NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Clinical guideline
CG101: Management of chronic obstructive pulmonary disease in adults in primary and secondary care

Publication date
June 2010

Surveillance report for GE (post-consultation)
July 2014

Key findings

			Potential impact on guidance	
			Yes	**No**
Evidence identified from Evidence Update			✓	
Evidence identified from literature search				✓
Feedback from Guideline Development Group				✓
Anti-discrimination and equalities considerations				✓
No update	Rapid update	Standard update	Transfer to static list	Change review cycle
✓				

Surveillance recommendation
GE is asked to consider the following proposal which was consulted on for two weeks:

- The COPD guideline should not be considered for an update at this time.

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Surveillance review of CG101: Management of chronic obstructive pulmonary disease in adults in primary and secondary care

Background information

Guideline issue date: 2010
4 year review: 2014

NCC: National Clinical Guidelines Centre

Four year surveillance review

1. An Evidence Update was produced for the guideline in 2012 and was used as a source of evidence for the review proposal. The Evidence Update indicated that there is currently insufficient new evidence to invalidate the majority of the guideline recommendations. However, the Evidence Update identified three areas: (a) delivery of tiotropium via mist inhaler; (b) indacaterol inhaled therapy and (c) complex patient education programmes and suggested that there may be an impact on current guideline recommendations. The evidence was considered alongside the new evidence identified for the 4 year surveillance review and was deemed unlikely to impact on the current guideline recommendations:
    a. Delivery of tiotropium via mist inhaler and indacaterol inhaled therapy: The guideline does not give preference to either tiotropium or a long-acting beta2 agonist (such as indacaterol) and publication of longer term studies comparing patient-orientated outcomes for tiotropium and indacaterol with other active treatments for COPD would enable their place in therapy to be more clearly established.
    b. Complex patient education programmes: in terms of patient education programmes, further research on the specific components of educational programmes in action plans that are most likely to improve patient outcomes would be pertinent before considering in the guideline.

2. For the 4 year Surveillance Review, a search to identify randomised controlled trials (RCTs) and systematic reviews was carried out for studies published between 15 June 2011 (the end of the search period for the Evidence Update) and 7 January 2014 and relevant abstracts were assessed. Clinical feedback was also obtained from members of the guideline development group (GDG) through a questionnaire survey.

3. No new evidence was identified through the literature search which would invalidate the guidance recommendations.

4. The GDG clinical adviser felt that an update of the COPD guideline should wait until further research outcomes are available, largely related to drug therapy positioning, and particularly related to comparison of long-acting beta2 agonists and long-acting antimuscarinics with long-acting beta2 agonists and inhaled corticosteroids in addition to the role of roflumilast in exacerbation prevention.

Ongoing research

5. Patients are currently being recruited for a 52-week study comparing the effects of indacaterol/glycopyrronium and fluticasone/salmeterol on exacerbations in people with moderate to very severe COPD (ClinicalTrials.gov NCT01782326). In addition to important patient-oriented outcome data, this study is likely to provide better longer-term comparative safety data for the two treatments.

Anti-discrimination and equalities considerations

6. None identified.

Implications for other NICE programmes

7. None identified.

Summary of stakeholder feedback

8. Stakeholders were consulted about the following proposals over a two week consultation period:

The COPD guideline should not be considered for an update at this time.

9. In total, thirteen stakeholders commented on the surveillance review proposal recommendation during the two week consultation period. The table of stakeholder comments can be viewed in Appendix 1.

10. Eight stakeholders agreed with the surveillance review proposal to not update the guidance at this time, four stakeholders disagreed and one stakeholder did not state a definitive decision.

11. The stakeholders that disagreed with the decision not to update the guidance generally felt:
    a. The sections on drug therapy, specifically LAMA/LABA and LABA/ICS combinations could be updated due to new evidence and the availability of new licensed combinations over the next 12 months. New evidence was identified through the surveillance review relating to LABA/ICS combination therapy however, it was concluded that the new evidence is in line with the evidence currently included in the guideline. In terms of LAMA/LABA, new evidence was identified which indicated benefits in some outcomes. The guideline currently recommends the use of LABA plus LAMA where use of inhaled corticosteroids is declined or not tolerated and the new evidence identified through the surveillance review would not impact on this. The guideline was unable to make a recommendation on the use of LABA plus LAMA in those already taking a LAMA. Currently, there is still insufficient consistent evidence available to determine whether there is an added benefit of dual therapy over LAMA monotherapy.
    b. The guideline should take account of medicines management and provide guidance on a set colour coding for medications. NICE acknowledges that there is a vast array of medications available for the treatment of COPD however, as these are implementation issues rather than issues relating to clinical management they should be addressed at a local level.

12. Comments were provided by one stakeholder suggesting that workplace exposure and an association with COPD has been excluded from the original scope. However, the guideline already acknowledges that other factors, particular occupational exposures, may also contribute to the development of COPD. The guideline scope includes identification of early disease to facilitate preventative approaches and this would be relevant to all people who have signs and symptoms of COPD regardless of the cause. Furthermore, guidance on assessment for occupational therapy is provided as the Guideline Development Group felt that occupational therapy assessment should certainly form part of a multidisciplinary assessment and planning package prior to discharge from hospital.

13. One stakeholder highlighted that there may be inequalities in the provision of pulmonary rehabilitation for people with COPD. However, the guideline recommends that pulmonary rehabilitation should be made available to all appropriate people with COPD (see recommendation 84) including those who have had a recent hospitalisation for an acute exacerbation and failure to follow the guideline recommendations is a local implementation issue.

Conclusion

14. Through the 4 year surveillance review of CG101 and subsequent consultation with stakeholders no new evidence was identified which may potentially change the direction of current guideline recommendations. The proposal is not to update the guideline at this time.

Surveillance recommendation

15. GE is asked to consider the following proposal which was consulted on for two weeks:

- The COPD guideline should not be considered for an update at this time.

Mark Baker – Centre Director
Sarah Willett – Associate Director
Emma McFarlane – Technical Adviser

Centre for Clinical Practice
July 2014

Appendix 1 Surveillance review consultation

Surveillance review consultation comments table
6-19 May 2014

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
Department of Health	no substantive comments to make, regarding this consultation			Thank you for your comment.
NHS England	no substantive comments to make regarding this consultation			Thank you for your comment.
NHS England	Agree		I am happy with the decision not to review the COPD guidelines for the present with the caveat that there are several new pharmaceutical products due for licence soon and the guidelines will need to be reviewed in the next year or so.	Thank you for your comment. The next surveillance review of CG101 will be in 2016.
Novartis Pharmaceuticals UK Ltd	Agree			Thank you for your comment.
The Royal College of Anaesthetists	Agree			Thank you for your comment.
ACPRC – Association of Chartered Physiotherapists in	Agree			Thank you for your comment.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
Respiratory Care				
GORDS (Group of Occupational Respiratory Disease Specialists)	Disagree	The current document makes no mention of the interface between COPD and work. There are two broad issues that we believe require inclusion; (i) A significant proportion of COPD is associated with exposures to harmful workplace inhaled exposures. A better future understanding of the nature of these, and how to control these, is important to reduce the future burden of this condition. As smoking rates fall, non smoking causes of COPD such as occupational exposures will become proportionately more important as modifiable causes of COPD. Future interventions to reduce certain inhaled causes may be as important as other clinical interventions currently used to treat the symptoms and natural history of COPD. Further work is needed to	The GORDS group believes that the two areas for inclusion into the guidance are important. There is now a substantial body of global evidence, including evidence form the UK, to support an association between COPD and workplace exposures. Workers with COPD also may require particular workplace considerations to allow them to work well currently, and to retain their future employment. Certain references supporting these statements are found here; Davison AG, Fayers PM, Taylor AJ, Venables KM, Darbyshire J, Pickering CA, Chettle DR, Franklin D, Guthrie CJ, Scott MC, et al. Cadmium fume inhalation and emphysema. Lancet 1988 Mar 26;1(8587):663-7. Hnizdo E, Vallyathan V , Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence. Occup Environ Med 2003;60:267-243. Hnizdo E, SluisCremer GK, Abramowitz JA , Emphysema type in relation to silica dust exposure in South African gold miners. Am Rev Respir Dis 1991;143:1241-1247,	Thank you for providing references to support your comments. The majority of the papers were published outwith the date period of our review (which included studies published June 2011 – January 2014 only) therefore, we were unable to consider them at this surveillance point. Of the three studies that were published within the date period of the surveillance review, one met the study type inclusion criteria of RCTs and systematic reviews (Cullinan P, 2012). From an assessment of the abstract, this review implies that there may be an increased risk of COPD from certain exposures (such as coal mine dust and welding fume) although no statistics are reported in the abstract. However, the guideline already acknowledges that other factors, particular occupational exposures, may also contribute to the development of COPD. The guideline scope includes identification of early disease to facilitate preventative approaches

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
		identify how best to effect these appropriate changes at work. (ii) Workers with COPD may require particular consideration from their employers, to allow them to continue to work with minimal sickness absence and presenteeism. There are very few studies assessing how best to support those with COPD at work, and the consequences of leaving employment due to chronic respiratory ill health. With changing population demographics, older workers will be required to, and may wish to, work for longer; this will lead to a greater proportion of this part of the workforce having to deal with the consequences of respiratory ill health, including COPD.	Oxman AD, Muir DC, Shannon HS, Stock SR, Hnizdo E, Lange HJ , Occupational dust exposure and chronic obstructive pulmonary disease. A systematic overview of the evidence. Am Rev Respir Dis 1993;148:38-48. Kodgule R, Salvi S. Exposure to biomass smoke as a cause for airway disease in women and children. Curr Opin Allergy Clin Immunol 2012 Feb;12(1):82-90. American Thoracic Society Statement. Occupational contribution to the burden of airway disease. Am J Respir Crit Care Med 2003;167(5):787-797. Blanc PD, Toren K. Occupation in chronic obstructive pulmonary disease and chronic bronchitis: an update. Int J Tuberc Lung Dis 2007;11(3):251-7. Blanc PD, Iribarren C, Trupin L, et al. Occupational exposures and the risk of COPD: dusty trades revisited. Thorax 2009;64(1):6-12. Darby AC, Waterhouse JC, Stevens V, Billings CG, Billings CG, Burton CM, Young C, Wight J, Blanc PD, Fishwick D. Chronic obstructive pulmonary disease among residents of an historically industrialised area. Thorax 2012 Oct;67(10):901-7.	and this would be relevant to all people who have signs and symptoms of COPD regardless of the cause. Guidance on assessment for occupational therapy is provided as the Guideline Development Group felt that occupational therapy assessment should certainly form part of a multidisciplinary assessment and planning package prior to discharge from hospital. In addition, advice on accessing social services is provided in the guideline.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			Cullinan P. Occupation and chronic obstructive pulmonary disease (COPD). Br Med Bull 2012;104:143-61. Harber P, Tashkin DP, Simmons M, et al. Effect of occupational exposures on decline of lung function in early chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007;176(10):994-1000. Blanc PD, Eisner MD, Trupin L, et al. The Association between Occupational Factors and Adverse Health Outcomes in Chronic Obstructive Pulmonary Disease. J Occup Environ Med 2004;61(8):661-7. Matheson MC, Benke G, Raven J, Sim MR, Kromhout H, Vermeulen R, Johns DP, Walters EH, Abramson MJ. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. Thorax 2005 Aug;60(8):645-51. Eisner MD, Yelin EH, Trupin L, Blanc PD. The influence of chronic respiratory conditions on health status and work disability. Am J Public Health 2002 Sep;92(9):1506-13.	
Cochrane Airways Review Group	Agree			Thank you for your comment.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
Boehringer Ingelheim UK Ltd	Disagree		There are several recently licensed fixed dosed combinations (FDC) that will become available in the next 12 months. Their place in the management of COPD and subsequent use by healthcare professionals should be clearly defined by the NICE COPD guidelines. Several Phase III trials using different LAMA/LABA FDC show consistent significant improvements in several outcomes including trough FEV1, TDI, SGRQ and exacerbation rates compared to placebo. In addition LAMA/LABA FDC consistently show either significant or numerical improvement in these outcomes compared to LAMA or LABA monotherapy without an increase in adverse events, suggesting that they should have a place in guidelines alongside LABA or LAMA monotherapy. It is important for NICE to continue to provide national guidance as to how these new FDC, which include new molecules not available previously, should be used appropriately. Currently, the inhaled corticosteroids / long acting β2 agonist (ICS/LABA) FDC combination is widely prescribed for COPD patients, although not always appropriately in line with current evidence. It is well recognised that ICS carry a risk of non-fatal pneumonia for patients with COPD which in turn affects the patient	Thank you for your comment. Through the surveillance review new evidence was identified which indicated benefits in some outcomes for combination therapy with a LABA and a LAMA. The guideline currently recommends the use of LABA plus LAMA where use of inhaled corticosteroids is declined or not tolerated and no evidence was identified which would impact on this. The guideline was unable to make a recommendation on the use of LABA plus LAMA in those already taking a LAMA. Currently, there is still insufficient consistent evidence available to determine whether there is an added benefit of dual therapy over LAMA monotherapy and this will be evaluated again in the next surveillance review. New evidence was identified through the surveillance review relating to LABA/ICS combination therapy. It was concluded that the identified new evidence is broadly in line with the evidence currently included in the guideline particularly

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			population which may derive benefit. We would recommend a review of the current guidelines to provide more clarity for primary care physicians as to where the risk-benefit of ICS in COPD is in favour of the patient.	in relation to improved FEV1, reduction in exacerbations and increased risk of pneumonia with this treatment. This area will be examined again in the next surveillance review.
			3. We would like to address the comment on page 6 “The results of a network meta-analysis indicated that tiotropium Soft Mist Inhaler was associated with a universally increased risk of overall death (particularly in people with more severe COPD) compared with placebo, tiotropium HandiHaler, LABA and LABA-ICS.” We would also like to address the comment on page 13: “one meta-analysis indicated that there may be safety issues with tiotropium when delivered via mist inhaler” The TIOSPIR study, an RCT including over 17,000 COPD patients, demonstrated that Spiriva® Respimat® 5 µg and Spiriva® HandiHaler® 18 µg showed similar survival outcomes as measured by all-cause mortality (Hazard ratio for all-cause mortality including vital status follow up: 0.957 (95% CI, 0.84 to 1.09; percentage of deaths 7.4% and 7.7% respectively). Specifically in patients with a history of cardiac arrhythmia (1,221 patients), Spiriva® Respimat®	Thank you for highlighting the TIOSPIR study which suggests, from an assessment of the abstract, that the tiotropium Respimat inhaler was noninferior to tiotropium HandiHaler with respect to the risk of death. However, considering the new evidence together, the risk of death with the tiotropium Soft Mist Inhaler is currently inconsistent. The guideline currently recommends the use of a LAMA for managing stable COPD and does not indicate the use of a specific LAMA or delivery system. Through the surveillance review a study comparing tiotropium with LABAs found the LAMA to be more effective whilst other studies comparing tiotropium with a range of LABA treatments indicated that these have comparable efficacy. At this time, there is insufficient evidence that conclusively indicates

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			5 µg and Spiriva® HandiHaler® 18 µg showed similar impact on survival as measured by all-cause mortality; hazard ratio, 0.81 (95% CI, 0.58 to 1.12, percentage of deaths 10.6% and 12.9% respectively). We would recommend that this RCT data (the largest RCT to be conducted in COPD to date with safety as the primary end point) be included in the data considered for the guidelines update. Ref: N Engl J Med 2013. DOI: 10.1056/NEJMoa1303342.	superiority of one treatment over the other and additional larger studies with longer term follow-up are needed.
British Thoracic Society	Agree		The British Thoracic Society agrees that the decision not to review the Guideline at this time is sensible - but this decision should be reviewed again in a year. The following comments may be relevant for future revisions. 1) More evidence is needed around the inhaled drugs compared to current treatment 2) Tai Chi probably belongs in physiotherapy rather than “complementary”	Thank you for your comment. The next surveillance review of CG101 will be in 2016. Systematic review evidence relating to inhaled drugs for COPD will be considered at the 6 year review of the guideline. Thank you, this will be considered at the next surveillance review of the guideline.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			3) Physical activity promotion may need to be a distinct question (separate from PR)	Thank you, this will be considered at the next surveillance review of the guideline.
			4) The LVRS section is a bit disengaged! Although not RCT data the fact that morbidity / mortality is lower in real life than in historical trials http://www.ncbi.nlm.nih.gov/pubmed/24715121 and that clinician estimates of the risks of LVRS are excessive http://bmjopenrespres.bmj.com/content/1/1/e000023.full ought to be highlighted. I note that the only trial that the reviewers look at is not actually of lung volume reduction surgery at all but of valve placement. There ought to be a separate section in the next draft of guidelines for bronchoscopic techniques and ongoing research should include trials with valves and coils. 5) Some specific sections on managing comorbidities ought to be included in the next version	Thank you for highlighting two studies. Unfortunately as these are not RCTs or systematic reviews we are unable to consider them as part of our surveillance review. Lung volume reduction surgery will be considerd again at the next review of the guideline.
			The ongoing research section mentions only one trial – we assume there hasn't been a systematic attempt to review this.	The trial described in the ongoing research section was identified from the ESNM33 Chronic obstructive pulmonary disease: indacaterol/glycopyrronium (Ultibro Breezhaler) issued February 2014. No systematic search to identify all relevant ongoing trials was

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				undertaken as part of the surveillance review. Further detail on the interim clinical guideline surveillance process and methods can be viewed here: http://publications.nice.org.uk/interim-clinical-guideline-surveillance-process-and-methods-guide-2013-pmg16
Teva UK Limited	Agree			Thank you for your comment.
Association of Respiratory Nurse Specialists & Royal College of Nursing	Disagree		Clearly a robust literature review and overview of the evidence is supplied in the guidance which highlights a number of key points in relation to the care of COPD patients. There are also a number of studies which highlight some of the newer drugs that have come into the respiratory field since the guidelines were previous updated. The suggestions outlined in the guidance suggest that there are no significant changes to make to the guidelines. We believe that a focus on the guidelines should be around the implementation of the current guidelines and highlighting their use within clinical practice. However, we believe that the guidelines should be updated to take into account the following points: 1. Medicines management – there are a	Thank you for your comment. The individual comments have been addressed individually below. Thank you for bringing the issues of

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			number of different devices which are coming to market and while choice is important for patients and which we fully support, there is a lack of availability of placebo inhalers to demonstrate to patients, and for patients to use which can make it difficult for practitioners to obtain a suitable device to use and demonstrate to patients. With the availability of more long-acting beta(2) agonists (LABA) & long-acting muscarinic agtagonist (LAMA's) and combination inhalers we are concerned around the prescribing of these and how choices are made now and in the future. 2. Colour Coding - We understand there is no set colour coding for medications within the UK,and recently there has been wider spread concern around the introduction of Relvar® ▼(fluticasone furoate / vilanterol) Ellipta®, mainly the colour of the cap of the inhaler device which is Blue, which many patients and healthcare professionals associate with SABD, which Relvar is clearly not as a combination inhaler, secondly, there name Relvar' is similar to that of 'reliever', and we are concerned that patients may take an accidental increase in this drug. 3. Pulmonary rehabilitation - ARNS & RCN agree with a CDG questionnaire that states	medicines management and colour coding to our attention. However, these are implementation issues rather than issues relating to clinical management and should be addressed at a local level. The guideline recommends that inhalers should be prescribed only after patients have received training in the use of the device and have demonstrated satisfactory technique. Furthermore, it is recommended that patients should have their ability to use an inhaler device regularly assessed by a competent healthcare professional and, if necessary, should be re-taught the correct technique. Failure to follow the guidance recommendations is a local implementation issue. The guideline recommends that

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			that there are inequalities in the provision of pulmonary rehabilitation specifically for COPD patients, and agree that this is true representation with some areas still not providing patient's with PR.	Pulmonary rehabilitation should be made available to all appropriate people with COPD (see recommendation 84) including those who have had a recent hospitalisation for an acute exacerbation. Failure to follow the guidance recommendations is a local implementation issue.
			4. Classification - One of the recommendations that ARNS & RCN have is regarding the classification of severity of COPD diagnosis. while the we completely agree with the introduction of the 4 classifications of Mild – Very Severe, we would like the work, of the GOLD Global Strategy for the diagnosis, management and prevention of COPD (2014) and the COPD assessment which looks at impact of COPD, including spirometric measurement, risks, breathlessness and exacerbations to be considered as a useful tool in the future NICE guidance and hope that these have been considered within the NICE update.	Thank you for highlighting the GOLD Global Strategy for the diagnosis, management and prevention of COPD (2014). The GOLD criteria was utilised in the 2010 update of the COPD guideline however, no new evidence relating to GOLD was identified in this current surveillance review.
			We would also like to highlight that there was a GDG feedback indicating that there is now more awareness of the risk of pneumonia with inhaled corticosteroid use, whilst we believe this to be	The guideline includes a recommendation which states: be aware of the potential risk of developing side effects (including

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			true, we do not think that this is universally understood across the broader community of healthcare professionals, and again would support a greater emphasis around the implications of guidelines in practice. Finally we believe that there must be a stronger emphasis on the role of public health and spirometry for at risk patients, along with a greater emphasis on end of life/supportive care for people living with advanced disease, such as the role of advanced directives. Nurses have a key role in providing hospital and community care and in supporting a more integrated approach to the care of people living with COPD and that this should be emphasised in future updates with the relevant supporting research. Thank-you.	non-fatal pneumonia) in people with COPD treated with inhaled corticosteroids and be prepared to discuss with patients. It was concluded that the new evidence identified through the surveillance review would not impact on this recommendation. Spriometry is currently recommended for use in diagnosing COPD. Specifically, the guideline recommends that all health professionals involved in the care of people with COPD should have access to spirometry and be competent in the interpretation of the results. No new evidence was identified through the surveillance review which would impact on these recommendations. In terms of end of life/supportive care, the guideline recommends that 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. Limited evidence on palliative care was

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
				identified through the surveillance review and it was felt that the new evidence was unlikely to impact on the current recommendation.
GlaxoSmithKline	Disagree		*Whilst GSK understand that the surveillance list of published evidence up to January 2014 may not lead to a decision to update the guidance at this time, there have been new therapies for COPD licensed in late 2013 and in 2014 which could lead to significant changes in COPD practice. There is now a once daily ICS/LABA licensed and LAMA/LABA combination therapies also gained their licences, giving new treatment options for COPD patients and physicians.* *There will be a substantial amount of data published during 2014 to contribute to the evidence base in a review, and any GSK data not yet published would also be made available to the clinical guidelines group. Please find below the publications planned in COPD from GSK in 2014.* *If the decision is to not update the guidelines at this time point (at the 8 year review), GSK would strongly suggest that the guidelines should be updated at the 10 year review.*	Thank you for your comment and for supplying a list of future publications. Through the surveillance review of CG101 we identified a number of studies evaluating ICS/LABA and LAMA/LABA combination therapies for COPD. In terms of ICS/LABA we concluded that the identified new evidence is broadly in line with the evidence currently included in the guideline particularly in relation to improved FEV1, reduction in exacerbations and increased risk of pneumonia. New evidence was also identified through the surveillance review relating to LAMA/LABA combination therapies which generally indicated benefits in some outcomes. The guideline currently recommends the use of LABA plus LAMA where use of inhaled corticosteroids is declined or not tolerated and no evidence was identified which would impact on this. The guideline was unable to make a recommendation on the

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			 Intended publications Anoro 20  COPD intended publications Relvar 2(	use of LABA plus LAMA in those already taking a LAMA. The reference that was submitted through consultation (Decramer et al., 2014) indicated an improvement in lung function for LAMA/LABA treatment compared with LAMA monotherapy although follow-up was only 24 weeks. Long-term comparative data is needed to confirm the results obtained. However, we agree that there is a vast amount of research in this area which is why CG101 will remain on the active surveillance list and drug treatment will be evaluated again at the next surveillance review.
College of Occupational Therapists	Agree		I am only able to comment on the elements that are relevant to my area of expertise and experience in pulmonary rehabilitation. I would agree that the evidence highlight during the surveillance process does not point to a need to change the current guidance. However, I note there are two areas not considered by this process: the delivery of COPD care bundles and post exacerbation pulmonary rehabilitation. I would recommend	Thank you for your comment. No new evidence was identified during the surtveillance review on the delivery of COPD care bundles and post exacerbation pulmonary rehabilitation. However, these areas will be examined in the next review of the guideline.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			that these are considered in future reviews.	

Appendix 2 Decision matrix

The table below provides summaries of the evidence for key questions for which studies were identified.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
101-01: 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?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-02: In individuals where the diagnosis of COPD is considered and spirometry is conducted, what are the sensitivity and specificity of a fixed ratio FEV1/FVC compared with the lower limit of normal FEV1/FVC ratio to diagnose COPD?			
None identified.	A systematic review was identified which found that the prevalence of spirometry-based COPD is greater when using the fixed value of FEV1/FVC in comparison to using the lower limit of normal (LLN).[1] As such, the review concluded that using the LLN of FEV1/FVC may underestimate COPD.	One GDG member suggested the need to consider the importance of the use of LLN rather than fixed FEV1/FVC ratio to define obstructive spirometry.	The guideline states that use of LLN was considered impractical due to lack of predictive equations and reference values for post bronchodilator FEV1 and FVC values and further research would be required to confirm the role of LNN in COPD diagnosis.
101-03: Is routine assessment using multidimensional severity assessment indices (e.g. BODE) more predictive of outcomes compared with FEV1 alone?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-04: 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?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
101-05: 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?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-06: 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?			
<u>LAMA vs. LABA</u> *Tiotropium vs. salmeterol* One RCT comparing the LAMA tiotropium (18 micrograms once daily) with the LABA salmeterol (50 micrograms twice daily) found that time to the first exacerbation was greater with tiotropium (187 days) versus salmeterol (145 days).[2] The Evidence Update reported that interpretation of this evidence in the context of the guideline is complicated by the fact that patients were allowed to continue treatment with inhaled corticosteroids during the study. As tiotropium plus ICS is not a regimen recommended in the guideline the Evidence Update was unable to conclude on the potential effect this evidence may have on current recommendations.	<u>Tiotropium versus salmeterol</u> One RCT which compared the effect of salmeterol with tiotropium on muscular efficiency in COPD found that endurance time after tiotropium treatment was significantly higher than that after placebo, whereas endurance time after salmeterol treatment was not higher than that after placebo.[6] <u>Tiotropium versus indacaterol</u> One meta-analysis evaluating the safety and efficacy of indacaterol in COPD with treatment duration of >=12 weeks found that indacaterol was superior to tiotropium, and placebo at weeks 12, 26, and 52.[7] Similarly, one systematic review found that compared with tiotropium, indacaterol showed statistically and clinically significant reductions in the use of rescue medication and dyspnea whilst trough FEV1 was significantly higher at the end of treatment with indacaterol than with other LABAs.[8] An RCT reported that the effects of indacaterol and tiotropium on FEV1 and FVC were statistically significant compared with placebo with both treatments having a similar bronchodilator effect. Finally, a post-hoc analysis of	Feedback from the GDG highlighted that there are now more data on the choice between LABA and LAMA as first line therapy and also about the safety of inhaled corticosteroids and bronchodilators.	In summary, some evidence comparing LAMA versus LABA indicates that the LABA indacaterol is non-inferior to the LAMA tiotropium and may be superior in certain outcomes. Conversely, a study comparing tiotropium with LABAs found the LAMA to be more effective whilst other studies comparing tiotropium with a range of LABA treatments indicated that these have comparable efficacy. Currently there is insufficient evidence that conclusively indicates superiority of one treatment over the other and, from an assessment

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
Indacaterol vs. tiotropium INTENSITY, was a 3-month non-inferiority RCT which compared indacaterol 150 micrograms and tiotropium 18 micrograms, both once daily.[3] The mean difference in TDI score between the two treatments was less than the MCID of 1 point indicated by the guideline. INHANCE was a 26-week RCT including patients who received indacaterol 150 or 300 micrograms or placebo daily, or open-label tiotropium 18 micrograms once daily.[4] At week 12, both doses of indacaterol improved trough FEV compared to placebo. Both indacaterol doses were stated to be statistically significant for non-inferiority to tiotropium for trough FEV at 12 weeks. However, the 40 ml difference in improvement in mean trough FEV over placebo between tiotropium and indacaterol was substantially less than than MCID of 100 ml indicated by CG101. Indacaterol vs. salmeterol Indacaterol 150 micrograms daily was compared with salmeterol 50	pooled data from clinical studies found that both indacaterol and tiotropium had similar effects in people with less dyspnoea however, indacaterol mproved trough FEV1, transition dyspnoea index total score at week 26 and decreased the risk of COPD exacerbations compared to placebo in people with more dyspnoea.[9] Tiotropium versus indacaterol; salmeterol; formoterol A post-hoc analysis investigated efficacy and safety of indacaterol compared with placebo and other long-acting bronchodilators (formoterol, salmeterol, open-label tiotropium) in patient subgroups defined by COPD severity.[10] All active treatments significantly improved trough FEV1 and dyspnoea compared with placebo although indacaterol had the best overall efficacy in GOLD II and GOLD III subgroups. Furthermore, the results of an individual patient data network meta-analysis indicated that indacaterol was at least as efficacious as formoterol and comparable to tiotropium and salmeterol regarding FEV1.[11] Tiotropium versus LABA One systematic review compared the efficacy of tiotropium bromide alone versus LABA alone for COPD.[12] Tiotropium was more effective than LABAs as a group in preventing COPD exacerbations and disease-related hospitalisations, although there were no statistical differences between groups in overall		of the abstracts it is not clear what the FEV1% of the included populations was. 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 and it is unlikely that the new evidence would change this recommendation.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
micrograms twice daily in INSIST, a 12-week RCT.[5] Indacaterol was statistically superior to salmeterol for trough FEV at 12 weeks. Indacaterol also produced a statistically superior improvement in TDI but this was less than the MCID of 1 point indicated by CG101. The Evidence Update concluded that indacaterol therapy may be a potential consideration for future reviews of CG101.	hospitalisation rates or mortality during the study periods. In addition, one systematic review compared the risk of overall and cardiovascular death in people with COPD receiving tiotropium Soft Mist Inhaler, tiotropium HandiHaler, LABAs, inhaled corticosteroids (ICS), and LABA-ICS combination with at least a 6-month treatment duration.[13] The results of a network meta-analysis indicated that tiotropium Soft Mist Inhaler was associated with a universally increased risk of overall death (particularly in people with more severe COPD) compared with placebo, tiotropium HandiHaler, LABA and LABA-ICS. LABA-ICS was associated with the lowest risk of death among all treatments no excess risk was noted for tiotropium HandiHaler or LABA. <u>Salmeterol versus GSK961081</u> One RCT compared GSK961081, a bifunctional molecule demonstrating both muscarinic antagonist and beta-agonist activities, with salmeterol and placebo.[14] The results indicated that GSK961081 showed statistically and clinically significant differences from placebo in all doses and regimens for trough FEV1 on day 29 however, further research on investigating the long-term impact of this agent is needed.		
101-07: 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?			

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
A meta-analysis investigated the safety and efficacy of combined LABA plus ICS versus LABA monotherapy in stable COPD.[15] Compared with LABA monotherapy, LABA plus ICS did not significantly reduce severe exacerbations or all-cause mortality. These findings largely agree with the TORCH study of LABA plus ICS, which did not establish a clear link between the combination regimen and reduced mortality versus LABA alone but did find that exacerbations were reduced.[16] The Evidence Update concluded that the evidence suggests that LABA plus ICS reduce moderate exacerbations, in line with the intent of this regimen in CG101, and are associated with a known risk of pneumonia as already stated in current guidance. However it remains unclear if mortality is reduced. It was felt that this evidence is unlikely to affect current guideline recommendations.	<u>Inhaled corticosteroid plus LABA versus LABA alone</u> Two Cochrane systematic reviews indicated that combined inhaled corticosteroids and LABA for COPD led to fewer exacerbations of COPD.[17,18] There was no significant difference in mortality between people on combined inhalers and those on LABA although pneumonia was more common in the combination group.[17] Conversely, one RCT concluded that two bronchodilators decreased hyperinflation significantly more than one bronchodilator and an inhaled corticosteroid.[19] <u>Beclometasone plus LABA</u> The results of a Cochrane systematic review and a small RCT indicated that a combination of beclomethasone and formoterol improved total lung capacity and dyspnea in people with COPD but there was also an indication that combination therapy leads to a significantly increased rate of exacerbations leading to hospitalisation.[20,21] <u>Fluticasone plus salmeterol</u> One RCT comparing inhaled fluticasone/salmeterol combination (FSC) in mild to moderate COPD reported that, compared with placebo, FSC improved FEV1 and inspiratory capacity but did not change dyspnea intensity.[22] Furthermore, the results of a post-hoc cluster analysis indicated that salmeterol/fluticasone propionate significantly reduced the annual rate of moderate/severe exacerbations as	Clinical feedback stated that recent data indicates 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. In addition, the GDG made reference to newer LABAs, LAMAs, LAMA-LABA and LABA-ICS treatments, indicating there may be a requirement to review stratification of therapies and health economics. Finally, the GDG highlighted that a very large mortality trial with LABA-ICS drugs should report by 2016.	In summary, the identified new evidence is broadly in line with the evidence currently included in the guideline particularly in relation to improved FEV1, reduction in exacerbations and increased risk of pneumonia.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	compared with salmeterol alone.[23] <u>Mometasone furoate plus formoterol fumarate</u> Three RCTs reported that combination of mometasone furoate and formoterol fumarate improved lung function and reduced exacerbations in people with COPD.[24-26] <u>Budesonide plus formoterol</u> The results of 4 RCTs and one systematic review indicated that budesonide/formoterol combination therapy improved lung function and COPD symptoms and may reduce exacerbation rates although pneumonia was more common.[27-32] Conversely, the results of a network meta-analysis comparing the efficacy of indacaterol to combined formoterol and budesonide and salmeterol and fluticasone for the treatment of COPD indicated higher change from baseline in FEV1 in the indacaterol group.[33] <u>Fluticasone furoate plus vilanterol</u> Four RCTs evaluating fluticasone furoate plus vilanterol for COPD indicated that this treatment improved FEV1 and may reduce COPD exacerbations.[34-37]		
101-08: 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?			
None identified.	No new evidence identified.	None identified.	No relevant evidence

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
			identified.
101-09: 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?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-10: 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?			
None identified.	Four RCTs and two 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.[38-43] Conversely, a Cochrane systematic review assessing the relative effects of inhaled corticosteroid plus LABA and tiotropium alone identified only limited data and concluded that there was uncertainty regarding the long-term benefits and risks of triple therapy.[44]	None identified.	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.
101-11: 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?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-12: 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?			
None identified.	<u>Tiotropium plus LABA</u> The results of two RCTs and a Cochrane systematic review comparing tiotropium plus LABA with LABA or LAMA alone were mixed.[45-47] The review found no	None identified.	In summary, the identified new evidence generally indicated benefits in some outcomes for combination

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	significant differences between the groups for several outcomes including exacerbations, symptom scores, serious adverse events, and withdrawals.[47] One RCT reported improved inspiratory muscle strength compared with LABA[45] whilst another RCT indicated that dual therapy improved walking distance compared with LAMA but there was no significant difference in FEV1 between the two groups.[46] <u>Indacaterol plus glycopyrronium</u> Two RCTs reported that combination treatment with indacaterol and glycopyrronium induced sustained bronchodilation compared with placebo[48] and reduced the rate of moderate to severe exacerbations versus glycopyrronium.[49] <u>Umeclidinium plus vilanterol</u> The efficacy and safety of the LAMA/LABA combination umeclidinium/vilanterol (UMEC/VI) compared with monotherapies in people with COPD was evaluated in an RCT.[50] All active treatments produced significant improvements in trough FEV 1 compared with placebo although increases with UMEC/VI were significantly greater than with monotherapies.		therapy with a LABA and a LAMA. The guideline currently recommends the use of LABA plus LAMA where use of inhaled corticosteroids is declined or not tolerated and no evidence was identified which would impact on this. The guideline was unable to make a recommendation on the use of LABA plus LAMA in those already taking a LAMA. Currently, there is still insufficient consistent evidence available to determine whether there is an added benefit of dual therapy over LAMA monotherapy.
101-13: 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?			
A meta-analysis compared a combined	A post-hoc analysis[52] and four RCTs indicated	None identified.	This new evidence

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
regimen of the long-acting muscarinic antagonist (LAMA) tiotropium plus a LABA (formoterol) with tiotropium alone in stable COPD.[51] 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.	improvements in dyspnea[53], FEV1[54,55] and exercise capacity[56] in people with COPD being treated with a LAMA plus LABA. This new evidence supports the guideline recommendations which state 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.		supports the guideline recommendations which state 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.
101-14: 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?			
None identified.	An RCT comparing salmeterol-fluticasone with indacaterol combined with glycopyrronium in people with moderate to severe COPD reported significantly higher FEV1 in the indacaterol/glycopyrronium group.[57] NICE has published an Evidence Summary (ESNM33 Chronic obstructive pulmonary disease: indacaterol/glycopyrronium (Ultibro Breezhaler)) on the indacaterol/glycopyrronium (Ultibro Breezhaler) which is the first LABA/LAMA combination inhaler to be approved for COPD. It is licensed as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD and is expected to be launched in the UK in quarter 2, 2014. Although some	The GDG stated that there is more data to come out on patient reported outcomes and exacerbations with dual bronchodilation as the issue is whether dual bronchodilation should be used in preference to LABA/ICS in more severe disease. These studies are currently on going and will not report before 2015. It was suggested tha these studies are important for positioning PDE4 (roflumilast) inhibitors	During development of the guideline the GDG decided not to make a recommendation due to lack of evidence. Although one RCT was identified in the surveillance review comparing LABA+LAMA versus LABA+ICS, further research is needed to confirm the results obtained over a longer time period. In addition, ESNM33 Chronic obstructive pulmonary

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	small statistically significant improvements in lung function, dyspnoea (breathlessness), 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 and the Evidence Summary concluded that indacaterol/glycopyrronium's place in therapy is currently difficult to assess. Patients are currently being recruited for a 52-week study comparing the effects of indacaterol/glycopyrronium and fluticasone/salmeterol on exacerbations in people with moderate to very severe COPD and this study is likely to provide better longer-term comparative safety data for the 2 treatments.	and it may be pertinent to wait untill these studies are published before considering an update.	disease: indacaterol/glycopyrronium (Ultibro Breezhaler) highlighted that long-term comparative data is likely to be provided by an ongoing trial comparing indacaterol/glycopyrronium and fluticasone/salmeterol.
101-15: 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?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-16: 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?			
None identified.	One RCT comparing a single-dose of salbutamol/ipratropium + flunisolide added to regular treatment found no improvement in endurance time in people with COPD.[58] This study did not compare the intervention with an active treatment, such as a LAMA or a LABA and therefore is unlikely to impact the recommendations.	None identified.	The identified study did not compare the intervention with an active treatment, such as a LAMA or a LABA and therefore is unlikely to impact the recommendations.
101-17: What is the clinical and cost effectiveness of mucolytic agents vs. placebo in people with stable COPD?			

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-18: 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?			
None identified.	No new evidence identified.	Clinical feedback indicated that further studies are in development to examine the effect of early pulmonary rehabilitation post exacerbation.	No relevant evidence identified.
101-19: What is a useful, robust definition of COPD?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-20: Must the definition of COPD include the presence of airflow obstruction?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-21: Must the definition of COPD include reversibility criteria?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-22: Must the definition of COPD discuss causation and pathophysiology?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-23: What is the current and future burden of COPD in England & Wales?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-24: Can COPD be detected before the onset of symptoms?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
101-25: What factors can be used to identify patients opportunistically as being at risk of having COPD?*			
None identified. A meta-analysis found that the presence of residential dampness and mould may be linked with both bronchitis and respiratory tract infections.[59] Several limitations were identified with the study design however, the EUAG felt that the evidence suggests that dampness and mould in the home 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. Some patients with COPD may feel that their ill health is linked to domestic mould or dampness, and in light of this evidence further research may be warranted. This is an area that is not currently addressed by CG101.	One RCT compared the effectiveness of two strategies for population-based early detection of COPD.[60] In the practice-managed condition, the practice was responsible for the whole procedure, while in the patient-managed condition, patients were responsible for calculating their Respiratory Health Screening Questionnaire (RHSQ) risk score and applying for a spirometry test. The results indicated that more new COPD patients were detected in the practice-managed condition (36%) than in the patient-managed condition (18%). One study investigated the impact of the COPD Assessment Test (CAT) on the quality of primary care consultations in COPD patients.[61] The results indicated that the CAT did aid physician assessment of COPD.	None identified.	Further research is required to confirm the results of these studies before considering the COPD Assessment Test and other strategies for detection of COPD for inclusion in the guideline.
101-26: What methods can be used to confirm the diagnosis in patients identified opportunistically as being at risk of having COPD?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-27: Does early diagnosis of COPD affect the success of smoking cessation therapy?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
101-28: What are the aims of COPD management?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-29: What symptoms are suggestive of a diagnosis of COPD?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-30: What other conditions may present with similar symptoms/signs/results?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-31: In patients with suspected COPD, what are the most effective diagnostic criteria?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-32: What clinical signs are useful (confirm or refute the diagnosis) in stable COPD?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-33: What are the most appropriate tests in a patient with suspected COPD to confirm the diagnosis?*			
None identified.	One meta-analysis evaluated the accuracy of computed tomography (CT) in diagnosing COPD and reported that CT may improve the accuracy of diagnosis.[62] A CT scan is already recommended as a tool to aid investigations in some circumstances and this new evidence supports that recommendation. One systematic review evaluated the use of (18)F-fluorodeoxyglucose positron emission tomography ((18)F-FDG-PET) in the management of COPD.[63] The results indicated that (18)F-FDG-PET) may be useful in differentiating COPD from other diseases. However, further research is needed before considering for inclusion in the guideline.	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.	A CT scan is already recommended as a tool to aid investigations in some circumstances and the identified new evidence supports that recommendation. In terms of (18)F-FDG-PET), further research is needed before considering for inclusion in the guideline.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
101-34: What is the role of spirometry in the diagnosis of COPD?			
None identified.	The quality and reproducibility of spirometry in people with COPD was assessed within a trial.[64] The quality of spirometry in this trial was found to be acceptable and improved over time.	None identified.	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.
101-35: Where and by whom should spirometry be performed in order to maximise reliable and valid test result outcomes?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-36: What is the role of reversibility testing in the diagnosis of COPD?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-37: What is the role of reversibility testing in the prediction of response to COPD drugs?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-38: What is the role of other lung function tests in the diagnosis of COPD? (IRC, TLCO,KCO, Lung Volumes)*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-39: How should the severity of stable COPD be assessed?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-40: In patients with stable COPD, how should the (initial) management plan be determined?*			

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-41: Which patients with stable COPD should be referred for specialist advice?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-42: Which patients with stable COPD should be referred for an oxygen assessment?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-43: What is the most appropriate smoking cessation strategy in patients with stable COPD?			
<u>Benefits of stopping smoking</u> A meta-analysis examined decline in FEV among never smokers, continued smokers, ex-smokers and quitters (those who discontinued smoking between recruitment and follow up) but was unable to confirm the relative benefits of smoking cessation at different stages of COPD severity.[65] However, an observational study found that patients continuing to smoke were at greater risk of marked disease progression irrespective of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage.[66] Furthermore, the EUAG felt that established link between smoking and death from cardiovascular disease adds further weight to this argument.[67]	Two RCTs[69,70] and a systematic review[71] found that varenicline was an efficacious smoking cessation strategy although it may be associated with an increased risk of psychiatric side effects.[71] Furthermore, a probabilistic sensitivity analysis from the perspective of the healthcare systems of Spain (base case), the UK, France, Germany, Greece and Italy suggested varenicline had a high probability (>95%) of being cost-effective at a threshold of 30,000/QALY.[72] Furthermore, two systematic reviews[73,74] reported that psychosocial interventions combined with pharmacotherapy may be effective in smoking cessation although the effect was not statistically significant in one review.[74] Lastly, a cost-effectiveness analysis based on an RCT investigated the cost-effectiveness of a high-intensity smoking cessation program (SmokeStop Therapy; SST) versus a medium-intensity treatment (Minimal Intervention Strategy for Lung patients [LMIS]) for	None identified.	Taken together, this new evidence supports the current guideline recommendation which states: unless contraindicated, offer NRT, varenicline or bupropion, as appropriate, to people who are planning to stop smoking combined with an appropriate support programme to optimise smoking quit rates for people with COPD.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
The Evidence Update concluded that these studies strenghthen the messages on smoking cessation in the guideline and indicate that even in severe COPD, stopping smoking may be of benefit. <u>Smoking cessation therapy</u> A network meta-analysis found that smoking cessation counselling (SCC) plus nicotine replacement therapy (NRT) was deemed most effective with SCC plus antidepressant in second place.[68] The Evidence Update concluded that SCC plus either NRT or antidepressant both are equally effective smoking cessation interventions to offer patients, and there is little evidence for the superiority of high-intensity over low-intensity counselling. The guideline currently recommends that pharmacological therapy with appropriate support should be offered and the evidence included in the Evidence Update was deemed unlikely to impact on this recommendation.	COPD.[75] The high-intensive SST was more cost-effective than the medium-intensive LMIS after 1 year. However, as the components of the programmes were not reported in the abstract any impact on the guideline is unclear.		
101-44: Which patients with stable COPD should be treated with short-acting beta2-agonists? How should the effects of this treatment be assessed?			
None identified.	No new evidence identified.	None identified.	No relevant evidence

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
			identified.
101-45: Which patients with stable COPD should be treated with short-acting anticholinergics? How should the effects of this treatment be assessed?			
None identified.	An RCT assessed the effectiveness of nurse-initiated use of albuterol metered-dose inhaler for relieving the signs and symptoms of acute exacerbations of COPD.[76] The oxygen saturation and symptom of dyspnoea improved in the albuterol group but not in the control group.	None identified.	The new evidence is unlikely to change the direction of the recommendation which states that short-acting bronchodilators, as necessary, should be the initial empirical treatment for the relief of breathlessness and exercise limitation.
101-46: Which patients with stable COPD should be treated with long-acting beta2-agonists? How should the effects of this treatment be assessed?			
<u>LABA vs. placebo</u> *Indacaterol vs. placebo* The INDORSE trial, a 26-week extension to INHANCE, was conducted among patients randomised to either dose of indacaterol or to placebo in that trial.[77] Difference in trough FEV from placebo at 52 weeks was 170 ml for patients receiving indacaterol 150 micrograms and 180 ml for patients receiving indacaterol 300 micrograms. Hazard ratios for time to first exacerbation were not	Eighteen RCTs[39,80-96], two post-hoc analyses[10,97] and three systematic reviews[98-100] were identified which indicated that LABAs are effective in people with COPD. Studies comparing different LABAs generally indicated that indacaterol may be more effective[11,28,101-103] although systematic reviews indicated that the efficacy of indacaterol was similar to other LABAs including formoterol and salmeterol.[104,105] The use of LABAs in people with FEV1 ≥ 50% predicted is recommended in people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators and no evidence was identified which	None identified.	Since the guideline was published additional LABAs (including indacaterol) have been licensed for use in the UK however, the studies comparing LABAs have reported inconsistent results. Therefore, there is currently insufficient consistent evidence to include details on the use of specific LABAs in the guideline.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
statistically significantly different from placebo, although exacerbation rates were lower in the indacaterol groups. <u>LABA vs. LABA</u> *Indacaterol vs. formoterol* The INVOLVE RCT was included which compared indacaterol 300 and 600 micrograms once daily, formoterol 12 micrograms twice daily and placebo for 52-weeks.[78] Both doses of indacaterol produced increases in FEVover placebo 100 ml greater than that produced by formoterol, but the clinical relevance of this difference was questioned by the European Medicines Agency. All active treatments were statistically significantly superior to placebo. *Indacaterol vs. salmeterol* Indacaterol 150 micrograms daily was compared with salmeterol 50 micrograms twice daily in INSIST, a 12-week RCT.[5] Indacaterol was statistically superior to salmeterol for trough FEV at 12 weeks. Indacaterol also produced a statistically superior improvement in TDI but this was less	would change the direction of this recommendation.		

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
than the MCID of 1 point indicated by CG101. Indacaterol 150 micrograms daily was compared with salmeterol 50 micrograms twice daily and placebo in INLIGHT-2, a 6-month RCT. (2011).[79] Indacaterol improved trough FEV compared with placebo at 12 weeks. Indacaterol produced a statistically superior improvement in TDI at 4 weeks and 12 weeks, but not at 26 weeks. This is less than the MCID of 1 point indicated in CG101. *Indacaterol vs. formoterol and salmeterol* A safety meta-analysis pooled data from all published and unpublished studies of indacaterol in COPD of at least 12 weeks duration completed at the time of the analysis.[4] The risks of acute respiratory serious adverse events (leading to hospitalisation, intubation, or death), and major adverse cardiovascular events were not significantly different from placebo with any of the active treatments. The Evidence Update concluded that			

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
indacaterol therapy may be a potential consideration for future reviews of CG101.			
101-47: Which patients with stable COPD should be treated with long-acting anticholinergics? How should the effects of this treatment be assessed?			
A meta-analysis[106] and an RCT included in the analysis[107] found no increased risk of cardiovascular events or mortality when tiotropium was delivered via a dry-powder inhaler compared with placebo. The results of one meta-analysis indicated that there may be safety issues with tiotropium when delivered via mist inhaler (Spiriva Respimat).[108] The Evidence Update concluded that the potential safety issues with tiotropium via mist inhaler may be a consideration for future reviews of CG101, particularly for patients with cardiovascular disease. A Rapid Review by the Medicines Prescribing Centre describes the increased risk of safety issues when using tiotropium but advices health professionals looking after people with COPD should continue to follow NICE guidance [*long-acting bronchodilator (either a*	Twenty one RCTs[109-129] and five systematic reviews[130-134] were identified which indicated that LAMAs are effective in people with COPD. Furthermore, a cost-utility analysis 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%.[135] Studies which compared LAMAs suggested that tiotropium may be more effective[136] whilst others reported that tiotropium and aclidinium may be comparable.[137,138] In other studies there was an indication that concomitant treatment of two LAMAs[139] or a SAMA/LAMA[140] may be efficacious although the risk of adverse events was greater.[139]	None identified.	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. Since the guideline was published additional LAMAs (including aclidinium) have been licensed for use in the UK however, the studies comparing LAMAs have reported inconsistent results. NICE has published two Evidence

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
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]. NICE does not give preference to either tiotropium or LABA. The MPC advises health professionals to follow current MHRA advice on tiotropium Respimat. This 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 by Boehringer Ingelheim Pharmaceuticals was underway to investigate concerns with tiotropium delivery via mist inhaler. This study is now stated as completed on Clinicaltrials.gov and a relevant publication is provided: Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B, Dusser D, Joseph E, Kattenbeck S, Koenen-Bergmann M, Pledger G, Calverley P; TIOSPIR Investigators. Tiotropium Respimat inhaler and the risk of death in COPD. N Engl J Med. 2013 Oct			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 bromide and glycopyrronium bromide with other active treatments for COPD would enable their place in therapy to be more clearly established. Currently there is insufficient consistent evidence to include details on the use of specific LAMAs in the guideline.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
17;369(16):1491-501. doi: 10.1056/NEJMoa1303342. Epub 2013 Aug 30. Results indicated that tiotropium Respimat at a dose of 5 µg or 2.5 µg had a safety profile and exacerbation efficacy similar to those of tiotropium HandiHaler at a dose of 18 µg in patients with COPD.			
101-48: Which patients with stable COPD should be treated with methylxanthines / PDE4 inhibitors? How should the effects of this treatment be assessed?			
The Evidence Update highlighted that NICE technology appraisal 244 has recently recommended roflumilast 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. The Evidence Update states that this should be referred to as the latest guidance.	The included new evidence on PDE4 inhibitors was mixed with some systematic reviews and RCTs reporting only a modest benefit or insufficient evidence of benefit[141-146] whilst other studies indicated the efficacy and safety of roflumilast for COPD.[147-151] The results of a network meta-analysis indicated that the combination of roflumilast plus LAMA exhibited the largest treatment effects, and had the highest probability of being the best first-line treatment.[152] The majority of the studies included people with different disease severity, compared roflumilast to placebo as opposed to active treatment and many indicated that further research is needed to confirm the long-term benefits and harms of PDE4 inhibitors for COPD.	Clinical feedback indicated that studies on PDE4 inhibitors, particularly roflumilast, are ongoing.	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 has been developed (TA244 Roflumilast for the management of severe chronic obstructive pulmonary disease, 2012) which states: • Roflumilast is recommended only in the context of research as part of a clinical

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
			trial for adults with severe chronic obstructive pulmonary disease (COPD) (for the purposes of this guidance defined as forced expiratory volume in 1 second [FEV1] post-bronchodilator less than 50% predicted) associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment. • Such research should be designed to generate robust evidence about the benefits of roflumilast as an

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
			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. • People receiving roflumilast should have the option to continue treatment until they and their clinicians consider it appropriate to stop. This Technology Appraisal has been included in the COPD pathway within the oral therapy section for the treatment of stable COPD.
101-49: Which patients with stable COPD should be treated with inhaled steroids? How should the effects of this treatment be assessed?			

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
None identified.	A Cochrane systematic review assessing the efficacy and safety of inhaled corticosteroids in stable patients with COPD indicated that this intervention leads to a reduced rate of exacerbations, reduced rate of decline in quality of life and possibly reduced rate of decline in FEV1 although there was an increase in rate of pneumonia.[153] Similarly, a benefit of inhaled fluticasone propionate monotherapy was observed in a small RCT.[154] Nonetheless, the results of a systematic review indicated that withdrawing inhaled corticosteroids in routine practice does not result in important deterioration in patient outcomes in people with COPD.[155] Additionally, a Cochrane systematic review reported no significant difference in the number of patients experiencing exacerbations or the rate of exacerbations per patient year between inhaled corticosteroids and LABAs.[156] Lastly, a systematic review reported that currently available economic evaluations indicate differences in cost effectiveness between COPD maintenance therapies.[157] Two Cochrane systematic reviews reported an increase in rate of pneumonia following use of inhaled steroids[153,158] whilst the results of another systematic review indicated that inhaled corticosteroids use was not consistently associated with reduced mortality from pneumonia in people with COPD.[159] An increased fracture risk was reported in one systematic review.[160]	GDG feedback indicated there is now more awareness of pneumonia with inhaled corticosteroid use.	The identified new evidence is broadly in line with the recommendation in the guideline which states 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. 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 advice about inhaled steroids as monotherapy. Insufficient consistent new evidence was identified to suggest that monotherapy with inhaled corticosteroids should be reassessed.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
101-50: Which patients with stable COPD should be treated with oral steroids? How should the effects of this treatment be assessed?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-51: What is the role of combination therapy in patients with stable COPD? How should the effects of this treatment be assessed?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-52: What are the most appropriate delivery systems for giving inhaled therapy to patients with stable COPD?			
None identified.	One systematic review reported that the Respimat inhaler does not provide any additional clinical benefit to that provided by other inhaler devices in the management of COPD.[161] One crossover RCT assessed the safety and efficacy of a new oscillatory device as add-on therapy for COPD reporting that this device was found to improve 6 minute walk performance, pulmonary function and HRQoL.[162] Lastly, one RCT evaluated patient satisfaction, device usage, and long-term safety of Ipratropium bromide/albuterol Respimat inhaler (CVT-R) compared to ipratropium bromide/albuterol metered-dose inhaler (CVT-MDI).[163] Time to first COPD exacerbation was slightly longer in the CVT-R group compared to the other treatment groups, although it did not reach statistical significance.	None identified.	The identified new evidence evaluated a range of different delivery systems but, although the studies reported on 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.
101-53: Which patients with stable COPD benefit from nebulised therapy compared to other delivery mechanisms?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-54: What is the role of mucolytic therapy in patients with stable COPD?			
None identified.	No new evidence identified.	None identified.	No relevant evidence

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
			identified.
101-55: In patients with stable COPD, what is the comparative efficacy of mucolytic therapy?			
None identified.	One Cochrane review investigated whether treatment with mucolytics reduces the frequency of exacerbations in COPD.[164] The results indicated that in people with COPD, treatment with a mucolytic produced a small reduction in acute exacerbations, but had little or no effect on the overall quality of life. Furthermore, one RCT compared high-dose N-acetylcysteine (NAC) compared with placebo for stable COPD.[165] At 1 year, there was a significant improvement in forced expiratory flow, forced oscillation technique and a significant reduction in exacerbation frequency in the NAC group.	None identified.	In summary, the identified new evidence included N-acetylcysteine (a drug currently without a UK marketing authorisation for use as a mucolytic) and comparisons were with placebo (and not other known effective therapies). As such, there is currently insufficient new evidence to recommend the routine use of mucolytics primarily for the purpose of preventing exacerbations therefore, the current guideline recommendations are unlikely to be impacted.
101-56: In patients with stable COPD, does mucolytic therapy reduce morbidity?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-57: What is the role of antioxidant therapy in patients with stable COPD?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
101-58: In patients with stable COPD, what is the comparative efficacy of antioxidant therapy?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-59: In patients with stable COPD, does antioxidant therapy reduce morbidity?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-60: What is the role of antitussive therapy in patients with stable COPD?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-61: In patients with stable COPD, what is the comparative efficacy of antitussive therapy?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-62: In patients with stable COPD, does antitussive therapy reduce morbidity?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-63: What is the role of 1-antitrypsin replacement therapy in patients with stable COPD?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-64: What is the role of antibiotic therapy in patients with stable COPD?			
None identified.	Four systematic reviews[166-169] and two RCTs[170,171] investigated the use of prophylactic antibiotics to prevent exacerbations of COPD. The studies generally indicated that the frequency of exacerbations was reduced in the antibiotic treatment groups compared with placebo and adverse events were greater although no significant effect on mortality was reported. One review indicated that the specific antibiotic used and the length of therapy (more than 6 months) had an impact on exacerbation frequency.[169]	None identified.	From an assessment of abstracts it was not clear whether the studies included patients with the same level of severity of COPD (mild, moderate, severe or very severe) which would impact on the exacerbation risk. Further research is needed in

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
			specific COPD populations to determine whether the benefits of prophylactic antibiotic treatment outweigh the risk of adverse events before considering updating the current recommendation which states that there is insufficient evidence to recommend prophylactic antibiotic therapy in the management of stable COPD.
101-65: What are the benefits of pulmonary rehabilitation programmes for patients with stable COPD?			
None identified.	Several RCTs reported beneficial effects of pulmonary rehabilitation in people with COPD including improvements in walking distance and leg strength[172]; improvement in the 6 minute walk test and QoL[173] and improvements in the affective and impact domains of dyspnea.[174] Furthermore, the results of a systematic review indicated that pulmonary rehabilitation promotes behavioural changes towards health promotion in people with COPD.[175] Conversely, the results of one RCT did not show meaningful changes in QoL, exercise tolerance, pulmonary function or exacerbation after a one-year, community based	None identified.	The identified new evidence broadly supports the use of pulmonary rehabilitation in people with COPD and is in line with the current recommendations which state that pulmonary rehabilitation should be offered.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	rehabilitation programme.[176] One systematic review reported a lack of perceived benefit of pulmonary rehabilitation, travel and transport as factors influencing both uptake and completion.[177]		
101-66: In stable COPD patients referred for pulmonary rehabilitation programmes, what is the optimal course content, setting & duration?			
<u>Duration</u> The Evidence Update included a systematic review which evaluated the optimal duration of pulmonary rehabilitation in people with COPD.[178] The review reported limited evidence which suggested that longer duration rehabilitation programmes are of greater benefit than those of a shorter length. The Evidence Update concluded that although some of the evidence suggested greater benefit of longer rehabilitation programmes, limitations of the review including the absence of a meta-analysis, and lack of clinical significance with some outcomes, meant that current recommendations in CG101 are unlikely to be affected. <u>Setting</u> The Evidence Update included a trial which compared pulmonary	<u>Duration</u> One systematic review reported that rehabilitation programs showed positive effects on all of the outcomes evaluated, except for mortality[183] whilst a Cochrane systematic review concluded that integrated disease management programmes or interventions in people with COPD reduced hospitalisation days.[184] One RCT indicated that a long-term pulmonary rehabilitation programme may result in improvements in physical capabilities and HRQoL compared to standard care.[185] Potential barriers to uptake of pulmonary rehabilitation programmes in people with COPD were investigated in a systematic review and included changing health status, personal issues, lack of support, external factors and ongoing smoking.[186] <u>Setting</u> The effectiveness of in-home rehabilitation programs (including aerobic conditioning or functional strength training) for individuals with COPD considered homebound was assessed in an RCT.[187] Both groups had significant improvements in the CRQ-dyspnea domain whilst depression scores although a significant	One GDG questionnaire respondent felt there are inequalities in access to services specifically that COPD patients do not have equal access to pulmonary rehabilitation.	In summary, new evidence was identified focusing on individual components of pulmonary rehabilitation programmes with the results indicating a benefit specifically from exercise, neuromuscular electrical stimulation and whole body vibration training. This 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

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
rehabilitation in a hospital versus community setting.[179] The results suggested that there seems to be no clinical or cost benefit of community-based 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. Course content A meta-analysis looked at the effect of inspiratory muscle training (IMT) in patients with COPD.[180] Significant improvements were found in a number of outcomes including maximal inspiratory muscle strength and respiratory muscle endurance time. One review also investigated IMT as part of a systematic review of home-based physiotherapy interventions.[181] The Evidence Update concluded that although the analysis suggested that home-based IMT may be effective, because of potential limitations of the evidence (limited numbers of patients and treatment heterogeneity between studies), more research is needed to determine whether IMT can be added	improvement in walking distance was observed in the aerobic conditioning group only. Course content *Ambulatory oxygen use* The effect of ambulatory oxygen use during pulmonary rehabilitation for COPD was evaluated in an RCT.[188] Patients in the oxygen group demonstrated a significantly greater mean improvement in endurance walking distance than those in the pulmonary rehabilitation only group. *Pharmacological therapies during pulmonary rehabilitation* One RCT comparing inhaled procaterol on exercise therapy for pulmonary rehabilitation with rehabilitation alone in COPD suggested that those receiving inhaled procaterol showed significant improvement of 6 minute walking distance and St. George's respiratory questionnaire scores.[189] Additionally, the efficacy and safety of adding ghrelin to pulmonary rehabilitation was evaluated in two RCTs.[190,191] Both studies reported improvement in exercise outcomes although the difference compared with placebo was not signfificant. *Neuromuscular electrical stimulation* The results of four small RCTs indicated that neuromuscular electrical stimulation may have a beneficial effect in preventing muscle function		should incorporate a programme of physical training, disease education, nutritional, psychological and behavioural intervention.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
to or substituted for standard pulmonary rehabilitation techniques, before firm recommendations can be made. The EUAG felt the evidence suggests the potential of IMT in pulmonary rehabilitation, but may not yet provide definitive answers as to whether IMT should be added to other forms of rehabilitation, and especially as to whether there is a subgroup of patients with inspiratory muscle weakness who may benefit. As such, the Evidence Update noted that further research is needed to evaluate IMT and whether those with muscle weakness can feasibly be identified and treated effectively with this intervention. An RCT investigated the effect of Nordic walking (a walking technique involving specialised poles) on daily physical activities in people with COPD.[182] This was considered preliminary evidence suggesting that Nordic walking may be a useful addition to current pulmonary rehabilitation strategies but larger studies are needed comparing the	deterioration in people with COPD.[192-195] *Whole body vibration training* Two RCTs reported a significant increase in the 6 minute walking test in people with COPD who received whole body vibration training during pulmonary rehabilitation programmes.[196,197] *Respiratory training* One RCT reported beneficial effects on the 6 minute walking distance and dyspnoea of a respiratory training programme as pulmonary rehabilitation for COPD.[198] In addition, a Cochrane systematic review 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.[199] Lastly, an RCT comparing singing classes to 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.[200] *Exercise sessions* A large amount of evidence on exercise was identified which generally indicated a beneficial effect as part of a pulmonary rehabilitation programme in COPD.[201-203] Specific effective exercise interventions included water based training[204-206]; an aerobic physical training		

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
intervention with other techniques, and looking at additional, longer term outcomes such as survival, resource usage and patient satisfaction. The EUAG felt are no current implications for CG101.	programme[207]; arm exercise training[208,209]; urban walking circuits[210]; combined strength training and endurance training[211-213]; floor exercises[214]; resistance training.[215] Lastly, the results of a Cochrane systematic review indicated no significant differences in endurance time improvement and six minute walk distance improvement following higher or lower-intensity training.[216] *Manual therapy* A systematic review concluded there was insufficient evidence on manual therapy to recommend this as an approach for COPD[217] whilst a small-scale RCT indicated only small improvements in distance walked and dyspnea levels in people receiving manual therapy and exercise.[218] Lastly, one RCT evaluating the effect of rib cage mobilisation on lung function in people with COPD found that this intervention increased FEV1/FVC ratio and Dyspnea index significantly compared with a control group.[219] *Structured education* The effectiveness of a structured education pulmonary rehabilitation programme compared with usual care on the health status of people with COPD was evaluated in an RCT.[220] Participants allocated to the intervention group had statistically significant higher mean change total Chronic Respiratory Questionnaire scores. In addition, the cost-effectiveness of a structured education pulmonary rehabilitation programme		

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	compared with usual care for COPD was assessed in one study however, no evidence was identified when effectiveness was measured in QALYS gained.[221] *Improving mobility* One RCT evaluated the use of a rollator compared with a modern draisine in improving mobility in people with COPD.[222] Walking with the modern draisine resulted in a higher 6 minute walking distance compared with walking with the rollator whilst oxygen uptake, oxygen saturation and Borg symptom score were comparable between the two walking aids.		
101-67: Which patients with stable COPD should be referred for pulmonary rehabilitation and when?			
One RCT examined the safety and efficacy of a home-based pulmonary rehabilitation programme for patients with very severe COPD on long-term oxygen therapy (LTOT).[223] This study was considered to reinforce the recommendation in CG101 that pulmonary rehabilitation should be offered to all patients who consider themselves functionally disabled by COPD, and serves as a reminder that this may extend to those even with the most severe disease on LTOT. A Cochrane review found that	The results of three RCTs indicated potential benefit of pulmonary rehabilitation in people had recently had an acute exacerbation of COPD.[225-227] Furthermore, the results of a systematic review 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.[228]	None identified.	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.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
pulmonary rehabilitation significantly reduced hospital admissions and mortality in patients who had recently experienced an exacerbation.[224] The EUAG felt that this evidence reinforces the value of post-exacerbation rehabilitation and may be a consideration in future reviews of CG101, although the included trials were small.			
101-68: In patients with stable COPD, are there benefits in repeated pulmonary rehabilitation attendances?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-69: In patients with stable COPD how can right heart failure / chronic salt and water retention be identified?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-70: In patients with stable COPD what therapies can be used to manage right heart failure / chronic salt and water retention?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-71: In patients with stable COPD how can pulmonary hypertension be identified?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-72: In patients with stable COPD what therapies can be used to manage pulmonary hypertension?*			
None identified.	One RCT evaluated the effect of atorvastatin compared to placebo on the treatment of pulmonary hypertension in people with COPD.[229] No significant differences in pulmonary hypertension, 6 minute walking distance or spirometry parameters were	None identified.	In summary, atorvastatin and sildenafil showed no benefit for people with pulmonary hypertension and further study on the

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	observed between the two groups. Furthermore, the results of one RCT indicated that addition of sildenafil did not improve the results of pulmonary rehabilitation in patients with COPD and pulmonary hypertension.[230]		long term benefits and harms of these treatments would be needed before considering for inclusion in the guideline.
101-73: How are patients with stable COPD affected by anxiety and / or depression?			
None identified.	The results of systematic reviews indicated that depressive symptoms were more common among people with COPD compared with control groups.[231-233] A systematic review 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 disorder, panic disorder, specific phobia and social phobia.[234]	None identified.	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.
101-74: In patients with stable COPD, how can anxiety and depression be identified?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-75: How can anxiety and depression in stable COPD patients be managed? (Pharmacological & non-pharmacological)			
None identified.	One RCT assessed the effects of an uncertainty management intervention incorporating a cognitive behavioural intervention on uncertainty, anxiety, depression, and quality of life in people with COPD.[235] Compared with the control group, the intervention group showed significant improvement in uncertainty, coping strategy, anxiety, depression, and the mental	Clinical feedback suggests that management of anxiety and depression remains very varied.	The recommendations on treatment and management of depression in adults with a chronic physical health problem in CG91 updated the recommendations

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	health domains of QOL. The efficacy of a personalised intervention for depression and COPD (PID-C) compared with treatment as usual was evaluated in a trial and was found to lead to a higher remission rate and a greater reduction in depressive symptoms compared to the control group.[236] Finally, a systematic review reported that psychological and/or lifestyle interventions were associated with small reductions in symptoms of depression whilst multi-component exercise training was the only intervention associated with significant treatment effects for depression.[237]		within CG101 although the guideline noted the importance of offering psychological and psycho-social interventions before considering anti-depressant drugs.
101-76: What is the significance of nutritional problems in both stable and acute exacerbations of COPD?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-77: In patients with stable COPD, how can nutritional problems be identified?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-78: In patients with stable COPD, how can nutritional problems be managed?			
None identified.	Three systematic reviews and two RCTs reported benefits of nutritional support in people with COPD across a range of outcomes.[238-242] However, an RCT evaluating the effect of fruit and vegetable intake in moderate-to-severe COPD reported no significant effect on airway or systemic oxidative stress and inflammation.[243] The evidence on the role of supplementation in people with COPD was mixed with studies reporting an	None identified.	In general, the evidence on nutritional support in people with COPD is favourable however, there is currently insufficient conclusive evidence to provide more detailed recommendations on specific nutritional supplements in this

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	increase in lean body mass and exercise tolerance with Creatine + Coenzyme Q-Ter[244]; improved physical performance and muscle strength with essential amino acids[245]; less severe and shorter exacerbation episodes with Echinacea purpurea[246]; improved exercise performance after magnesium IV loading[247] but no difference in outcomes with vitamin D.[248,249] Conversley, a post-hoc subgroup analysis of an RCT found that patients receiving vitamin D had significantly larger improvements in inspiratory muscle strength and maximal oxygen uptake although improvements in quadriceps strength or six minutes walking distance were not significantly different from the effects in the placebo group.[250]		population. The current guideline recommendations are unlikely to be impacted.
101-79: Do self-management plans & patient education affect concordance with treatment and improve outcomes in patients with stable COPD?			
A Cochrane review investigated the effect of action plans involving limited patient education only for exacerbations of COPD.[251] The evidence suggested that a single, short educational session is unlikely to benefit health outcomes. A more complex programme was examined in a multicentre RCT of patients with severe COPD.[252] Patients in the treatment arm received a single 1–1.5 hour education session, an	<u>Self-management programmes</u> Several studies reported that self-management support programmes for people with COPD feasible and effective for a number of outcomes including improving inhaler technique and improving exercise endurance.[253-265] Conversely, an RCT evaluating the efficacy of a comprehensive care management programme reported that this intervention did not reduce COPD-related hospitalisations compared to a control group.[266] Additionally, the results of another RCT indicated that a comprehensive self-management	None identified.	*Self-management programmes* Generally, the identified new evidence is supportive of self-management programmes for people with COPD which is in line with the guideline recommendations. *Telecare* The identified new

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
action plan for self-treatment of exacerbations, and monthly follow-up calls from a case manager. The Evidence Update concluded that this evidence in terms of the incorporation of case management and structured action plans, particularly for higher risk patients, may be a consideration for future reviews of CG101.	programme did not show long term benefits over usual care alone in COPD patients in general practice.[267] An RCT comparing three different care modes: self-management, regular monitoring by a practice nurse, and care provided by the GP at the patient's own initiative (usual care) in COPD found that patients receiving usual care experienced the highest continuity of care however, no relationship was found between continuity of care and changes in QoL.[268] Lastly, a systematic review of educational programmes for people with COPD found that smoking cessation; medication; exercise; breathing strategies; exacerbations; and stress management were the most common topics.[269] <u>Telecare</u> A large amount of new evidence was identified focusing on telecare services for people with COPD in the community. Several studies reported a significant reduction in hospital admissions among people with COPD randomised to telecare.[270-273] Similarly, the results of one RCT indicated a significant decrease in dyspnea intensity in people using a telehealth video for teaching pursed-lips breathing in COPD.[274] Conversely, the results of other RCTs and systematic reviews reported no benefit of telecare services compared with usual care for people with COPD.[275-281] Finally, an RCT assessing the benefits of telephone-delivered health mentoring in community-based COPD found that QoL did not differ compared with the usual		evidence included different populations with varying severity of COPD whilst the specific components of the interventions are likely to differ considerably across the studies. The evidence is mixed with some studies reporting a benefit of a telecare intervention and others indicating that there is no benefit compared with usual care. Further research is needed to clarify the role of telehealthcare in the COPD population before considering for inclusion in the guideline. *Individualised plans* The guideline recommends that patients given self-management plans should be advised to contact a health care professional if they do not improve and no new evidence was identified

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	care group although self-management capacity increased.[282] <u>Individualised plans</u> Two RCTs were identified evaluating the use of individualised action plans on COPD exacerbation rates. One RCT reported that adherence to a written action plan significantly reduced exacerbation recovery time whilst the second RCT found no difference in exacerbation rates when using an individualised care plan versus care as usual.[283,284]		which would impact on this recommendation. An RCT included in the Evidence Update indicated that an action plan including educational sessions and follow-up calls from a case manager is beneficial in severe COPD. However, further research on the specific components of educational programmes in action plans would be pertinent before considering in the guideline.
101-80: What is the role of oxygen therapy in patients with stable COPD?*			
None identified.	The symptomatic benefit of home oxygen therapy in mildly or non-hypoxaemic people with COPD with dyspnoea who do not meet the criteria for long-term oxygen therapy was evaluated in a Cochrane systematic review.[285] The review reported that oxygen can relieve dyspnoea in mildly and non-hypoxaemic people with COPD who would not otherwise qualify for home oxygen therapy. In addition, the long-term effect of ambulatory oxygen combined with pulmonary rehabilitation in COPD was evaluated in an RCT.[286]	None identified.	Taken together these studies are unlikely to change the direction of the recommendations on oxygen therapy.

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	The results indicated no additional benefit of adding ambulatory oxygen to a pulmonary rehabilitation programme.		
101-81: In patients with stable COPD, what is the best method of oxygen supply?*			
None identified.	Four RCTs focusing on oxygen supply were identified.[287-290] All four studies compared different types of oxygen supply methods in people with various stages of COPD.	None identified.	The identified new evidence is unlikely to impact the current guideline recommendations.
101-82: In patients with stable COPD, what are the benefits of short burst oxygen?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-83: In patients with stable COPD, what are the benefits of portable oxygen?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-84: In patients with stable COPD, what are the criteria for continuous oxygen therapy?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-85: What is the role of immunisation in patients with stable COPD?			
A Cochrane review examined the use of injectable vaccines against pneumococcal infections in patients with COPD.[291] The results indicated that pneumococcal vaccination did not significantly reduce the likelihood of developing pneumonia compared with controls. The EUAG felt that the results of the review appear to be	No new evidence identified.	None identified.	Larger, well designed clinical trials are needed to determine whether newer polyvalent vaccines reduce the likelihood of people with COPD developing pneumonia.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
counter to the recommendations in CG101 that pneumococcal vaccination should be offered to all patients with COPD. However, the Evidence Update states that any potential impact on current guidance may be limited by the quality of the evidence; two included studies were abstracts from which only the published abstract data were used, and two studies were from the 1980s, when only 14-valent vaccines were used (modern vaccines are 23-valent). It was concluded that larger, well designed clinical trials are therefore needed of the newer polyvalent vaccines in COPD (although this may be difficult in the UK where the 5-yearly pneumococcal vaccine has become standard practice).			
101-86: What is the role of non-invasive ventilation in patients with stable COPD?			
None identified.	Four systematic reviews[292-295] and two RCTs[296,297] reported mixed results of non-invasive ventilation for stable COPD with some demonstrating small improvements and others indicating no significant effect.	None identified.	The guideline currently recommends that only people who have chronic hypercapnic respiratory failure who have required assisted ventilation (whether invasive or non-invasive) during an exacerbation or who are

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
			hypercapnic or acidotic on long-term oxygen therapy should be referred to a specialist centre for consideration of long-term non-invasive ventilation and no new evidence was identified to suggest expanding this population.
101-87: What management strategies can be used to provide palliative care in the end stages of COPD?			
None identified.	Limited new evidence on palliative care was identified. One systematic review indicated that there is limited evidence for health service coordination in palliative care services[298] whilst another review reported that many people with COPD had not had end of life care conversations with their healthcare professional.[299] Lastly, the results of an RCT indicated that discussions about end of life care increased when patients gave feedback about their preference for such conversations.[300]	Clinical feedback highlighted that integration of palliative care services are under investigation.	Taken together, this new evidence is unlikely to impact on the guideline recommendation on palliative care which states that 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.
101-88: How should the long term care of patients with stable COPD be organised in order to maximise patient outcomes?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-89: Where (Primary care versus secondary care) should the long term care of patients with stable COPD be organised in order to maximise patient			

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
outcomes?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-90: How often should the long term care of patients with stable COPD be reviewed in order to maximise patient outcomes?*			
None identified.	One systematic review reported that chronic care management has the potential to improve outcomes of care in COPD however, no specific details on when reviews should be carried out was provided.[301] As such, no new evidence was identified which would impact the current recommendations on follow-up of patients with COPD.	None identified.	No new evidence was identified which would impact the current recommendations on follow-up of patients with COPD.
101-91: In patients with stable COPD, what is the role of respiratory nurse specialists?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-92: What is the role of respiratory physiotherapy in the management of patients with stable COPD?			
None identified.	Two RCTs[302,303] and a systematic review[304] evaluated different breathing techniques for COPD. All three studies reported a benefit of the techniques tested including pursed lips breathing, a diaphragmatic breathing training programme and active breathing techniques.	None identified.	This new evidence is supportive of the recommendation which states that patients with excess sputum should be taught an active cycle of breathing techniques.
101-93: What is the role of lung surgery in patients with stable COPD?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-94: In patients with stable COPD, what is the operation of choice (bullectomy, lung volume reduction, transplantation) in reducing morbidity or mortality?*			
None identified.	One RCT was identified which compared complete unilateral with partial bilateral lung volume reduction in	None identified.	The guideline currently recommends that patients

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	people with severe lung emphysema.[305] At 30 days and 90 days, significant differences were seen in pulmonary function tests and 6 minute walking distance, as well as in dyspnea score and QoL, in favour of unilateral treatment. 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. However, this 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.		with severe COPD who remain breathless despite medical therapy and rehabilitation should be referred for consideration of lung volume reduction surgery. However, 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.
101-95: In patients with stable COPD, what are the referral criteria for lung surgery?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-96: What is a robust and useful definition of an exacerbation of COPD?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-97: What symptoms are suggestive of an exacerbation of COPD?*			

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-98: What other conditions present with similar symptoms?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-99: What are the factors known to cause exacerbations of COPD?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-100: What is known about the consequences (short & long term outcome impact) of having an exacerbation (chest episodes, infective episodes) of COPD?*			
A meta-analysis found that a severe exacerbation needing hospitalisation resulted in a weighted mean case-fatality rate of 15.6% with an average in-hospital mortality rate of 6.7%.[306] The Evidence Update concluded that the study indicates the potentially high risk of dying around the time of an acute exacerbation, and that the critical period appears to extend beyond the duration of the hospitalisation. It was felt that this evidence is unlikely to affect CG101, but emphasises the risks associated with severe exacerbations (in particular the continued elevated risk after discharge), which should be managed according to current guidance.	No new evidence identified.	Clinical feedback indicated that work has been published about predicting exacerbations and the use of the DECAF score for mortality in COPD.	New evidence is unlikely to impact on guideline recommendations.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
An observational cohort study was considered to provide further context, noting that exacerbations increased with the severity of COPD.[307] It was also found that a history of exacerbations appeared to be the best predictor of exacerbations at all stages of disease. Taken together, the EUAG felt that two studies show that those with a history of exacerbations and more severe disease may potentially be more likely to experience exacerbations with increased frequency, and that exacerbations may be associated with a high risk of death, even after discharge.			
101-101: What clinical signs are useful (confirm or refute) in making a diagnosis and assessing the severity of an exacerbation of COPD?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-102: What are the most appropriate tests in a patient with suspected exacerbation of COPD?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-103: What are the most appropriate tests to confirm the diagnosis of an exacerbation of COPD?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-104: What are the most appropriate tests to assist in the management of an exacerbation of COPD?*			

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-105: In patients with an exacerbation of COPD, what are the most appropriate tests to assess severity?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-106: In patients with an exacerbation of COPD, what are the most appropriate tests to monitor recovery?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-107: Which patients with an exacerbation of COPD benefit from admission to hospital?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-108: Are bronchodilators useful / effective in the treatment of patients with an exacerbation of COPD?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-109: Which patients with an exacerbation of COPD should be treated with bronchodilators?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-110: Are oral steroids useful / effective in the treatment of patients with an exacerbation of COPD?			
None identified.	<u>Oral corticosteroids</u> One RCT was identified which compared oral prednisone with etanercept, a tumour necrosis factor (TNF) antagonist, for acute exacerbations of COPD.[308] Rates of treatment failure at 90 days were similar in the prednisone and etanercept groups, as were measures of dyspnoea and quality of life whilst subgroup analysis revealed fewer treatment failures if people were treated with prednisone compared with etanercept.	None identified.	In summary, the identified new evidence supports the current guideline which recommends the use of corticosteroids for exacerbations of COPD and states that a course of corticosteroid treatment should not be longer than 14 days as there is no advantage in prolonged

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	Systemic corticosteroids One RCT compared intravenous (IV) followed by oral methylprednisolone with IV hydrocortisone followed by oral prednisolone in people with acute exacerbations of COPD.[309] Mortality, need for mechanical ventilation and acute exacerbation within 2 weeks of discharge were not significantly different between the two groups. However, at 2 weeks, a significant improvement in FEV1 was observed in the group receiving IV followed by oral methylprednisolone. Similarly, one meta-analysis found that systemic corticosteroids were associated with a significant reduction in the treatment failure rate and an improvement in FEV1.[310] One RCT evaluated the efficacy and safety of intravenous methylprednisolone compared with placebo in patients with an exacerbation of COPD who were receiving ventilatory support.[311] Corticosteroid treatment was associated with a significant reduction in the median duration of mechanical ventilation. One systematic review[312] and an RCT[313] 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 the shorter treatment was non-inferior to longer treatment.		therapy.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
101-111: Which patients with an exacerbation of COPD should be treated with oral steroids?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-112: Which delivery systems should be used for giving inhaled therapy to patients with an exacerbation of COPD?*			
None identified.	One small-scale RCT evaluated whether the AeroEclipse II breath-activated nebulizer (BAN) would produce greater bronchodilator responses than a continuous flow small-volume nebulizer (SVN) in patients with exacerbations of COPD.[314] The results indicated that the breath-activated nebuliser was more effective in reducing lung hyperinflation and respiratory frequency. The guideline currently recommends that both nebulisers and hand-held inhalers can be used to administer inhaled therapy during exacerbations of COPD and that the choice of delivery system should reflect the dose of drug required, the ability of the patient to use the device and the resources available to supervise the administration of the therapy. No specific guidance on type of nebuliser is given in the guideline however, further research in this area is needed before determining any impact on the recommendations.	None identified.	The guideline currently recommends that both nebulisers and hand-held inhalers can be used to administer inhaled therapy during exacerbations of COPD and that the choice of delivery system should reflect the dose of drug required, the ability of the patient to use the device and the resources available to supervise the administration of the therapy. No specific guidance on type of nebuliser is given in the guideline however, further research in this area is needed before determining any impact on the recommendations.
101-113: Are antibiotics useful / effective in the treatment of patients with an exacerbation of COPD?			
None identified.	The results of two Cochrane systematic reviews and	Clinical feedback stated that	Antibiotics are currently

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	an RCT indicated that antibiotics for acute exacerbations of COPD significantly reduced treatment failure[315] and mortality[316] whilst median time to the next exacerbation was significantly longer compared with placebo.[317] There was also an indication that the benefit of antibiotic treatment improved as the degree of severity of the exacerbation increased.[315]	newer evidence has been published on use of prophylactic antibiotics (macrolides) in reducing time to further exacerbation.	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.
101-114: Which patients with an exacerbation of COPD should be treated with antibiotics?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-115: Which patients with an exacerbation of COPD should be treated with oxygen (how much and how monitored, including use during transfer to hospital)?*			
One RCT examined titrated versus high flow oxygen treatment in the prehospital (ambulance/paramedic) setting.[318] 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[319] that 'oxygen is a treatment for hypoxaemia, not breathlessness' and 'oxygen (should) be prescribed according to a target saturation range'. The evidence also appears to agree with current recommendations in	One RCT evaluating whether titrated oxygen via nasal prongs in the pre-hospital setting impacts on mortality in people with a suspected acute exacerbation of COPD reported that using titrated oxygen to maintain SpO(2) between 88% and 92% reduced the risk of mortality by 58%.[289]	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 and this new evidence is unlikely to impact on this recommendation.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
CG101 that oxygen should be given to keep the saturation level within the individualised target range. Furthermore, a comment piece summarising the latest evidence on high-concentration oxygen therapy in COPD affirmed that the preferred initial treatment in acute exacerbations of COPD is oxygen titration.[320]			
101-116: What is the role of theophylline in patients with exacerbations of COPD?			
None identified.	Two small-scale RCTs evaluated the addition of theophylline to inhaled corticosteroids (fluticasone propionate)/bronchodilator therapy (ICS)[321] or long-acting inhaled beta-agonist (LABA) and long-acting anti-cholinergic bronchodilator therapy (LAMA)[322] in people with COPD. ICS plus theophylline resulted in a non-significant increase in FEV1 whilst addition of theophylline to LAMA/LABA treatment improved exercise duration although there were no significant observed differences in resting lung function or measures of dyspnea between the two treatment groups. The guideline acknowledged the need to monitor plasma levels when using theophylline and their potential to interact with other medications however, these issues were not reported in the new evidence. As such, the identified new studies are unlikely to impact on the recommendations which state that theophylline should only be used after a trial of	None identified.	The guideline acknowledged the need to monitor plasma levels when using theophylline and their potential to interact with other medications however, these issues were not reported in the new evidence. As such, the identified new studies are unlikely to impact on the recommendations which state that theophylline should only be used after a trial of short-acting bronchodilators and long-acting bronchodilators, or

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	short-acting bronchodilators and long-acting bronchodilators, or in patients who are unable to use inhaled therapy, as there is a need to monitor plasma levels and interactions.		in patients who are unable to use inhaled therapy, as there is a need to monitor plasma levels and interactions.
101-117: What is the role of respiratory stimulants in patients with exacerbations of COPD?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-118: What is the role of therapies for managing right heart failure / chronic salt and water retention in patients with exacerbations of COPD?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-119: Which patients with exacerbations of COPD require non-invasive ventilation?			
None identified.	Eight RCTs[323-330] and a systematic review[331] evaluating non-invasive ventilation in people with COPD were identified. The studies were mixed evaluating different protocols for non-invasive ventilation, different settings and different COPD states.	None identified.	Non-invasive ventilation is currently recommended as the treatment of choice for persistent hypercapnic ventilatory failure during exacerbations despite optimal medical therapy and no new evidence was identified which would impact this recommendation.
101-120: 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?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
101-121: Which patients with exacerbations of COPD require IPPV / ITU care?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-122: 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.			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-123: What multi professional team membership is effective in providing hospital-at-home / assisted discharge schemes for patients with exacerbations of COPD?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-124: In patients with an exacerbation of COPD, what criteria are useful in assessing the suitability of and planning for home treatment / early discharge?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-125: In patients with an exacerbation of COPD, what is the optimal duration of home care?			
Hospital at home A Cochrane review investigated home care by outreach nursing for COPD.[332] A pooled analysis of eight studies found mortality was not significantly reduced at 12 months. The EUAG felt that heterogeneity between studies may limit any conclusions and there is unlikely to be an impact on current recommendations in CG101. To further investigate the movement of long-term follow-up services into the community, longer and larger well-designed studies are needed looking	Three RCTs[333-335] and a systematic review[336] assessing home care for people with COPD reported a benefit of home care compared with usual care. Two RCTs evaluating hospital discharge policies reported mixed results with one stating that there was no clear evidence to determine whether early assisted discharge (discharged after 3 days and treated at home by community nurses for 4 days) is more effective compared with 7 days of inpatient hospital treatment.[337] Conversely, the results of one RCT indicated that coordination of discharge from hospital reduces hospitalisations in people with COPD.[338]	Clinical feedback indicated that home care is now widely advocated.	Taken together, this new evidence is unlikely to impact the guideline which recommends home care.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
at clearly defined populations and intervention types.			
101-126: What is the role of respiratory physiotherapy in the management of exacerbations of COPD?			
None identified.	One RCT evaluating the effectiveness of manual chest physiotherapy (MCP) in acute exacerbations of COPD reported no significant difference in the St Georges Respiratory Questionnaire for patients who did, or did not receive MCP.[339] Conversely, a Cochrane systematic review reported that airway clearance techniques were associated with small but significant short-term reductions in the need for increased ventilatory assistance in people experiencing acute exacerbations of COPD.[340]	None identified.	Further research is needed to confirm the benefits and harms of these respiratory physiotherapy techniques before considering for inclusion in the guideline.
101-127: Which patients with COPD benefit from referral to palliative care services?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-128: Which patients with COPD benefit from referral to occupational therapists?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-129: Which patients with COPD benefit from referral to social services?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-130: 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?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-131: In patients with stable COPD and their relatives / carer, what effect does education have on morbidity, quality of life, advanced directives or mortality measures?			
None identified.	No new evidence identified.	None identified.	No relevant evidence

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
			identified.
101-132: Do cultural factors modify the uptake of COPD care?			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
101-133: What advice should be given to patients with COPD who wish to travel?*			
None identified.	One small-scale RCT compared alveolar hypoxia induced in a hypobaric chamber (HC) with a hypoxia-altitude simulation test (HAST) in people with COPD.[341] 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 but this is unlikely to impact the recommendations as they refer the reader directly to the BTS document rather than incorporate the recommendations.	None identified.	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 but this is unlikely to impact the recommendations as they refer the reader directly to the BTS document rather than incorporate the recommendations.
101-134: How should the fitness for surgery of patients with COPD be assessed?*			
None identified.	No new evidence identified.	None identified.	No relevant evidence identified.
Areas not currently covered in the guideline			
The role of acupuncture in management of COPD			

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
None identified.	Three RCTs evaluated the use of acupuncture for management of COPD. Two RCTs comparing acupuncture with sham reported improvements in dyspnea[342] and the 6 minute walk distance during exercise[343] after 12 weeks of therapy. Conversely, one RCT found that the addition of acupuncture to pulmonary rehabilitation did not add significant benefit in QoL scores, dyspnea or exercise capacity compared to pulmonary rehabilitation alone.[344]	None identified.	Additional, large-scale studies reporting on a range of outcomes are required to confirm the role of acupuncture in management of COPD.
The role of other drug treatments in the management of COPD			
None identified.	RCTs evaluating other drug treatments for COPD generally reported no beneficial effect of a 5-lipoxygenase inhibitor[345,346]; a neutrophil elastase[347,348]; selective MMP-9 and MMP-12 inhibitors[349]; melatonin[350]; sildenafil[351,352]; bisoprolol[353]; magnesium[354] or a selective CRTh2 (DP2) receptor antagonist.[355] Small benefits in people with COPD were reported for fentanyl citrate[356]; a p38 inhibitor[357]; N-acetyl cysteine[358] and furosemide.[359] However, these were small studies carried out in people with differing severity of COPD.	None identified.	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.
The role of stem cell therapy in the management of COPD			
None identified.	One RCT conducted an initial evaluation of the potential efficacy of systemic mesenchymal stem cells (MSC) administration to patients with moderate to severe COPD.[360] Compared with vehicle control, no	None identified.	Further research in larger studies is required before considering this therapy for inclusion in the

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	significant difference in frequency of exacerbations or adverse events was observed.		guideline.
The role of alternative and complementary therapies in management of COPD			
None identified.	Stable COPD ***Huangqi formulae*** One systematic review evaluated the efficacy and safety of oral Huangqi formulae for the treatment of stable COPD.[361] Compared with conventional therapy (CT) alone, oral Huangqi formulae plus CT resulted in improvements in SGRQ total score, COPD-related symptoms and reduction of frequency of exacerbations although the included studies were considered to be methodologically weak. ***Tai chi Qigong*** Three RCTs compared a Tai chi Qigong (TCQ) programme with exercise or usual care in people with COPD.[362-364] Improvements in respiratory functions[362], exercise capacity and QoL[363,364] were observed in the TCQ group. One of the studies reported no changes in dyspnea and fatigue levels among the three groups.[364] ***Health qigong*** The efficacy of health qigong (HQG), a traditional Chinese exercise, as an adjunct home exercise programme in people with chronic COPD was investigated in an RCT.[365] Some improvement in functional capacity was observed in the HQG group.	None identified.	Overall, the identified new evidence is heterogeneous evaluating a range of different complementary remedies in people with differing levels of severity of COPD. Further research is needed to confirm the results obtained and to determine the long-term effects of therapies before considering for inclusion in the guideline.

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	Herbal medicine One systematic review was identified assessing the efficacy of Chinese herbal medicine for stable COPD[366] in addition to five small RCTs evaluating traditional Chinese medicine[367,368], bakumondoto, Kampo medicine[369], Chinese Yam and epimedium[370] and EPs 7630, a herbal drug preparation from the roots of Pelargonium sidoides.[371] In all the studies, some improvements were observed in the range of outcome measures reported. In the study evaluating EPs 7630 the incidence of minor gastrointestinal adverse events was higher in the EPs 7630 group.[371] Furthermore, one systematic review evaluated the efficacy of Jianpi therapy in Traditional Chinese Medicine (TCM) for treatment of stable COPD indicating that the results are encouraging but more research is needed.[372] ***Bufei Yishen Granule (BFYSG) combined with Shufei Tie acupoint sticking therapy*** Three RCTs compared the efficacy of Bufei Yishen Granule (BFYSG) combined with Shufei Tie acupoint sticking therapy in people with COPD.[373-375] Improvements in frequency and duration of acute exacerbation and scores of daily living ability[373,375], higher scores in ESQ-COPD domains including clinical symptoms and effect of therapy[374], 6 minute walking distance and dyspnea grade[373] were observed in the intervention group. One of the studies reported no differences between the experimental and control		

Conclusions from Evidence Update (February 2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (April 2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (April 2014)
	group in FVC, FEV1, FEV1% and adverse events.[373] ***Tai Chi*** A meta-analysis was identified which assessed the role of Tai Chi (TC) in management of COPD.[376] Improvements in dyspnea and FEV1 were observed in the TC group. <u>Exacerbations of COPD</u> One systematic review assessed the effectiveness and safety of modified Dachengqi Decoction (MDD) combined with conventional treatment for treating acute exacerbations of COPD.[377] The results indicated that MDD shortened the duration of mechanical ventilation although adverse events were reported. However, the included studies were considered to be methodologically weak. Overall, the identified new evidence is heterogeneous evaluating a range of different complementary remedies in people with differing levels of severity of COPD. Further research is needed to confirm the results obtained and to determine the long-term effects of therapies before considering for inclusion in the guideline.		

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