients with stable COPD should be treated with inhaled steroids? How should the effects of this treatment be assessed? (2004; 1.2.2.2–1.2.2.3)			
Surveillance decision This review question should not be updated; however, a footnote could be added to the guideline to outline potential adverse events related to inhaled steroids			
4-year surveillance (2014) A Cochrane systematic review[196] which assessed the safety and efficacy of ICS therapy in patients with stable COPD reported that treatment improved the rate of decline in FEV1 and quality of life. Authors reported that ICS therapy reduced COPD exacerbation rates but increased pneumonia rates. The results of another systematic review[197] indicated that withdrawing ICSs in routine practice did not result in considerable deterioration in patient outcomes. Additionally, a Cochrane systematic review[198] reported no significant differences in the percentage of patients experiencing exacerbations or the rate of exacerbations per patient year between ICSs and LABAs). Lastly, a systematic review[199] reported that economic evaluations indicated differences in cost	A systematic review[202] assessed the risk of pneumonia in patients with COPD who were receiving inhaled steroids by evaluating studies which compared budesonide or fluticasone with placebo, or studies which compared budesonide or fluticasone in combination with a LABA versus the same LABA as monotherapy. Compared with placebo, fluticasone increased non-fatal serious adverse pneumonia events (requiring hospital admission) and no evidence suggested that this outcome was reduced by delivering it in combination with salmeterol or vilanterol. Similar effects were reported for budesonide. An indirect	Topic experts suggested 1 RCT[96]. In this RCT patients with moderate to severe COPD received triple therapy (tiotropium plus salmeterol plus fluticasone) over a 6 week period. Subsequently, patients were randomly assigned to continue triple therapy or to discontinue ICS (fluticasone) treatment in 3 steps, over 12 weeks. No significant difference in the period of time to first moderate to severe COPD exacerbation was observed between groups; demonstrating non-inferiority. At 18 week follow-up, patients who discontinued ICS treatment had significantly greater reductions in trough FEV1 measurements than	New evidence is consistent with guideline recommendations The identified new evidence is broadly in line with the recommendation in the guideline which states that clinicians should 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. Currently, it is unclear how European-level discussions will impact on guideline recommendations. As a result, there is a need to await feedback from the MHRA. When the guideline was updated in 2010, the GDG felt that the evidence reviewed relating to combination therapy of inhaled

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
effectiveness between COPD maintenance therapies. Two Cochrane systematic reviews[196,198] reported an increase in rate of pneumonia following ICS usage whereas the results of another systematic review[200] indicated that ICS usage was not consistently associated with reduced mortality from pneumonia in people with COPD. An increased risk of fracture was reported in another systematic review[201]. GDG feedback indicated that there was more awareness of the risk of pneumonia due to ICS use. The identified new evidence was broadly in line with the recommendation in the guideline. When the guideline was updated in 2010, the GDG felt that the evidence reviewed relating to combination therapy of inhaled corticosteroids plus LABA superseded the previous evidence about inhaled steroid monotherapy. Insufficient evidence was identified that suggested that monotherapy with inhaled corticosteroids should be reassessed. **Evidence Update (2012)** No relevant evidence identified	comparison of budesonide versus fluticasone monotherapy revealed no significant differences with respect to serious adverse events or mortality. One systematic review[203] indicated that treatment with either ICS plus LABA or ICS alone resulted in an increased risk of pneumonia; however, no effect on pneumonia related mortality was reported. A systematic review[204] which compared the effectiveness of ICS with placebo reported no significant differences in in survival rates between groups. Furthermore, patients treated by ICS were significantly less likely to develop an exacerbation episode than those who received placebos. A systematic review[205] evaluated the risk of TB and influenza in patients treated by ICS. Authors reported that patients treated by ICS had a significantly higher risk of developing TB than those who didn't receive ICS treatment. Furthermore, the number needed to harm to cause 1 additional TB event was lower for patients with	those who continued triple therapy. A similar difference was observed at 52 week follow-up. No change in dyspnoea and minor changes in health status (not specified) occurred in the ICS discontinuation group. In an RCT[208]of patients with COPD treated by medium- or high-dose ICS therapy, significantly greater improvements in COPD assessment test scores and FEV1 measurements were reported in the high-dose ICS group at 1 year follow-up. Furthermore acute exacerbation rates were lower in the high-dose ICS group. No significant difference in pneumonia rates were observed between groups. Topic experts felt that the role of ICS treatment needs further discussion. One expert highlighted that there is more evidence about potential adverse events related to ICS treatment. Another expert stated that studies show that ICS withdrawal had no effect on exacerbation frequency in patients with severe COPD but small changes occurred on FEV1 values. Three topic experts raised	corticosteroids plus LABA superseded the previous evidence about inhaled steroids as monotherapy. Insufficient new evidence was identified to suggest that this should be reassessed. It was considered that a footnote could be added to the guideline to outline potential adverse events related to inhaled corticosteroid therapy.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	COPD treated with ICSs in endemic areas than for those in non-endemic areas (909 vs 1,667, respectively). No significant difference in the risk of influenza was reported between patients treated by ICS and those not treated by ICS. One meta-analysis[206] was performed to determine whether treatment with ICSs increased the risk of tuberculosis in people with chronic respiratory disease. A subgroup analysis, which focussed on patients with COPD, revealed that ICSs increased the risk of tuberculosis. A network meta-analysis[84] pooled data from RCTs which assessed the efficacy of LABA, LAMA and ICS, alone or in combination, versus each other or placebo. Analysis of cardiovascular-related mortality revealed that Triamcinolone acetonide was the most harmful medication according to the Surface Under the Cumulative Ranking (SUCRA) curve. Analysis also revealed that salmeterol plus fluticasone and fluticasone were likely to increase the risk of pneumonia in	concerns about the risk of pneumonia in patients with severe COPD while 2 experts highlighted the risk of diabetes onset and progression. A Drug Safety Update was published in 2010, lighting the risk of psychological and behavioural side effects associated with inhaled steroids. Furthermore, The MHRA informed NICE's Medicines Prescribing Programme that safety issues relating to inhaled corticosteroids are under consideration at a European level and could affect considerations in the UK.	

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	comparison to placebo. One network meta-analysis[207] evaluated the cost effectiveness of pharmacotherapies (not adequately defined) in moderate to severe COPD. At the threshold of $40,000 per QALY, ICS, LAMA and placebo each had a 56%, 19%, and 21% probability of being cost effective.		
101 – 48 Which patients with stable COPD should be treated with oral steroids? How should the effects of this treatment be assessed? (2004; 1.2.3.1–1.2.3.2)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 49 What is the role of combination therapy in patients with stable COPD? How should the effects of this treatment be assessed? (2004; 1.2.2.4–1.2.2.10)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 50 What are the most appropriate delivery systems for giving inhaled therapy to patients with stable COPD? (2004; 1.2.2.11–1.2.2.17)			
Surveillance decision This review question should not be updated; however, a footnote could be added to the guideline to outline potential cardiovascular adverse events related to Respimat and Handihaler inhalers.			
4-year surveillance (2014) A systematic[209] review reported that the Respimat inhaler did not add any additional clinical benefit to that of other inhaler devices in the management of COPD. One crossover RCT[210] assessed the safety and efficacy of a new oscillatory device as add-on therapy for COPD and reported that the device improved 6 minute walk test distances, pulmonary function and HRQoL. Lastly, an RCT[211] reported that an Ipratropium bromide plus salbutamol Respimat inhaler produced greater increases in the time to first COPD exacerbation than an ipratropium bromide plus salbutamol metered-dose inhaler: however, the results were not statistically significant. Although studies reported on clinical outcomes, no evidence was identified relating to handling of the devices, ease of use and patient preference. As a result, the new evidence was considered unlikely to change guideline recommendations. **Evidence Update (2012)** No relevant evidence identified	In 1 systematic review[212] the death rate of patients treated by a dry powder tiotropium inhaler was significantly lower than the death rate of patients who received placebo. Conversely, the death rate of patients treated by a soft-mist tiotropium inhaler was significantly higher than the death rate of patients who received placebo. One systematic review[213] compared 2 types of tiotropium inhalers: the handihaler metered-dose inhaler and the respimat soft mist inhaler. Authors reported that limited, early studies suggested a potential increase in cardiovascular and general mortality associated with tiotropium handihaler, but these data were outweighed by subsequent larger trials, real-life studies and meta-analyses which proved the opposite. It is unclear from the abstract whether any pooled	The MPP highlighted a Drug Safety Update (February 2015) which stated that clinicians should 'take the risk of cardiovascular side effects into account when prescribing tiotropium delivered via Respimat or Handihaler to patients with certain cardiac conditions, who were excluded from clinical trials of tiotropium',	New evidence is unlikely to impact on guideline recommendations The guideline currently states: "1.2.2.11 In most cases bronchodilator therapy is best administered using a hand-held inhaler device (including a spacer device if appropriate). [2004] 1.2.2.12 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. [2004]" The guideline does not recommend which types of handheld inhalers should be used. The identified new evidence evaluated a range of different delivery systems. Although the studies reported clinical outcomes, no evidence was identified relating to handling of the devices, ease of use and patient preference. The new evidence is unlikely to impact on the current guideline recommendations; however, a footnote could be added to the guideline to outline

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	analysis was performed.		potential cardiovascular adverse events related to Respimat and Handihaler inhalers.
101 – 51 Which patients with stable COPD benefit from nebulised therapy compared to other delivery mechanisms? (2004; 1.2.2.18–1.2.2.23)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 52 What is the role of mucolytic therapy in patients with stable COPD? (2004; 1.2.3.7–1.2.3.9)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	A meta-analysis[214] assessing the efficacy of N-acetylcysteine (NAC) in patients with bronchitis or COPD reported that NAC significantly and consistently reduced exacerbations: the protective effect was more apparent in patients without evidence of airway obstruction. Authors stated that NAC was well tolerated and the risk of adverse reactions was not dose-dependent.	Topic experts stated that more data on the role of NAC in preventing COPD exacerbations is becoming available.	New evidence is unlikely to impact on guideline recommendations. The guideline recommends that mucolytic drugs should not be routinely used to prevent exacerbations in people with COPD. Similar to literature reviewed in the 2010 update of the guideline, the identified new evidence compared mucolytic agents with placebo (and not other known effective therapies). As a result, there is insufficient new evidence to recommend the routine use

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	A systematic review[97] of RCTs which compared oral mucolytic therapy versus placebo reported a reduction in the number of exacerbations in patients treated by mucolytic therapy. Compared with placebo, mucolytic therapy was associated with improved quality of life, a reduction in the number of hospitalisations, and a reduction in the days of disability per participant per month. One systematic review[215] evaluated the effects of low-dose and high-dose NAC on COPD. Authors reported high-dose NAC reduced the total number of exacerbations and the proportion of patients with at least 1 exacerbation (unclear if comparisons were made with placebo). Low-dose NAC showed no benefit in the total number of exacerbations. Furthermore, neither high nor low-dose NAC treatment produced improvements in FEV1 measurements.		of mucolytic agents ahead of other therapies for preventing exacerbations.
101 – 53 In patients with stable COPD, what is the comparative efficacy of mucolytic therapy? (2004; 1.2.3.7–1.2.3.9)			
Surveillance decision			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
This review question should not be updated.			
4-year surveillance (2014) A Cochrane review[216] investigated whether treatment with mucolytics reduced the frequency of exacerbations in COPD. The results indicated that mucolytic reduced the frequency of acute exacerbations, but had little or no effect on the overall quality of life. An RCT[217] of patients with stable COPD treated with N-acetylcysteine (NAC) compared or placebo, reported significant improvements in forced expiratory flow, forced oscillation technique and exacerbation frequency in the NAC group. The identified new evidence compared N-acetylcysteine with placebo (and not other known effective therapies). As such, there was insufficient new evidence to recommend the routine use of mucolytics primarily for the purpose of preventing exacerbations. **Evidence Update (2012)** No relevant evidence identified	A meta-analysis[214] assessing the efficacy of NAC in patients with bronchitis or COPD reported that NAC significantly and consistently reduced exacerbations: the protective effect was more apparent in patients without evidence of airway obstruction. Authors stated that NAC was well tolerated and the risk of adverse reactions was not dose-dependent. A systematic review[97] of RCTs which compared oral mucolytic therapy versus placebo reported a reduction in the number of exacerbations in patients treated by mucolytic therapy. Compared with placebo, mucolytic therapy was associated with improved quality of life, a reduction in the number of hospitalisations, and a reduction in the days of disability per participant per month.	Topic experts highlighted the following RCT: In an RCT[98] of patients with moderate to severe COPD treated by N-acetylcysteine or placebo, the exacerbation rate was 1·16 exacerbations per patient-year in the N-acetylcysteine group and 1·49 exacerbations per patient-year in the placebo group at 1 year follow-up ($p<0.05$). The occurrence of adverse events was similar in both treatment arms, with acute COPD exacerbation being the most common serious adverse event. Topic experts stated that more data on the role of NAC in preventing COPD exacerbations is becoming available.	New evidence is unlikely to impact on guideline recommendations. The guideline recommends that mucolytic drugs should not be routinely used to prevent exacerbations in people with COPD. Similar to literature reviewed in the 2010 update of the guideline, the identified new evidence compared mucolytic agents with placebo (and not other known effective therapies). As a result, there is insufficient new evidence to recommend the routine use of mucolytic agents ahead of other therapies for preventing exacerbations
101 – 54 In patients with stable COPD, does mucolytic therapy reduce morbidity? (2004; 1.2.3.7–1.2.3.9)			
Surveillance decision			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 55 What is the role of antioxidant therapy in patients with stable COPD? (2004; 1.2.3.10)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 56 In patients with stable COPD, what is the comparative efficacy of antioxidant therapy? (2004; 1.2.3.10)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 57 In patients with stable COPD, does antioxidant therapy reduce morbidity? (2004; 1.2.3.10)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 58 What is the role of antitussive therapy in patients with stable COPD? (2004; 1.2.3.11)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 59 In patients with stable COPD, what is the comparative efficacy of antitussive therapy? (2004; 1.2.3.11)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 60 In patients with stable COPD, does antitussive therapy reduce morbidity? (2004; 1.2.3.11)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 61 What is the role of 1-antitrypsin replacement therapy in patients with stable COPD? (2004; 1.2.3.11)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 62 What is the role of antibiotic therapy in patients with stable COPD? (2004; 1.2.3.12)			
Surveillance decision This review question should be updated.			
4-year surveillance (2014) Four systematic reviews[218-221] and 2 RCTs[222,223] evaluated the prophylactic use of antibiotics to prevent COPD exacerbations. The studies generally indicated that the frequency of	A systematic review[224] indicated that prophylactic use of macrolide antibiotics could reduce the frequency of exacerbations in patients with COPD. Subgroup analysis showed	Topic experts stated that growing concerns about antibiotic resistance mean that considerations need to be made about the long-term use of antibiotics for prevention of COPD	New evidence identified that may change current recommendations Current recommendations state that there is insufficient evidence to recommend

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
exacerbations was reduced in the antibiotic treatment groups compared with placebo. The occurrence of adverse events was greater in antibiotic treatment arms but no significant effect on mortality was reported. One review[221] indicated that the specific antibiotic used as well as the length of therapy (more than 6 months) had a positive impact on exacerbation frequency. It was not clear whether the studies included patients with the similar levels of COPD severity. As a result, it was considered that further research was needed in specific COPD populations to determine whether the benefits of prophylactic antibiotic treatment outweigh the risk of adverse events. **Evidence Update (2012)** No relevant evidence identified	only 6 to 12 months of erythromycin or azithromycin therapy is effective. Moreover, among studies with 6 to 12 months of azithromycin therapy, both daily dosing regimens and intermittent regimens significantly reduced exacerbation rates.	exacerbations. Topic experts felt that is a clinically important topic because macrolides have been used extensively in people with COPD, particularly for those with chronic bronchitis and exacerbations. Experts suggested that clear guidance is needed to confirm or refute benefit in sub-groups, and highlight the significant risk of side effects.	prophylactic antibiotic therapy in the management of stable COPD. The identified new evidence indicates some benefits of antibiotic prophylaxis delivered for 6 to 12 months. Conversely, topic experts have raised concerns about the long-term (duration not specified) use of antibiotic prophylaxis, Further discussions are needed to clarify the role of antibiotic therapy in people with stable COPD.
101 – 63 What are the benefits of pulmonary rehabilitation programmes for patients with stable COPD? (2004; 1.2.8.1–1.2.8.5)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) Several RCTs reported beneficial effects of pulmonary rehabilitation in people with COPD including improvements in walking distance and leg strength[225]; improvement in the 6 minute walk test and QoL[226] and improvements in the	One systematic review[231] of RCTs compared the efficacy of pulmonary rehabilitation with that of usual care in people with COPD. Significantly greater improvements in all domains of the Chronic Respiratory	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations The identified new evidence broadly supports the use of pulmonary rehabilitation in people with COPD. This is in line with the current recommendations which state that

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
affective and impact domains of dyspnoea[227]. Furthermore, the results of a systematic review[228] indicated that pulmonary rehabilitation promotes behavioural changes towards health promotion in people with COPD. Conversely, the results of one RCT[229] did not show meaningful changes in QoL, exercise tolerance, pulmonary function or exacerbation after a one-year, community based rehabilitation programme. One systematic review[230] reported a lack of perceived benefit of pulmonary rehabilitation, travel and transport as factors influencing both uptake and completion. The identified new evidence broadly supported the use of pulmonary rehabilitation in people with COPD and was in line with the recommendations. **Evidence Update (2012)** No relevant evidence identified	Questionnaire and the St. George's Respiratory Questionnaire were reported in the pulmonary rehabilitation group. Furthermore, pulmonary rehabilitation yielded significantly greater improvements in functional exercise and maximal exercise compared with usual care. In relation to functional exercise, capacity, the 6 minute walk test distance the treatment effect was greater than the threshold of clinical significance.		pulmonary rehabilitation should be made available to all appropriate people with COPD including those who have had a recent hospitalisation for an acute exacerbation.
101 – 64 In stable COPD patients referred for pulmonary rehabilitation programmes, what is the optimal course content, setting & duration? (2004; 1.2.8.1–1.2.8.5)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) Course content: In an RCT[232] of patients with COPD treated by	Course content: One systematic review[276] assessed RCTs that compared non-invasive	One topic expert stated that community services provide pulmonary rehabilitation but transport	New evidence is unlikely to impact on guideline recommendations The new evidence mainly assessed

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
pulmonary rehabilitation plus ambulatory oxygen or pulmonary rehabilitation alone, significantly greater improvements in endurance walking distance were reported in the ambulatory oxygen group. An RCT[233] reported that patients who received inhaled procaterol during pulmonary rehabilitation had significantly greater improvements in 6 minute walk test distances and St. George's respiratory questionnaire scores than those who received pulmonary rehabilitation alone. Additionally, 2 RCTSs[234,235] reported that adding ghrelin to pulmonary rehabilitation improved exercise outcomes although no significant differences in outcomes were observed when comparisons were made with placebo groups. The results of 4 small RCTs[236-239] indicated that neuromuscular electrical stimulation may have a beneficial effect in preventing muscle function deterioration in people with COPD. Two RCTs[240,241] reported a significant increase in the 6 minute walk test distances in people with COPD who received whole body vibration training during pulmonary rehabilitation programmes. One RCT[242] reported that a respiratory training programme produced considerable	ventilation (NIV) during exercise training (as part of pulmonary rehabilitation) with exercise training alone or exercise training with sham NIV. Greater improvements in FEV1, training intensity, isoload lactate levels and endurance exercise capacity were observed in the active NIV group; however, there was no difference between interventions in other measures of exercise capacity. No significant differences in dyspnoea severity and quality of life were observed between groups. In another systematic review[277], NIV during exercise training (as part of pulmonary rehabilitation) produced significant improvements in heart rate, work load and oxygen consumption. A systematic review[278] assessed groups of patients who received Expiratory Muscle Training (EMT) plus Inspiratory Muscle Training (IMT) or EMT alone and compared them with controls groups. Both treatment groups produced greater improvements in maximum respiratory pressure and maximum	is not provided for those who need it, leading to some patients not being able to attend treatment sessions. No additional information was provided.	individual components of pulmonary rehabilitation programmes with results indicating a benefit from exercise (including traditional Chinese exercise and resistance training), neuromuscular electrical stimulation, and whole body vibration training. The new evidence is generally supportive of the current recommendation which states 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.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
improvements in dyspnoea severity and 6 minute walk test distances. In addition, a Cochrane systematic review[243] reported that breathing exercises may be useful in improving exercise tolerance in selected individuals with COPD who are unable to undertake exercise training but the evidence was not conclusive to recommend as a central intervention for COPD management. Lastly, an RCT[244] which compared the effect of singing classes with that of a film club reported a difference in the physical component score of the SF-36 but no difference in breathing control measures, exercise capacity or daily physical activity. A large amount of evidence on exercise was identified. The evidence generally reported a beneficial effect as part of a pulmonary rehabilitation programme in people with COPD[245-247]. Specific effective exercise interventions included water based training[248-250]; an aerobic physical training programme[251]; arm exercise training[252,253]; urban walking circuits[254]; combined strength training and endurance training[255-257]; floor exercises[258]; resistance training[259]. Lastly, the results of a Cochrane systematic review which compared high- and low-intensity training indicated no significant differences in improvements in endurance times and 6 minute walk test distances between	inspiratory pressure than control groups, with the EMT plus IMT group showing the yielding the greatest improvements. Not significant difference in dyspnoea severity and 6 minute walk test distances were observed between EMT alone and control group: no data were provided for the EMT plus IMT group. One systematic review[279] assessed the potential benefits of traditional Chinese exercises (Qigong and/or Tai chi) for pulmonary rehabilitation. When compared against conventional exercise or no exercise groups, weighted mean differences in FEV1 measurements and 6 minute walk test distances were in favour of the Chinese exercise group. A meta-analysis[280] of RCTs which assessed the effects of neuromuscular electrical stimulation in patients with COPD reported the intervention was associated with significant improvements in dyspnoea scores (comparator groups were not specified). No significant changes in quadriceps strength, muscle fibre characteristics and 6 minute walk test		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
groups[260]. One systematic review[261] concluded that there was insufficient evidence on manual therapy to recommend this as an approach for managing COPD. Furthermore, a small-scale RCT[262] reported small improvements in distances walked and dyspnoea levels in people receiving manual therapy and exercise. One RCT[263] which assessed the effect of rib cage mobilisation in people with COPD found that the intervention significantly improved FEV1/FVC ratios and dyspnoea index scores. An RCT[264] compared the effectiveness of a structured education pulmonary rehabilitation programme with that of usual care. Participants allocated to the intervention group had significantly greater mean changes in Chronic Respiratory Questionnaire scores. Another study[265] compared the cost-effectiveness of a structured education pulmonary rehabilitation programme with usual care and found no benefit in relation to QALYS gained. One RCT[266] evaluated the use of a rollator compared with a modern draisine in improving mobility in people with COPD. Higher 6 minute walk test distances were reported in the draisine group whereas oxygen uptake, oxygen saturation and Borg symptom scores were comparable	distances were associated with the intervention. A systematic review[281] evaluated the effects of resistance training on people with COPD pooling data from trials which compared resistance training with no exercise OR compared resistance training plus endurance training with endurance training alone. Compared with no exercise, resistance training produced significant improvements in dyspnoea, skeletal muscle strength and percent of predicte4d FEV1. Compared with endurance training alone, resistance training plus endurance training lead to significant better improvements in skeletal muscle strength as well as improvements in all domains of the St George Respiratory Questionnaire (SGRQ). There were no significant differences in 6 minute walk test distance, 6 minute pegboard and ring test, maximum exercise work load, and maximum oxygen consumption between the 2 groups. Another systematic review[282] comparing resistance training plus endurance		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
between groups. Setting: In an RCT[267] of home-bound patients who received aerobic conditioning or functional strength training, significant improvements in CRQ-dyspnoea domain scores were reported in both groups. A significant improvement in walking distances was reported in the in the aerobic conditioning group. Duration: A systematic review[268] reported that rehabilitation programs had positive effects on all outcome measures evaluated apart from mortality. Furthermore, a Cochrane systematic review[269] concluded that integrated disease management programmes or interventions reduced hospitalisation days. One RCT[270] indicated that a long-term pulmonary rehabilitation programme resulted in greater improvements in physical capabilities and HRQoL compared to standard care. One GDG questionnaire respondent felt there were inequalities in access to pulmonary rehabilitation services. This new evidence was supportive of the recommendation which states that pulmonary rehabilitation programmes should include	training with endurance training alone reported a significant increase in leg muscle strength favouring combination training whereas meta-analysis showed equal improvements in HRQoL, walking distance and exercise capacity. One systematic review[283] reported no clinically important difference between resistance training and endurance training: the abstract did not specify what outcome measures were assessed. Finally, a systematic review[284] indicated that whole body vibration training improved exercise capacity in people with COPD. <u>Setting:</u> One systematic review[231] compared hospital-based pulmonary rehabilitation programmes with community-based programmes for managing COPD. Authors reported significantly greater improvements in Chronic Respiratory Questionnaire scores for dyspnoea, fatigue, emotional function and mastery in the hospital-based group. No significant		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
multicomponent, multidisciplinary interventions, which are tailored to the individual patient's needs. **Evidence Update (2012)** Course content: A meta-analysis[271] reported significant improvements in maximal inspiratory muscle strength and respiratory muscle endurance times in patients with COPD who received inspiratory muscle training (IMT). IMT was also investigated as part of a systematic review[272] of home-based physiotherapy interventions. Although the analysis suggested that home-based IMT may be effective, potential limitations of the evidence (high heterogeneity and small sample sizes) lead to the conclusion that more research was needed to determine whether IMT could be added to or substituted for standard pulmonary rehabilitation techniques. The EUAG felt the evidence highlighted the potential benefit of IMT in pulmonary rehabilitation, but could not provide definitive answers as to whether IMT should be added to other forms of rehabilitation. Furthermore there was limited evidence on whether there is a subgroup of patients with inspiratory muscle weakness who could benefit. As such, the Evidence Update noted that further research was	difference in SGRQ scores were observed between groups. A meta-analysis[285] that included RCTs of patients with COPD treated by home-based pulmonary rehabilitation or 'non-intervention', reported significantly better improvements in dyspnoea, HRQoL, exercise capacity and pulmonary function in the intervention group at 12 week follow-up. No significant differences in maximal workload, hospital admission, cost of care, or mortality were observed between groups.		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
needed. An RCT[273] was identified which assessed the effect of Nordic walking (a walking technique involving specialised poles) on daily physical activities in people with COPD. The EUAGE felt the study provided preliminary evidence that Nordic walking could be a useful addition to pulmonary rehabilitation strategies but larger comparative studies which assess long-term outcomes (such as survival, resource usage and patient satisfaction are needed. Setting: The Evidence Update included a trial [274] which compared pulmonary rehabilitation delivered in hospital and community settings. The results suggested that there was no clinical or cost benefit of community-based rehabilitation over hospital-based rehabilitation, and the venue may be best determined by local access preferences and transport links. This evidence was considered to reinforce current recommendations in CG101. Duration: The Evidence Update included a systematic review[275] which evaluated the optimal duration of pulmonary rehabilitation in people with COPD. The review suggested that longer duration rehabilitation programmes were of greater benefit			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
than shorter programmes. Limitations of the review, including the absence of a meta-analysis and lack of clinical significance with some outcomes, meant that recommendations in CG101 were unlikely to be affected.			
101 – 65 Which patients with stable COPD should be referred for pulmonary rehabilitation and when? (2004; 1.2.8.1–1.2.8.5)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) Three RCTs[286-288] indicated potential benefit of pulmonary rehabilitation in people recently had an acute COPD exacerbation. Furthermore, the results of a systematic review[289] indicated that supervised exercise programmes after pulmonary rehabilitation are likely to be more effective than usual care for preserving exercise capacity in the medium term but not in the long term. The new evidence was broadly supportive of the recommendation which states that pulmonary rehabilitation should be made available to all appropriate people with COPD including those who have had a recent hospitalisation for an acute exacerbation. **Evidence Update (2012)**	A systematic review[292] of RCTs compared the efficacy of pulmonary rehabilitation with usual care in patients with mild symptoms of COPD (Medical Research Council dyspnea scale scores less than 1). Pulmonary rehabilitation conferred a significantly greater improvement in the 6 minute walk test distances than usual care; however, this was not considered clinically significant. Authors also reported a significant improvement in HRQoL in the short-term. No difference in mortality was observed between groups.	None identified relevant to this question.	New evidence is consistent with guideline recommendations The new evidence is broadly supportive of the recommendation which states that pulmonary rehabilitation should be made available to all appropriate people with COPD including those who have had a recent hospitalisation for an acute exacerbation.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
CG101 recommended that pulmonary rehabilitation should be offered to all patients who consider themselves functionally disabled by COPD. The Evidence Update suggested that the recommendation was reinforced by an RCT[290] which evaluated the safety and efficacy of a home-based pulmonary rehabilitation programme for patients with very severe COPD on long-term oxygen therapy (LTOT). A Cochrane review[291] by found that pulmonary rehabilitation significantly reduced hospital admissions and mortality in patients who had recently experienced an exacerbation. The EUAG felt that the evidence reinforced the value of post-exacerbation rehabilitation and may be considered in future reviews of CG101, although the included trials were small.			
101 – 66 In patients with stable COPD, are there benefits in repeated pulmonary rehabilitation attendances? (2004; 1.2.8.1–1.2.8.5)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 67 In patients with stable COPD how can right heart failure / chronic salt and water retention be identified? (2004; 1.2.7.1–1.2.7.2)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 68 In patients with stable COPD what therapies can be used to manage right heart failure / chronic salt and water retention? (2004; 1.2.7.3–1.2.7.5)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 69 In patients with stable COPD how can pulmonary hypertension be identified? (2004; not linked to a specific guideline recommendation)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	One meta-analysis[293] compared the prevalence of cardiovascular disease in people with COPD with matched controls or random samples from the general population. Compared with	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations The identified study does not provide any conclusive evidence of how pulmonary

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	the non-COPD population, patients with COPD were more likely to be diagnosed with cardiovascular disease; including ischaemic heart disease, cardiac dysrhythmia, heart failure, diseases of the pulmonary circulation, and diseases of the arteries. Additionally, hypertension, diabetes, and ever smoking were reported more often in people with COPD.		hypertension can be identified in people with COPD. Instead the study, confirms the association between COPD and cardiovascular disease.
101 – 70 In patients with stable COPD what therapies can be used to manage pulmonary hypertension? (2004;1.2.7)			
Surveillance decision This review question should be updated.			
4-year surveillance (2014) An RCT[294] of patients with pulmonary hypertension secondary to COPD treated by atorvastatin or placebo, reported no significant differences in pulmonary hypertension measurements, 6 minute walk test distances or spirometry parameters between groups. Furthermore, another RCT[295] indicated that addition of sildenafil did not improve the results of pulmonary rehabilitation in patients with COPD and pulmonary hypertension. Identified studies revealed that atorvastatin and sildenafil provided no benefit for people with	In 1 systematic review[296], patients with pulmonary hypertension, secondary to COPD, treated by statins were compared with those who were not receiving treatment (controls). Analysis revealed that patients treated by statins had a lower risk of mortality than controls. The pooled hazard ratio for all-cause mortality was 0.81 ($p<0.05$). The pooled hazard ratios for cardiovascular-related, cancer-related, and respiratory-related	None identified relevant to this question.	New evidence identified that may change current recommendations. Currently, CG101 makes no recommendations on the use of statins for managing pulmonary hypertension in people with COPD. In contrast to evidence from 1 RCT identified during the 4-year review, new evidence from 2 systematic reviews identified in this 6-year review suggests considerable benefits to patient outcomes.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
pulmonary hypertension. It was considered that further research on the long-term benefits and harms of statins would be needed before considering amendments to the guideline. **Evidence Update (2012)** No relevant evidence identified	mortality were 0.52 (p>0.05), 0.57 (p>0.05) and 0.55 (p<0.05), respectively. Another systematic review[297] indicated that treatment with either bosentan or sildenafil significantly increased exercise capacity and reduced pulmonary arterial pressure in patients with pulmonary hypertension secondary to COPD. No improvements in hypoxemia and quality of life were observed. Authors stated that 'dyspnoea was alleviated or at least not aggravated'.		
101 – 71 How are patients with stable COPD affected by anxiety and / or depression? (2004; 1.2.12.5)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) Systematic reviews indicated that depressive symptoms were more common among people with COPD compared with control groups[298-300]. One systematic review[301] evaluating the prevalence of specific anxiety disorders in patients with COPD reported that the prevalence of clinical anxiety ranged from 10-55% among in-patients and 13-46% among out-patients with COPD and included generalised anxiety	A systematic review[302] reported that anxiety and depression in COPD led to a significant increase in the likelihood of being hospitalised. The comorbidities also led to increased length of stay and a greater risk of mortality following discharge. One systematic review[303] reported that anxiety reduced physical	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations The identified new evidence highlighted the potential for people with COPD to present with symptoms of depression and anxiety. This is in line with the guideline which recommends that healthcare professional should be alert to the presence of depression in patients with COPD.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
disorder, panic disorder, specific phobia and social phobia. The new evidence highlighted the potential for people with COPD to present with symptoms of depression and anxiety. This is in line with the guideline. **Evidence Update (2012)** No relevant evidence identified	activity/performance in people with COPD. Depression had less of an effect on physical activity but was associated with higher dropout rates from pulmonary rehabilitation programmes. One systematic review[304] reported that depression was associated with increased mortality in people with COPD. Depression was also associated with an increase in COPD exacerbations. A systematic review[305] of prospective cohort studies which assessed the impact of depression and anxiety in people with COPD reported that there was a significant correlation between depression and HRQoL at 1-year follow-up (pooled r=0.48). Additionally there was a significant correlation between anxiety and HRQoL at 1-year follow-up (pooled r=0.36).		
101 – 72 In patients with stable COPD, how can anxiety and depression be identified? (2004; 1.2.12.5)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014)	No relevant evidence identified.	None identified relevant to this	No new evidence was identified that would

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified		question.	affect recommendations.
101 – 73 How can anxiety and depression in stable COPD patients be managed? (Pharmacological & non-pharmacological) (2004; 1.2.12.5)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) One RCT[306] assessed the effects of an uncertainty management intervention which incorporated a cognitive behavioural intervention on uncertainty, anxiety, depression, and overall quality of life in people with COPD. Compared with the control group, the intervention group showed significant improvements in uncertainty, coping strategy, anxiety, depression, and the mental health domains of quality of life. One trial[307] compared patients with COPD who a personalised intervention for depression (PID-C) and those who received usual care. PID-C was found to lead to a higher remission rate and a greater reduction in depressive symptoms compared to the control group. Finally, a systematic review[308] reported that psychological and/or lifestyle interventions were associated with small reductions in symptoms of depression whereas multi-component exercise training was the only intervention associated with significant	A meta-analysis[309] which assessed cognitive behavioural therapy for anxiety and depression in COPD reported small improvements in symptoms for both comorbidities but changes were not statistically significant. In another systematic review[310], relaxation therapy (not specified) was found to have a slight effect (borderline significant) on both anxiety and depression. One systematic review[311]evaluated the effectiveness of yoga programmes for individuals with various chronic diseases, including COPD. Compared with usual care, yoga failed to relieve symptoms of anxiety in people with COPD.	Topic experts stated that poor physical health increases the risk of mental illness and there is increasing evidence indicating a close relationship with obstructive lung diseases such as COPD and mental health problems. Experts suggested that there is a potential benefit of Cognitive Behavioural Therapy in reducing anxiety and depression in people with COPD. Furthermore, there is new evidence which is being prepared for publication.	New evidence is unlikely to impact on guideline recommendations The recommendations on treatment and management of depression in adults with a chronic physical health problem in CG91 updated the recommendations within CG101 although the guideline noted the importance of offering psychological and psycho-social interventions before considering anti-depressant drugs. The identified studies evaluated a variety of psychological and psycho-social interventions; however, no significant improvements in depression or anxiety were reported. As a result, the new evidence is unlikely to impact on guideline recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
treatment effects for depression. Clinical feedback suggested that management of anxiety and depression varied. It was considered that the new evidence was unlikely to impact on guideline recommendations. **Evidence Update (2012)** No relevant evidence identified	A systematic review[312] identified RCTs of people with COPD who received interventions that combined exercise training and psychological strategies. When compared with control conditions (usual care or waiting lists), standardised mean differences for dyspnoea, anxiety, depression, quality of life and functional exercise capacity consistently favoured interventions which included both exercise and psychological components.		
101 – 74 What is the significance of nutritional problems in both stable and acute exacerbations of COPD? (2004; 1.2.12.6–1.2.12.7)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	One systematic review[313], explored the associated between host serum 25-hydroxy vitamin D (25(OH)D) and the susceptibility and severity of COPD. Pooled analysis of case-control studies revealed that people with COPD had lower 25(OH)D levels than controls whereas analysis of cohort studies indicated no significant difference between groups. No significant difference in 25(OH)D	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations The identified study did not provide conclusive evidence of an association between vitamin D levels and COPD severity. Further research is needed to confirm the significance of nutritional problems in both stable and acute exacerbations of COPD.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	deficiency rates was observed between people with COPD and controls. The deficiency rate of 25(OH)D in people with moderate to severe COPD was significantly lower than those with mild COPD.		
101 – 75 In patients with stable COPD, how can nutritional problems be identified? (2004; 1.2.12.6–1.2.12.7)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 76 In patients with stable COPD, how can nutritional problems be managed? (2004; 1.2.12.6–1.2.12.7)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) Three systematic reviews and 2 RCTs highlighted potential benefits associated with nutritional support in people with COPD [314-318]. Although, 1 RCT[319] which evaluated the effect of fruit and vegetable intake in people with moderate-to-severe COPD reported no significant effect on airway or systemic oxidative	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
stress and inflammation. Evidence on the role of supplementation in was mixed. Studies reported an increase in lean body mass and exercise tolerance with Creatine + Coenzyme Q-Ter [320]; improved physical performance and muscle strength with essential amino acids[321]; less severe and shorter exacerbation episodes with Echinacea purpurea[322]; improved exercise performance after magnesium IV loading[323]. Two studies reported no significant improvements in outcomes after vitamin D supplementation[324,325]. Conversely, a post-hoc subgroup analysis[326] of an RCT found that patients who received vitamin D had significantly larger improvements in inspiratory muscle strength and maximal oxygen uptake although improvements in quadriceps strength and 6 minute walk test distances were not significantly different from the effects in the placebo group. In general, the evidence on nutritional support in people with COPD was favourable; however, there was insufficient conclusive evidence to provide more detailed recommendations on specific nutritional supplements in this population. **Evidence Update (2012)** No relevant evidence identified			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 77 Do self-management plans & patient education affect concordance with treatment and improve outcomes in patients with stable COPD? (2004; 1.2.12.18–1.2.12.25)			
Surveillance decision This review question should be updated.			
4-year surveillance (2014) Several studies reported that self-management support programmes improved various outcomes in people with COPD, including inhaler technique and exercise endurance[327-339]. Conversely, an RCT[340] reported that a comprehensive care management programme failed to reduce COPD related hospitalisations compared to usual care. The results of another RCT[341] indicated no long term benefits associated with a comprehensive self-management programme delivered in general practice. An RCT[342] of patients who recieved a self-management intervention, regular monitoring by a practice nurse or care provided by the GP (usual care), reported that patients who received usual care experienced the highest continuity of care; however, no relationship was found between continuity of care and changes in quality of life. Finally, a systematic review[343] of educational programmes for people with COPD found that smoking cessation, medication; exercise, breathing	One systematic review[361] aimed to assess whether self-management interventions in COPD improved health outcomes and reduced healthcare utilisation. Compared with usual care, self-management produced greater improvements in dyspnoea scores, HRQoL scores and respiratory-related hospitalisation rates. No significant effects on 6 minute walk test distances, all-cause hospitalisation rates and mortality rates were reported. A systematic review[362] which evaluated the clinical- and cost-effectiveness of self-management support after hospital discharge identified no evidence of benefit to admissions, mortality and most other health outcomes (not specified). A modest improvement in HRQoL was observed. Economic modelling revealed that self-management (delivered within 6 weeks of discharge) was more costly and resulted in better outcomes (683 cost	Topic experts stated that self-management interventions are variably effective and further research is needed. One expert highlighted that there is some evidence that tele-health programmes to enhance self-management have not worked. Some experts also highlighted that a lot of NHS activity has been focused on prevention of admission of patients with chronic disease, including COPD: there is some uncertainty about the effectiveness (including cost effectiveness) and safety of such approaches.	New evidence identified that may change current recommendations. The guideline currently states that 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. Generally, the new identified evidence highlighted that self-management interventions improved various outcomes in people with COPD. Furthermore, 2 systematic reviews highlighted that tele-monitoring reduced healthcare utilisation and improved health-related outcomes. Authors also reported reduced healthcare costs for patients who utilised tele-monitoring programmes. This is an area which is currently not addressed by the guideline.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
strategies, exacerbations, and stress management were the most common topics. A large amount of new evidence was identified that evaluated telecare services for people with COPD. Several studies reported significant reductions in hospital admissions[344-347]. Additionally, an RCT[348] reported that a telehealth video which taught pursed-lips breathing produced significant reductions in dyspnoea severity. Conversely, the results of other RCTs and systematic reviews reported no benefit of telecare services compared with usual care[349-355]. Finally, an RCT[356] reported no significant difference in quality of life outcome measures between people who received telephone-delivered mentoring and those who received usual care. Two RCTs evaluated the effect of individualised action plans on COPD exacerbation rates. One RCT[357] reported that adherence to a written action plan significantly reduced exacerbation recovery time while the second RCT[358] found no significant difference in exacerbation rates in comparison to usual care. Generally, the identified new evidence was supportive of self-management programmes	difference and 0.0831 QALY gain) than usual care. Individual component analyses revealed that only exercise improved HRQoL. A systematic review[363] pooled data from RCTs which evaluated self-management interventions in patients with COPD who were recently discharged from hospital after an acute exacerbation. Compared with control, usual care or other intervention, self-management interventions produced greater improvements in St George's Respiratory Questionnaire scores. No significant differences in hospital admissions and all-cause mortality were observed between groups. A systematic review[364] which included 9 trials evaluated whether home tele-monitoring reduced healthcare utilisation and improved health-related outcomes of patients with COPD. Authors reported a trend to reduced healthcare costs in the tele-monitoring group. Additionally, the intervention was associated with a reduced number of exacerbations and a significant increase in quality of life. One systematic review[365] pooled data		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
for people with COPD which is in line with the guideline **Evidence Update (2012)** A Cochrane review[359] investigated the effect of action plans which focussed on education on COPD. The evidence suggested that a single, short educational session was unlikely to benefit health outcomes. Additionally, an RCT[360] examined a complex programme which involved a single 1–1.5 hour education session, an action plan for self-treatment of exacerbations, and monthly follow-up calls from a case manager. The Evidence Update concluded that the incorporation of case management and structured action plans, particularly for higher risk patients, may be a consideration for future reviews of CG101.	from studies which compared tele-healthcare with ordinary care, exercise training and/or education. Significantly greater improvements in FEV1 were associated with tele-healthcare. No significant differences in physical capacity and dyspnoea were observed between groups. A systematic review of RCTs[366] assessed the effectiveness of Integrated Disease Management (IDM) programmes which incorporated self-management, exercise and nutrition components. When compared with controls, people who underwent IDM programmes had significantly greater improvements in HRQoL scores and 6-minute walk test distances. Additionally, reductions in the proportion of patients with more than 1 respiratory related hospital admission and the duration of hospitalisation were reported in the IDM group. One systematic review[367] reported that complex interventions were associated with a 32% reduction in the use of urgent healthcare (Full details about component interventions were not provided). When study effects were		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	assessed according to individual components of the complex interventions, significant effects were seen for general education, exercise and relaxation therapy. One systematic review[368] assessed the impact of Chronic Disease Management programmes (including exercise, self-management and structured follow-up) on mortality in patients with COPD. Authors reported no impact of CDM on mortality.		
101 – 78 What is the role of oxygen therapy in patients with stable COPD? (2004; 1.2.5.1–1.2.5.18)			
Surveillance decision This review question should be updated.			
4-year surveillance (2014) A Cochrane systematic review[369] indicated that home oxygen therapy could relieve dyspnoea in mildly and non-hypoxaemic people with COPD who would not otherwise qualify for home oxygen therapy. Additionally, an RCT[370] reported that there was no additional benefit of adding ambulatory oxygen to pulmonary rehabilitation in people with COPD. It was considered that these studies were unlikely to change the direction of the	A Cochrane review[371] assessed the efficacy of ambulatory oxygen in patients with COPD who were not hypoxaemic at rest and did not meet criteria for long-term oxygen therapy (LTOT). The review included RCTs that compared ambulatory oxygen against placebo air cylinders, usual medical care or co-intervention. Significantly greater improvements in dyspnoea and fatigue were reported in the oxygen group. There was no	The Medicines and Prescribing Programme highlighted that the British Thoracic society's guidelines on oxygen therapy were updated in April 2015 and appear to be consistent with the NICE 2010 guidance.	New evidence identified that may change current recommendations. Current guideline recommendations state that LTOT is indicated in patients with COPD who have a PaO2 less than 7.3 kPa when stable or a PaO2 greater than 7.3 kPa and less than 8 kPa when stable and one of: secondary polycythaemia, nocturnal hypoxaemia (oxygen saturation of arterial blood [SaO2] less than 90% for more than 30% of the time), peripheral oedema or

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
recommendations on oxygen therapy. **Evidence Update (2012)** No relevant evidence identified	evidence of any effect on survival, and limited benefits were observed for exercise capacity. Another systematic review[372] assessed whether oxygen therapy relieved dyspnoea in patients with mild or non-hypoxemic COPD. Compared with 'medical air', oxygen therapy significantly reduced dyspnoea. Subgroup analysis revealed that dyspnoea was reduced by continuous oxygen during exertion but not short-burst oxygen therapy.		pulmonary hypertension. Evidence identified at both 4-year and 6-year review time points suggest that there is some benefit in giving oxygen therapy to people who would not normally meet the criteria for LTOT (people with mild COPD who are non-hypoxaemic at rest).
101 – 79 In patients with stable COPD, what is the best method of oxygen supply? (2004; 1.2.5.16–1.2.5.18)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) Four RCTs focusing on oxygen supply were identified[373-376]. All four studies evaluated the potential benefit of different methods of oxygen supply in people with various stages of COPD. It was considered that the new evidence was unlikely to impact on guideline recommendations. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 80 In patients with stable COPD, what are the benefits of short burst oxygen? (2004; 1.2.5.1–1.2.5.18)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 81 In patients with stable COPD, what are the benefits of portable oxygen? (2004; 1.2.5.10–1.2.5.18)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 82 In patients with stable COPD, what are the criteria for continuous oxygen therapy? (2004; 1.2.5.4)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 83 What is the role of immunisation in patients with stable COPD? (2004; 1.2.9.1)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** A Cochrane systematic review[377] concluded that pneumococcal vaccinations did not significantly reduce the likelihood of developing pneumonia when compared against controls. The EUAG felt that the results of the review contradicted recommendations in CG101 (pneumococcal vaccination should be offered to all patients with COPD) but felt that any potential impact on guidance may be limited by the quality of included studies. Two studies were abstracts from which only the published abstract data were used. Furthermore, 2 studies were outdated and used older vaccines. It was concluded that larger, well designed clinical trials were needed (although this may be difficult in the UK where the 5-yearly pneumococcal vaccine has become standard practice).	One systematic review[378] aimed to assess the effectiveness of an oral, whole-cell, non-typeable Haemophilus influenzae (NTHi) vaccine in protecting against recurrent acute exacerbations of chronic bronchitis or COPD. When compared with placebo, the vaccine group produced a non-significant reduction in the incidence of exacerbations. Meta-analysis of the need for antibiotic therapy revealed a significant (80%) increase in antibiotic courses per person in the placebo group. There were no significant differences in hospitalisation rates and mortality rates between groups. Adverse events were reported in all included trials, with a point estimate suggestive that they occurred more frequently in the vaccine group; however, the result was not statistically significant.	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. CG101 recommends that both pneumococcal and influenza vaccinations should be offered to all patients with COPD. The new evidence suggests H. influenza vaccinations fail to prevent acute COPD exacerbations. More research is needed to assess the effectiveness of vaccinations for various bacterial or viral infections.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 84 What is the role of non-invasive ventilation in patients with stable COPD? (2004; 1.2.6.1)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) Four systematic reviews[379-382] and 2 RCTs[383,384] reported mixed results of non-invasive ventilation for stable COPD with some demonstrating small improvements and others indicating no significant effect. It was considered that the new evidence was unlikely to impact on the guideline recommendations. **Evidence Update (2012)** No relevant evidence identified	One systematic review[276] assessed RCTs that compared non-invasive ventilation (NIV) during exercise training (as part of pulmonary rehabilitation) with exercise training alone or exercise training with sham NIV. Greater improvements in FEV1, training intensity, isoload lactate levels and endurance exercise capacity were observed in the active NIV group; however, there was no difference between interventions for other measures of exercise capacity. No significant differences in dyspnoea severity and quality of life were observed between groups. A network meta-analysis[385] compared outcomes of patients with COPD who received Nocturnal Non-invasive Positive Pressure Ventilation (NIPPV) with outcomes of controls. No significant differences in PaCO2, PaO2, 6 minute walk test distance,	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations The guideline currently recommends that only people who have chronic hypercapnic respiratory failure and have required assisted ventilation (whether invasive or non-invasive) during an exacerbation or who are hypercapnic or acidotic on long-term oxygen therapy should be referred to a specialist centre for consideration of long-term NIV. The identified studies assessed NIV in different settings and provided inconclusive evidence of benefit. As a result, further research is needed to confirm the role of NIV in patients with stable COPD.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	HRQOL, FEV1, FVC, maximal inspiratory pressure and sleep efficiency were reported between the NIPPV and control group at 3 and 12 month follow-up. Sub group analyses revealed significantly better PaCO2 levels in patients ventilated with IPAP levels of at least 18 cm H2O, patients who used NIPPV for at least 5 hours per night and patients with baseline PaCO2 of at least 55 mmHg when compared to patients with lower IPAP levels, poorer compliance or lower levels of hypercapnia. One systematic review[386] aimed to assess the clinical- and cost-effectiveness of domiciliary NIV in patients with COPD. In patients with stable COPD domiciliary NIV produced small but non-significant beneficial trends in hospitalisations and quality of life but no improvement in survival was identified. For post-hospital patients, no benefit from NIV could be shown in terms of survival. No cost-effectiveness studies of domiciliary NIV were identified.		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 85 What management strategies can be used to provide palliative care in the end stages of COPD? (2004; 1.2.12.8–1.2.12.9)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) One systematic review[387] indicated that there was limited evidence on health service coordination in palliative care services, while another review[388] reported that many people with COPD had not received end of life care conversations with their healthcare professional. Lastly, the results of an RCT[389] indicated that discussions about end of life care increased when patients gave feedback about their preference for such conversations. Clinical feedback highlighted that integration of palliative care services are under investigation. Taken together, it was considered that the new evidence was unlikely to impact on the guideline recommendation on palliative care: 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. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. During the previous surveillance review, it was considered that evidence identified was unlikely to change guideline recommendation on palliative care: 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.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 86 How should the long term care of patients with stable COPD be organised in order to maximise patient outcomes? (2004; 1.2.12.1–1.2.12.3, 1.2.14.1–1.2.14.5)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 87 Where (Primary care versus secondary care) should the long term care of patients with stable COPD be organised in order to maximise patient outcomes? (2004; not linked to a specific guideline recommendation)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 88 How often should the long term care of patients with stable COPD be reviewed in order to maximise patient outcomes? (2004; 1.2.14.1–1.2.14.5)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) One systematic review[390] reported that chronic care management had the potential to improve	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
outcomes of care in COPD; however, no specific details about when reviews should be carried out were provided. The guideline currently states that patients with COPD should be reviewed at least once per year, or more frequently if indicated. It was considered that the new evidence was unlikely to impact on guideline recommendations. **Evidence Update (2012)** No relevant evidence identified			Only 1 potentially relevant study was identified during the previous surveillance review; however, there was insufficient evidence to change guideline recommendations.
101 – 89 In patients with stable COPD, what is the role of respiratory nurse specialists? (2004; 1.2.12.3)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 90 What is the role of respiratory physiotherapy in the management of patients with stable COPD? (2004; 1.2.12.4)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) Data from RCTs[391,392] and 1 systematic review[393] highlighted the potential benefit of various	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. Evidence identified during the previous

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
breathing techniques (including pursed lips breathing, diaphragmatic breathing and active breathing) in managing COPD. The new evidence was supportive of the recommendation which states that patients with excess sputum should be taught an active cycle of breathing techniques. **Evidence Update (2012)** No relevant evidence identified			review was supportive of the guideline recommendation which states that patients with excess sputum should be taught an active cycle of breathing techniques.
101 – 91 What is the role of lung surgery in patients with stable COPD? (2004; 1.2.10.1–1.2.10.3)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	In a systematic review[394] of RCTs, bronchoscopic lung volume reduction using endobronchial valves was compared with sham surgery and standard medications for treatment of advanced emphysema. Compared with standard medications, endobronchial valves yielded greater improvements in FEV1 measurements, Modified Medical Research Council dyspnoea scale scores, cycle ergometry workloads and 6 minute walk test distances. Endobronchial valves were found to	Topic experts highlighted that studies on Lung Volume Reduction Surgery using airway valves for treatment of emphysematous COPD have shown some short-term clinical benefit. One topic expert suggested that no satisfactory long-term randomised controlled trial is currently available; as a result, it may be worth producing a narrative comment	New evidence is consistent with guideline recommendations. The COPD guideline generally recommends surgery for patients who are breathless and have a single large bulla on CT scan or patients with severe COPD who remain breathless with marked restrictions of their activities of daily living despite maximal medical therapy. Most of the studies that were included in the 2 identified systematic reviews generally included patients with advanced/severe emyphysema.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	increase the rate of haemoptysis but did not increase the incidence of mortality, respiratory failure, empyema, pneumonia, or pneumothorax. No significant difference in the overall complication rate was observed in patients treated by endobronchial valves and those treated by standard medications or sham surgery. A second systematic review[395] assessed the efficacy of bronchoscopic lung volume reduction surgery using endobronchial valves. Patients treated by endobronchial valves had significant improvements in FEV1 measurements, 6 minute walk test distances, cycle workload and St George's Respiratory Questionnaire scores compared with patients who received medical treatment only.		
101 – 92 How should the fitness for surgery of patients with COPD be assessed? (2004; 1.2.13.1–1.2.13.3)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014)	No relevant evidence identified.	None identified relevant to this	No new evidence was identified that would

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified		question.	affect recommendations.
101 – 93 In patients with stable COPD, what is the operation of choice (bullectomy, lung volume reduction, transplantation) in reducing morbidity or mortality? (2004; 1.2.10.1–1.2.10.3)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) One RCT[396] was identified which compared unilateral with partial lung volume reduction in people with severe emphysema. Significantly greater improvements dyspnoea scores, pulmonary function tests, 6 minute walk test distances and quality of life were reported in the unilateral treatment group. There was no means of determining the comparative effectiveness of lung volume reduction surgery as the investigators did not compare it against other surgical techniques. As a result, it was considered that the new evidence was unlikely to impact on guideline recommendations. **Evidence Update (2012)** Significant differences in Pulmonary function tests and 6 minute walk test distanced	One systematic review[397] different methods of bronchoscopic lung volume reduction; including one-way valves, sealants (Biologic lung volume reduction) lung volume reduction coils, airway bypass stents, and bronchial thermal vapour ablation. All interventions apart from airway bypass stents produced improvements in the lung function tests (not specified), 6 minute walk test distances, and St George's Respiratory Questionnaire scores. The sealant approach produced the most significant improvements and was the least associated with major treatment-related complications	Topic experts stated that recent studies on Lung Volume Reduction Surgery using airway valves for treatment of emphysematous COPD have shown some short-term clinical benefit. One topic expert suggested that no satisfactory long-term RCT is currently available; as a result, it may be worth producing a narrative comment.	New evidence is unlikely to impact on guideline recommendations The guideline currently recommends that patients with severe COPD who remain breathless despite medical therapy and rehabilitation should be referred for consideration of lung volume reduction surgery. The identified study did not compare lung volume reduction surgery with other techniques such as lung transplantation or bullectomy and is more related to specific techniques for lung volume reduction surgery. Further research is needed to determine an impact on the current recommendations on lung surgery.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 94 In patients with stable COPD, what are the referral criteria for lung surgery? (2004; 1.2.10.1–1.2.10.3)			
Surveillance decision This review question should be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	A systematic review[398] evaluated the efficacy of one-way endobronchial valves in patients with advanced emphysema with or without intact fissures on lung imaging. Meta-analyses revealed that patients with intact fissures had significantly greater improvements in of FEV1, 6 minute walk test distances and St George's Respiratory Questionnaire scores than those without intact fissures. A sub-group analysis of patients with intact fissures revealed significantly better outcomes in patients with lobar occlusion compared to those without occlusion. In a second systematic review[395], a sub-group analysis highlighted that patients with complete fissures who had surgery had greater improvements in FEV1 than controls (patients who received medical treatment) at 6 and 12 months. No significant difference was observed between patients with incomplete	None identified relevant to this question.	New evidence identified that may change current recommendations. CG101 recommends that 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: • FEV1 more than 20% predicted • PaCO2 less than 7.3 kPa • upper lobe predominant emphysema • TLCO more than 20% predicted. The identified new evidence highlights an additional criterion (intact fissures on lung imaging) which could be used to determine whether patients should be referred for lung surgery.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	fissures and controls.		
101 – 95 Which patients with COPD benefit from referral to palliative care services? (2004; 1.2.12.2, 1.2.12.8–1.2.12.10)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 96 Which patients with COPD benefit from referral to occupational therapists? (2004; 1.2.12.11–1.2.12.12)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 97 Which patients with COPD benefit from referral to social services? (2004; 1.2.12.13)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
Evidence Update (2012) No relevant evidence identified			
101 – 98 What information / education / support is needed for stable COPD patients and their families to understand and cope with the diagnosis, treatment and outcome in COPD? (2004; 1.2.12.18–1.2.12.20)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 99 In patients with stable COPD and their relatives / carer, what effect does education have on morbidity, quality of life, advanced directives or mortality measures? (2004; 1.2.12.18–1.2.12.20)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 100 Do cultural factors modify the uptake of COPD care? (2004; not linked to a specific guideline recommendation)			
Surveillance decision This review question should not be updated.			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 101 What advice should be given to patients with COPD who wish to travel? (2004; 1.2.12.14–1.2.12.16)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) A small-scale RCT[399] compared alveolar hypoxia induced in a hypobaric chamber (HC) with a hypoxia-altitude simulation test (HAST). The results indicated that the HAST may be used to identify patients needing supplemental oxygen during air travel. The guideline currently recommends that all patients on LTOT or with FEV1 < 50% predicted who are planning air travel should be assessed in line with British Thoracic Society (BTS) recommendations. There is now a 2011 version which supersedes the 2002 version referenced in the guideline. It was deemed unlikely to impact the recommendations as recommendations refer the reader directly to the BTS document rather than incorporate the recommendations. **Evidence Update (2012)**	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
No relevant evidence identified			
Management of exacerbations of COPD			
101 – 102 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? (2010; 1.2.8.1)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified. Clinical feedback indicated that further studies were in development to examine the effect of early pulmonary rehabilitation post exacerbation. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	Topic experts highlighted an RCT[400] of 389 patients with COPD exacerbations who received an early pulmonary rehabilitation intervention or usual care within 48 hours of admission to hospital. Significant improvements in physical performance and health status were observed within each group after hospital discharge. No significant differences in physical performance and health status were observed between groups at 1 year follow-up. The proportion of patients who were readmitted to hospital at least once within the following year was 62% in the pulmonary rehabilitation group and 58% in the usual care group. Authors reported that the mortality rate was higher in the pulmonary rehabilitation group at 1 year follow-	New evidence is unlikely to impact on guideline recommendations. The guideline states that pulmonary rehabilitation should be made available to all appropriate people with COPD including those who have had a recent hospitalisation for an acute exacerbation. The identified evidence highlights some benefit of early pulmonary rehabilitation but treatment was delivered within 48 hours of hospital admission rather than upon hospital discharge. As a result, there was insufficient evidence to consider reviewing guideline recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
		up. One topic expert felt that evidence of the potential benefits of pulmonary rehabilitation after hospitalisation may result in changes to recommendations. Another expert stated that community services provide pulmonary rehabilitation but transport is not provided for those who need it, leading to some patients not being able to attend meetings.	
101 – 103 What is a robust and useful definition of an exacerbation of COPD? (2004; 1.3.1)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 104 What symptoms are suggestive of an exacerbation of COPD? (2004; 1.3.1)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
Evidence Update (2012) No relevant evidence identified			
101 – 105 What other conditions present with similar symptoms? (2004; not linked to a specific guideline recommendation)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 106 What are the factors known to cause exacerbations of COPD? (2004; not linked to a specific guideline recommendation)			
Surveillance decision This review question should be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	Two systematic reviews[401,402] explored whether there was an association between viral infections and COPD exacerbations. One review[401] reported that the weighted overall prevalence of respiratory viruses in patients with acute COPD exacerbations was 39.3% whereas the rate in patients with stable COPD was 13.6%. Rhinovirus was the most common virus, with a weighted prevalence of 14.8%. In the other	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. The guideline makes no reference to factors known to cause exacerbations of COPD. The identified new evidence highlights an association between viral infections and acute COPD exacerbations. The guideline could be updated to highlight these associations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	systematic review[402], rhino-/enteroviruses (16.4%), RSV (9.9%) and influenza (7.8%) were the most prevalent viruses. Adenovirus (2.1%), hMPV (2.8%) and bocaviruses (0.6%) were the least prevalent viruses in people with acute exacerbations.		
101 – 107 What is known about the consequences (short & long term outcome impact) of having an exacerbation (chest episodes, infective episodes) of COPD? (2004; not linked to a specific guideline recommendation)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** A meta-analysis[403] reported that people with severe COPD exacerbations who needed hospitalisation had a weighted mean case-fatality rate of 15.6% with an average in-hospital mortality rate of 6.7%. The Evidence Update stated that evidence was unlikely to affect CG101, but emphasised the risks associated with severe exacerbations (in particular the continued elevated risk after discharge), which should be managed according to current guidance. An observational cohort study[404] highlighted that	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. Evidence identified in the Evidence Update was relevant to the clinical question; however, the EUAG felt that more supportive evidence was needed to make recommendations in the guideline. No additional supportive evidence was identified during both 4-year and 6-year surveillance reviews.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
exacerbations increased with the severity of COPD: It was also found that a history of exacerbations appeared to be the best predictor of exacerbations at all stages of disease. The EUAG felt that identified studies showed that people with a history of exacerbations and more severe disease may be more likely to experience exacerbations more often, and that exacerbations may be associated with a higher risk of death, even after discharge. Clinical feedback indicated that work was going to be published on methods of predicting exacerbations and predicting hospital mortality (including evaluations of the DECAF scoring system). It was considered that the identified evidence was unlikely to impact on guideline recommendations			
101 – 108 What clinical signs are useful (confirm or refute) in making a diagnosis and assessing the severity of an exacerbation of COPD? (2004; 1.3.2.1)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 109 What are the most appropriate tests in a patient with suspected exacerbation of COPD? (2004; 1.3.3.1, 1.3.3.2)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	One systematic review[405] of 10 observational studies reported a positive correlation between circulating leptin concentrations and tumour necrosis factor levels in people with COPD exacerbations. No correlation correlation between circulating leptin concentrations and tumour necrosis factor levels were observed in people with stable COPD.	Topic experts highlighted that recent published evidence suggests that systemic inflammatory markers and biomarkers, including eosinophils, may have a role in predicting exacerbation risk and related outcomes.	New evidence is unlikely to impact on guideline recommendations. More conclusive evidence is needed to confirm the diagnostic/predictive accuracy of using leptin concentrations to identify people with COPD exacerbations.
101 – 110 What are the most appropriate tests to confirm the diagnosis of an exacerbation of COPD? (2004; 1.3.3.1, 1.3.3.2)			
Surveillance decision This review question should not be updated.			
No relevant evidence identified. **4-year surveillance (2014)** No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
101 – 111 What are the most appropriate tests to assist in the management of an exacerbation of COPD? (2004; 1.3.3.1, 1.3.3.2)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 112 In patients with an exacerbation of COPD, what are the most appropriate tests to assess severity? (2004; 1.3.3.1, 1.3.3.2)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 113 In patients with an exacerbation of COPD, what are the most appropriate tests to monitor recovery? (2004; 1.3.10.1–1.3.10.4)			
Surveillance decision This review question should not be updated.			
No relevant evidence identified. **4-year surveillance (2014)** No relevant evidence identified **Evidence Update (2012)**	Two systematic reviews[406,407] assessed whether elevated troponins were predictive of mortality (in-hospital, short term, and longer-term) among patients admitted with COPD	Topic experts that recent published evidence suggests that systemic inflammatory markers and biomarkers, including eosinophils, may have a role in predicting	New evidence is unlikely to impact on guideline recommendations Only 1 of the 2 identified systematic reviews performed a meta-analysis which included

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
No relevant evidence identified	exacerbations. One review[406] reported that the risk of mortality increased with increasing troponin levels in most included studies. No pooled/statistical analysis of data was performed. In the other review[407] pooled analysis revealed a significant association between elevated troponin levels and all-cause mortality. Furthermore, the troponin subunit Tn-T appeared to be more helpful in predicting all-cause mortality than Tn-I.	exacerbation risk and related outcomes.	studies 8. Further research is needed to confirm the diagnostic accuracy of using troponin levels to predict risk of mortality in people with COPD.
101 – 114 Which patients with an exacerbation of COPD benefit from admission to hospital? (2004; 1.3.2.1)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	Topic experts highlighted that a lot of NHS activity has been focused on prevention of admission of patients with chronic disease, including COPD: there is some uncertainty about the effectiveness (including cost effectiveness) and safety of such approaches.	No new evidence was identified that would affect recommendations. Although topic experts suggested that interventions which attempt to prevent hospital admissions are considered ineffective (please refer to 101-77), no evidence was identified which highlighted what type of patients with COPD exacerbations would benefit from admission

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
			to hospital.
101 – 115 Are bronchodilators useful / effective in the treatment of patients with an exacerbation of COPD? (2004; 1.3.5.1–1.3.5.5)			
Surveillance decision This review question should not be updated.			
No relevant evidence identified. **4-year surveillance (2014)** No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 116 Which patients with an exacerbation of COPD should be treated with bronchodilators? (2004; 1.3.5.1–1.3.5.5)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 117 Are oral steroids useful / effective in the treatment of patients with an exacerbation of COPD? (2004; 1.3.5.6–1.3.5.14)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014)	One systematic review[414], assessed	MPP confirmed that the increased	New evidence is consistent with guideline

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
An RCT[408] compared oral prednisone with etanercept, (a tumour necrosis factor antagonist), for acute COPD exacerbations. No significant differences in measures of dyspnoea, quality of life and treatment failure rates were observed between groups at 90 day follow-up. Subgroup analysis revealed that patients with serum eosinophils >2% at exacerbation tended to experience fewer treatment failures if treated with prednisone compared with etanercept. One RCT[409] assessed patients with acute COPD exacerbations treated by intravenous (IV) hydrocortisone followed by oral methylprednisolone or oral prednisolone. No significant differences in mortality rates, the need for mechanical ventilation and acute exacerbation rates were observed between groups within 2 weeks of discharge. After 2 weeks, a significant improvement in FEV1 was observed in the group that received IV hydrocortisone followed by oral methylprednisolone. Similarly, 1 meta-analysis[410] found that systemic corticosteroids were associated with a significant reduction in the treatment failure rate and an improvement in FEV1 measurements. An RCT[411] of patients with acute COPD exacerbations, who were receiving ventilatory support, reported that IV methylprednisolone was	the safety and efficacy of systemic corticosteroids for COPD exacerbation by making comparisons with placebo or standard treatment (not specified). A significant increase in treatment success rates was reported when corticosteroids were used. No significant difference in success rates were observed between ICU patients who received corticosteroids and those who didn't (controls): however, a significantly better success rate was observed in non-ICU patients who received corticosteroids than controls. Overall, there was no difference in the mortality rate between the steroid-treated group and controls but the rate of adverse events increased significantly with corticosteroid administration. Treatment with systemic corticosteroids significantly increased the risk of hyperglycaemic episodes requiring initiation or alteration of insulin therapy. Another systematic review[415] assessed the effects of systemic corticosteroids for treating acute COPD exacerbations and	risk of hyperglycaemia is a well-known adverse event associated with systemic steroids.	recommendations The identified new evidence highlights benefits associated with oral steroid therapy and is broadly supportive of guideline recommendations: notably, the recommendation that a course of corticosteroid treatment should not be longer than 14 days as there is no advantage in prolonged therapy.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
more effective than placebo at reducing the duration of mechanical ventilation. One systematic review[412] and an RCT[413] compared shorter duration with (seven days or fewer) with longer duration (more than seven days) systemic corticosteroid therapy for exacerbations of COPD and found that shorter treatment was non-inferior to longer treatment. The guideline states that a course of corticosteroid treatment should not be longer than 14 days as there is no advantage in prolonged therapy. It was considered that the identified new evidence supported the guideline recommendations. **Evidence Update (2012)** No relevant evidence identified	subsequently made comparisons between parental and oral administration. Systemic corticosteroids reduced the risk of treatment failure and relapse, compared with placebo. Furthermore, systemic corticosteroids produced greater improvements in FEV1 measurements (within 72 hours) than placebo: this benefit was not observed at later time points. Analysis of safety revealed that the likelihood of adverse events increased with corticosteroid treatment. Thirty day mortality rates were not reduced by treatment with systemic corticosteroid. Comparison of parenteral versus oral treatment showed no significant difference in treatment failure, relapse or mortality. A systematic review[416] compared the efficacy of short-duration (up to 7 days) and long-duration (longer than 7 days) systemic corticosteroid treatments in adults with COPD. Pooled analysis of 4 studies revealed no significant differences in treatment failure, relapse and adverse event rates between short-duration and		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	longer duration treatment. Furthermore, no significant difference in time to next exacerbation and length of hospital stay were observed between groups. Finally, one systematic review[417] of RCTs aimed to examine the effects of anabolic steroids in patients with COPD. Compared with controls, patients treated by anabolic steroids had significantly greater improvements in body weight, fat-free mass, St. George's Respiratory Questionnaire total scores. Apparent improvements in maximal inspiratory and expiratory pressure were not significant. Compared with controls, patients treated by anabolic steroids had significantly worse handgrip strength, 6 minute walk test distances, FEV1, PaO2 and PaCO2 measurements.		
101 – 118 Which patients with an exacerbation of COPD should be treated with oral steroids? (2004; 1.3.5.6–1.3.5.14)			
Surveillance decision This review question should not be updated.			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
No relevant evidence identified. **4-year surveillance (2014)** No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 119 Which delivery systems should be used for giving inhaled therapy to patients with an exacerbation of COPD? (2004; 1.3.5.1–1.3.5.5)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) An RCT[418] of patients with COPD exacerbations treated by a breath-activated nebulizer or a continuous flow small-volume nebulizer, reported greater improvements in lung hyperinflation and respiratory frequency in the breath-activated nebulizer group. It was noted that no specific guidance on type of nebuliser is outlined in the guideline and further research in this area is needed before determining any impact on the recommendations. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 120 Are antibiotics useful / effective in the treatment of patients with an exacerbation of COPD? (2004; 1.3.5.15–1.3.5.18)			
Surveillance decision			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
This review question should not be updated.			
4-year surveillance (2014) Data from 2 Cochrane systematic reviews and 1 RCT indicated that antibiotic treatment of acute COPD exacerbations significantly reduced treatment failure [419] and mortality [420] and resulted in greater improvements in the median time to next exacerbation when compared with placebo [421]. There was also evidence that the benefit of antibiotic treatment improved as exacerbation severity increased[419]. Clinical feedback stated that newer evidence has been published on use of prophylactic antibiotics (macrolides) in reducing time to further exacerbation. Antibiotics are recommended for treatment of exacerbations of COPD associated with a history of more purulent sputum and no new evidence was identified which would have changed the direction of the recommendation. **Evidence Update (2012)** No relevant evidence identified	A systematic review[422] assessed RCTs which compared moxifloxacin against comparator agents (not specified) in patients with acute COPD exacerbations. A superior 'microbiological success' rate was reported in the moxifloxacin group. No significant difference in treatment success rates was reported between groups when analysis was restricted to intention-to-treat or clinically evaluable populations. Furthermore, no significant difference in adverse event rates was reported between groups.	Topic experts stated that growing concerns about antibiotic resistance mean that considerations need to be made about the long-term use of antibiotics for prevention of COPD exacerbations.	New evidence is unlikely to impact on guideline recommendations Antibiotics are currently recommended for treatment of exacerbations of COPD associated with a history of more purulent sputum and no new evidence was identified which would change the direction of this recommendation.
101 – 121 Which patients with an exacerbation of COPD should be treated with antibiotics? (2004; 1.3.5.15–1.3.5.18)			
Surveillance decision This review question should not be updated.			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 122 Which patients with an exacerbation of COPD should be treated with oxygen (how much and how monitored, including use during transfer to hospital)? (2004; 1.3.6.1–1.3.6.4)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) One RCT[374] assessed whether titrated oxygen via nasal prongs, delivered in a pre-hospital setting, affected mortality in people with suspected acute COPD exacerbations. Authors reported that maintaining arterial oxygen saturation levels between 88% and 92% reduced the risk of mortality by 58%. The GDG highlighted that national (BTS) guidance on use of oxygen in acute illness has been updated. The guideline recommends that oxygen should be given to keep the SaO2 within the individualised target range. It was considered that the new evidence was unlikely to impact on this recommendation. **Evidence Update (2012)**	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
The Evidence update highlighted 1 RCT[423] which compared titrated oxygen with high flow oxygen treatment in a prehospital (ambulance/paramedic) setting. The Evidence Update concluded that the evidence appeared to support the assertion in the British Thoracic Society's guideline for emergency oxygen use in adult patients[424] that 'oxygen is a treatment for hypoxaemia, not breathlessness' and 'oxygen (should) be prescribed according to a target saturation range'. The evidence also appeared to agree with current recommendations in CG101 that oxygen should be given to keep the saturation level within the individualised target range.			
101 – 123 What is the role of theophylline in patients with exacerbations of COPD? (2004; 1.3.5.19–1.3.5.21)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) Two RCTs evaluated the addition of theophylline to ICS therapy[425] or LAMA plus LABA therapy combination[426] in people with COPD. Treatment with ICS plus theophylline resulted in a non-significant increase in FEV1. The addition of theophylline to LAMA plus LABA treatment significantly improved exercise duration but there were no significant differences in resting lung	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. The 4-year review outlined 2 areas of interest: the need to monitor plasma levels and potential interactions with other medications when using theophylline. No relevant new evidence was identified.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
function or dyspnoea scores between the two treatment groups. The guideline acknowledged the need to monitor plasma levels and potential interactions with other medications when using theophylline. It was decided that these issues were not evaluated in the new evidence. **Evidence Update (2012)** No relevant evidence identified			
101 – 124 What is the role of respiratory stimulants in patients with exacerbations of COPD? (2004; 1.3.5.22)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 125 What is the role of therapies for managing right heart failure / chronic salt and water retention in patients with exacerbations of COPD? (2004; 1.2.7.3–1.2.7.5)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)**	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
No relevant evidence identified			
101 – 126 Which patients with exacerbations of COPD require non-invasive ventilation? (2004; 1.3.7.1–1.3.7.3)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) Eight RCTs[427-434] and a systematic review[435] evaluated non-invasive ventilation in people with COPD. The studies evaluated different non-invasive ventilation protocols which were used to treat various severities of COPD in different settings. Non-invasive ventilation is recommended as the treatment of choice for persistent hypercapnic ventilatory failure during exacerbations despite optimal medical therapy. No new evidence was identified which would impact this recommendation. **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. Studies identified during the 4 year surveillance review evaluated different non-invasive ventilation protocols but did not assess which types of patients would benefit from treatment. As a result, it was considered that they would not impact on guideline recommendations.
101 – 127 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? (2004; 1.3.7.1–1.3.7.3)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014)	A meta-analysis[436] compared non-	None identified relevant to this	New evidence is unlikely to impact on

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	invasive ventilation (NIV) with conventional oxygen therapy, after planned extubation in medical intensive care unit (ICU). Results indicated that NIV produced significantly greater reductions in reintubation rates.	question.	guideline recommendations The identified new evidence is not directly related to the clinical question. Although the new study demonstrates that NIV confers benefits over oxygen therapy in an ICU setting, no comparisons were made with other hospital settings. Recommendations in CG101 do not specify where NIV should be performed. Instead the guideline states 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'.
101 – 128 Which patients with exacerbations of COPD require IPPV / ITU care? (2004; not linked to a specific guideline recommendation)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 129 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? (2004; 1.3.4.1–1.3.4.4)			
Surveillance decision			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	Topic experts highlighted that a lot of NHS activity has been focused on prevention of admission of patients with chronic disease, including COPD. There is some uncertainty about the effectiveness (including cost effectiveness) and safety of such approaches.	No new evidence was identified that would affect recommendations.
101 – 130 What multi professional team membership is effective in providing hospital-at-home / assisted discharge schemes for patients with exacerbations of COPD? (2004; 1.3.4.1–1.3.4.4)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
101 – 131 In patients with an exacerbation of COPD, what criteria are useful in assessing the suitability of and planning for home treatment / early discharge? (2004; 1.3.11.1–1.3.11.7)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
Evidence Update (2012) No relevant evidence identified			
101 – 132 In patients with an exacerbation of COPD, what is the optimal duration of home care? (2004; 1.3.4.3)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) Three RCTs [437-439] and a systematic review[440] which assessed home care for people with COPD, reported a benefit of home care over usual care. Two RCTs which evaluated hospital discharge policies reported mixed results. One RCT[441] stated that there was no evidence that early assisted discharge (discharged after 3 days and treated at home by community nurses for 4 days) was more effective than 7 days of inpatient hospital treatment. The other RCT[442] indicated that coordination of discharge from hospital reduced hospitalisations in people with COPD. Clinical feedback indicated that home care is now widely advocated. It was considered that the new evidence was unlikely to impact on the recommendations. **Evidence Update (2012)** A Cochrane systematic review[443] reported that home care of people with COPD, by outreach nurses, conferred no significant reductions in	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
mortality rates at 12 months. The EUAG felt that heterogeneity between studies limited any conclusions. They felt that larger, well-designed studies that assessed clearly defined populations and interventions, over longer periods of time, were needed.			
101 – 133 What is the role of respiratory physiotherapy in the management of exacerbations of COPD? (2004; 1.3.9.1)			
Surveillance decision This review question should not be updated.			
4-year surveillance (2014) An RCT[444] which evaluated the effectiveness of manual chest physiotherapy in patients with acute COPD exacerbations reported no significant difference in improvements in St Georges Respiratory Questionnaire scores between patients who received manual chest physiotherapy and those who did not. Conversely, a Cochrane systematic review[445] reported that airway clearance techniques were associated with small but significant short-term reductions in the need for ventilatory assistance in people with acute COPD exacerbations. It was considered that the evidence was unlikely to impact on guideline recommendations and further research is needed to confirm the benefits and harms of respiratory physiotherapy	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
techniques. **Evidence Update (2012)** No relevant evidence identified			
Areas not currently covered in the guideline			
NQ – 01 The role of acupuncture in management of COPD			
Surveillance decision This review question should not be added.			
4-year surveillance (2014) Three RCTs evaluated the use of acupuncture for management of COPD. Two RCTs which compared acupuncture with sham reported improvements in dyspnoea[446] and the 6 minute walk test distances[447] after 12 weeks of therapy. Conversely, one RCT[448] found that the addition of acupuncture to pulmonary rehabilitation did not add significant benefit in QoL, dyspnoea or exercise capacity compared to pulmonary rehabilitation alone. It was considered that, large-scale studies reporting a range of outcomes were needed to confirm the role of acupuncture in management of COPD. **Evidence Update (2012)** No relevant evidence identified	A systematic review[449] assessed the efficacy of acupuncture and related therapies (not specified) for treatment of COPD. Compared with placebo, acupuncture improved HRQoL, St George's Respiratory Questionnaire scores, dyspnoea scale scores, and 6 minute walk test distance. No benefit was seen on measures of lung function when acupuncture therapies were compared with either placebo or drug therapy.	None identified relevant to this question.	New evidence is unlikely to impact on the guideline The identified systematic review pooled data from studies which assessed various types of acupuncture and other related therapies. Additional, large-scale studies reporting a range of outcome measures are required to confirm the role of acupuncture in management of COPD.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
NQ – 02 The role of other drug treatments in the management of COPD			
Surveillance decision This review question should not be added.			
<u>4-year surveillance (2014)</u> RCTs evaluating other drug treatments for COPD generally reported no beneficial effect of a 5-lipoxygenase inhibitor[450,451]; a neutrophil elastase [452,453]; selective MMP-9 and MMP-12 inhibitors [454]; melatonin [455]; sildenafil [456,457]; bisoprolol [458]; magnesium [459] or a selective CRTh2 (DP2) receptor antagonist[460]. Small benefits in people with COPD were reported for fentanyl citrate[461]; a p38 inhibitor[462]; N-acetyl cysteine[463] and furosemide [464]. However, these were small studies carried out in people with differing severity of COPD. It was considered that the new evidence was unlikely to impact on the guideline and further research was needed to determine the long-term benefits and harms of these drug treatments **<u>Evidence Update (2012)</u>** No relevant evidence identified	A systematic review[465] aimed to estimate the efficacy and safety of opioids on refractory breathlessness, exercise capacity, and HRQL in COPD. Improvements in breathlessness were reported in patients who were treated by systemic or nebulised opioids. Opioids did not affect exercise capacity and HRQoL could not be analysed. Another systematic review[466] evaluated the effects of OM-85BV (an extract of different bacterial species frequently responsible for respiratory infections) in patients with COPD. OM-85BV resulted in greater reductions in antibiotic usage and exacerbation rates when compared against placebo. Authors stated that OM-85BV 'was not significantly associated with duration of hospitalization, severity of acute exacerbation, and total adverse	None identified relevant to this question.	New evidence is unlikely to impact on the guideline Each systematic review explored different drug therapies. Furthermore, systematic reviews pooled data from studies which included heterogeneous populations of patients with various COPD severities. Further research is needed to determine the long-term benefits and harms of these drug treatments in people with COPD before considering for inclusion in the guideline.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	events. One systematic review[467] of 4 RCTs assessed the efficacy of magnesium sulphate in patients with COPD. Authors reported that intravenous magnesium sulphate had no immediate bronchodilatory effect; however it appeared to potentiate the bronchodilatory effect of inhaled LABAs. Patients treated by magnesium sulphate had a greater increase in the peak expiratory flow rate (PEFR) at 30 and 45 minutes compared to those who received placebo. However, no significant differences in dyspnoea scores, hospital admission rates, or emergency department readmission rates were observed between groups. No significant differences in improvements in FEV1 after 90 mins were observed between patients treated by nebulized magnesium sulphate plus salbutamol and those who received nebulized salbutamol plus placebo. Furthermore, there was no significant difference in hospitalisation rates between groups. A systematic review[468] which		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	assessed the effect of beta-blockers on mortality and exacerbation rates in patients with COPD reported that treatment significantly decreased the risk of overall mortality and exacerbation of COPD. One systematic review[469] of RCTs aimed to assess whether anti-leukotriene agents were effective in treating patients with COPD. Authors reported that anti-leukotriene agents failed to improve FEV1 and FVC measurements and had no effect on inflammatory marker levels (no comparator group was specified). Significant improvements in dyspnoea and sputum were attributable to anti-leukotriene therapy.		
NQ – 03 The role of stem cell therapy in the management of COPD			
Surveillance decision This review question should not be added.			
4-year surveillance (2014) One RCT[470] evaluated the efficacy of systemic mesenchymal stem cell administration in patients with moderate to severe COPD. Compared with vehicle control, no significant differences in the frequency of exacerbations and adverse events	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
were observed. It was considered that the new evidence was unlikely to impact on the guideline and larger studies were required before considering this therapy for inclusion in the guideline. **Evidence Update (2012)** No relevant evidence identified			
NQ – 04 The role of alternative and complementary therapies in management of COPD			
Surveillance decision This review question should not be added.			
4-year surveillance (2014) One meta-analysis revealed that treatment with Tai Chi resulted in improvements in dyspnoea and FEV1 measurements. Three RCTs compared a Tai chi Qigong (TCQ) programme against exercise or usual care in people with COPD[471-473]. Improvements in respiratory functions[474], exercise capacity[472] and QoL[473] were observed in the TCQ group. One of the studies reported no changes in dyspnoea and fatigue levels among the 3 groups[472]. An RCT investigated the efficacy of health qigong, a traditional Chinese exercise, as an adjunct home exercise programme in people with chronic COPD[475]. Authors reported some	Herbal medicines: A systematic review[487] which compared Chinese herbal medicine (Astragalus membranaceus, Panax ginseng and Cordyceps sinensis) plus routine pharmacotherapy with routine pharmacotherapy alone, reported significantly better BODE index scores and 6 minute walk test distances in the Chinese herbal medicine group. In 1 systematic review[488], patients with COPD treated by Yupingfeng formula plus conventional medications (not specified) were	None identified relevant to this question.	New evidence is unlikely to impact on the guideline CG101 does not make recommendations on the role of alternative and complementary therapies in management of COPD. A considerable amount of evidence on alternative and complementary therapies was identified. Although there appears to be some improvements in subjective and objective outcome measures, the new evidence is extremely heterogeneous; studies evaluated a wide range of different complementary remedies in people with differing levels of severity of COPD.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
improvement in functional capacity in the health qigong group. Three systematic reviews and 5 RCTs evaluated the safety and efficacy of traditional Chinese herbal medicines for treating stable COPD; all of which reported some improvements in the range of outcome measures reported[476-482]. One systematic review[477] compared the efficacies of oral Huangqi formulae, oral Huangqi formulae plus conventional therapy (CT) and CT alone. Greater improvements in SGRQ scores, COPD related symptoms and exacerbation rates were observed in the Oral Huangqi formulae plus CT group, although some of the included studies were deemed methodologically weak. One systematic review[483] evaluated the efficacy of Jianpi therapy in traditional Chinese medicine for treatment of stable COPD indicating that the results are encouraging but more research is needed. In 1 RCT[482], the incidence of gastrointestinal adverse was higher in people who received a herbal drug preparation from the roots of Pelargonium sidoides. Three RCTs[479,484,485] compared the efficacy of Bufei Yishen Granule (BFYSG) combined with Shufei Tie acupoint sticking therapy in people with COPD. Improvements were observed in the frequency and duration of acute exacerbations, and scores of daily living ability[484,485]. Higher	compared with patients treated by Western medications alone. Authors reported that significantly better FEV1 values, 6 minute walk test distances, 'effective rates' (not defined), serum IgA levels and serum IgG levels were reported when Yupingfeng formula was combined with conventional medications. No significant difference in serum IgE levels was reported between groups. A systematic review[489] which assessed the efficacy of Chinese medicines in COPD reported that Dang shen formulae yielded significantly greater improvements in FEV1 than conventional pharmacotherapy. Additional analysis revealed that patients who received Dang shen formulae, in combination with conventional pharmacotherapy, had significantly better 6 minute walk test distances, St. Georges Respiratory Questionnaire (SGRQ) scores and exacerbation rates than those who received conventional pharmacotherapy alone. Three additional systematic reviews[490-492] evaluated the efficacy		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
scores were also reported in ESQ-COPD domains including clinical symptoms and effect of therapy[479], 6 minute walk test distance and dyspnea grade[484] in the intervention group. One study[478] reported no significant differences in FVC, FEV1, FEV1% and adverse events rates between study arms. A systematic review[486] reported that modified Dachengqi Decoction combined with conventional treatment shortened the duration of mechanical ventilation in patients with acute exacerbations of COPD. Some adverse events were reported. Furthermore, the included studies were considered to be methodologically weak. The 4-year review concluded that the evidence was heterogeneous and evaluated a range of different complementary remedies in people with differing levels of severity of COPD. The identified new evidence was heterogeneous; evaluating a range of different complementary remedies in people with differing levels of COPD severity. It was considered that the new evidence was unlikely to impact on the guideline. **Evidence Update (2012)** No relevant evidence identified	of herbal medicine (not specified) as an adjunct to conventional COPD medicine. Compared with conventional medicine, herbal medicine produced significantly greater improvements in clinical symptoms and quality of life (total score, activity score, and impact score of the SGRQ[490]. Furthermore, significant improvements in FEV1 measurements, arterial blood gas levels[492] and exacerbation rates[491] were reported when Chinese medications were combined with conventional medicines. No significant differences in FEV1, FEV%, FVC, and FEV1/FVC values were observed between groups[490,491]. One systematic review[493] compared patients treated by Chinese herbal medicine with a heterogeneous control group (patients who received pharmacotherapy, placebo, or no treatment). Adverse events occurred in 1.4% of patients in the Chinese herbal medicine group and in 1.8% of patients in the control group. Nausea was the most frequently reported adverse event in either group.		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	Alternative exercises: One systematic review[279] assessed the potential benefits of traditional Chinese exercises (Qigong and/or Tai Chi) for pulmonary rehabilitation. When compared against conventional exercise or no exercise groups, weighted mean differences in FEV1 measurements and 6 minute walk test distances were in favour of the Chinese exercise group. Another systematic review[494] reported that people with COPD who practiced Tai Chi or qipong had significantly greater improvements in 6-minute walk test distances, FEV1 measurements, predicted FEV1 percentages, and SGRQ scores than their counterparts who did no excercise. A systematic review[495] which evaluated the effectiveness of Tai Chi, reported greater improvements in 6 minute walk test distances, SGRQ scores and Chronic Respiratory Disease Questionnaire scores when compared with 'no-exercise'. When Tai Chi was compared with physical exercise (not defined), significantly greater improvements in SGRQ		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	scores were observed in the Tai Chi group but no difference in 6 minute walk test distances were observed between groups. One systematic review[496], reported that yoga training significantly improved FEV1 measurements and 6 minute walk test distances in people with COPD; however, no significant effects on PaO2 and PacO2 were reported. Another systematic review[311], reported that yoga failed to relieve symptoms of anxiety when compared with usual care. Psychological interventions: One systematic review[497] assessed the impact of supplementing medical treatment with psychological interventions in people with COPD. Overall psychosocial interventions produced significant improvements in psychological outcomes (not specified). Subgroup analysis, according to intervention type, revealed that cognitive behavioural therapy appeared to be effective in improving psychological outcomes.		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	Only mind-body interventions (such as mindfulness-based therapy, yoga, and relaxation) were found to have a significant effect on physical outcomes (not specified). Another systematic review[312] identified RCTs of people with COPD who received interventions that combined exercise training and psychological strategies. Comparisons were made with controls (usual care or waiting lists) or active comparators (education, exercise or psychological interventions alone). When compared with control conditions, standardised mean differences for dyspnoea, anxiety, depression, quality of life and functional exercise capacity consistently favoured interventions which included both exercise and psychological components. When compared with active comparators, standardised mean differences for dyspnoea, anxiety and exercise capacity favoured interventions which included both exercise and psychological components.		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	Auditory stimuli: One systematic review[498] assessed the efficacy of Distractive Auditory Stimuli (DAS) in patients with COPD under 3 conditions: during exercise training, during exercise testing, and for symptom management at rest. DAS was found to increased exercise capacity when applied over at least 2 months of exercise training (unclear if significant). Furthermore, HRQoL improved only after a training duration of 3 months. No improvement in dyspnoea was observed when DAS was used as a symptom management strategy at rest.		
Research recommendations			
RR – 01 In people with COPD, does pulmonary rehabilitation during hospital admission for exacerbation and/or in the early recovery period (within 1 month of an exacerbation) improve quality of life and reduce hospitalisations and exacerbations compared to a later (defined as after 1 month) pulmonary rehabilitation programme?			
Surveillance decision This research recommendation will be considered again at the next surveillance point.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)**	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
No relevant evidence identified			
RR – 02 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?			
Surveillance decision This research recommendation will be considered again at the next surveillance point.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	Topic experts stated that there is a need to review the role of multidimensional assessments of COPD severity. They highlighted various multidimensional severity assessment tools, such as GOLD, DECAF, CAT, BODE and DOSE.	No new evidence was identified that would affect this research recommendation.
RR – 03 In people with COPD, does triple therapy improve outcomes when compared with single or double therapy?			
Surveillance decision This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	A network meta-analysis[84] pooled data from RCTS which assessed the efficacy of LABA, LAMA and ICS, alone or in combination, versus each other or placebo. The combination of tiotropium, formoterol and budesonide was found to be the most effective intervention according to the Surface Under the Cumulative Ranking (SUCRA) curve. Salmeterol plus	None identified relevant to this question.	The guideline currently recommends that triple therapy should be offered as step-up treatment if symptoms or exacerbations persisted on current therapy and no new evidence was identified which would change the direction of this recommendation.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	fluticasone was more effective in reducing mortality than placebo, formoterol and fluticasone alone. In the same study, analysis of cardiovascular-related mortality revealed that Triamcinolone acetonide was the most harmful medication. Analysis also revealed that salmeterol plus fluticasone and fluticasone were likely to increase the risk of pneumonia in comparison to placebo. In a systematic review[95] which compared tiotropium plus fluticasone propionate/salmeterol (triple therapy) against tiotropium alone, significantly better FEV1 measurements, exacerbation rates and HRQoL scores were reported in the triple therapy group. In 1 RCT[96] patients with moderate to severe COPD received triple therapy (tiotropium plus salmeterol plus fluticasone) over a 6 week period. Subsequently, patients were randomly assigned to continue triple therapy or discontinue ICS (fluticasone) treatment in 3 steps, over 12 weeks. No significant		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	difference in the period of time to first moderate to severe COPD exacerbation was observed between groups; demonstrating non-inferiority. At 18 week follow-up, patients who discontinued ICS treatment had significantly greater reductions in trough FEV1 measurements than those who continued triple therapy. A similar difference was observed at 52 week follow-up. No change in dyspnoea and minor changes in health status (not specified) occurred in the ICS discontinuation group.		
RR – 04 In people with COPD, does mucolytic drug therapy prevent exacerbations in comparison with placebo and other therapies?			
Surveillance decision This research recommendation will be considered again at the next surveillance point.			
4-year surveillance (2014) No relevant evidence identified **Evidence Update (2012)** No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.

References

1. Huber MB, Wacker ME, Vogelmeier CF et al. (2015) Excess costs of comorbidities in chronic obstructive pulmonary disease: a systematic review. PLoS ONE [Electronic Resource] 10:e0123292.

2. Mohamed Hoesein FA, Zanen P, and Lammers JW. (2011) Lower limit of normal or FEV1/FVC < 0.70 in diagnosing COPD: an evidence-based review. [Review]. Respiratory Medicine 105:907-915.

3. Gupta N, Pinto LM, Morogan A et al. (2014) The COPD assessment test: a systematic review. [Review]. European Respiratory Journal 44:873-884.

4. Haroon S, Jordan R, Takwoingi Y et al. (2015) Diagnostic accuracy of screening tests for COPD: a systematic review and meta-analysis. BMJ Open 5:e008133.

5. Soriano JB, Lamprecht B, Ramirez AS et al. (2015) Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data. The Lancet Respiratory Medicine 3:443-450.

6. Haroon SM, Jordan RE, O'Beirne-Elliman J et al. (2015) Effectiveness of case finding strategies for COPD in primary care: A systematic review and meta-analysis. npj Primary Care Respiratory Medicine.25 , 2015.Article Number: 15056.Date of Publication: 27 Aug 2015.

7. Dirven JAM, Tange HJ, Muris JWM et al. (2013) Early detection of COPD in general practice: Patient or practice managed? A randomised controlled trial of two strategies in different socioeconomic environments. Primary Care Respiratory Journal 22:331-337.

8. Gruffydd-Jones K, Marsden HC, Holmes S et al. (2013) Utility of COPD Assessment Test (CAT) in primary care consultations: a randomised controlled trial. Primary Care Respiratory Journal 22:37-43.

9. Fisk WJ, Eliseeva EA, and Mendell MJ. (2010) Association of residential dampness and mold with respiratory tract infections and bronchitis: A meta-analysis. Environmental Health: A Global Access Science Source 9.

10. Ryu JY, Sunwoo YE, Lee SY et al. (2015) Chronic Obstructive Pulmonary Disease (COPD) and Vapors, Gases, Dusts, or Fumes (VGDF): A Meta-analysis. Copd: Journal of Chronic Obstructive Pulmonary Disease 12:374-380.

11. Omland O, Wurtz ET, Aasen TB et al. (2014) Occupational chronic obstructive pulmonary disease: a systematic literature review. [Review]. Scandinavian Journal of Work, Environment & Health 40:19-35.

12. Bruske I, Thiering E, Heinrich J et al. (2014) Respirable quartz dust exposure and airway obstruction: a systematic review and meta-analysis. [Review]. Occupational & Environmental Medicine 71:583-589.

13. Byrne AL, Marais BJ, Mitnick CD et al. (2015) Tuberculosis and chronic respiratory disease: a systematic review. [Review]. International Journal of Infectious Diseases 32:138-146.

14. Wang L, Guan Y, Li Y et al. (2015) Association Between Chronic Respiratory Diseases and Helicobacter pylori: A Meta-Analysis. Archivos de Bronconeumologia 51:273-278.

15. Wang F, Liu J, Zhang Y et al. (2015) Association of Helicobacter pylori infection with chronic obstructive pulmonary disease and chronic bronchitis: a meta-analysis of 16 studies. Infectious Diseases 47:597-603.

16. Li JS, Zhang HL, Bai YP et al. (2012) Diagnostic value of computed tomography in chronic obstructive pulmonary disease: a systematic review and meta-analysis. [Review]. Copd: Journal of Chronic Obstructive Pulmonary Disease 9:563-570.

17. Zhu A, Ge D, Zhang J et al. (2014) Sputum myeloperoxidase in chronic obstructive pulmonary disease. European Journal of Medical Research 19:12.

18. Wei J, Xiong XF, Lin YH et al. (2015) Association between serum interleukin-6 concentrations and chronic obstructive pulmonary disease: a systematic review and meta-analysis. PeerJ 3:e1199.

19. Janssens W, Liu Y, Liu D et al. (2013) Quality and reproducibility of spirometry in COPD patients in a randomized trial (UPLIFT). Respiratory Medicine 107:1409-1416.

20. Vaart H, Postma DS, Grevink R et al. (2011) Bronchodilation improves endurance but not muscular efficiency in chronic obstructive pulmonary disease. SO: International journal of chronic obstructive pulmonary disease 6:229-235.

21. Jiang FM, Liang ZA, Zheng QL et al. (2013) Safety and efficacy of 12-week or longer indacaterol treatment in moderate-to-severe COPD patients: a systematic review. [Review]. Lung 191:135-146.

22. Rodrigo GJ and Neffen H. (2012) Comparison of indacaterol with tiotropium or twice-daily long-acting -agonists for stable COPD: a systematic review. [Review]. Chest 142:1104-1110.

23. Mahler DA, Buhl R, Lawrence D et al. (2013) Efficacy and safety of indacaterol and tiotropium in COPD patients according to dyspnoea severity. Pulmonary Pharmacology and Therapeutics 26:348-355.

24. Cope S, Capkun-Niggli G, Gale R et al. (2012) Efficacy of once-daily indacaterol relative to alternative bronchodilators in COPD: a patient-level mixed treatment comparison. Value in Health 15:524-533.

25. Chong J, Karner C, and Poole P. (2012) Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. [Review]. Cochrane Database of Systematic Reviews 9:CD009157.

26. Dong Y-H, Lin H-H, Shau W-Y et al. (2013) Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: Systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. Thorax 68:48-56.

27. Buhl R, Dunn LJ, Disdier C et al. (1-10-2011) Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. European Respiratory Journal 38:797-803.

28. Chapman KR, Rennard SI, Dogra A et al. (2011) Long-term safety and efficacy of indacaterol, a long-acting beta2-agonist, in subjects with COPD: a randomized, placebo-controlled study. Chest 140:68-75.

29. Korn S, Kerwin E, Atis S et al. (2011) Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: a 12-week study. Respiratory Medicine 105:719-726.

30. Kim JS, Park J, Lim SY et al. (2015) Comparison of clinical efficacy and safety between indacaterol and tiotropium in COPD: meta-analysis of randomized controlled trials. PLoS ONE [Electronic Resource] 10:e0119948.

31. Nannini LJ, Lasserson TJ, and Poole P. (2012) Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. [Review][Update of Cochrane Database Syst Rev. 2007;(4):CD006829; PMID: 17943918]. Cochrane Database of Systematic Reviews 9:CD006829.

32. Nannini LJ, Poole P, Milan SJ et al. (2013) Combined corticosteroid and long-acting beta2-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. SO: Cochrane Database of Systematic Reviews .

33. Magnussen H, Paggiaro P, Schmidt H et al. (2012) Effect of combination treatment on lung volumes and exercise endurance time in COPD. Respiratory Medicine 106:1413-1420.

34. De-Coster DA, Jones M, and Thakrar N. (2013) Beclometasone for chronic obstructive pulmonary disease. SO: Cochrane Database of Systematic Reviews .

35. Tzani P, Crisafulli E, Nicolini G et al. (2011) Effects of beclomethasone/formoterol fixed combination on lung hyperinflation and dyspnea in COPD patients. International Journal of Copd 6:503-509.

36. Guenette JA, Webb KA, and O'Donnell DE. (2013) Effect of fluticasone/salmeterol combination on dyspnea and respiratory mechanics in mild-to-moderate COPD. Respiratory Medicine 107:708-716.

37. Disantostefano RL, Li H, Rubin DB et al. (2013) Which patients with chronic obstructive pulmonary disease benefit from the addition of an inhaled corticosteroid to their bronchodilator? A cluster analysis. BMJ Open 3:2013.

38. Tashkin DP, Doherty DE, Kerwin E et al. (2012) Efficacy and safety characteristics of mometasone furoate/formoterol fumarate fixed-dose combination in subjects with moderate to very severe COPD: findings from pooled analysis of two randomized, 52-week placebo-controlled trials. International Journal of Copd 7:73-86.

39. Tashkin DP, Doherty DE, Kerwin E et al. (2012) Efficacy and safety of a fixed-dose combination of mometasone furoate and formoterol fumarate in subjects with moderate to very severe COPD: results from a 52-week Phase III trial. International Journal of Copd 7:43-55.

40. Doherty DE, Tashkin DP, Kerwin E et al. (2012) Effects of mometasone furoate/formoterol fumarate fixed-dose combination formulation on chronic obstructive pulmonary disease (COPD): results from a 52-week Phase III trial in subjects with moderate-to-very severe COPD. International Journal of Copd 7:57-71.

41. Fukuchi Y, Samoro R, Fassakhov R et al. (2013) Budesonide/formoterol via Turbuhaler versus formoterol via Turbuhaler in patients with moderate to severe chronic obstructive pulmonary disease: Phase III multinational study results. Respirology 18:866-873.

42. Zhong N, Zheng J, Wen F et al. (2012) Efficacy and safety of budesonide/formoterol via a dry powder inhaler in Chinese patients with chronic obstructive pulmonary disease. Current Medical Research and Opinion 28:257-265.

43. Sharafkhaneh A, Southard JG, Goldman M et al. (2012) Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. Respiratory Medicine 106:257-268.

44. Celli BR, Tashkin DP, Rennard SI et al. (2011) Bronchodilator responsiveness and onset of effect with budesonide/formoterol pMDI in COPD. SO: Respiratory medicine 105:1176-1188.

45. Cope S, Kraemer M, Zhang J et al. (2012) Efficacy of indacaterol 75 ug versus fixed-dose combinations of formoterol-budesonide or salmeterol-fluticasone for COPD: a network meta-analysis. International Journal of Copd 7:415-420.

46. Halpin DM, Gray J, Edwards SJ et al. (2011) Budesonide/formoterol vs. salmeterol/fluticasone in COPD: a systematic review and adjusted indirect comparison of pneumonia in randomised controlled trials. [Review]. International Journal of Clinical Practice 65:764-774.

47. Cope S, Capkun-Niggli G, Gale R et al. (2011) Comparative efficacy of indacaterol 150 ug and 300 ug versus fixed-dose combinations of formoterol + budesonide or salmeterol + fluticasone for the treatment of chronic obstructive pulmonary disease--a network meta-analysis. [Review]. International Journal of Copd 6:329-344.

48. Kerwin EM, Scott-Wilson C, Sanford L et al. (2013) A randomised trial of fluticasone furoate/vilanterol (50/25mug; 100/25mug) on lung function in COPD. Respiratory Medicine 107:560-569.

49. Martinez FJ, Boscia J, Feldman G et al. (2013) Fluticasone furoate/vilanterol (100/25; 200/25 mug) improves lung function in COPD: a randomised trial. Respiratory Medicine 107:550-559.

50. Dransfield MT, Bourbeau J, Jones PW et al. (2013) Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: Two replicate double-blind, parallel-group, randomised controlled trials. The Lancet Respiratory Medicine 1:210-223.

51. Lotvall J, Bakke PS, Bjermer L et al. (2012) Efficacy and safety of 4 weeks' treatment with combined fluticasone furoate/vilanterol in a single inhaler given once daily in COPD: A placebo-controlled randomised trial. SO: BMJ open 2:e000370.

52. Rodrigo GJ, Castro-Rodriguez JA, and Plaza V. (2009) Safety and efficacy of combined long-acting beta-agonists and inhaled corticosteroids vs long-acting beta-agonists monotherapy for stable COPD: a systematic review. Chest 136:1029-1038.

53. Calverley PM, Anderson JA, Celli B et al. (22-2-2007) Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. New England Journal of Medicine 356:775-789.

54. Kew KM, Dias S, and Cates CJ. (2014) Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. [Review]. Cochrane Database of Systematic Reviews 3:CD010844.

55. Oba Y and Lone NA. (2014) Comparative efficacy of inhaled corticosteroid and long-acting beta agonist combinations in preventing COPD exacerbations: a Bayesian network meta-analysis. [Review]. International Journal of Copd 9:469-479.

56. Rossi A, van der Molen T, Olmo Rd et al. (2014) INSTEAD: a randomised switch trial of indacaterol versus salmeterol/fluticasone in moderate COPD. European Respiratory Journal 44:1548-1556.

57. Vagaggini B, Nieri D, Malagrinò L et al. (2011) Acute administration of bronchodilators on exercise tolerance in treated COPD patients. SO: Pulmonary pharmacology & therapeutics 24:49-54.

58. Jayaram L, Wong C, McAuley S et al. (2013) Combined therapy with tiotropium and formoterol in chronic obstructive pulmonary disease: Effect on the 6-minute walk test. Copd: Journal of Chronic Obstructive Pulmonary Disease 10:466-472.

59. Canto ND, Ribeiro JP, Neder JA et al. (2012) Addition of tiotropium to formoterol improves inspiratory muscle strength after exercise in COPD. Respiratory Medicine 106:1404-1412.

60. Karner C and Cates CJ. (2012) Long-acting beta(2)-agonist in addition to tiotropium versus either tiotropium or long-acting beta(2)-agonist alone for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 4:CD008989.

61. Dahl R, Chapman KR, Rudolf M et al. (2013) Safety and efficacy of dual bronchodilation with QVA149 in COPD patients: The ENLIGHTEN study. Respiratory Medicine 107:1558-1567.

62. Wedzicha JA, Decramer M, Ficker JH et al. (2013) Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): A randomised, double-blind, parallel-group study. The Lancet Respiratory Medicine 1:199-209.

63. Donohue JF, Maleki-Yazdi MR, Kilbride S et al. (2013) Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. Respiratory Medicine 107:1538-1546.

64. Rodrigo GJ and Neffen H. (2015) A Systematic Review of the Efficacy and Safety of a Fixed-Dose Combination of Umeclidinium and Vilanterol for the Treatment of COPD. [Review]. Chest 148:397-407.

65. Farne HA and Cates CJ. (2015) Long-acting beta2-agonist in addition to tiotropium versus either tiotropium or long-acting beta2-agonist alone for chronic obstructive pulmonary disease. [Review]. Cochrane Database of Systematic Reviews 10:CD008989.

66. Oba Y, Sarva ST, and Dias S. (2015) Efficacy and safety of long-acting beta-agonist/long-acting muscarinic antagonist combinations in COPD: a network meta-analysis. Thorax 71:15-25.

67. Vincken W, Aumann J, Chen H et al. (2014) Efficacy and safety of coadministration of once-daily indacaterol and glycopyrronium versus indacaterol alone in COPD patients: the GLOW6 study. International journal of chronic obstructive pulmonary disease 9:215-228.

68. Beeh KM, Westerman J, Kirsten AM et al. (2015) The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease. Pulmonary Pharmacology & Therapeutics 32:53-59.

69. Singh D, Jones PW, Bateman ED et al. (2014) Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. BMC Pulm Med 14:178.

70. Celli B, Crater GF, Kilbride S FAU - Mehta R et al. (2014) Once-daily umeclidinium/vilanterol 125/25 mcg in COPD: a randomized, controlled study. Chest 145:981-991.

71. Tashkin DP and Varghese ST. (2011) Combined treatment with formoterol and tiotropium is more efficacious than treatment with tiotropium alone in patients with chronic obstructive pulmonary disease, regardless of smoking status, inhaled corticosteroid use, baseline severity, or gender. SO: Pulmonary pharmacology & therapeutics 24:147-152.

72. Abe T, Setoguchi Y, Kono Y et al. (2011) Effects of inhaled tiotropium plus transdermal tulobuterol versus tiotropium alone on impulse oscillation system (IOS)-assessed measures of peripheral airway resistance and reactance, lung function and quality of life in patients with COPD: A randomized crossover study. Pulmonary Pharmacology and Therapeutics 24:617-624.

73. Mahler DA, D'Urzo A, Bateman ED et al. (2012) Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison. Thorax 67:781-788.

74. Feldman G, Walker RR, Brooks J et al. (2012) 28-Day safety and tolerability of umeclidinium in combination with vilanterol in COPD: A randomized placebo-controlled trial. SO: Pulmonary pharmacology & therapeutics 25:465-471.

75. Nicolini A. (2012) Short term effects of tiotropium on COPD patients treated with long acting bronchodilators. Tanaffos 11:26-31.

76. Wang J, Jin D, Zuo P et al. (2011) Comparison of tiotropium plus formoterol to tiotropium alone in stable chronic obstructive pulmonary disease: a meta-analysis. Respirology (Carlton, Vic.) 16:350-358.

77. Rodrigo GJ and Plaza V. (2014) Efficacy and safety of a fixed-dose combination of indacaterol and Glycopyrronium for the treatment of COPD: a systematic review. [Review]. Chest 146:309-317.

78. Donohue JF, Niewoehner D, Brooks J et al. (2014) Safety and tolerability of once-daily umeclidinium/vilanterol 125/25 mcg and umeclidinium 125 mcg in patients with chronic obstructive pulmonary disease: results from a 52-week, randomized, double-blind, placebo-controlled study. Respiratory Research 15:78.

79. Maleki-Yazdi MR FAU - Kaelin T, Kaelin TF, Richard NF et al. (2014) Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: results of a 24-week, randomized, controlled trial. Respiratory Medicine 108:1752-1760.

80. Mahler DA, Decramer M, D'Urzo A et al. (2014) Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: the BLAZE study. European Respiratory Journal 43:1599-1609.

81. Beeh KM, Korn S, Beier J et al. (2014) Effect of QVA149 on lung volumes and exercise tolerance in COPD patients: The BRIGHT study. Respiratory Medicine 108:584-592.

82. Vogelmeier CF, Bateman ED, Pallante J et al. (2013) Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary

disease (ILLUMINATE): A randomised, double-blind, parallel group study. The Lancet Respiratory Medicine 1:51-60.

83. Horita N, Miyazawa N, Tomaru K et al. (2015) Long-acting muscarinic antagonist+long-acting beta agonist versus long-acting beta agonist+inhaled corticosteroid for COPD: A systematic review and meta-analysis. [Review]. Respirology 20:1153-1159.

84. Tricco AC, Strifler L, Veroniki AA et al. (2015) Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis. BMJ Open 5:e009183.

85. Singh D, Worsley S, Zhu CQ et al. (2015) Umeclidinium/vilanterol versus fluticasone propionate/salmeterol in COPD: a randomised trial. BMC Pulm Med 15:91.

86. Zhong N, Wang C, Zhou X et al. (2015) LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD. International journal of chronic obstructive pulmonary disease 10:1015-1026.

87. Frith PA, Thompson PJ, Ratnavadivel R et al. (2015) Glycopyrronium once-daily significantly improves lung function and health status when combined with salmeterol/fluticasone in patients with COPD: the GLISTEN studyΓÇöa randomised controlled trial. Thorax 70:519-527.

88. Jung KS, Park HY, Park SY et al. (2012) Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: a randomized controlled study. Respiratory Medicine 106:382-389.

89. Hoshino M and Ohtawa J. (2011) Effects of adding salmeterol/fluticasone propionate to tiotropium on airway dimensions in patients with chronic obstructive pulmonary disease. Respirology 16:95-101.

90. Rodrigo GJ, Plaza V, and Castro-Rodriguez JA. (2012) Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: A systematic review. Pulmonary Pharmacology and Therapeutics 25:40-47.

91. Gaebel K, McIvor RA, Xie F et al. (2011) Triple therapy for the management of COPD: a review. [Review]. Copd: Journal of Chronic Obstructive Pulmonary Disease 8:206-243.

92. Hanania NA, Crater GD, Morris AN et al. (2012) Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. Respiratory Medicine 106:91-101.

93. Hoshino M and Ohtawa J. (2013) Effects of tiotropium and salmeterol/fluticasone propionate on airway wall thickness in chronic obstructive pulmonary disease. Respiration 86:280-287.

94. Karner C and Cates CJ. (2011) The effect of adding inhaled corticosteroids to tiotropium and long-acting beta(2)-agonists for chronic obstructive pulmonary disease. [Review]. Cochrane Database of Systematic Reviews CD009039.

95. Liu Y, Shi H, Sun X et al. (2014) Benefits of adding fluticasone propionate/salmeterol to tiotropium in COPD: a meta-analysis. European Journal of Internal Medicine 25:491-495.

96. Magnussen H, Disse B, Rodriguez-Roisin R et al. (2014) Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD. New England Journal of Medicine 371:1285-1294.

97. Poole P, Chong J, and Cates CJ. (2015) Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. [Review][Update of Cochrane Database Syst Rev. 2012;8:CD001287; PMID: 22895919]. Cochrane Database of Systematic Reviews 7:CD001287.

98. Zheng JP, Wen FQ, Bai CX et al. (2014) Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial. The Lancet Respiratory Medicine 2:187-194.

99. Tashkin DP, Rennard S, Hays JT et al. (2011) Effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial. SO: Chest 139:591-599.

100. Tashkin DP, Rennard S, Taylor HJ et al. (2011) Lung function and respiratory symptoms in a 1-year randomized smoking cessation trial of varenicline in COPD patients. Respiratory Medicine 105:1682-1690.

101. Huang Y, Li W, Yang L et al. (2012) Long-term efficacy and safety of varenicline for smoking cessation: A Systematic review and meta-analysis of randomized controlled trials. Journal of Public Health (Germany) 20:355-365.

102. Lock K, Wilson K, Murphy D et al. (2011) A cost-effectiveness model of smoking cessation based on a randomised controlled trial of varenicline versus placebo in patients with chronic obstructive pulmonary disease. Expert Opinion on Pharmacotherapy 12:2613-2626.

103. Coronini-Cronberg S, Heffernan C, and Robinson M. (2011) Effective smoking cessation interventions for COPD patients: a review of the evidence. JRSM Short Reports 2:78.

104. Pires-Yfantouda R, Absalom G, and Clemens F. (2013) Smoking cessation interventions for COPD: A review of the literature. Respiratory Care 58:1955-1962.

105. Christenhusz LCA, Prenger R, Pieterse ME et al. (2012) Cost-effectiveness of an intensive smoking cessation intervention for COPD outpatients. Nicotine and Tobacco Research 14:657-663.

106. Lee PN and Fry JS. (2010) Systematic review of the evidence relating FEV1 decline to giving up smoking. BMC Medicine 8:84.

107. Strassmann R, Bausch B, Spaar A et al. (2009) Smoking cessation interventions in COPD: a network meta-analysis of randomised trials. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology 34:634-640.

108. Bartlett YK, Sheeran P, and Hawley MS. (2014) Effective behaviour change techniques in smoking cessation interventions for people with chronic obstructive pulmonary disease: a meta-analysis. British Journal of Health Psychology 19:181-203.

109. Kirsch F. (2015) A systematic review of quality and cost-effectiveness derived from Markov models evaluating smoking cessation interventions in patients with chronic obstructive pulmonary disease. Expert Review of Pharmacoeconomics & Outcomes Research 15:301-316.

110. Ho JKM and Yau WH. (2012) Nurse-initiated albuterol metered-dose inhaler for acute exacerbations of chronic obstructive pulmonary disease in an emergency department: A randomised controlled trial. Hong Kong Journal of Emergency Medicine 19:162-170.

111. Hanania NA, Feldman G, Zachgo W et al. (2012) The efficacy and safety of the novel long-acting 2 agonist vilanterol in patients with COPD: a randomized placebo-controlled trial. Chest 142:119-127.

112. Cazzola M, Rogliani P, Ruggeri P et al. (2013) Chronic treatment with indacaterol and airway response to salbutamol in stable COPD. Respiratory Medicine 107:848-853.

113. Cazzola M, Segreti A, Stirpe E et al. (2013) Effect of an additional dose of indacaterol in COPD patients under regular treatment with indacaterol. Respiratory Medicine 107:107-111.

114. Kew KM, Mavergames C, and Walters-Julia AE. (2013) Long-acting beta2-agonists for chronic obstructive pulmonary disease. SO: Cochrane Database of Systematic Reviews .

115. Beeh K-M, Wagner F, Khindri S et al. (2011) Effect of indacaterol on dynamic lung hyperinflation and breathlessness in hyperinflated patients with COPD. Copd: Journal of Chronic Obstructive Pulmonary Disease 8:340-345.

116. Bleecker ER, Siler T, Owen R et al. (2011) Bronchodilator efficacy and safety of indacaterol 150 ug once daily in patients with COPD: an analysis of pooled data. International Journal of Copd 6:431-438.

117. Hosoe M, Woessner R, Matsushima S et al. (2011) Efficacy, safety and pharmacokinetics of indacaterol in Caucasian and Japanese patients with chronic obstructive pulmonary disease: a comparison of data from two randomized, placebo-controlled studies. SO: Clinical drug investigation 31:247-255.

118. Jones PW, Mahler DA, Gale R et al. (2011) Profiling the effects of indacaterol on dyspnoea and health status in patients with COPD. Respiratory Medicine 105:892-899.

119. Kerwin EM, Gotfried MH, Lawrence D et al. (2011) Efficacy and tolerability of indacaterol 75 ug once daily in patients aged >=40 years with chronic obstructive pulmonary disease: results from 2 double-blind, placebo-controlled 12-week studies. Clinical Therapeutics 33:1974-1984.

120. O'Donnell DE, Casaburi R, Vincken W et al. (2011) Effect of indacaterol on exercise endurance and lung hyperinflation in COPD. Respiratory Medicine 105:1030-1036.

121. Decramer M, Rossi A, Lawrence D et al. (2012) Indacaterol therapy in patients with COPD not receiving other maintenance treatment. [Review][Erratum appears in Respir Med. 2013 Jan;107(1):160 Note: Dosage error in article text]. Respiratory Medicine 106:1706-1714.

122. Gotfried MH, Kerwin EM, Lawrence D et al. (2012) Efficacy of indacaterol 75 ug once-daily on dyspnea and health status: results of two double-blind, placebo-controlled 12-week studies. Copd: Journal of Chronic Obstructive Pulmonary Disease 9:629-636.

123. Kinoshita M, Lee SH, Hang LW et al. (2012) Efficacy and safety of indacaterol 150 and 300 g in chronic obstructive pulmonary disease patients from six Asian areas including Japan: a 12-week, placebo-controlled study. Respirology 17:379-389.

124. Bogdan MA, Aizawa H, Fukuchi Y et al. (2011) Efficacy and safety of inhaled formoterol 4.5 and 9 ug twice daily in Japanese and European COPD patients: phase III study results. BMC Pulmonary Medicine 11:51.

125. Brusasco V, Canonica GW, Negro RD et al. (2011) Formoterol by pressurized metered-dose aerosol or dry powder on airway obstruction and lung hyperinflation in partially reversible COPD. Journal of Aerosol Medicine and Pulmonary Drug Delivery 24:235-243.

126. van Noord JA, Smeets JJ, Drenth BM et al. (2011) 24-hour Bronchodilation following a single dose of the novel beta2-agonist olodaterol in COPD. Pulmonary Pharmacology and Therapeutics 24:666-672.

127. Cazzola M, Paggiaro P, Palange P et al. (2012) Onset of action of formoterol versus salmeterol via dry powder inhalers in moderate chronic obstructive pulmonary disease: a randomized, placebo-controlled, double-blind, crossover study. SO: Clinical drug investigation 32:147-155.

128. Kuna P, Ivanov Y, Trofimov VI et al. (2013) Efficacy and safety of AZD3199 vs formoterol in COPD: a randomized, double-blind study. Respiratory Research 14:64.

129. Decramer ML, Hanania NA, Lotvall JO et al. (2013) The safety of long-acting 2-agonists in the treatment of stable chronic obstructive pulmonary disease. [Review]. International Journal of Copd 8:53-64.

130. To Y, Kinoshita M, Lee SH et al. (2012) Assessing efficacy of indacaterol in moderate and severe COPD patients: a 12-week study in an Asian population. Respiratory Medicine 106:1715-1721.

131. Braido F, Baiardini I, Cazzola M et al. (2013) Long-acting bronchodilators improve Health Related Quality of Life in patients with COPD. Respiratory Medicine 107:1465-1480.

132. Han J, Dai L, and Zhong N. (2013) Indacaterol on dyspnea in chronic obstructive pulmonary disease: a systematic review and meta-analysis of randomized placebo-controlled trials. [Review]. BMC Pulmonary Medicine 13:26.

133. Mochizuki H, Nanjo Y, and Takahashi H. (2013) Better adherence to a transdermal tulobuterol patch than inhaled salmeterol in elderly chronic obstructive pulmonary disease patients. Geriatrics and Gerontology International 13:398-404.

134. Cope S, Donohue JF, Jansen JP et al. (2013) Comparative efficacy of long-acting bronchodilators for COPD - a network meta-analysis. Respiratory Research 14.

135. Laforce C, Aumann J, Teresa PL et al. (2011) Sustained 24-hour efficacy of once daily indacaterol (300 ?g) in patients with chronic obstructive pulmonary disease: a randomized, crossover study. SO: Pulmonary pharmacology & therapeutics 24:162-168.

136. Cope S, Capkun-Niggli G, Gale R et al. (2012) Efficacy of once-daily indacaterol relative to alternative bronchodilators in COPD: a patient-level mixed treatment comparison. Value in Health 15:524-533.

137. Chung VCH, Ma PHX, Hui DSC et al. (2013) Indacaterol for Chronic Obstructive Pulmonary Disease: Systematic Review and Meta-Analysis. PLoS ONE 8.

138. Wang J, Nie B, Xiong W et al. (2012) Effect of long-acting beta-agonists on the frequency of COPD exacerbations: a meta-analysis. [Review]. Journal of Clinical Pharmacy & Therapeutics 37:204-211.

139. Dahl R, Chung KF, Buhl R et al. (2010) Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. Thorax 65:473-479.

140. Korn S, Kerwin E, Atis S et al. (2011) Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: a 12-week study. Respiratory Medicine 105:719-726.

141. Kornmann O, Dahl R, Centanni S et al. (2011) Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. European Respiratory Journal 37:273-279.

142. Jones PW, Rennard SI, Agusti A et al. (2011) Efficacy and safety of once-daily aclidinium in chronic obstructive pulmonary disease. SO: Respiratory research 12:55.

143. Jones PW, Singh D, Bateman ED et al. (2012) Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. European Respiratory Journal 40:830-836.

144. Cooper CB, Celli BR, Jardim JR et al. (2013) Treadmill endurance during 2-year treatment with tiotropium in patients with COPD: A randomized trial. Chest 144:490-497.

145. Fogarty C, Hattersley H, Scala L et al. (2011) Bronchodilatory effects of NVA237, a once daily long-acting muscarinic antagonist, in COPD patients. SO: Respiratory medicine 105:337-342.

146. Fukuchi Y, Fernandez L, Kuo HP et al. (2011) Efficacy of tiotropium in COPD patients from Asia: a subgroup analysis from the UPLIFT trial.[Erratum appears in Respirology. 2011 Nov;16(8):1281]. Respirology 16:825-835.

147. Yoshimura K, Maekura R, Hiraga T et al. (2012) Effects of tiotropium on sympathetic activation during exercise in stable chronic obstructive pulmonary disease patients. International journal of chronic obstructive pulmonary disease 7:109-117.

148. D'Urzo A, Ferguson GT, Noord JA et al. (2011) Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. SO: Respiratory research 12:156.

149. Gelb AF, Fraser C, and Zamel N. (2011) Lack of protective effect of tiotropium vs induced dynamic hyperinflation in moderate COPD. SO: Respiratory medicine 105:755-760.

150. Maltais F, Celli B, Casaburi R et al. (2011) Aclidinium bromide improves exercise endurance and lung hyperinflation in patients with moderate to severe COPD. SO: Respiratory medicine 105:580-587.

151. Arievich H, Overend T, Renard D et al. (2012) A novel model-based approach for dose determination of glycopyrronium bromide in COPD. BMC Pulmonary Medicine 12:74.

152. Bateman E, Feldman G, Kilbride S et al. (2012) Efficacy and safety of the long-acting muscarinic antagonist GSK233705 delivered once daily in patients with COPD. SO: Clinical respiratory journal 6:248-257.

153. Fuhr R, Magnussen H, Sarem K et al. (2012) Efficacy of aclidinium bromide 400 ?g twice daily compared with placebo and tiotropium in patients with moderate to severe COPD. SO: Chest 141:745-752.

154. Kerwin E, Hébert J, Gallagher N et al. (2012) Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. SO: The European respiratory journal 40:1106-1114.

155. Kerwin EM, D'Urzo AD, Gelb AF et al. (2012) Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). Copd: Journal of Chronic Obstructive Pulmonary Disease 9:90-101.

156. Singh D, Magnussen H, Kirsten A et al. (2012) A randomised, placebo- and active-controlled dose-finding study of aclidinium bromide administered twice a day in COPD patients. Pulmonary Pharmacology and Therapeutics 25:248-253.

157. Tashkin DP, Celli BR, Decramer M et al. (2012) Efficacy of tiotropium in COPD patients with FEV1 >= 60% participating in the UPLIFT trial. Copd: Journal of Chronic Obstructive Pulmonary Disease 9:289-296.

158. Abrahams R, Moroni-Zentgraf P, Ramsdell J et al. (2013) Safety and efficacy of the once-daily anticholinergic BEA2180 compared with tiotropium in patients with COPD. Respiratory Medicine 107:854-862.

159. Decramer M, Maltais F, Feldman G et al. (2013) Bronchodilation of umeclidinium, a new long-acting muscarinic antagonist, in COPD patients. Respiratory Physiology and Neurobiology 185:393-399.

160. Gelb AF, Tashkin DP, Make BJ et al. (2013) Long-term safety and efficacy of twice-daily aclidinium bromide in patients with COPD. Respiratory Medicine 107:1957-1965.

161. Rennard SI, Scanlon PD, Ferguson GT et al. (2013) ACCORD COPD II: A randomized clinical trial to evaluate the 12-week efficacy and safety of twice-daily aclidinium bromide in chronic obstructive pulmonary disease patients. Clinical Drug Investigation 33:893-904.

162. Tal-Singer R, Cahn A, Mehta R et al. (15-2-2013) Initial assessment of single and repeat doses of inhaled umeclidinium in patients with chronic obstructive pulmonary disease: two randomised studies. European Journal of Pharmacology 701:40-48.

163. Karner C, Chong J, and Poole P. (2012) Tiotropium versus placebo for chronic obstructive pulmonary disease. [Review]. Cochrane Database of Systematic Reviews 7:CD009285.

164. Santus P, Di MF, Radovanovic D et al. (2012) Tiotropium: what came after the UPLIFT study. Expert Opinion on Pharmacotherapy 13:613-618.

165. Ulrik CS. (2012) Aclidinium bromide: Clinical Benefit in patients with moderate to severe COPD. Open Respiratory Medicine Journal 6:150-154.

166. Andrew WJ, Nealy KL, and Barrons RW. (2013) Aclidinium bromide: An alternative long-acting inhaled anticholinergic in the management of chronic obstructive pulmonary disease. Annals of Pharmacotherapy 47:1017-1028.

167. Hettle R, Wouters H, Ayres J et al. (2012) Cost-utility analysis of tiotropium versus usual care in patients with COPD in the UK and Belgium. Respiratory Medicine 106:1722-1733.

168. Cheyne L, Irvin-Sellers MJ, and White J. (2013) Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. SO: Cochrane Database of Systematic Reviews .

169. Beier J, Kirsten A-M, Mruz R et al. (2013) Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: Results from a 6-week, randomized, controlled phase iiib study. Copd: Journal of Chronic Obstructive Pulmonary Disease 10:511-522.

170. Karabis A, Lindner L, Mocarski M et al. (2013) Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as maintenance treatment of moderate to severe COPD patients: A systematic review and network meta-analysis. International Journal of Copd 8:405-423.

171. Cole JM, Sheehan AH, and Jordan JK. (2012) Concomitant use of ipratropium and tiotropium in chronic obstructive pulmonary disease. [Review]. Annals of Pharmacotherapy 46:1717-1721.

172. Gagnon P, Saey D, Provencher S et al. (2012) Walking exercise response to bronchodilation in mild COPD: a randomized trial. SO: Respiratory medicine 106:1695-1705.

173. Rodrigo GJ, Castro-Rodriguez JA, Nannini LJ et al. (2009) Tiotropium and risk for fatal and nonfatal cardiovascular events in patients with chronic obstructive pulmonary disease: systematic review with meta-analysis. Respiratory Medicine 103:1421-1429.

174. Tashkin DP, Celli B, Senn S et al. (9-10-2008) A 4-year trial of tiotropium in chronic obstructive pulmonary disease. New England Journal of Medicine 359:1543-1554.

175. Singh S, Loke YK, Enright PL et al. (2011) Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: Systematic review and meta-analysis of randomised controlled trials. BMJ (Clinical research ed.) 342.

176. Ni H, Soe Z, and Moe S. (2014) Aclidinium bromide for stable chronic obstructive pulmonary disease. [Review]. Cochrane Database of Systematic Reviews 9:CD010509.

177. Oba Y and Lone NA. (2015) Comparative efficacy of long-acting muscarinic antagonists in preventing COPD exacerbations: A network meta-analysis and meta-regression. Therapeutic Advances in Respiratory Disease.9 (1) (pp 3-15), 2015.Date of Publication: 05 Feb 2015. 3-15.

178. Cheyne L, Irvin-Sellers MJ, and White J. (2015) Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. [Review][Update of Cochrane Database Syst Rev. 2013;9:CD009552; PMID: 24043433]. Cochrane Database of Systematic Reviews 9:CD009552.

179. Rottenkolber M, Rottenkolber D, Fischer R et al. (2014) Inhaled beta-2-agonists/muscarinic antagonists and acute myocardial infarction in COPD patients. [Review]. Respiratory Medicine 108:1075-1090.

180. Chapman KR, Beeh KM, Beier J et al. (2014) A blinded evaluation of the efficacy and safety of glycopyrronium, a once-daily long-acting muscarinic antagonist, versus tiotropium, in patients with COPD: the GLOW5 study. BMC Pulmonary Medicine 14:4.

181. Taegtmeyer AB, Leuppi JD, and Kullak-Ublick GA. (2012) Roflumilast--a phosphodiesterase-4 inhibitor licensed for add-on therapy in severe COPD. [Review]. Swiss Medical Weekly 142:w13628.

182. Pan L, Guo YZ, Zhang B et al. (2013) Does roflumilast improve dyspnea in patients with chronic obstructive pulmonary disease? A meta-analysis. Journal of Thoracic Disease 5:422-429.

183. Reid DJ and Pham NT. (2012) Roflumilast: a novel treatment for chronic obstructive pulmonary disease. [Review]. Annals of Pharmacotherapy 46:521-529.

184. Rennard SI, Calverley PMA, Goehring UM et al. (2011) Reduction of exacerbations by the PDE4 inhibitor roflumilast - the importance of defining different subsets of patients with COPD. Respiratory Research 12.

185. Wedzicha JA, Rabe KF, Martinez FJ et al. (2013) Efficacy of roflumilast in the COPD frequent exacerbator phenotype. Chest 143:1302-1311.

186. O'Donnell DE, Bredenbröker D, Brose M et al. (2012) Physiological effects of roflumilast at rest and during exercise in COPD. SO: The European respiratory journal 39:1104-1112.

187. Oba Y and Lone NA. (2013) Efficacy and safety of roflumilast in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. [Review]. Therapeutic Advances in Respiratory Disease 7:13-24.

188. Bateman ED, Rabe KF, Calverley PMA et al. (2011) Roflumilast with long-acting beta2-agonists for COPD: Influence of exacerbation history. SO: European respiratory journal 38:553-560.

189. Chong J, Poole P, Leung B et al. (2011) Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. [Review]. Cochrane Database of Systematic Reviews CD002309.

190. Lee S-D, Hui DSC, Mahayiddin AA et al. (2011) Roflumilast in Asian patients with COPD: A randomized placebo-controlled trial. Respirology 16:1249-1257.

191. Pinner NA, Hamilton LA, and Hughes A. (2012) Roflumilast: a phosphodiesterase-4 inhibitor for the treatment of severe chronic obstructive pulmonary disease. [Review]. Clinical Therapeutics 34:56-66.

192. Mills EJ, Druyts E, Ghement I et al. (2011) Pharmacotherapies for chronic obstructive pulmonary disease: a multiple treatment comparison meta-analysis. Clinical Epidemiology 3:107-129.

193. Yan JH, Gu WJ, and Pan L. (2014) Efficacy and safety of roflumilast in patients with stable chronic obstructive pulmonary disease: a meta-analysis. Pulmonary Pharmacology & Therapeutics 27:83-89.

194. Martinez FJ, Calverley PMA, Goehring UM et al. (2015) Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. The Lancet 385:857-866.

195. Hanania NA, Calverley PMA, Dransfield MT et al. (2014) Pooled subpopulation analyses of the effects of roflumilast on exacerbations and lung function in COPD. Respiratory Medicine 108:366-375.

196. Yang IA, Clarke MS, Sim EH et al. (2012) Inhaled corticosteroids for stable chronic obstructive pulmonary disease. [Review][Update of Cochrane Database Syst Rev. 2007;(2):CD002991; PMID: 17443520]. Cochrane Database of Systematic Reviews 7:CD002991.

197. Nadeem NJ, Taylor SJ, and Eldridge SM. (2011) Withdrawal of inhaled corticosteroids in individuals with COPD--a systematic review and comment on trial methodology. [Review]. Respiratory Research 12:107.

198. Spencer S, Karner C, Cates CJ et al. (2011) Inhaled corticosteroids versus long-acting beta2-agonists for chronic obstructive pulmonary disease. SO: Cochrane Database of Systematic Reviews .

199. Rutten-van Molken MP and Goossens LM. (2012) Cost effectiveness of pharmacological maintenance treatment for chronic obstructive pulmonary disease: a review of the evidence and methodological issues. [Review]. Pharmacoeconomics 30:271-302.

200. Loke YK, Kwok CS, Wong JM et al. (2013) Chronic obstructive pulmonary disease and mortality from pneumonia: meta-analysis. [Review]. International Journal of Clinical Practice 67:477-487.

201. Loke YK, Cavallazzi R, and Singh S. (2011) Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. [Review]. Thorax 66:699-708.

202. Kew KM and Seniukovich A. (2014) Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. [Review]. Cochrane Database of Systematic Reviews 3:CD010115.

203. Liapikou A, Toumbis M, and Torres A. (2015) Managing the safety of inhaled corticosteroids in COPD and the risk of pneumonia. Expert Opinion on Drug Safety 14:1237-1247.

204. Karbasi-Afshar R, Aslani J, and Ghanei M. (2014) Efficacy and safety of inhaler steroids in COPD patients: Systematic review and meta-analysis of randomized placebo-controlled trials. [Review]. Caspian Journal of Internal Medicine 5:130-136.

205. Dong YH, Chang CH, Lin Wu FL et al. (2014) Use of inhaled corticosteroids in patients with COPD and the risk of TB and influenza: A systematic review and meta-analysis of randomized controlled trials. a systematic review and meta-analysis of randomized controlled trials. [Review]. Chest 145:1286-1297.

206. Ni S, Fu Z, Zhao J et al. (2014) Inhaled corticosteroids (ICS) and risk of mycobacterium in patients with chronic respiratory diseases: a meta-analysis. Journal of Thoracic Disease 6:971-978.

207. Thorlund K, Zafari Z, Druyts E et al. (2014) The impact of incorporating Bayesian network meta-analysis in cost-effectiveness analysis - a case study of pharmacotherapies for moderate to severe COPD. Cost Effectiveness & Resource Allocation 12:8.

208. Cheng SL, Su KC, Wang HC et al. (28-5-2014) Chronic obstructive pulmonary disease treated with inhaled medium- or high-dose corticosteroids: a prospective and randomized study focusing on clinical efficacy and the risk of pneumonia. Drug Des Devel Ther 8:601-607.

209. Ram FS, Carvallho CR, and White J. (2011) Clinical effectiveness of the Respimat inhaler device in managing chronic obstructive pulmonary disease: evidence when compared with other handheld inhaler devices. [Review]. International Journal of Copd 6:129-139.

210. Fridlender ZG, Arish N, Laxer U et al. (2012) Randomized controlled crossover trial of a new oscillatory device as add-on therapy for COPD. SO: COPD 9:603-610.

211. Ferguson GT, Ghafouri M, Dai L et al. (2013) COPD patient satisfaction with ipratropium bromide/albuterol delivered via Respimat: a randomized, controlled study. International Journal of Copd 8:139-150.

212. Karner C, Chong J, and Poole P. (2014) Tiotropium versus placebo for chronic obstructive pulmonary disease. [Review][Update of Cochrane Database Syst Rev. 2012;7:CD009285; PMID: 22786525]. Cochrane Database of Systematic Reviews 7:CD009285.

213. Mathioudakis AG, Chatzimavridou-Grigoriadou V, Evangelopoulou E et al. (2014) Comparative mortality risk of tiotropium administered via handihaler or respimat in COPD patients: are they equivalent?. [Review]. Pulmonary Pharmacology & Therapeutics 28:91-97.

214. Cazzola M, Calzetta L, Page C et al. (2015) Influence of N-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis. [Review]. European Respiratory Review 24:451-461.

215. Shen Y, Cai W, Lei S et al. (2014) Effect of high/low dose N-acetylcysteine on chronic obstructive pulmonary disease: a systematic review and meta-analysis. [Review]. Copd: Journal of Chronic Obstructive Pulmonary Disease 11:351-358.

216. Poole P, Black PN, and Cates CJ. (2012) Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. [Review][Update of Cochrane Database Syst Rev. 2010;(2):CD001287; PMID: 20166060]. Cochrane Database of Systematic Reviews 8:CD001287.

217. Tse HN, Raiteri L, Wong KY et al. (2013) High-dose N-acetylcysteine in stable COPD: the 1-year, double-blind, randomized, placebo-controlled HIACE study. Chest 144:106-118.

218. Donath E, Chaudhry A, Hernandez-Aya LF et al. (2013) A meta-analysis on the prophylactic use of macrolide antibiotics for the prevention of disease exacerbations in patients with Chronic Obstructive Pulmonary Disease. Respiratory Medicine 107:1385-1392.

219. Herath SC and Poole P. (2013) Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). SO: Cochrane Database of Systematic Reviews .

220. Lee JS, Park DA, Hong Y et al. (2013) Systematic review and meta-analysis of prophylactic antibiotics in COPD and/or chronic bronchitis. [Review]. International Journal of Tuberculosis & Lung Disease 17:153-162.

221. Yao G-Y, Ma Y-L, Zhang M-Q et al. (2013) Macrolide therapy decreases chronic obstructive pulmonary disease exacerbation: A meta-analysis. Respiration 86:254-260.

222. Albert RK, Connett J, Bailey WC et al. (25-8-2011) Azithromycin for prevention of exacerbations of COPD.[Erratum appears in N Engl J Med. 2012 Apr 5;366(14):1356]. New England Journal of Medicine 365:689-698.

223. Berkhof FF, Hertog NED, Uil SM et al. (2013) Azithromycin and cough-specific health status in patients with chronic obstructive pulmonary disease and chronic cough: A randomised controlled trial. Respiratory Research 14.

224. Ni W, Shao X, Cai X et al. (2015) Prophylactic use of macrolide antibiotics for the prevention of chronic obstructive pulmonary disease exacerbation: a meta-analysis. PLoS ONE [Electronic Resource] 10:e0121257.

225. Gottlieb V, Lyngso AM, Nybo B et al. (2011) Pulmonary rehabilitation for moderate COPD (GOLD 2)--does it have an effect? Copd: Journal of Chronic Obstructive Pulmonary Disease 8:380-386.

226. Liu X-D, Jin H-Z, Ng BHP et al. (2012) Therapeutic effects of qigong in patients with COPD: A randomized controlled trial. Hong Kong Journal of Occupational Therapy 22:38-46.

227. Wadell K, Webb KA, Preston ME et al. (2013) Impact of pulmonary rehabilitation on the major dimensions of dyspnea in COPD. Copd: Journal of Chronic Obstructive Pulmonary Disease 10:425-435.

228. De Sousa Pinto JM, Martin-Nogueras AM, Morano MTAP et al. (2013) Chronic obstructive pulmonary disease patients' experience with pulmonary rehabilitation: A systematic review of qualitative research. Chronic Respiratory Disease 10:141-157.

229. Roman M, Larraz C, Gomez A et al. (2013) Efficacy of pulmonary rehabilitation in patients with moderate chronic obstructive pulmonary disease: a randomized controlled trial. BMC Family Practice 14:21.

230. Keating A, Lee A, and Holland AE. (2011) What prevents people with chronic obstructive pulmonary disease from attending pulmonary rehabilitation? A systematic review. [Review]. Chronic Respiratory Disease 8:89-99.

231. McCarthy B, Casey D, Devane D et al. (2015) Pulmonary rehabilitation for chronic obstructive pulmonary disease. [Review][Update of Cochrane Database Syst Rev. 2006;(4):CD003793; PMID: 17054186]. Cochrane Database of Systematic Reviews 2:CD003793.

232. Dyer F, Callaghan J, Cheema K et al. (2012) Ambulatory oxygen improves the effectiveness of pulmonary rehabilitation in selected patients with chronic obstructive pulmonary disease. Chronic Respiratory Disease 9:83-91.

233. Hasegawa M, Dobashi K, Horie T et al. (2012) Influence of inhaled procaterol on pulmonary rehabilitation in chronic obstructive pulmonary disease. Respiratory Investigation 50:135-139.

234. Miki K, Maekura R, Nagaya N et al. (2012) Ghrelin treatment of cachectic patients with chronic obstructive pulmonary disease: a multicenter, randomized, double-blind, placebo-controlled trial. PLoS ONE 7:e35708.

235. Miki K, Maekura R, Nagaya N et al. (2013) Effects of Ghrelin Treatment on Exercise Capacity in Underweight COPD Patients: A substudy of a multicenter, randomized, double-blind, placebo-controlled trial of ghrelin treatment. BMC Pulmonary Medicine 13.

236. Giavedoni S, Deans A, McCaughey P et al. (2012) Neuromuscular electrical stimulation prevents muscle function deterioration in exacerbated COPD: a pilot study. Respiratory Medicine 106:1429-1434.

237. Abdellaoui A, Prefaut C, Gouzi F et al. (2011) Skeletal muscle effects of electrostimulation after COPD exacerbation: a pilot study. European Respiratory Journal 38:781-788.

238. Napolis LM, Corso SD, Neder JA et al. (2011) Neuromuscular electrical stimulation improves exercise tolerance in chronic obstructive pulmonary disease patients with better preserved fat-free mass. Clinics 66:401-406.

239. Vivodtzev I, Debigare R, Gagnon P et al. (2012) Functional and muscular effects of neuromuscular electrical stimulation in patients with severe COPD: a randomized clinical trial. Chest 141:716-725.

240. Gloeckl R, Heinzelmann I, Baeuerle S et al. (2012) Effects of whole body vibration in patients with chronic obstructive pulmonary disease--a randomized controlled trial. Respiratory Medicine 106:75-83.

241. Pleguezuelos E, Perez ME, Guirao L et al. (2013) Effects of whole body vibration training in patients with severe chronic obstructive pulmonary disease. Respirology 18:1028-1034.

242. Lin W-C, Yuan S-C, Chien J-Y et al. (2012) The effects of respiratory training for chronic obstructive pulmonary disease patients: A randomised clinical trial. Journal of Clinical Nursing 21:2870-2878.

243. Holland AE, Hill CJ, Jones AY et al. (2012) Breathing exercises for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 10:CD008250.

244. Lord VM, Hume VJ, Kelly JL et al. (2012) Singing classes for chronic obstructive pulmonary disease: a randomized controlled trial. BMC Pulmonary Medicine 12:69.

245. Reid WD, Yamabayashi C, Goodridge D et al. (2012) Exercise prescription for hospitalized people with chronic obstructive pulmonary disease and comorbidities: a synthesis of systematic reviews. International journal of chronic obstructive pulmonary disease 7:297-320.

246. Linneberg A, Rasmussen M, Buch TF et al. (2012) A randomised study of the effects of supplemental exercise sessions after a 7-week chronic obstructive pulmonary disease rehabilitation program. Clinical Respiratory Journal 6:112-119.

247. Cindy Ng LW, Mackney J, Jenkins S et al. (2012) Does exercise training change physical activity in people with COPD? A systematic review and meta-analysis. [Review]. Chronic Respiratory Disease 9:17-26.

248. McNamara RJ, McKeough ZJ, Mckenzie DK et al. (2013) Water-based exercise in COPD with physical comorbidities: A randomised controlled trial. European Respiratory Journal 41:1284-1291.

249. Souto-Araujo ZT, Miranda-Silva-Nogueira PA, Cabral EEA et al. (2012) Effectiveness of low-intensity aquatic exercise on COPD: A randomized clinical trial. SO: Respiratory medicine 106:1535-1543.

250. McNamara RJ, McKeough ZJ, McKenzie DK et al. (2013) Water-based exercise training for chronic obstructive pulmonary disease. SO: Cochrane Database of Systematic Reviews .

251. Marrara KT, Marino DM, Jamami M et al. (2012) Responsiveness of the six-minute step test to a physical training program in patients with COPD. Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia E Tisilogia 38:579-587.

252. McKeough ZJ, Bye PT, and Alison JA. (2012) Arm exercise training in chronic obstructive pulmonary disease: a randomised controlled trial. Chronic Respiratory Disease 9:153-162.

253. Pan L, Guo YZ, Yan JH et al. (2012) Does upper extremity exercise improve dyspnea in patients with COPD? A meta-analysis. [Review]. Respiratory Medicine 106:1517-1525.

254. Pleguezuelos E, Perez ME, Guirao L et al. (2013) Improving physical activity in patients with COPD with urban walking circuits. Respiratory Medicine 107:1948-1956.

255. Vonbank K, Strasser B, Mondrzyk J et al. (2012) Strength training increases maximum working capacity in patients with COPD - Randomized clinical trial comparing three training modalities. SO: Respiratory medicine 106:557-563.

256. Probst VS, Kovelis D, Hernandes NA et al. (2011) Effects of 2 exercise training programs on physical activity in daily life in patients with COPD. SO: Respiratory care 56:1799-1807.

257. Dias FD, Sampaio LMM, da Silva GA et al. (2013) Home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: A randomized clinical trial. International Journal of Copd 8:537-544.

258. de Souto Araujo ZT, de Miranda Silva Nogueira PA, Cabral EE et al. (2012) Effectiveness of low-intensity aquatic exercise on COPD: a randomized clinical trial. Respiratory Medicine 106:1535-1543.

259. Saey D and Ribeiro F. (2011) Resistance training preserves skeletal muscle function in patients with COPD who are hospitalised with an acute exacerbation. Journal of Physiotherapy 57:194.

260. Zainuldin R, Mackey MG, and Alison JA. (2011) Optimal intensity and type of leg exercise training for people with chronic obstructive pulmonary disease. SO: Cochrane Database of Systematic Reviews .

261. Heneghan NR, Adab P, Balanos GM et al. (2012) Manual therapy for chronic obstructive airways disease: a systematic review of current evidence. [Review]. Manual Therapy 17:507-518.

262. Engel RM, Vemulpad SR, and Beath K. (2013) Short-term effects of a course of manual therapy and exercise in people with moderate chronic obstructive pulmonary disease: A preliminary clinical trial. Journal of Manipulative and Physiological Therapeutics 36:490-496.

263. Shakil-ur-Rehman S, Rehman M, Siddique FA et al. (2013) The efficacy of rib cage obilization on lung function in COPD patients. Rawal Medical Journal 38:36-39.

264. Casey D, Murphy K, Devane D et al. (2013) The effectiveness of a structured education pulmonary rehabilitation programme for improving the health status of people with moderate and severe chronic obstructive pulmonary disease in primary care: The PRINCE cluster randomised trial. Thorax 68:922-928.

265. Gillespie P, O'Shea E, Casey D et al. (2013) The cost-effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease in primary care: The PRINCE cluster randomised trial. BMJ Open 3.

266. Vaes AW, Annegarn J, Meijer K et al. (2012) The effects of a "new" walking aid on exercise performance in patients with COPD: a randomized crossover trial. Chest 141:1224-1232.

267. McFarland C, Willson D, Sloan J et al. (2012) A randomized trial comparing 2 types of in-home rehabilitation for chronic obstructive pulmonary disease: a pilot study. Journal of geriatric physical therapy (2001) 35:132-139.

268. Wehrmeister FC, Knorst M, Jardim JR et al. (2011) Pulmonary rehabilitation programs for patients with COPD. [Review]. Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia E Tisilogia 37:544-555.

269. Kruis AL, Smidt N, Assendelft-Willem JJ et al. (2013) Integrated disease management interventions for patients with chronic obstructive pulmonary disease. SO: Cochrane Database of Systematic Reviews .

270. Baumann HJ, Kluge S, Rummel K et al. (2012) Low intensity, long-term outpatient rehabilitation in COPD: a randomised controlled trial. Respiratory Research 13:86.

271. Gosselink R, De Vos J, van den Heuvel SP et al. (2011) Impact of inspiratory muscle training in patients with COPD: what is the evidence? The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology 37:416-425.

272. Thomas MJ, Simpson J, Riley R et al. (2010) The impact of home-based physiotherapy interventions on breathlessness during activities of daily living in severe COPD: a systematic review. Physiotherapy 96:108-119.

273. Breyer MK, Breyer-Kohansal R, Funk GC et al. (2010) Nordic Walking improves daily physical activities in COPD: A randomised controlled trial. Respiratory Research 11.

274. Waterhouse JC, Walters SJ, Oluboyede Y et al. (2010) A randomised 2 x 2 trial of community versus hospital pulmonary rehabilitation for chronic obstructive pulmonary disease followed by telephone or conventional follow-up. Health Technology Assessment 14:1-164.

275. Beauchamp MK, Janaudis-Ferreira T, Goldstein RS et al. (2011) Optimal duration of pulmonary rehabilitation for individuals with chronic obstructive pulmonary disease - A systematic review. Chronic Respiratory Disease 8:129-140.

276. Menadue C, Piper AJ, van 't Hul AJ et al. (2014) Non-invasive ventilation during exercise training for people with chronic obstructive pulmonary disease. [Review]. Cochrane Database of Systematic Reviews 5:CD007714.

277. Ricci C, Terzoni S, Gaeta M et al. (2014) Physical training and noninvasive ventilation in COPD patients: a meta-analysis. [Review]. Respiratory Care 59:709-717.

278. Neves LF, Reis MH, Plentz RD et al. (2014) Expiratory and expiratory plus inspiratory muscle training improves respiratory muscle strength in subjects with COPD: systematic review. [Review]. Respiratory Care 59:1381-1388.

279. Ng BH, Tsang HW, Ng BF et al. (2014) Traditional Chinese exercises for pulmonary rehabilitation: evidence from a systematic review. [Review]. Journal of Cardiopulmonary Rehabilitation & Prevention 34:367-377.

280. Pan L, Guo Y, Liu X et al. (2014) Lack of efficacy of neuromuscular electrical stimulation of the lower limbs in chronic obstructive pulmonary disease patients: a meta-analysis. [Review]. Respirology 19:22-29.

281. Liao WH, Chen JW, Chen X et al. (2015) Impact of Resistance Training in Subjects With COPD: A Systematic Review and Meta-Analysis. Respiratory Care 60:1130-1145.

282. Iepsen UW, Jorgensen KJ, Ringbaek T et al. (2015) A combination of resistance and endurance training increases leg muscle strength in COPD: An evidence-based recommendation based on systematic review with meta-analyses. Chronic Respiratory Disease 12:132-145.

283. Iepsen UW, Jorgensen KJ, Ringbaek T et al. (2015) A Systematic Review of Resistance Training Versus Endurance Training in COPD. Journal of Cardiopulmonary Rehabilitation & Prevention 35:163-172.

284. Gloeckl R, Heinzelmann I, and Kenn K. (2015) Whole body vibration training in patients with COPD: A systematic review. Chronic Respiratory Disease 12:212-221.

285. Liu XL, Tan JY, Wang T et al. (2014) Effectiveness of home-based pulmonary rehabilitation for patients with chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials. Rehabilitation Nursing Journal 39:36-59.

286. Puhan MA, Spaar A, Frey M et al. (2012) Early versus late pulmonary rehabilitation in chronic obstructive pulmonary disease patients with acute exacerbations: a randomized trial. Respiration 83:499-506.

287. Ko FW, Dai DL, Ngai J et al. (2011) Effect of early pulmonary rehabilitation on health care utilization and health status in patients hospitalized with acute exacerbations of COPD. Respirology 16:617-624.

288. Tang CY, Blackstock FC, Clarence M et al. (2012) Early rehabilitation exercise program for inpatients during an acute exacerbation of chronic obstructive pulmonary disease: A randomized controlled trial. Journal of cardiopulmonary rehabilitation and prevention 32:163-169.

289. Beauchamp MK, Evans R, Janaudis-Ferreira T et al. (2013) Systematic review of supervised exercise programs after pulmonary rehabilitation in individuals with COPD. Chest 144:1124-1133.

290. Fernandez AM, Pascual J, Ferrando C et al. (2009) Home-based pulmonary rehabilitation in very severe COPD: Is it safe and useful? Journal of cardiopulmonary rehabilitation and prevention 29:325-331.

291. Puhan MA, Gimeno-Santos E, Scharplatz M et al. (2011) Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews CD005305.

292. Rugbjerg M, Iepsen UW, Jorgensen KJ et al. (2015) Effectiveness of pulmonary rehabilitation in COPD with mild symptoms: a systematic review with meta-analyses. [Review]. International Journal of Copd 10:791-801.

293. Chen W, Thomas J, Sadatsafavi M et al. (2015) Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. The Lancet Respiratory Medicine 3:631-639.

294. Moosavi SAJ, Raji H, Faghankhani M et al. (2013) Evaluation of the effects of atorvastatin on the treatment of secondary pulmonary hypertension due to chronic obstructive pulmonary diseases: A randomized controlled trial. Iranian Red Crescent Medical Journal 15:649-654.

295. Blanco I, Santos S, Gea J et al. (2013) Sildenafil to improve respiratory rehabilitation outcomes in COPD: A controlled trial. European Respiratory Journal 42:982-992.

296. Horita N, Miyazawa N, Kojima R et al. (2014) Statins reduce all-cause mortality in chronic obstructive pulmonary disease: a systematic review and meta-analysis of observational studies. Respiratory Research 15:80.

297. Chen X, Tang S, Liu K et al. (2015) Therapy in stable chronic obstructive pulmonary disease patients with pulmonary hypertension: a systematic review and meta-analysis. Journal of Thoracic Disease 7:309-319.

298. Atlantis E, Fahey P, Cochrane B et al. (2013) Bidirectional associations between clinically relevant depression or anxiety and COPD: A systematic review and meta-analysis. Chest 144:766-777.

299. Zhang MW, Ho RC, Cheung MW et al. (2011) Prevalence of depressive symptoms in patients with chronic obstructive pulmonary disease: a systematic review, meta-analysis and meta-regression. [Review]. General Hospital Psychiatry 33:217-223.

300. Doyle T, Palmer S, Johnson J et al. (2013) Association of anxiety and depression with pulmonary-specific symptoms in chronic obstructive pulmonary disease. International Journal of Psychiatry in Medicine 45:189-202.

301. Willgoss TG and Yohannes AM. (2013) Anxiety disorders in patients with COPD: A systematic review. Respiratory Care 58:858-866.

302. Pooler A and Beech R. (2014) Examining the relationship between anxiety and depression and exacerbations of COPD which result in hospital admission: a systematic review. [Review]. International Journal of Copd 9:315-330.

303. Li LS, Caughey GE, and Johnston KN. (2014) The association between co-morbidities and physical performance in people with chronic obstructive pulmonary disease: a systematic review. [Review]. Chronic Respiratory Disease 11:3-13.

304. Salte K, Titlestad I, and Halling A. (2015) Depression is associated with poor prognosis in patients with chronic obstructive pulmonary disease - a systematic review. Danish Medical Journal 62:2015.

305. Blakemore A, Dickens C, Guthrie E et al. (2014) Depression and anxiety predict health-related quality of life in chronic obstructive pulmonary disease: systematic review and meta-analysis. [Review]. International Journal of Copd 9:501-512.

306. Jiang X and He G. (2012) Effects of an uncertainty management intervention on uncertainty, anxiety, depression, and quality of life of chronic obstructive pulmonary disease outpatients. Research in Nursing and Health 35:409-418.

307. Alexopoulos GS, Kiosses DN, Sirey JA et al. (2013) Personalised intervention for people with depression and severe COPD. British Journal of Psychiatry 202:235-236.

308. Coventry PA, Bower P, Keyworth C et al. (2013) The effect of complex interventions on depression and anxiety in chronic obstructive pulmonary disease: systematic review and meta-analysis. [Review]. PLoS ONE [Electronic Resource] 8:e60532.

309. Smith SM, Sonego S, Ketcheson L et al. (2014) A review of the effectiveness of psychological interventions used for anxiety and depression in chronic obstructive pulmonary disease. BMJ open respiratory research 1:e000042.

310. Volpato E, Banfi P, Rogers SM et al. (2015) Relaxation Techniques for People with Chronic Obstructive Pulmonary Disease: A Systematic Review and a Meta-Analysis. Evidence-Based Complementary & Alternative Medicine: eCAM 2015:628365.

311. Desveaux L, Lee A, Goldstein R et al. (2015) Yoga in the Management of Chronic Disease: A Systematic Review and Meta-analysis. [Review]. Medical Care 53:653-661.

312. Wiles L, Cafarella P, and Williams MT. (2015) Exercise training combined with psychological interventions for people with chronic obstructive pulmonary disease. Respirology 20:46-55.

313. Zhu B, Zhu B, Xiao C et al. (2015) Vitamin D deficiency is associated with the severity of COPD: a systematic review and meta-analysis. International Journal of Copd 10:1907-1916.

314. Ferreira IM, Brooks D, White J et al. (2012) Nutritional supplementation for stable chronic obstructive pulmonary disease. [Review][Update of Cochrane Database Syst Rev. 2005;(2):CD000998; PMID: 15846608]. Cochrane Database of Systematic Reviews 12:CD000998.

315. Collins PF, Elia M, and Stratton RJ. (2013) Nutritional support and functional capacity in chronic obstructive pulmonary disease: a systematic review and meta-analysis. [Review]. Respirology 18:616-629.

316. Collins PF, Stratton RJ, and Elia M. (2012) Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. [Review]. American Journal of Clinical Nutrition 95:1385-1395.

317. Gurgun A, Deniz S, Argin M et al. (2013) Effects of nutritional supplementation combined with conventional pulmonary rehabilitation in muscle-wasted chronic obstructive pulmonary disease: a prospective, randomized and controlled study. Respirology 18:495-500.

318. Wang H, X, Hua WJ, Xia Y et al. (2011) Therapeutic effects of low carbohydrate and high fat enteral nutrition combined with parenteral nutrition in treatment of patients with chronic obstructive pulmonary disease undergoing mechanical ventilation. SO: Journal of Shanghai Jiaotong University (Medical Science) 31:1628-1631.

319. Baldrick FR, Elborn JS, Woodside JV et al. (2012) Effect of fruit and vegetable intake on oxidative stress and inflammation in COPD: a randomised controlled trial. SO: The European respiratory journal 39:1377-1384.

320. Marinari S, Manigrasso MR, and De BF. (2013) Effects of nutraceutical diet integration, with coenzyme Q10 (Q-Ter multicomposite) and creatine, on dyspnea, exercise tolerance, and quality of life in COPD patients with chronic respiratory failure. Multidisciplinary Respiratory Medicine 8:40.

321. Dal Negro RW, Testa A, Aquilani R et al. (2012) Essential amino acid supplementation in patients with severe COPD: A step towards home rehabilitation. Monaldi Archives for Chest Disease - Pulmonary Series 77:67-75.

322. Isbaniah F, Wiyono WH, Yunus F et al. (2011) Echinacea purpurea along with zinc, selenium and vitamin C to alleviate exacerbations of chronic obstructive pulmonary disease: Results from a randomized controlled trial. Journal of Clinical Pharmacy and Therapeutics 36:568-576.

323. Amaral AF, Gallo L, Jr., Vannucchi H et al. (2012) The effect of acute magnesium loading on the maximal exercise performance of stable chronic obstructive pulmonary disease patients. Clinics (Sao Paulo, Brazil) 67:615-622.

324. Lehouck A, Mathieu C, Carremans C et al. (2012) High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: A randomized trial. Annals of Internal Medicine 156:105-120.

325. Bjerk SM, Edgington BD, Rector TS et al. (2013) Supplemental vitamin D and physical performance in COPD: a pilot randomized trial. International Journal of Copd 8:97-104.

326. Hornikx M, Remoortel H, Lehouck A et al. (2012) Vitamin D supplementation during rehabilitation in COPD: a secondary analysis of a randomized trial. SO: Respiratory research 13:84.

327. Taylor SJ, Sohanpal R, Bremner SA et al. (2012) Self-management support for moderate-to-severe chronic obstructive pulmonary disease: a pilot randomised controlled trial. British Journal of General Practice 62:e687-e695.

328. Bucknall CE, Miller G, Lloyd SM et al. (2012) Glasgow supported self-management trial (GSuST) for patients with moderate to severe COPD: Randomised controlled trial. BMJ (Online) 344.

329. Kiser K, Jonas D, Warner Z et al. (2012) A randomized controlled trial of a literacy-sensitive self-management intervention for chronic obstructive pulmonary disease patients. Journal of General Internal Medicine 27:190-195.

330. Ninot G, Moullec G, Picot MC et al. (2011) Cost-saving effect of supervised exercise associated to COPD self-management education program. SO: Respiratory medicine 105:377-385.

331. Wakabayashi R, Motegi T, Yamada K et al. (2011) Efficient integrated education for older patients with chronic obstructive pulmonary disease using the Lung Information Needs Questionnaire. Geriatrics and Gerontology International 11:422-430.

332. Ho C-F, Maa S-H, Shyu Y-I et al. (2012) Effectiveness of paced walking to music at home for patients with COPD. Copd: Journal of Chronic Obstructive Pulmonary Disease 9:447-457.

333. Jarab AS, AlQudah SG, Khdour M et al. (2012) Impact of pharmaceutical care on health outcomes in patients with COPD. International Journal of Clinical Pharmacy 34:53-62.

334. Siddique HH, Olson RH, Parenti CM et al. (2012) Randomized trial of pragmatic education for low-risk COPD patients: impact on hospitalizations and emergency department visits. International Journal of Copd 7:719-728.

335. Tan JY, Chen JX, Liu XL et al. (2012) A meta-analysis on the impact of disease-specific education programs on health outcomes for patients with chronic obstructive pulmonary disease. Geriatric Nursing 33:280-296.

336. Effing T, Zielhuis G, Kerstjens H et al. (2011) Community based physiotherapeutic exercise in COPD self-management: a randomised controlled trial. SO: Respiratory medicine 105:418-426.

337. Liu F, Cai H, Tang Q et al. (2013) Effects of an animated diagram and video-based online breathing program for dyspnea in patients with stable COPD. Patient Preference and Adherence 7:905-913.

338. Pomidori L, Contoli M, Mandolesi G et al. (2012) A simple method for home exercise training in patients with chronic obstructive pulmonary disease: One-year study. SO: Journal of cardiopulmonary rehabilitation and prevention 32:53-57.

339. Jonsdottir H. (2013) Self-management programmes for people living with chronic obstructive pulmonary disease: a call for a reconceptualisation. [Review]. Journal of Clinical Nursing 22:621-637.

340. Fan VS, Gaziano JM, Lew R et al. (15-5-2012) A comprehensive care management program to prevent chronic obstructive pulmonary disease hospitalizations: a randomized, controlled trial.[Summary for patients in Ann Intern Med. 2012 May 15;156(10):I-30; PMID: 22586018]. Annals of Internal Medicine 156:673-683.

341. Bischoff EWMA, Akkermans R, Bourbeau J et al. (2012) Comprehensive self management and routine monitoring in chronic obstructive pulmonary disease patients in general practice: Randomised controlled trial. BMJ (Online) 345.

342. Uijen AA, Bischoff EW, Schellevis FG et al. (2012) Continuity in different care modes and its relationship to quality of life: a randomised controlled trial in patients with COPD. British Journal of General Practice 62:e422-e428.

343. Stoilkova A, Janssen DJA, and Wouters EFM. (2013) Educational programmes in COPD management interventions: A systematic review. Respiratory Medicine 107:1637-1650.

344. Dinesen B, Haesum LK, Soerensen N et al. (2012) Using preventive home monitoring to reduce hospital admission rates and reduce costs: A case study of telehealth among chronic obstructive pulmonary disease patients. Journal of Telemedicine and Telecare 18:221-225.

345. McLean S, Nurmatov U, Liu JL et al. (2011) Telehealthcare for chronic obstructive pulmonary disease. [Review]. Cochrane Database of Systematic Reviews CD007718.

346. McLean S, Nurmatov U, Liu JL et al. (2012) Telehealthcare for chronic obstructive pulmonary disease: Cochrane Review and meta-analysis. [Review]. British Journal of General Practice 62:e739-e749.

347. Pare G, Poba-Nzaou P, Sicotte C et al. (2013) Comparing the costs of home telemonitoring and usual care of chronic obstructive pulmonary disease patients: A randomized controlled trial. European Research in Telemedicine 2:35-47.

348. Nield M and Hoo GW. (2012) Real-time telehealth for COPD self-management using SkypeTM. Copd: Journal of Chronic Obstructive Pulmonary Disease 9:611-619.

349. Chau JP, Lee DT, Yu DS et al. (2012) A feasibility study to investigate the acceptability and potential effectiveness of a telecare service for older people with chronic obstructive pulmonary disease. International Journal of Medical Informatics 81:674-682.

350. Jodar-Sanchez F, Ortega F, Parra C et al. (2013) Implementation of a telehealth programme for patients with severe chronic obstructive pulmonary disease treated with long-term oxygen therapy. Journal of Telemedicine & Telecare 19:11-17.

351. Bolton CE, Waters CS, Peirce S et al. (2011) Insufficient evidence of benefit: a systematic review of home telemonitoring for COPD. [Review]. Journal of Evaluation in Clinical Practice 17:1216-1222.

352. Pinnock H, Hanley J, McCloughan L et al. (2013) Effectiveness of telemonitoring integrated into existing clinical services on hospital admission for exacerbation of chronic obstructive pulmonary disease: Researcher blind, multicentre, randomised controlled trial. BMJ (Online) 347.

353. Antoniades NC, Rochford PD, Pretto JJ et al. (2012) Pilot study of remote telemonitoring in COPD. Telemedicine journal and e-health : the official journal of the American Telemedicine Association 18:634-640.

354. Pedone C, Chiurco D, Scarlata S et al. (2013) Efficacy of multiparametric telemonitoring on respiratory outcomes in elderly people with COPD: a randomized controlled trial. BMC Health Services Research 13:82.

355. Nguyen HQ, Donesky D, Reinke LF et al. (2013) Internet-based dyspnea self-management support for patients with chronic obstructive pulmonary disease. Journal of Pain and Symptom Management 46:43-55.

356. Walters J, Cameron-Tucker H, Wills K et al. (2013) Effects of telephone health mentoring in community-recruited chronic obstructive pulmonary disease on self-management capacity, quality of life and psychological morbidity: A randomised controlled trial. BMJ Open 3.

357. Bischoff EW, Hamd DH, Sedeno M et al. (2011) Effects of written action plan adherence on COPD exacerbation recovery. SO: Thorax 66:26-31.

358. Trappenburg JC, Monninkhof EM, Bourbeau J et al. (2011) Effect of an action plan with ongoing support by a case manager on exacerbation-related outcome in patients with COPD: a multicentre randomised controlled trial. Thorax 66:977-984.

359. Walters-Julia AE, Turnock AC, Walters EH et al. (2010) Action plans with limited patient education only for exacerbations of chronic obstructive pulmonary disease. Walters.Julia AE., Turnock.Allison.C, Walters.E.Haydn., Wood.Baker.Richard.Action plans.with limited.patient education only.for exacerbations.of chronic obstructive pulmonary disease.Cochrane Database of Systematic Reviews: Reviews 2010 Issue 5 John Wi .

360. Rice KL, Dewan N, Bloomfield HE et al. (2010) Disease management program for chronic obstructive pulmonary disease a randomized controlled trial. American journal of respiratory and critical care medicine 182:890-896.

361. Zwerink M, Brusse-Keizer M, van der Valk PD et al. (2014) Self management for patients with chronic obstructive pulmonary disease. [Review][Update of Cochrane Database Syst Rev. 2007;(4):CD002990; PMID: 17943778]. Cochrane Database of Systematic Reviews 3:CD002990.

362. Jordan RE, Majothi S, Heneghan NR et al. (2015) Supported self-management for patients with moderate to severe chronic obstructive pulmonary disease (COPD): an evidence synthesis and economic analysis. Health Technology Assessment (Winchester, England) 19:1-516.

363. Majothi S, Jolly K, Heneghan NR et al. (2015) Supported self-management for patients with COPD who have recently been discharged from hospital: a systematic review and meta-analysis. International Journal of Copd 10:853-867.

364. Cruz J, Brooks D, and Marques A. (2014) Home telemonitoring effectiveness in COPD: a systematic review. [Review]. International Journal of Clinical Practice 68:369-378.

365. Lundell S, Holmner A, Rehn B et al. (2015) Telehealthcare in COPD: a systematic review and meta-analysis on physical outcomes and dyspnea. Respiratory Medicine 109:11-26.

366. Kruis AL, Smidt N, Assendelft WJ et al. (2014) Cochrane corner: is integrated disease management for patients with COPD effective?. [Review]. Thorax 69:1053-1055.

367. Dickens C, Katon W, Blakemore A et al. (2014) Complex interventions that reduce urgent care use in COPD: a systematic review with meta-regression. [Review]. Respiratory Medicine 108:426-437.

368. Peytremann-Bridevaux I, Taffe P, Burnand B et al. (2014) Mortality of patients with copd participating in chronic disease management programmes: A happy end? Thorax.69 (9) (pp 865-866), 2014.Date of Publication: September 2014. 865-866.

369. Uronis H, McCrory DC, Samsa G et al. (2011) Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease. [Review]. Cochrane Database of Systematic Reviews CD006429.

370. Ringbaek T, Martinez G, and Lange P. (2013) The long-term effect of ambulatory oxygen in normoxaemic COPD patients: a randomised study. Chronic Respiratory Disease 10:77-84.

371. Ameer F, Carson KV, Usmani ZA et al. (2014) Ambulatory oxygen for people with chronic obstructive pulmonary disease who are not hypoxaemic at rest. [Review][Update of Cochrane

Database Syst Rev. 2002;(2):CD000238; PMID: 12076387]. Cochrane Database of Systematic Reviews 6:CD000238.

372. Uronis HE, Ekstrom MP, Currow DC et al. (2015) Oxygen for relief of dyspnoea in people with chronic obstructive pulmonary disease who would not qualify for home oxygen: a systematic review and meta-analysis. [Review]. Thorax 70:492-494.

373. Casaburi R, Porszasz J, Hecht A et al. (2012) Influence of lightweight ambulatory oxygen on oxygen use and activity patterns of COPD patients receiving long-term oxygen therapy. SO: COPD 9:3-11.

374. Ntoumenopoulos G. (2011) Using titrated oxygen instead of high flow oxygen during an acute exacerbation of chronic obstructive pulmonary disease (COPD) saves lives. SO: Journal of Physiotherapy 57:55.

375. Rice KL, Schmidt MF, Buan JS et al. (2011) AccuO2 oximetry-driven oxygen-conserving device versus fixed-dose oxygen devices in stable COPD patients. Respiratory Care 56:1901-1905.

376. Moore RP, Berlowitz DJ, Denehy L et al. (2011) A randomised trial of domiciliary, ambulatory oxygen in patients with COPD and dyspnoea but without resting hypoxaemia. SO: Thorax 66:32-37.

377. Walters-Julia AE, Smith S, Poole P et al. (2010) Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. Walters.Julia AE., Smith Sabin., Poole.Phillippa., Granger.Robert H, Wood.Baker.Richard.Injectable.vaccines for preventing pneumococcal.infection in patients.with chronic obstructive pulmonary disease.Cochrane Database of Systematic Reviews: Reviews 201 .

378. Teo E, House H, Lockhart K et al. (2014) Haemophilus influenzae oral vaccination for preventing acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease. [Review]. Cochrane Database of Systematic Reviews 9:CD010010.

379. Chen H, Liang BM, Xu ZB et al. (2011) Long-term non-invasive positive pressure ventilation in severe stable chronic obstructive pulmonary disease: a meta-analysis. Chinese Medical Journal 124:4063-4070.

380. Shi J-X, Xu J, Sun W-K et al. (2013) Effect of noninvasive, positive pressure ventilation on patients with severe, stable chronic obstructive ulmonary disease: A meta-analysis. Chinese Medical Journal 126:140-146.

381. Struik FM, Lacasse Y, Goldstein R et al. (2013) Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease. [Review][Update of Cochrane Database Syst Rev. 2002;(3):CD002878; PMID: 12137664]. Cochrane Database of Systematic Reviews 6:CD002878.

382. Ramsay M and Hart N. (2013) Current opinions on non-invasive ventilation as a treatment for chronic obstructive pulmonary disease. Current Opinion in Pulmonary Medicine 19:626-630.

383. Bhatt SP, Peterson MW, Wilson JS et al. (2013) Noninvasive positive pressure ventilation in subjects with stable COPD: A randomized trial. International Journal of Copd 8:581-589.

384. Rodrigues MK, Oliveira MF, Soares A et al. (2013) Additive effects of non-invasive ventilation to hyperoxia on cerebral oxygenation in COPD patients with exercise-related O2 desaturation. Clinical Physiology and Functional Imaging 33:274-281.

385. Struik FM, Lacasse Y, Goldstein RS et al. (2014) Nocturnal noninvasive positive pressure ventilation in stable COPD: a systematic review and individual patient data meta-analysis. [Review]. Respiratory Medicine 108:329-337.

386. Dretzke J, Blissett D, Dave C et al. (2015) The cost-effectiveness of domiciliary non-invasive ventilation in patients with end-stage chronic obstructive pulmonary disease: a systematic review and economic evaluation. Health Technology Assessment (Winchester, England) 19:1-246.

387. Disler RT, Currow DC, Phillips JL et al. (2012) Interventions to support a palliative care approach in patients with chronic obstructive pulmonary disease: an integrative review. [Review]. International Journal of Nursing Studies 49:1443-1458.

388. Momen N, Hadfield P, Kuhn I et al. (2012) Discussing an uncertain future: End-of-life care conversations in chronic obstructive pulmonary disease. A systematic literature review and narrative synthesis. Thorax 67:777-780.

389. Au DH, Udris EM, Engelberg RA et al. (2012) A randomized trial to improve communication about end-of-life care among patients with COPD. SO: Chest 141:726-735.

390. Lemmens KMM, Lemmens LC, Boom JHC et al. (2013) Chronic care management for patients with COPD: A critical review of available evidence. Journal of Evaluation in Clinical Practice 19:734-752.

391. Yamaguti WP, Claudino RC, Neto AP et al. (2012) Diaphragmatic breathing training program improves abdominal motion during natural breathing in patients with chronic obstructive pulmonary disease: A randomized controlled trial. Archives of Physical Medicine and Rehabilitation 93:571-577.

392. Bhatt SP, Luqman-Arafath TK, Gupta AK et al. (2013) Volitional pursed lips breathing in patients with stable chronic obstructive pulmonary disease improves exercise capacity. Chronic Respiratory Disease 10:5-10.

393. Ides K, Vissers D, De BL et al. (2011) Airway clearance in COPD: need for a breath of fresh air? A systematic review. [Review][Erratum appears in COPD. 2011 Dec;8(6):468 Note: Vissers, Dick [corrected to Vissers, Dirk]]. Copd: Journal of Chronic Obstructive Pulmonary Disease 8:196-205.

394. Liu H, Xu M, Xie Y et al. (2015) Efficacy and safety of endobronchial valves for advanced emphysema: a meta analysis. Journal of Thoracic Disease 7:320-328.

395. Choi M, Lee WS, Lee M et al. (2015) Effectiveness of bronchoscopic lung volume reduction using unilateral endobronchial valve: a systematic review and meta-analysis. International Journal of Copd 10:703-710.

396. Eberhardt R, Gompelmann D, Schuhmann M et al. (2012) Complete unilateral vs partial bilateral endoscopic lung volume reduction in patients with bilateral lung emphysema. Chest 142:900-908.

397. Iftikhar IH, McGuire FR, and Musani AI. (2014) Efficacy of bronchoscopic lung volume reduction: a meta-analysis. [Review][Erratum appears in Int J Chron Obstruct Pulmon Dis. 2014;9:685]. International Journal of Copd 9:481-491.

398. Iftikhar IH, McGuire FR, and Musani AI. (2014) Predictors of efficacy for endobronchial valves in bronchoscopic lung volume reduction: A meta-analysis. [Review]. Chronic Respiratory Disease 11:237-245.

399. Akero A, Edvardsen A, Christensen CC et al. (2011) COPD and air travel: oxygen equipment and preflight titration of supplemental oxygen. Chest 140:84-90.

400. Greening NJ, Williams JEA, Hussain SF et al. (8-7-2014) An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. BMJ 349:g4315.

401. Wu X, Chen D, Gu X et al. (2014) Prevalence and risk of viral infection in patients with acute exacerbation of chronic obstructive pulmonary disease: a meta-analysis. Molecular Biology Reports 41:4743-4751.

402. Zwaans WA, Mallia P, van Winden ME et al. (2014) The relevance of respiratory viral infections in the exacerbations of chronic obstructive pulmonary disease-a systematic review. [Review]. Journal of Clinical Virology 61:181-188.

403. Hoogendoorn M, Hoogenveen RT, Rutten-van Molken MP et al. (2011) Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology 37:508-515.

404. Hurst JR, Vestbo J, Anzueto A et al. (16-9-2010) Susceptibility to exacerbation in chronic obstructive pulmonary disease. New England Journal of Medicine 363:1128-1138.

405. Zhou L, Yuan C, Zhang J et al. (2014) Circulating leptin concentrations in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. Respiration.86 (6) (pp 512-522), 2014.Date of Publication: January 2014. 512-522.

406. Chaudary N and Geraci SA. (2014) Prognostic value of cardiac-specific troponins in chronic obstructive pulmonary disease exacerbations: a systematic review. [Review]. Journal of the Mississippi State Medical Association 55:40-44.

407. Pavasini R, d'Ascenzo F, Campo G et al. (15-7-2015) Cardiac troponin elevation predicts all-cause mortality in patients with acute exacerbation of chronic obstructive pulmonary disease: Systematic review and meta-analysis. International Journal of Cardiology 191:187-193.

408. Aaron SD, Vandemheen KL, Maltais F et al. (2013) TNF antagonists for acute exacerbations of COPD: a randomised double-blind controlled trial. Thorax 68:142-148.

409. Aggarwal P, Wig N, and Bhoi S. (2011) Efficacy of two corticosteroid regimens in acute exacerbation of chronic obstructive pulmonary disease. International Journal of Tuberculosis & Lung Disease 15:687-692.

410. Cheng T, Gong Y, Guo Y et al. (2013) Systemic corticosteroid for COPD exacerbations, whether the higher dose is better? A meta-analysis of randomized controlled trials. Clinical Respiratory Journal 7:305-318.

411. Alía I, Cal MA, Esteban A et al. (2011) Efficacy of corticosteroid therapy in patients with an acute exacerbation of chronic obstructive pulmonary disease receiving ventilatory support. SO: Archives of internal medicine 171:1939-1946.

412. Walters-Julia AE, Wang W, Morley C et al. (2011) Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. SO: Cochrane Database of Systematic Reviews .

413. Leuppi JD, Schuetz P, Bingisser R et al. (2013) Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: The REDUCE randomized clinical trial. JAMA - Journal of the American Medical Association 309:2223-2231.

414. Abroug F, Ouanes I, Abroug S et al. (2014) Systemic corticosteroids in acute exacerbation of COPD: a meta-analysis of controlled studies with emphasis on ICU patients. [Review]. Annals of Intensive Care 4:32.

415. Walters JA, Tan DJ, White CJ et al. (2014) Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. [Review][Update of Cochrane Database Syst Rev. 2009;(1):CD001288; PMID: 19160195]. Cochrane Database of Systematic Reviews 9:CD001288.

416. Walters JA, Tan DJ, White CJ et al. (2014) Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. [Review][Update of Cochrane Database Syst Rev. 2011;(10):CD006897; PMID: 21975757]. Cochrane Database of Systematic Reviews 12:CD006897.

417. Pan L, Wang M, Xie X et al. (2014) Effects of anabolic steroids on chronic obstructive pulmonary disease: a meta-analysis of randomised controlled trials. PLoS ONE [Electronic Resource] 9:e84855.

418. Haynes JM. (2012) Randomized controlled trial of a breath-activated nebulizer in patients with exacerbation of COPD. SO: Respiratory care 57:1385-1390.

419. Vollenweider DJ, Jarrett H, Steurer-Stey CA et al. (2012) Antibiotics for exacerbations of chronic obstructive pulmonary disease. SO: Cochrane Database of Systematic Reviews .

420. Ram-Felix SF, Rodriguez RR, Granados NA et al. (2011) Antibiotics for exacerbations of chronic obstructive pulmonary disease. SO: Cochrane Database of Systematic Reviews .

421. Llor C, Moragas A, Hernandez S et al. (2012) Efficacy of antibiotic therapy for acute exacerbations of mild to moderate chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine 186:716-723.

422. Liu KX, Xu B, Wang J et al. (2014) Efficacy and safety of moxifloxacin in acute exacerbations of chronic bronchitis and COPD: a systematic review and meta-analysis. Journal of Thoracic Disease 6:221-229.

423. Austin M, Wood-Baker R, Wills K et al. (2010) High flow oxygen increases mortality in COPD patients in a pre-hospital setting: A RCT. Internal Medicine Journal 40:2-3.

424. O'Driscoll BR, Howard LS, and Davison AG. (2008) British Thoracic Society Guideline for emergency oxygen use in adult patients. Thorax 63 (suppl 6):1-68.

425. Boyacy H, Pala A, Argun BS et al. (2011) The effects of inhaled steroid and theophylline on systemic inflammation in COPD. SO: European Journal of Inflammation 9:241-248.

426. Voduc N, Alvarez GG, Amjadi K et al. (2012) Effect of theophylline on exercise capacity in COPD patients treated with combination long-acting bronchodilator therapy: a pilot study. International Journal of Copd 7:245-252.

427. Antonaglia V, Ferluga M, Molino R et al. (2011) Comparison of noninvasive ventilation by sequential use of mask and helmet versus mask in acute exacerbation of chronic obstructive pulmonary disease: a preliminary study. Respiration 82:148-154.

428. De BL, Vos W, Dieriks B et al. (2011) The effects of long-term noninvasive ventilation in hypercapnic COPD patients: a randomized controlled pilot study. International journal of chronic obstructive pulmonary disease 6:615-624.

429. Di MF, Centanni S, Bellone A et al. (2011) Optimization of ventilator setting by flow and pressure waveforms analysis during noninvasive ventilation for acute exacerbations of COPD: A multicentric randomized controlled trial. Critical Care 15.

430. Duiverman ML, Wempe JB, Bladder G et al. (2011) Two-year home-based nocturnal noninvasive ventilation added to rehabilitation in chronic obstructive pulmonary disease patients: a randomized controlled trial. Respiratory Research 12:112.

431. Funk GC, Breyer MK, Burghuber OC et al. (2011) Long-term non-invasive ventilation in COPD after acute-on-chronic respiratory failure. SO: Respiratory medicine 105:427-434.

432. Khilnani GC, Galle AD, Hadda V et al. (2011) Non-invasive ventilation after extubation in patients with chronic obstructive airways disease: a randomised controlled trial. SO: Anaesthesia and intensive care 39:217-223.

433. Kirakli C, Ozdemir I, Ucar ZZ et al. (2011) Adaptive support ventilation for faster weaning in COPD: a randomised controlled trial. European Respiratory Journal 38:774-780.

434. Duan J, Tang X, Huang S et al. (2012) Protocol-directed versus physician-directed weaning from noninvasive ventilation: The impact in chronic obstructive pulmonary disease patients. Journal of Trauma and Acute Care Surgery 72:1271-1275.

435. Smith TA, Davidson PM, Lam LT et al. (2012) The use of non-invasive ventilation for the relief of dyspnoea in exacerbations of chronic obstructive pulmonary disease; a systematic review. [Review]. Respirology 17:300-307.

436. Bajaj A, Rathor P, Sehgal V et al. (2015) Efficacy of noninvasive ventilation after planned extubation: A systematic review and meta-analysis of randomized controlled trials. [Review]. Heart & Lung 44:150-157.

437. Wang Y, Haugen T, Steihaug S et al. (2012) Patients with acute exacerbation of chronic obstructive pulmonary disease feel safe when treated at home: a qualitative study. SO: BMC pulmonary medicine 12:45.

438. Utens CMA, Goossens LMA, Smeenk FWJM et al. (2012) Early assisted discharge with generic community nursing for chronic obstructive pulmonary disease exacerbations: Results of a randomised controlled trial. BMJ Open 2.

439. Zwar NA, Hermiz O, Comino E et al. (2012) Care of patients with a diagnosis of chronic obstructive pulmonary disease: a cluster randomised controlled trial. The Medical journal of Australia 197:394-398.

440. Jeppesen E, Brurberg KG, Vist GE et al. (2012) Hospital at home for acute exacerbations of chronic obstructive pulmonary disease. [Review][Update of Cochrane Database Syst Rev. 2003;(4):CD003573; PMID: 14583984]. Cochrane Database of Systematic Reviews 5:CD003573.

441. Goossens LM, Utens CM, Smeenk FW et al. (2013) Cost-effectiveness of early assisted discharge for COPD exacerbations in The Netherlands. Value in Health 16:517-528.

442. Lainscak M, Kadivec S, Kosnik M et al. (2013) Discharge coordinator intervention prevents hospitalizations in patients with COPD: a randomized controlled trial. Journal of the American Medical Directors Association 14:450-456.

443. Wong CX, Smith BJ, and Carson KV. (2010) Home care by outreach nursing for chronic obstructive pulmonary disease: A systematic review. Respirology (Carlton, Vic.) 15:A19.

444. Cross JL, Elender F, Barton G et al. (2012) Evaluation of the effectiveness of manual chest physiotherapy techniques on quality of life at six months post exacerbation of COPD (MATREX): a randomised controlled equivalence trial. BMC Pulmonary Medicine 12:33.

445. Osadnik CR, McDonald CF, Jones AP et al. (2012) Airway clearance techniques for chronic obstructive pulmonary disease. [Review]. Cochrane Database of Systematic Reviews 3:CD008328.

446. Moon KT. (2012) Adjunctive acupuncture reduces COPD-related dyspnea. American Family Physician 86.

447. Suzuki M, Muro S, Ando Y et al. (11-6-2012) A randomized, placebo-controlled trial of acupuncture in patients with chronic obstructive pulmonary disease (COPD): the COPD-acupuncture trial (CAT). Archives of Internal Medicine 172:878-886.

448. Deering BM, Fullen B, Egan C et al. (2011) Acupuncture as an adjunct to pulmonary rehabilitation. Journal of cardiopulmonary rehabilitation and prevention 31:392-399.

449. Coyle ME, Shergis JL, Huang ET et al. (2014) Acupuncture therapies for chronic obstructive pulmonary disease: a systematic review of randomized, controlled trials. [Review]. Alternative Therapies in Health & Medicine 20:10-23.

450. Bernstein JA, Liu N, Knorr BA et al. (2011) MK-0633, a potent 5-lipoxygenase inhibitor, in chronic obstructive pulmonary disease. SO: Respiratory medicine 105:392-401.

451. Woodruff PG, Albert RK, Bailey WC et al. (2011) Randomized trial of zileuton for treatment of COPD exacerbations requiring hospitalization. SO: COPD 8:21-29.

452. Vogelmeier C, Aquino TO, O'Brien CD et al. (2012) A randomised, placebo-controlled, dose-finding study of AZD9668, an oral inhibitor of neutrophil elastase, in patients with chronic obstructive pulmonary disease treated with tiotropium. Copd: Journal of Chronic Obstructive Pulmonary Disease 9:111-120.

453. Kuna P, Jenkins M, O'Brien CD et al. (2012) AZD9668, a neutrophil elastase inhibitor, plus ongoing budesonide/formoterol in patients with COPD. SO: Respiratory medicine 106:531-539.

454. Dahl R, Titlestad I, Lindqvist A et al. (2012) Effects of an oral MMP-9 and -12 inhibitor, AZD1236, on biomarkers in moderate/severe COPD: A randomised controlled trial. Pulmonary Pharmacology and Therapeutics 25:169-177.

455. de Matos Cavalcante AG, de Bruin PF, de Bruin VM et al. (2012) Melatonin reduces lung oxidative stress in patients with chronic obstructive pulmonary disease: a randomized, double-blind, placebo-controlled study. Journal of Pineal Research 53:238-244.

456. Lederer DJ, Bartels MN, Schluger NW et al. (2012) Sildenafil for chronic obstructive pulmonary disease: a randomized crossover trial. Copd: Journal of Chronic Obstructive Pulmonary Disease 9:268-275.

457. Rao RS, Singh S, Sharma BB et al. (2011) Sildenafil improves six-minute walk distance in chronic obstructive pulmonary disease: a randomised, double-blind, placebo-controlled trial. The Indian journal of chest diseases & allied sciences 53:81-85.

458. Mainguy V, Girard D, Maltais F et al. (15-7-2012) Effect of bisoprolol on respiratory function and exercise capacity in chronic obstructive pulmonary disease. American Journal of Cardiology 110:258-263.

459. Edwards L, Shirtcliffe P, Wadsworth K et al. (2013) Use of nebulised magnesium sulphate as an adjuvant in the treatment of acute exacerbations of COPD in adults: a randomised double-blind placebo-controlled trial. Thorax 68:338-343.

460. Snell N, Foster M, and Vestbo J. (2013) Efficacy and safety of AZD1981, a CRTH2 receptor antagonist, in patients with moderate to severe COPD. Respiratory Medicine 107:1722-1730.

461. Jensen D, Alsuhail A, Viola R et al. (2012) Inhaled fentanyl citrate improves exercise endurance during high-intensity constant work rate cycle exercise in chronic obstructive pulmonary disease. Journal of Pain and Symptom Management 43:706-719.

462. MacNee W, Allan RJ, Jones I et al. (2013) Efficacy and safety of the oral p38 inhibitor PH-797804 in chronic obstructive pulmonary disease: a randomised clinical trial. Thorax 68:738-745.

463. Mahmoud Abd El HA, Mohammed El WL, Mohammed El HH et al. (2013) High dose N-acetyl cysteine improves inflammatory response and outcome in patients with COPD exacerbations. Egyptian Journal of Chest Diseases and Tuberculosis 62:51-57.

464. Motahar Vahedi HS, Mahshidfar B, Rabiee H et al. (2013) The adjunctive effect of nebulized furosemide in COPD exacerbation: A randomized controlled clinical trial. Respiratory Care 58:1873-1877.

465. Ekstrom M, Nilsson F, Abernethy AA et al. (2015) Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review. Annals of the American Thoracic Society 12:1079-1092.

466. Pan L, Jiang XG, Guo J et al. (2015) Effects of OM-85 BV in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. Journal of Clinical Pharmacology 55:1086-1092.

467. Shivanthan MC and Rajapakse S. (2014) Magnesium for acute exacerbation of chronic obstructive pulmonary disease: A systematic review of randomised trials. Annals of Thoracic Medicine 9:77-80.

468. Du Q, Sun Y, Ding N et al. (2014) Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: a meta-analysis of observational studies. PLoS ONE [Electronic Resource] 9:e113048.

469. Lee JH, Kim HJ, and Kim YH. (2015) The Effectiveness of Anti-leukotriene Agents in Patients with COPD: A Systemic Review and Meta-analysis. Lung 193:477-486.

470. Weiss DJ, Casaburi R, Flannery R et al. (2013) A placebo-controlled, randomized trial of mesenchymal stem cells in COPD. Chest 143:1590-1598.

471. Chan AW, Lee A, Suen LK et al. (2011) Tai chi Qigong improves lung functions and activity tolerance in COPD clients: a single blind, randomized controlled trial. SO: Complementary therapies in medicine 19:3-11.

472. Chan AWK, Lee A, Lee DTF et al. (2013) The sustaining effects of Tai chi Qigong on physiological health for COPD patients: A randomized controlled trial. Complementary Therapies in Medicine 21:585-594.

473. Chan AWK, Lee A, Lee DTF et al. (2013) Evaluation of the sustaining effects of tai chi qigong in the sixth month in promoting psychosocial health in copd patients: A single-blind, randomized controlled trial. The Scientific World Journal 2013.

474. Chan AW, Lee A, Suen LK et al. (2011) Tai chi Qigong improves lung functions and activity tolerance in COPD clients: a single blind, randomized controlled trial. SO: Complementary therapies in medicine 19:3-11.

475. Ng BH, Tsang HW, Jones AY et al. (2011) Functional and psychosocial effects of health qigong in patients with COPD: a randomized controlled trial. Journal of Alternative & Complementary Medicine 17:243-251.

476. An X, Zhang AL, May BH et al. (2012) Oral chinese herbal medicine for improvement of quality of life in patients with stable chronic obstructive pulmonary disease: A systematic review. Journal of Alternative and Complementary Medicine 18:731-743.

477. Wu L, Chen Y, Xu Y et al. (2013) Oral huangqi formulae for stable chronic obstructive pulmonary disease: A systematic review and meta-analysis. Evidence-based Complementary and Alternative Medicine 2013.

478. Li S-Y, Li J-S, Wang M-H et al. (2012) Effects of comprehensive therapy based on traditional Chinese medicine patterns in stable chronic obstructive pulmonary disease: A four-center, open-label, randomized, controlled study. BMC Complementary and Alternative Medicine 12.

479. Li J-S, Xie Y, Yu X-Q et al. (2013) An evaluation of self-efficacy and satisfaction with the effectiveness of Bu-Fei Yi-Shen granule combined with acupoint sticking therapy in patients with chronic obstructive pulmonary disease. European Journal of Integrative Medicine 5:313-325.

480. Mukaida K, Hattori N, Kondo K et al. (15-6-2011) A pilot study of the multiherb Kampo medicine bakumondoto for cough in patients with chronic obstructive pulmonary disease. Phytomedicine 18:625-629.

481. Zhao YL, Song HR, Fei JX et al. (2012) The effects of Chinese yam-epimedium mixture on respiratory function and quality of life in patients with chronic obstructive pulmonary disease. Jun. SO: Journal of traditional Chinese medicine / Chung i tsa chih ying wen pan 32:203-207.

482. Matthys H, Pliskevich DA, Bondarchuk OM et al. (2013) Randomised, double-blind, placebo-controlled trial of EPs 7630 in adults with COPD. Respiratory Medicine 107:691-701.

483. Gao Z, Liu Y, Zhang J et al. (2013) Effect of Jianpi therapy in treatment of chronic obstructive pulmonary disease: a systematic review. [Review]. Journal of Traditional Chinese Medicine 33:1-8.

484. Li J-S, Li S-Y, Yu X-Q et al. (2012) Bu-Fei Yi-Shen granule combined with acupoint sticking therapy in patients with stable chronic obstructive pulmonary disease: A randomized, double-blind, double-dummy, active-controlled, 4-center study. Journal of Ethnopharmacology 141:584-591.

485. Xie Y, Li JS, Yu XQ et al. (2013) Effectiveness of Bufei Yishen Granule combined with acupoint sticking therapy on quality of life in patients with stable chronic obstructive pulmonary disease. Chinese Journal of Integrative Medicine 19:260-268.

486. Wu R, Fengjie Z, Li Y et al. (2013) Modified Dachengqi Decoction combined with conventional treatment for treating acute exacerbation of chronic obstructive pulmonary disease: A systematic review based on randomized controlled trials. Evidence-based Complementary and Alternative Medicine 2013.

487. Chen X, May B, Di YM et al. (2014) Oral Chinese herbal medicine combined with pharmacotherapy for stable COPD: a systematic review of effect on BODE index and six minute walk test. [Review]. PLoS ONE [Electronic Resource] 9:e91830.

488. Zhong Y, Wang X, Xu G et al. (2014) Modified Yupingfeng formula for the treatment of stable chronic obstructive pulmonary disease: a systematic review of randomized controlled trials. [Review]. African journal of traditional, complementary, & alternative medicines 11:1-14.

489. Shergis JL, Liu S, Chen X et al. (2015) Dang shen [Codonopsis pilosula (Franch.) Nannf] herbal formulae for chronic obstructive pulmonary disease: a systematic review and meta-analysis. [Review]. Phytotherapy Research 29:167-186.

490. Chen HY, Ma CH, Cao KJ et al. (2014) A systematic review and meta-analysis of herbal medicine on chronic obstructive pulmonary diseases. Evidence-Based Complementary & Alternative Medicine: eCAM 2014:925069.

491. Haifeng W, Hailong Z, Jiansheng L et al. (2015) Effectiveness and safety of traditional Chinese medicine on stable chronic obstructive pulmonary disease: A systematic review and meta-analysis. [Review]. Complementary Therapies in Medicine 23:603-611.

492. Liu S, Shergis J, Chen X et al. (2014) Chinese herbal medicine (weijing decoction) combined with pharmacotherapy for the treatment of acute exacerbations of chronic obstructive pulmonary disease. [Review]. Evidence-Based Complementary & Alternative Medicine: eCAM 2014:257012.

493. Coyle M, Shergis JL, Liu S et al. (2015) Safety of chinese herbal medicine for chronic obstructive pulmonary disease. [Review]. Evidence-Based Complementary & Alternative Medicine: eCAM 2015:380678.

494. Ding M, Zhang W, Li K et al. (2014) Effectiveness of t'ai chi and qigong on chronic obstructive pulmonary disease: a systematic review and meta-analysis. [Review]. Journal of Alternative & Complementary Medicine 20:79-86.

495. Wu W, Liu X, Wang L et al. (2014) Effects of Tai Chi on exercise capacity and health-related quality of life in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. [Review]. International Journal of Copd 9:1253-1263.

496. Liu XC, Pan L, Hu Q et al. (2014) Effects of yoga training in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Journal of Thoracic Disease 6:795-802.

497. Farver-Vestergaard I, Jacobsen D, and Zachariae R. (2015) Efficacy of psychosocial interventions on psychological and physical health outcomes in chronic obstructive pulmonary disease: a systematic review and meta-analysis. [Review]. Psychotherapy & Psychosomatics 84:37-50.

498. Lee AL, Desveaux L, Goldstein RS et al. (2015) Distractive Auditory Stimuli in the Form of Music in Individuals With COPD: A Systematic Review. [Review]. Chest 148:417-429.