Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Chiesi Ltd	Algorithm	General	General	The guideline recommends offering triple therapy (LAMA+LABA+ICS) only to those who remain breathless or have exacerbations despite taking a LABA+ICS. However, no additional pharmacological recommendation is provided for those who still remain breathless or have exacerbations despite using a dual bronchodilator therapy (LABA+LAMA). There is evidence to support the use of triple therapy over and above both a mono and dual bronchodilator in providing additional exacerbation reduction and improved quality of life: The TRINITY study showed a significant 20% reduction in the rate of moderate-to-severe exacerbations (RR: 0.80, 95% CI 0.69-0.92; p=0.0025) with single inhaler triple therapy (beclometasone/formoterol/glycopyrronium) than tiotropium alone, and more patients in the triple therapy group were responders in terms of SGRQ total score (decrease from baseline ≥4units) at both week 26 (OR: 1.32, p=0.0024) and week 52 (OR:1.33, p=0.0019).[1] The TRIBUTE study showed a significant 15% reduction in the rate of moderate-to-severe exacerbations (RR: 0.848, 95% CI 0.723-0.995, p=0.043) and an improvement in mean SGRQ total score (adjusted mean difference: -1.68, p≤0.001) with single inhaler triple therapy (beclometasone/formoterol/glycopyrronium) compared to a dual bronchodilator (indacaterol/glycopyrronium). It is worth noting that these results were found in patients without a current diagnosis of asthma, [2] thereby supporting the use of triple therapy in patients without asthmatic features.	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the publication of a number of large new RCTs (including the ones you have cited) it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm. Treatment switching between dual therapies and treatment de-escalation were not within the scope of the current update, and therefore the committee was not able to make recommendations on these topics.

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				The IMPACT study showed similar beneficial effects with a 25% reduction in the rate of moderate-to-severe exacerbations (RR: 0.75, 95% CI 0.70 to 0.81, p<0.001) and an improvement in mean SGRQ total score (mean difference: -1.8, 95% CI -2.6 to -1.0, p<0.001) with single inhaler triple therapy (fluticasone furoate/umeclidinium/vilanterol) compared to a dual bronchodilator (umeclidinium/vilanterol). [3] The algorithm suggests the only option for patients without asthmatic features currently uncontrolled on a LABA+LAMA are options such as surgery. Given this approach may not be necessary in the majority of patients, we would advocate allowing for pharmacological escalation and de-escalation of therapies where appropriate in the algorithm to include use of LABA+ICS and triple therapy before consideration of options such as surgery. [1] Vestbo et al. Lancet, 2017; 389(10082): 1919-1929 [2] Papi et al. Lancet, 2018; 391(10125): 1076-1084 [3] Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680	
Boehringer-Ingelheim Ltd	Algorithm	General	General	It would be clearer to add PRN in the 'Offer SABA or SAMA' in the algorithm, to reflect the 'as necessary' clause in section 1.2.7 (page 14 of the draft guideline). Further to the existing guidance, BI would recommend that a statement be included to assist prescribers to decide when a patient should transition from as needed short-acting bronchodilator therapy to a long-acting maintenance therapy. Presently, both the existing and draft guidelines recommend a transition to long-acting maintenance therapy if the patient remains breathless or has exacerbations, however it is possible through continued use of a short-acting bronchodilator a patient could potentially control their symptoms. The GOLD 2018 management strategy suggests a similar approach, though specifically states that use of short-acting bronchodilators on a regular basis is not generally recommended (full document, page 46). Similarly, the UK PCRS recommend that	Thank you for your comment. The committee agreed that this wording would improve clarity and 'to use if needed' has been added to the algorithm. The committee discussed the suggestion for an additional statement to assist prescribers to decide when a patient should transition from as needed short-acting bronchodilator therapy to a long-acting maintenance therapy. They decided that the wording of the existing recommendations were sufficient for this as they already include the information to move the patient to a long-acting therapy if they remain breathless or have exacerbations despite using a short-acting bronchodilator. The committee concluded that this was sufficiently clear to ensure that people whose symptoms

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				'for people using SABA regularly ensure other medicines are prescribed and optimised to reduce breathlessness'. Finally, the National Review of Asthma Deaths (NRAD) specifically highlighted the overuse of SABA therapy in asthma and whilst asthma is an entirely separate disease, it is likely that behaviours will remain similar across disease areas with respect to potential overuse of SABAs when it would be appropriate to initiate or optimise maintenance therapy. BI would therefore recommend that a statement similar to 'Patients who are regularly using short-acting therapy should be considered for long-acting maintenance therapy' in section 1.2.7.	could be controlled using short-acting bronchodilator would not be switched to a long-acting therapy prematurely. The committee recognised that overuse of SABAs could be problematic, but were unable to add the requested recommendation because the section on SAMA and SABA use was not within the scope of this update.
Boehringer-Ingelheim Ltd	Algorithm	General	General	In the algorithm, following on from 'Consider LABA+ ICS' the guideline suggests 'Person still breathless or has exacerbations despite further treatment? Consider LAMA+ LABA + ICS)'. It would be useful to further elaborate on what 'still breathless' means as well as defining the type and number of exacerbations per year. Nearly all COPD patients will experience breathlessness and exacerbations over the course of their disease, but this does not necessarily mean they all need to be escalated to triple therapy. We also recommend adding 'Review' to the algorithm after LAMA/LABA and LAMA/LABA/ICS to highlight that the risk/benefit of pharmacological therapies should be reviewed on a regular basis.	Thank you for your comments. This part of the pathway covering the transition from LABA+ICS to LAMA+LABA+ICS is based on an existing triple therapy recommendation. Triple therapy was out of the scope of this update and, as a result, the committee are unable to be more specific about this transition. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs (including the ones you have cited) it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.

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09/07/2018 – 06/08/2018

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					The committee did not review the evidence for the follow-up of people with COPD. This was out of scope of the update as it has been covered in the section of the guideline entitled 'Follow-up of people with COPD'. There is a recommendation to review people at least once a year and this refers to a table which list includes the 'effects of each drug treatment'. However, the committee agreed that reviewing inhaled therapies was an important issue, and this has been added to the algorithm to highlight this.
Boehringer-Ingelheim Ltd	Algorithm	General	General	BI consider that with respect to the algorithm itself, the specific design of the algorithm is such that a viewer may consider the two pathways for non-asthmatic features or asthmatic features as having equal weighting, i.e. a comparable number of patients would be in each group. Evidence suggests that the number of patients exacerbating with high eosinophils (>300 cells/µl) is approximately 20% (WISDOM study sub analysis, Watz et al, Lancet Respiratory Medicine 2016; 4, 390-398) and therefore a greater number of patients should be on the non-asthmatic feature pathway: we would recommend that this is highlighted in some way specifically on the algorithm, either by the size of the arrows/boxes or by a text note.	Thank you for your comment. The committee agreed that the majority of patients were expected to be treated with LAMA+LABA (and this is reflected in the resource impact assessment produced alongside the guideline), but noted that since the algorithm was designed to be used in individual cases, it was not necessary to visually reflect this on the algorithm.
Boehringer-Ingelheim Ltd	Algorithm	General	General	This algorithm is written for newly diagnosed COPD patients. There is no guidance on how to optimise inhaler therapies in existing COPD patients. We recommend that NICE include a statement to suggest that patients that are currently suitably maintained on LAMA monotherapy remain on monotherapy unless they demonstrate increased symptoms/breathlessness. These patients should be reviewed on an individual basis, and switched to LAMA/LABA if deemed appropriate by their healthcare professionals.	Thank you for your comment. The committee agreed with the importance of this issue and an additional recommendation has been added to the guideline, stating that people whose symptoms are well controlled on treatment when the guideline is published should be allowed to continue that treatment until they are their clinician agree it is appropriate to change.
Boehringer-Ingelheim Ltd	Algorithm	General	General	BI recommend that guidance is given on ICS withdrawal in patients who do not meet the outlined criteria.	Thank you for your comments. The topic of ICS withdrawal is not within the scope of this update and, as a result, we are

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				No guidance is given with respect to withdrawing ICS from patients who have never demonstrated asthmatic features or steroid responsiveness with their COPD yet have been prescribed ICS-containing therapy. There are various strategies that are currently recommended locally and it would be valuable for healthcare professionals who wish to step their patients down from ICS-containing and curate this knowledge. Current evidence suggests that ICS withdrawal is feasible in stable patients, provided that they remain on regular bronchodilator treatment. There is a growing body of evidence, both observational and randomised controlled trials, investigating the effects of withdrawing ICS from COPD patients at various levels of exacerbation risk. • INSTEAD showed that patients with moderate COPD and a low risk of exacerbations can be switched from a LABA/ICS to LABA without symptom deterioration or an increase in exacerbation risk (Rossi et al. 2014. Eur Respir J 44(6): 1548-56) • OPTIMO demonstrated that in a real life setting, ICS can be withdrawn in patients with moderate COPD at low risk of exacerbations provided that they remain on adequate bronchodilator treatment (Rossi et al. 2014. Respir Res 15:77) • WISDOM reported that in patients with severe COPD receiving LAMA/LABA, the risk of moderate or severe exacerbations was similar among those who discontinued inhaled glucocorticoids and those who continued glucocorticoid therapy (Magnussen et al. 2014. N Engl J Med 371(14): 1285-94). • SUNSET showed that in patients without frequent exacerbations on long term triple therapy, the direct de-escalation to LAMA/LABA led to a small decrease in lung function, but no difference in exacerbations	unable to change the previous recommendations or add new recommendations to this section of the guideline. We have passed the information about the INSTEAD, OPTIMO, WISDOM, DACCORD and SUNSET trials to our surveillance team to help inform subsequent updates of this guideline.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

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09/07/2018 – 06/08/2018

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				(Chapman et al. 2018. Am J Respir Crit Care Med 198(3): 329-339) • DACCORD demonstrated in a prospective, non-interventional to year study, that ICS may be withdrawn in a real life setting without increased risk of exacerbations in patients managed in primary and secondary care (Vogelmeier et al. 2017 Int J Chron Obstruct Pulmon Dis 12: 487-494) Given the growing amount of evidence, and interest in withdrawing inappropriate use of ICS in COPD, BI would like to see guidance on ICS withdrawal included in the guidelines. We suggest NICE recommend therapy reviews for individuals currently on either LABA/ICS or LAMA/LABA/ICS who have either never exhibited or do not currently (e.g. in the previous year) exhibit "ICS responsiveness".	
AstraZeneca UK	Algorithm	General	General	Based on comments no 2 (see above), we suggest to amend the explanation of asthmatic features/responsiveness to steroids as follow: *Asthmatic features/features suggesting steroid responsiveness – The patient must have at least one of the below features: • any previous, secure diagnosis of asthma or of atopy, • or a higher blood eosinophil count (eosinophil count > 0.10 x 10^9 cells/L and upwards), • or a substantial variation in FEV1 over time (at least 400 ml) • or substantial diurnal variation in peak expiratory flow (at least 20%).	Thank you for your comment. The committee discussed the inclusion of a threshold to define a higher eosinophil count, but concluded that based on the evidence available it was not possible to define a specific threshold or to decide whether single or repeated measurement of eosinophils should be carried out. In particular, they noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. The other bullets listed are identical to the ones already included in the existing definition.
AstraZeneca UK	Algorithm	General	General	Based on comment no 5 we propose adding triple therapy with a LABA, LAMA and ICS to the pathway of patients without features of asthma and not responsive to steroids, for patients who develop exacerbations despite taking LAMA+LABA.	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify

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					updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
AstraZeneca UK	Algorithm	General	General	AstraZeneca suggests the inclusion of the option to use roflumilast after appropriate inhaled therapy recommendations in the proposed treatment algorithm. In particular, we suggest rewording the sentence in the following way: "Explore further treatment options, such as roflumilast and later on surgery, if needed (see guideline)". Roflumilast has been recommended by NICE as add-on to triple inhaled therapy in patients with severe COPD and with a history of 2 or more exacerbations in the previous year (NICE TA-461)[10]. Roflumilast is also recommended by GOLD (Global Initiative for Chronic Obstructive Lung Disease) COPD Guidelines as the preferred add-on therapy for people with severe COPD who continue to have exacerbations despite treatment with triple therapy, particularly if they had at least 1 hospitalisation for an exacerbation in the previous year[11]. In light of the above, we believe that the recommendation to consider roflumilast after triple inhaled therapy should be specifically included in the algorithm.	Thank you for your comment. The committee decided to keep the list of further treatment options to a minimum as there was insufficient space to list them all. As a result, they included a reference to refer to the COPD guideline, which in turn links to the appraisal for roflumilast for treating COPD here instead (where roflumilast is mentioned). The committee included surgery here as they wanted to highlight that lung volume reduction surgery may be an option for more people with COPD, following the new recommendations that look at referral criteria for consideration for these interventions. Based on consultation feedback we have removed this example to prevent undue weight being given to a single treatment.

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Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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Glaxo SmithKline	Algorithm, Evidence Review F, Evidence review 6	 43 47	 25-36 35-36	<u>*Suggested revision*</u> GSK is concerned about the clinical phenotype of patients with COPD and 'features of asthma', because – as acknowledged by the review committee – there is "no economic or clinical evidence on inhaled therapy for patients with COPD and features of asthma". We are concerned that implementation of this guidance will be challenging with regard to identification of patients with asthmatic features and the confusion that may arise from a patient being labelled with both COPD and asthma. GSK therefore recommends that instead of using the asthmatic/non-asthmatic features classification, the algorithm is updated to reflect a wide and robust evidence base in which the severity and frequency of exacerbations is key to guiding the use of ICS-regimens. Reduction in the future risk of exacerbations is one of the key treatment strategies employed by GOLD and should be reflected in this guideline. GSK would also like to highlight that the draft COPD algorithm and definition of 'COPD with asthmatic features' is not aligned to NICE's own guidance on the management of Asthma (*Asthma: diagnosis, monitoring and chronic asthma management published November 2017*). Specifically, in the method of diagnosis and objective tests employed (described in Algorithm C of the Asthma guideline) as well as in the principles of pharmacological management described in Section 1.5. Overall the algorithm in its current form differs substantially from the GOLD guidelines (2018) algorithm and it is important to ensure clinicians have a clear view based on an aligned framework of assessing and diagnosing patients to ensure maximum utility of the guidance. GSK believe that this can be achieved by ensuring options for treatment in the algorithm are guided by exacerbation	Thank you for your comments. The committee were aware that not everyone with COPD who is steroid responsive has asthma and chose asthmatic features/features suggesting steroid responsiveness to try to avoid suggesting that this responsiveness was confined to people with COPD and asthma. They discussed the difficulties in identifying which people with COPD are steroid responsive in great detail and are aware that there isn't a standard definition in clinical use. As a result, they tried to list a range of factors that would be recognisable to a clinician. The committee wrote research recommendations to stimulate research into defining this population of people more clearly. The committee is aware that the definition of 'COPD with asthmatic features' is not aligned to NICE's own guidance on the management of asthma. The committee intends the LABA+ICS recommendation to apply to people with COPD and asthma or people with COPD who are steroid responsive and, as a result, there is no reason that this should be aligned with a guideline that is intended for people with asthma alone. Based on the economic and clinical evidence, dual therapy was more effective than monotherapy across a range of outcomes, and LAMA+LABA was the most effective option for people with both a low and a high risk of exacerbations, based on previous exacerbation history. However, the committee recognised that there was an absence of evidence for the most effective long-acting therapies for people with COPD and asthma and they made a consensus recommendation to try to cover this population of people. They also included another research recommendation to try to address this issue. The committee noted that there were a specific subset of people with COPD in whom it would be inappropriate to use a regimen not containing inhales

				history rather than by the presence or absence of asthmatic features. As acknowledged in Evidence Review E, exacerbations are life changing and lead to poor outcomes. Specifically, the strongest predictor of a patient's future exacerbation frequency is the number of exacerbations they have had in the previous year. • Exacerbations are more frequent (and more severe) as severity of COPD increases (*Hurst et al 2010*) • COPD exacerbations are a contributing factor to disease progression (*Hurst et al 2010*) Beyond this, COPD exacerbations – especially those resulting in hospitalisation – are associated with an increased risk of mortality (*Suissa et al 2012)* • The 5-year mortality rate following a hospitalised COPD exacerbation is approximately 50%. • The rate of death also increases between successive severe exacerbations with a 1.9-times higher risk of mortality after the second exacerbation leading to hospitalisation As per the IMPACT and TRIBUTE data described above, triple therapy has an important role to play in reducing exacerbations and the social and economic costs associated with this.	steroids, and that these people likely would not be included in the RCTs identified, as it would not be ethical to randomise them to a treatment strategy not involving inhaled steroids. The committee therefore concluded that, although the reviewed evidence supported the use of LAMA+LABA in people with both a low and high risk of future exacerbations, it was appropriate to include a consensus recommendation to cover the subset of people in whom inhaled steroids are a necessary part of treatment. The committee concluded that the algorithm and guideline are an accurate representation of the findings of the clinical and economic analysis, which has taken previous exacerbation history into account, coupled with the clinical expertise of the committee in the absence of evidence concerning people with COPD and asthma or people with COPD who are steroid responsive. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.

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Chiesi Ltd	Economic Report	19		The economic report suggests that 10% of patients might be prescribed ICS as monotherapy despite being off-licence for patients with COPD. Given the financial pressures with NHS budgets, could including the costs of an off-licence therapy encourage prescribing purely for cost saving reasons?	Thank you for your comment. This section relates to assumptions regarding cost calculations for patients who progress to triple therapy (LAMA+LABA+ICS). We make the assumption that, in 10% of patients, triple therapy is delivered using two devices: a LAMA+LABA inhaler and an ICS inhaler. We are not implying that any patients would have ICS monotherapy with no other long-acting bronchodilation. Nor are we making recommendations on the format in which triple therapy should be delivered - this assumption is simply meant to reflect current practice according to the committee's experience.
Novartis	Economic report	41	Table 35	Thank you for the opportunity to comment on this draft Clinical Guideline. The guideline recommendations are evidence-based, clear and should add considerable value to clinical practice in the field of COPD. We have some comments on the guideline documents below which may enhance the understanding of the guideline by practitioners and assist with its implementation. It is not clear, why LABA+LAMA should result in higher mortality rate compared to LABA+ICS. Please could the source data and method for calculating treatment-specific differences in mortality rate be explained in more detail?	Thank you for your comment. The values you refer to were calculated by applying treatment outcomes for mortality from the network meta-analysis conducted in the clinical evidence review to baseline standardised mortality ratios. It should be noted that these values were only used in the model for 'Option C' (treatment-specific differences in adverse events and mortality included). As discussed in the model report and Evidence Review F, the committee concluded that such differences in mortality did not seem clinically plausible, and therefore preferred results of the economic model which did not implement treatment effects on mortality.
Pulmonx Corporation	Evidence review	7	15	We think it would be useful for the reader if the date the literature search was ended (February 2018) would be mentioned here also, and not only in the appendix. This is an essential information that clearly places the document in time. Relevant to the discussion on endobronchial valves, an additional multicentre RCT with follow-up out to a year was published after the literature search was performed: Criner et al ; A Multicenter RCT of Zephyr® Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE); AJRCCM Articles in Press. Published on 22-May-2018 as 10.1164/rccm.201803-0590OC.	Thank you for your comment. The end date of the literature search has now been added to the clinical evidence information in the introduction in each chapter. The publication date of the article referenced is after the date limit criteria of this guideline. However, we have looked at the article and are confident that the results would not substantially alter the findings and conclusions of this review, or the recommendations made in the guideline.

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Primary Care Respiratory Society	Evidence review	15 +16	25 + 6	We are concerned that this recommendation may imply that ICS combinations are appropriate for patients who remain breathless but do not necessarily exacerbate due to the wording 'remain breathless or have exacerbations'. It should read 'and have exacerbations' as there is no place for ICS combinations in patients who are breathless but do not exacerbate with no evidence of asthma. Also, NICE has continued to recommend that use of ICS in patients who have continuing breathlessness despite the lack of evidence of benefit in the economic evaluation - see 1.2.12 and 1.2.14. This keeps open the route for everyone who has COPD to end up on triple therapy again as in NICE 2010! Where is the evidence for this and has NICE factored in the cost of everyone ending up on triple therapy again? The studies show some improvement in FEV1 with ICS (or rather, a fall when withdrawn), but we are not aware of any significant change in breathlessness.	Thank you for your comments. Based on the clinical and economic evidence, the committee concluded that for the majority of people with COPD the most effective treatment was LABA+LAMA and they expected that most people would follow this pathway for treatment. The committee recommended LABA+ICS for people who have COPD with asthmatic features/features of steroid responsiveness. They defined the meaning of this term carefully to try to ensure that people who would respond to steroids were not denied them, but made a 'consider' recommendation to reflect the shortage of evidence about the nature of this population. It was not their intention that LABA+ICS be prescribed for people who remain breathless or have exacerbations unless they also had features that suggested asthma/steroid responsiveness. The evidence base for this review mainly consisted of trials that excluded people with COPD and asthma and, as a result, the economic model was based on a COPD population alone. The committee had to draw on their clinical experience to try to recommend appropriate treatments for people with COPD and asthmatic features/ features suggesting steroid responsiveness. They also made a research recommendation on this topic to highlight the lack of information available. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated.

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					A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
Primary Care Respiratory Society	Evidence review	45	6/7	This recommendation will be a challenging change in practice because we are not sure how the markers of eosinophil count can be utilised to support consideration of an asthmatic element as it isn't clear what is meant by higher eosinophil count.	Thank you for your comment. The committee discussed the inclusion of a threshold to define a higher eosinophil count, but concluded that based on the evidence available it was not possible to define a specific threshold. In particular, they noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. However, the accompanying research recommendation to address which features predict inhaled corticosteroid responsiveness most accurately in people with COPD could provide information on this topic and help improve the definition of asthmatic features/features suggesting steroid responsiveness in future updates of the guideline.
Pulmonx Corporation	Evidence review - clinical evidence tables	68	Short title	Davey (2014) should be replaced with Davey (2015)	Thank you for your comment. The date has been amended to 2015.
Pulmonx Corporation	Evidence review - clinical evidence tables	70	Study characteristics, 6th line	"millimetres" should be "millilitres"	Thank you for your comment. All values for FEV1 have been updated to millilitres.
Pulmonx Corporation	Evidence review - clinical	75	Study characteristics	"millimetres" should be "millilitres"	Thank you for your comment. All values for FEV1 have been updated to millilitres.

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	evidence tables		, 5th line		
Pulmonx Corporation	Evidence review - clinical evidence tables	75	Study characteristics , 7th line	"Steps mean/day Walk intensity" should be "metres"	Thank you for your comment. The 6 minute walk units have been changed to metres.
Pulmonx Corporation	Evidence review - clinical evidence tables	77	Study characteristics , 4th line from bottom of page	"millimetres" should be "millilitres"	Thank you for your comment. All values for FEV1 have been updated to millilitres.
Pulmonx Corporation	Evidence review - clinical evidence tables	89	Study characteristics , 4th line	"millimetres" should be "millilitres"	Thank you for your comment. All values for FEV1 have been updated to millilitres.
Pulmonx Corporation	Evidence review – committee discussion	26	24	Since the literature search by NICE in February 2018, an additional RCT, reporting on 12 months follow-up in 190 patients was published.	Thank you for your comment. Unfortunately the publication date of the article referenced is after the date limit criteria of this guideline (February 2018). However, we have looked at the article and are confident that the results would not substantially alter the findings and conclusions of this review, or the recommendations made.
Pulmonx Corporation	Evidence review – committee discussion	26	37	Of note, the quality of the evidence was considered very low because of the inclusion of patients with collateral ventilation in both the EU and US cohorts of the VENT trial. These data introduced a high level of inconsistency in the outcomes because their study population was not comparable to the study population of the four other RCTs. As discussed by the committee on page 22, current practice excludes patients with collateral ventilation. Excluding the 2 VENT cohorts from the evaluation should result in a conclusion	Thank you for your comment. The committee discussed the VENT trial and agreed it was appropriate to conduct a sensitivity analysis excluding the results from this study, and this has now been added to the evidence statements for this chapter. The results, whilst somewhat more positive for this population, were not substantively different and it was concluded that no changes to the recommendations were necessary.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

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09/07/2018 – 06/08/2018

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				that the grade of evidence is higher. (As indicated on page 22, line 5, the evidence is already moderate in this patient population.)	
Pulmonx Corporation	Evidence review – committee discussion	26	30 to 35	The inclusion criteria for the study population in the VENT EU cohort (Herth et al, 2012) were identical to the inclusion criteria of the VENT US cohort (Sciurba et al, 2010), as indeed they are both from the same protocol. Therefore we believe it should follow that the VENT US study should also be considered of limited relevance to current practice and be excluded from the evaluation of the overall evidence. Doing so, the study populations of the 4 remaining RCTs are much more comparable and the trial results more consistent.	Thank you for your comment. The committee discussed the VENT trial and agreed it was appropriate to conduct a sensitivity analysis excluding the results from this study, and this has now been added to the evidence statements for this chapter. The results, whilst somewhat more positive for this population, were not substantively different and it was concluded that no changes to the recommendations were necessary.
Pulmonx Corporation	Evidence review statements	21/22	General	This section refers to the quality of the evidence associated with endobronchial valves as ranging between very low and high. We think this section could be made clearer by focusing solely on those clinical studies including the current target population: patients suffering from heterogeneous or homogenous emphysema without collateral ventilation between the target lobe and the adjacent lobes. Both VENT cohorts (Sciurba et al, 2010 and Herth et al, 2012) should thus be excluded from the evaluation since they did not prospectively evaluate the presence of collateral ventilation and exclude the patients with collateral ventilation. Doing so, the results for the different outcomes measures are much more consistent and correspond to those obtained in the current target population.	Thank you for your comment. The committee discussed the VENT trial and agreed it was appropriate to conduct a sensitivity analysis excluding the results from this study, and this has now been added to the evidence statements for this chapter. The results, whilst somewhat more positive for this population, were not substantively different and it was concluded that no changes to the recommendations were necessary.
Pulmonx Corporation	Evidence review - summary of clinical studies included	12/13	Table 3	Outcomes: improvement in FEV1 can be expressed in volume or % predicted measures. The “millimetres” in the FEV1 outcomes section for Davey, Klooster, Sciurba and Valipour should be replaced by “millilitres”.	Thank you for your comment. All values for FEV1 have been updated to millilitres.
Pulmonx Corporation	Evidence review - summary of clinical studies included	12/13	Table 3	Outcomes section for the study by Klooster et al, 2015: the exercise capacity in this paper is measured using the 6 minutes walking distance expressed in meters; the paper does not report 6 minutes walking distance expressed in steps mean/day walk intensity. We propose to replace “steps mean/day walk intensity” by “meters”.	Thank you for your comment. The 6 minute walk units have been changed to metres.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Pulmonx Corporation	Evidence review - summary of clinical studies included	12	Table 3	Short Title, 1st line: The article by Davey et al was published in 2015, not 2014	Thank you for your comment. The date has been amended to 2015.
Teva UK	Evidence review 6	24	3–12	We agree that these are reasonable conclusions from the RCT evidence reviewed. Indeed, the findings of the meta-analysis of studies reporting data for LABA+LAMA vs LAMA are in agreement with other published reviews considering RCT evidence from studies comparing dual and single-agent long-acting inhaled bronchodilator therapy, e.g. Thomas et 2017,[3] Price 2016,[7] and Anzueto 2018.[8] However, we have concerns about extrapolating these trial data to routine clinical practice and the development of guidelines. Firstly, although the results of the meta-analysis suggest statistically significant differences in favour of LAMA+LABA vs LAMA for some parameters, the mean differences between the two treatments do not exceed the minimally important difference for the efficacy parameters for which the mean difference is reported. Thus the mean difference for FEV1 at 3 months was 0.07 (95% CI, 0.06, 0.08) litre vs the MID of 0.1 litre;[9] the mean difference for TDI at 3 months was 0.48 (95% CI, 0.34, 0.62) vs the MID of 1 point;[10] and the mean difference for SGRQ score was –1.74 (95% CI, –2.31, –1.18) vs the MID of 4 points.[11] This indicates that there are no clinically meaningful differences in the improvements in lung function, symptoms and HRQoL achieved with LAMA+LABA compared with LAMA alone. As such, the clinical evidence does not support recommending LAMA+LABA over LAMA, especially in low-risk patients. Secondly, these data do not imply that dual therapy is the best option for all COPD patients. COPD is a heterogeneous condition; thus, the response to treatment is likely to differ between patients.	Thank you for your comments. We are glad that you agree with the findings of the meta-analysis. Although, the MID is not exceeded for some of the outcomes comparing LAMA+LABA to LAMA alone, this does not mean that the changes in these outcomes were not clinically meaningful as the MIDs were determined by comparing an intervention to placebo and it is to be expected that the difference in effectiveness between 2 related treatments would be smaller than for either compared to placebo alone. In addition, the conclusion that LAMA+LABA was the most clinically and cost effective first long-acting bronchodilator therapy was based on an economic model that synthesised the benefits and harms across a number of outcomes. The committee are aware of the variation in responses to treatment by people with COPD, but the guideline is aimed at providing guidance for the treatment of an average patient and cannot cover every possible scenario. It is intended that the healthcare professional tailor treatment to the individual using this information. From the results of the NMA, LAMA+LABA was the most effective treatment for the average person with COPD and this was consistent for both low and high risk groups based on previous exacerbation history. In the absence of clinical trials directly comparing the treatment pathway of LAMA to LAMA+LABA versus initiation on LAMA+LABA, the economic model was used to simulate the possible treatment journeys of an average patient. This

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				Clinical trials aim to involve a more homogeneous population than that seen in routine clinical practice. Indeed, according to a recent review of RCTs of fixed dose dual-combination bronchodilators, these studies have largely involved patients with more severe disease, e.g. moderate-to-severe air flow limitation (GOLD 2010 classification); severe-to-very-severe or moderate-to-very-severe disease and one or more exacerbations in the past year.[7] Thus the superior efficacy outcomes for dual therapy versus monotherapy reported in clinical trials may only be evident for patients with more severe disease, as recruited into these studies. Differences in efficacy outcomes between LABA+LAMA vs LAMA are likely to be less evident and possibly not clinically relevant in patients with less severe disease, but studies in such patient populations have not been performed. The studies identified in the NICE review were divided into high risk (patients hospitalized for COPD exacerbation within 12 months of study entry) and low risk groups, based on previous exacerbation history. (Of note, the GOLD classification considers two categories regarding exacerbation history – Stage C and D require ≥2 previous exacerbations or ≥1 exacerbation leading to hospitalisation; Stage A and B correspond to 0 or 1 exacerbation not leading to hospitalization.) However, only two of the studies which reported data for the comparison of LABA+LAMA vs LAMA were classified as involving high-risk populations and data for the two subgroups were generally similar. This may suggest that the criteria used in the NICE analysis to define low risk patients may not be stringent enough to identify patients who would respond to LAMA monotherapy, probably reflecting the fact that studies comparing single- and dual-agent therapy have not been performed in patients with mild disease. Thirdly, the comparison of relevance (and that considered in the economic evaluation) is a strategy involving initiation of therapy with LABA+LAMA or initiation of therapy with LAMA and moving to LAMA+LABA (i.e. LAMA to LAMA+LABA) if symptoms or exacerbations are not adequately controlled on LAMA alone. No	looked at several scenarios including starting treatment on LAMA, and stepping up to LAMA+LAMA if required. Thus, while there may be no clinical data that can be directly used to inform treatment guidelines, there is evidence from an economic model that supports the recommendations made by the committee. The actual effectiveness of a therapy in practice is likely to be less than that seen during a clinical trial, but that should apply to both bronchodilators being compared in a trial and should not therefore introduce bias in favour of one treatment over another. The usefulness of clinical trials lies in their extrapolation from a trial setting to routine clinical practice and any caveats about efficacy and safety outcomes apply to all trial data that is used in this manner. The committee were aware of the GOLD recommendations, but their decisions were made according to the NICE 2017 guideline manual and took into account the evidence provided. Although this may differ to the recommendations provided by GOLD the committee were confident that their recommendations were a reflection of the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend dual therapy as the most clinically and cost-effective option

				clinical trials have compared these two strategies. Thus, there are no clinical data that can be directly used to inform treatment guidelines. Fourthly, protocol-specified management in prospective clinical trials is unlikely to correspond to routine clinical practice. Thus monitoring, scheduling of patient assessments and management of adverse events are likely to differ in routine clinical practice compared with in a clinical trial and may have a bearing on treatment outcomes. This is a further reason why efficacy and safety outcomes as reported in clinical trials are unlikely to correspond exactly to clinical practice and means caution should be applied when extrapolating from a trial setting to routine clinical practice. This is borne in mind in the 2018 GOLD guidelines. This document reviews the available evidence for LABA+LAMA combinations and states that superior improvements in lung function and PROs have been reported for combinations vs monotherapy. However, the guidelines recommend a step-up approach to the management of patients with stage A-C disease, escalating therapy from monotherapy to dual therapy in patients with persistent symptoms or further exacerbations. Initiation with dual therapy is only recommended for patients with stage D disease. We therefore suggest that: • The available clinical data suggest that there is no clinically meaningful benefit for LAMA+LABA vs LAMA monotherapy – including in terms of terms of lung function, symptoms or HRQoL – as evident from the mean differences reported for a meta-analysis of the studies identified in the systematic review • Caution should be exercised when extrapolating from RCT data to make recommendations to guide clinical practice, and should be interpreted in the light of clinical considerations such as	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				patient heterogeneity, differences in clinical practice and the need to tailor therapy to the individual patient • This is supported by the internationally accepted GOLD guidelines and other national guidelines, both in COPD and other conditions, where clinical considerations are taken into account in addition to the evidence from clinical trials. Thus, the findings of the literature review and the meta-analysis should be interpreted to suggest that LAMA+LABA has a role in the management of patients with more severe disease, e.g. GOLD stage D at treatment initiation, or who experience symptoms and exacerbations on LAMA. However, a proportion of patients should initiate therapy with LAMA monotherapy and should be escalated to combination therapy only if appropriate based on response to monotherapy.	
Alpha-1 UK Support Group	Evidence review D	6	24	Table 1 PICO: The listing of "Alpha-1 antitrypsin" in the section "other tests" is misleading. Alpha-1 antitrypsin is a protein but not a test as such. We recommend that this wording is replaced by the specific diagnostic tests for alpha-1 antitrypsin deficiency that is referred to here, such as "serum alpha-1 antitrypsin levels", or further diagnostic tests such as phenotyping or genotyping for alpha-1 antitrypsin deficiency.	Thank you for your comment. We have amended the table to clarify this issue by referring to serum alpha 1-antitrypsin.
Boehringer-Ingelheim Ltd	Evidence Review D	26	5	The authors report that GOLD 2017 was evaluated in the clinical evidence review; however there is no mention of the prognostic value of this classification. This should be included as a research recommendation.	Thank you for your comment. We have corrected the legend for the table of included studies as no studies reporting GOLD 2017 were included in this review. The committee discussed whether to make a research recommendation in this area, but agree that since such research is already ongoing (e.g. Gedeberg et al (2018) that looked at the prediction of mortality in people with COPD using GOLD 2017) and was likely to continue, it was not necessary to make a research recommendation on this topic.
Alpha-1 UK Support Group	Evidence review D	44	5	Table Review protocol for confirming COPD diagnosis: The listing of "Alpha-1 antitrypsin" in the section "other tests" is misleading. Alpha-1 antitrypsin is a protein but not a test as such. We recommend that	Thank you for your comment. We have amended the table to clarify this issue by referring to serum alpha 1-antitrypsin.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				this wording is replaced by the specific diagnostic tests for alpha-1 antitrypsin deficiency that is referred to here, such as "serum alpha-1 antitrypsin levels", or further diagnostic tests such as phenotyping or genotyping for alpha-1 antitrypsin deficiency.	
Glaxo SmithKline	Evidence Review F And Appendix H	11-23 614-18		<u>*Summary of comments on Economic Model*</u> GSK have reviewed the economic model developed in support of the COPD guideline development. We are concerned that a significant body of clinical evidence published after November 2017 has not been included in the COPD model inputs and therefore the model conflicts with more recent clinical evidence. We would like to make the following comments on the economic model used: GSK is concerned that the model design does not explicitly address the impact of "asthmatic features" which feature prominently in the treatment algorithm. Nor does the model address how exacerbation history influences either disease progression or decisions to step up or switch treatment. It is therefore unclear the extent to which the model results have informed the guideline in these respects. GSK is also concerned that the effect on FEV_1 for triple therapy is less than the value used for LAMA+LABA when considering transition probabilities to less severe COPD health states. This is both counter-intuitive and contrary to recent clinical evidence, and could have produced anomalous results for strategies where patients are initiated on (or stepped-up to) LABA+LAMA therapy, since patients may be worse off (with respect to FEV_1) if they subsequently step up to triple therapy. Because of concerns with the modelled treatment effect on FEV1 for triple therapy, GSK would question the validity of using the results of the scenario analyses where step-up to triple is prohibited, and where the probability of the LABA+LAMA strategy being cost-	Thank you for your comment. To address your points in order: *"We are concerned that a significant body of clinical evidence published after November 2017 has not been included in the COPD model inputs…"* – The economic model used the latest available evidence at the time of development to inform the effectiveness of triple therapy. Please note that the model was used to assess the cost effectiveness of mono and dual therapy only, and triple therapy was not part of the decision space. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm. *"GSK is concerned that the model design does not explicitly address the impact of "asthmatic features" which feature prominently in the treatment algorithm"* - No clinical evidence was identified on treatment of patients with features of both

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				effective was higher, to support or inform the recommendation that patients do not receive triple therapy after LABA+LAMA in the algorithm.	COPD and asthma, and therefore economic modelling was not conducted for this group of patients. The committee's decision to recommend LABA+ICS for patients with asthmatic features was based on two factors: (1) evidence in patients with COPD shows that dual therapy is generally more effective than monotherapy (2) asthmatic features suggest steroid responsiveness, so it is logical that patients with features of both COPD and asthma should be treated with a regimen containing an ICS. *"GSK is also concerned that the effect on FEV1 for triple therapy is less than the value used for LAMA+LABA when considering transition probabilities to less severe COPD health states."* – As discussed, the latest available evidence at the time of development was used to inform the effectiveness of triple therapy. We will incorporate the newly published evidence when assessing the cost-effectiveness of triple therapy in the latest update. We were confident that data on the clinical effectiveness of triple therapy used in the economic model did not produce anomalous results, since the conclusions of the analysis did not change in the scenario analysis where stepping up to triple therapy was not permitted. Please note that the objective of this scenario analysis was not to produce recommendations on triple therapy, but to ensure that the conclusions on the cost effectiveness of mono and dual therapy were robust.
Glaxo SmithKline	Evidence Review F And Algorithm	43-44; 314-382	Lines 37-48 and 1-31	*Abbreviations used:* *BDP* *Beclomethasone* *DPI* *Dry powder inhaler* *FF* *Fluticasone* furoate *FOR* *Formeterol*	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				GLY Glycopyrronium *MDI Metered dose inhaler* *SGRQ St Georges Respiratory Questionnaire* *UMEC Umeclidinium* *VI Vilanterol* <u>*Suggested revision*</u> GSK request that NICE take into account a significant body of clinical trial evidence published since November 2017; namely, data from IMPACT and TRIBUTE (*Lipson et al 2018* and *Papi et al. 2018*). Importantly, these studies demonstrate the clinically meaningful benefit of triple therapy (ICS/LAMA/LABA) vs. dual therapies (LAMA/LABA and LABA/ICS) in patients with a history of exacerbations. Omission of this noteworthy data will mean that the guidance is immediately outdated upon publication. Moreover, the current NICE draft guidelines indicate that the ceiling of pharmacological treatment is LAMA/LABA in patients with no features of asthma despite the findings that at least 40-50% of patients with no history of asthma continue to exacerbate after one year based on data from the FLAME trial, which was within scope of the draft guidance. Building on FLAME, IMPACT demonstrates that combining ICS to LAMA/LABA significantly reduces the rate of moderate/severe exacerbations and severe hospitalised exacerbations as well as showing a signal to reduce all-cause mortality. In addition to improving patient care and health related quality of life, these important clinical outcomes may also lead to cost savings in primary and secondary care. GSKs main concern is that since November 2017 (the time parameter limiting evidence inclusion for this guideline revision) a	publication of a number of large new RCTs (including those you have cited) it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.

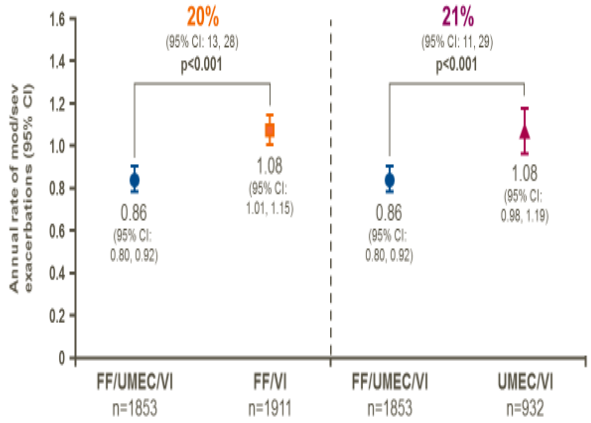
				substantial body of clinical evidence has been published which provides important clinically relevant information that needs to be taken into consideration; in particular, relating to the use of triple therapy in managing COPD patients with a history of exacerbations (*Lipson et al 2018* and *Papi et al. 2018*). Omission of this data from the evidence review will mean that the guideline is out of date even before it has been released. In the current draft of the guideline NICE recommend treatment approaches for patients which are not in line with the evidence base at the time of publication. As a result, the benefits of publishing an update to this guideline will be lost and there is the potential for significant confusion in the healthcare community when attempting to implement it. Recent data from two large RCTs (*Lipson 2018* and *Papi 2018*) which include in total 11,887 patients has shown that there is an incremental benefit from adding ICS to LAMA/LABA in COPD patients with a history of at least 1 moderate/severe exacerbation in past year. Hence, recommendations contained in the draft guidance for LAMA/LABA therapy to be the ceiling of pharmacological treatment in patients with no features of asthma who continue to be at risk of exacerbations presents a clinical concern. The incremental benefit of ICS combined to LAMA/LABA as part of single inhaler triple therapy is evident on a range of important outcomes including reductions in the rate of moderate/severe exacerbations, improvements in quality of life, improvements in lung function, and notably a reduction in severe hospitalised exacerbations and a signal on reducing all-cause mortality. *Evidence of triple therapy vs dual therapy (LAMA/LABA and LABA/ICS)* Although LAMA/LABA reduce exacerbation risk, approximately 40-50% of COPD patients receiving LAMA/LABA remain at risk of experiencing a moderate/severe exacerbation after one year	

				(*Wedzicha 2016*). IMPACT provides robust, consistent evidence for statistically significant improvements in a range of important outcomes with ICS/LAMA/LABA (FF/UMEC/VI) compared with LAMA/LABA (UMEC/VI) and ICS/LABA (FF/VI) in patients with COPD who have experienced ≥1 moderate/severe exacerbation in the past 12 months. IMPACT included 10,355 symptomatic COPD patients with a history of at least one moderate/severe exacerbation in the prior 12 months and compared single inhaler triple therapy FF/UMEC/VI with FF/VI and UMEC/VI over 52 weeks (Lipson 2018) delivered by dry powder inhaler (DPI). Single inhaler triple therapy FF/UMEC/VI showed statistically significant and clinically meaningful improvements on a range of important outcomes. In particular, FF/UMEC/VI versus UMEC/VI demonstrates: - 25% reduction in annual rate of moderate/severe exacerbations (p<0.001) - 34% reduction in annual rate of exacerbations leading to hospitalisation (p<0.001) - 42% reduction in the risk of on treatment all-cause mortality (p=0.011) - Significant improvement in lung function (54mls improvement in trough FEV1 at week 52, p<0.001) - Significant improvement in health-related quality of life at week 52 (SGRQ total score -1.8; P<0.001).	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				The benefit of triple therapy is seen in patients who have experienced one moderate/severe exacerbation in the last 12 months with a significant reduction in moderate/severe exacerbations of 20% versus FF/VI and 21% reduction versus UMEC/VI. Furthermore, this population is analogous to the population included in the FLAME study and demonstrates the benefits triple therapy can have over LAMA/LABA in the same population.  Figure 1 Moderate/severe exacerbations in patients experiencing 1 moderate/severe exacerbation in the last 12 months - *significant reduction with FF/UMEC/VI vs FF/VI and UMEC/VI* Data from the TRIBUTE study (Papi 2018) also demonstrates the benefits of triple therapy over LAMA/LABA. TRIBUTE is a study of 1,532 patients comparing twice daily single inhaler triple therapy	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				(BDP/FOR/GLY) delivered by the metered dose inhaler (MDI) device with the once daily LAMA/LABA (IND/GLY) delivered by the Breezhaler. There was a statistically significant 15% reduction in the rate of moderate/severe exacerbations in favour of the triple therapy compared with LAMA/LABA. Overall recent data indicate triple therapy is the preferred therapeutic approach compared to LAMA/LABA or ICS/LABA for symptomatic patients who have experienced an exacerbation in the past 12 months despite receiving a maintenance therapy.	
UK Clinical Pharmacy Association	Evidence review F	1	n/a	1. The statement 'Person still breathless or has exacerbations despite treatment?' needs to be quantified, as currently this is too vague and will lead to over-treatment. Symptomatic using CAT is better as more holistic assessment rather than merely just breathlessness (MRC). Need to define appropriate extent of COPD control to warrant stepping up treatment, e.g. symptoms (CAT >/=10)< breathlessness (MRC>/=3) and exacerbations (2 in 12months or 1 hospital admission). This will ensure that NICE guidelines are more in line with GOLD, so will maintain consistency compared to actual current UK practice 2. 'Asthmatic features' is the wrong terminology, as many COPD patients without asthma respond to ICS (E.g. TORCH 3.7% had reversibility, IMPACT 18%, TRIBUTE 13%). At best, this should be 'features of steroid responsiveness'. 3. Why are patients with 'asthmatic features' denied a LAMA, when the text of guideline (p51 14-19) says that the most cost-effective regimen to improve quality of life and reduce exacerbations is LAMA+LABA. LABA+ICS for 'asthma' who remain uncontrolled on SABA is not consistent with the NICE 2017 or BTS/SIGN 2016 asthma guidelines, which would recommend low dose ICS. The addition of LABA would be a second or first choice (respectively) add-on to low dose ICS. 4. It is a major failing that TRIBUTE and IMPACT have not been reviewed, so patients still symptomatic and/or exacerbating on	Thank you for your comments. 1. The committee discussed including additional information to assist prescribers to decide when a patient should transition from as needed short-acting bronchodilator therapy to a long-acting maintenance therapy. They decided that the wording of the existing recommendations were sufficient for this as they already include the information to move the patient to a long-acting therapy if they remain breathless or have exacerbations despite using a short-acting bronchodilator. The committee concluded that this was sufficiently clear to ensure that people whose symptoms could be controlled using short-acting bronchodilator would not be switched to a long-acting therapy prematurely. 2. The committee chose to use the term asthmatic features/features suggesting steroid responsiveness to highlight that people with COPD who do not have asthma may still respond to ICS. The definition of this term was kept deliberately broad by the committee and is provided in the algorithm footnote. 3. The clinical and economic evidence showed that the most effective treatment regimen was LABA+LAMA, but the committee concluded that it would be inappropriate to deny

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				LAMA+LAMA are denied further treatment, despite evidence from IMPACT and TRIBUTE demonstrating additional benefits of LAMA+LABA+ICS above LABA-LAMA in patients with high levels of COPD symptoms and frequent COPD exacerbations. 5. As the algorithm would be referred to more than the text of the document, there is a need to specify: (i) brand name prescribing to ensure consistent supply of inhaler device that the patients have been trained on and can use; and (ii) use of combination inhalers over separate inhalers as the cheapest / most cost-effective option for the NHS and patients. 6. 'Explore further treatments…' This box fails to acknowledge other COPD medicines such as mucolytic, roflumilast, 'prophylactic' antibiotics, so could be forgotten about very easily 7. The key at the bottom: '*Features suggesting steroid responsiveness….' doesn't match the title in the flow chart - i.e. 'Asthma features' is not the same as 'features suggesting steroid responsiveness'. This needs to be consistent.	people with asthmatic features/features suggesting steroid responsiveness treatment with ICS. They therefore recommended that these people be prescribed LABA+ICS. They would be able to move onto triple therapy using an existing recommendation if this treatment combination was insufficient. 4. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm. 5. Recommendations at the end of the inhaled combination therapies section cover the issues you have raised about brand name prescribing and cost, however, due to space constraints, we are limited in the amount of detail that can be covered in the algorithm. It is assumed that medical staff will consult the full guideline for more detail. **6.** The treatments you raise were not included as the list of further treatment options was not intended to be exhaustive. Based on consultation feedback we have removed the

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					surgery example to prevent undue weight being given to a single treatment. 7. The terminology in the algorithm around asthmatic features/features suggesting steroid responsiveness has been updated to be consistent with that used in the guideline.
Chiesi Ltd	Evidence review F	7	2	A combination of ICS + LABA + LAMA has not been included within the review question for inhaled therapy combinations. Given the proposed treatment algorithm suggests a position for triple therapy within the treatment pathway for patients with COPD, it is worrying that it's comparative effectiveness against other inhaled therapies has not been assessed. A strong body of evidence exists for triple therapy combinations and this should have been evaluated as part of the review process.	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
Chiesi Ltd	Evidence review F	11	7	Studies evidencing the efficacy and safety of triple therapy combinations have been excluded from the evidence review. We suggest including the following studies for review, to allow for the place of triple therapy within the algorithm to be fairly and accurately assessed: • TRILOGY study: Singh et al. Lancet, 2016; 388(10048): 963-973 • TRINITY study: Vestbo et al. Lancet, 2017; 389(10082): 1919-1929 • TRIBUTE study: Papi et al. Lancet, 2018; 391(10125): 1076-1084	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs (including those you have cited) it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				• IMPACT study: Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680 • FULFIL study: Lipson et al. Am J Respir Crit Care Med, 2017; 196(4):438-446	A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
Boehringer-Ingelheim Ltd	Evidence review F	24	4	It is stated in Evidence Review F that for LABA/LAMA vs LAMA there was 'no meaningful difference in the change in FEV_1, TDI or SGRQ score…'. However, the identified MIDs (Table 15, page 64, line 26) are all measurements that have all been originally designed to assess whether an active treatment was superior to a placebo treatment. It is only recently with the development of the LAMA/LABA class that these parameters, particularly TDI and SGRQ, have been used to aid in the assessment of a combination of two active drugs compared to a single active drug. Discussion with clinical experts around this issue has suggested that the MCIDs as presented here should not be applied when considering the efficacy of a combination compared to a monotherapy: as highlighted in the evidence review, LAMA/LABA combinations have consistently demonstrated statistically significant differences in lung function, TDI and SGRQ score compared to LAMA and LABA monotherapy. Assessing the MCID between LAMA/LABAs and LAMA or LABA monotherapy may be a useful recommendation for research.	Thank you for your comment. We are aware that the minimal important differences used in this review were originally designed to assess whether an active treatment was superior to a placebo treatment. In the absence of minimal important differences for comparing combinations of active drug treatments it was concluded that the existing minimal important differences would still provide useful information to the committee to help them with their discussion of the evidence. However, the guideline development group also highlighted the comparisons where significant differences between interventions were detected that fell below the minimal important difference thresholds. This can be seen clearly in the network meta-analysis summaries in appendix N. In addition, the use of an economic model allowed synthesis of the data across outcomes and did not rely on minimal important differences. We have added a sentence to the discussion of the benefits and harms section to clarify this point about minimal important differences. The committee decided not to make a research recommendation on this point because there were a number of higher priority issues for research that they felt should be addressed.
Chiesi Ltd	Evidence review F	38	26	Recommendation F5 for the use of LAMA+LABA+ICS is not evidenced base. No evidence on the comparative efficacy or safety of triple therapy has been evaluated in this evidence review.	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				We suggest including the following studies for review, to allow for the place of triple therapy within the algorithm to be fairly and accurately assessed: • TRILOGY study: Singh et al. Lancet, 2016; 388(10048): 963-973 • TRINITY study: Vestbo et al. Lancet, 2017; 389(10082): 1919-1929 • TRIBUTE study: Papi et al. Lancet, 2018; 391(10125): 1076-1084 • IMPACT study: Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680 • FULFIL study: Lipson et al. Am J Respir Crit Care Med, 2017; 196(4):438-446	was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs (including those you have cited) it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
Chiesi Ltd	Evidence review F	38	35	Many patients will have been historically trained to use pressurised metered dose (pMDI) inhalers. The proposed algorithm which only specifies LABA + LAMA use for those with no asthmatic features would mean a large number of patients would need additional training on how to use a potentially unfamiliar device type. Given the resources available, this may pose a challenge in training such a large number of patients.	Thank you for your comment. The committee did not intend that people currently using a LAMA inhaler would be switched automatically to a LAMA+LABA inhaler, rather that this change would occur if/when their symptoms were not controlled. This is reflected in recommendation 1.2.13. People starting long-acting therapy for the first time would begin with LAMA+LABA. Therefore, the numbers of people needing training in the use of new inhaler type should be fewer than in your comment as this will be a gradual process rather than a wholesale rapid switch.
Chiesi Ltd	Evidence review F	39	29	LAMA+LABA dual therapy is not indicated for the prevention of exacerbations. Therefore, giving direction to clinicians to prescribe off-label without highlighting this fact could have potential medico-legal consequences for prescribers and safety implications for patients. This impact on practice should be noted in this section of the evidence review. Guidance issued by the MHRA advises prescribers to “be satisfied that such use would better serve the patient’s needs than an	Thank you for your comment. The committee were confident, based on the large number of trials for these treatments measuring a wide range of outcomes (including breathlessness, exacerbations and adverse events) measured for all the treatment options, that the recommendations were an appropriate reflection of the clinical and economic evidence. The committee also concluded that these medicines are already in common use for people with COPD, and

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				appropriately licensed alternative before prescribing a medicine off-label"[1] Furthermore, regulators did not grant LABA+LAMA combination therapies with a licence for prevention of exacerbations due to insufficient evidence to support this indication. [2-5] [1] MHRA. 2009. Off-label or unlicensed use of medicines: prescribers' responsibilities. Available from: https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities [Accessed 12/07/18] [2] Duaklir Genuair 340/12 micrograms inhalation power. Summary of Product Characteristics. Feb 2018. [3] Anoro Ellipta 55/22 micrograms inhalation powder. Summary of Product Characteristics. July 2017. [4] Spiolto Respimat 2.5/2.5 micrograms, inhalation solution. Summary of Product Characteristics. March 2017. [5] Ultibro Breezhaler 85/43 micrograms, inhalation powder hard capsules. Summary of Product Characteristics. May 2018.	prescribers should be familiar with the benefits and risks associated with using them.
Chiesi Ltd	Evidence review F	40	3	The key outcome for people with COPD has been stated to be breathlessness. Whilst we do not disagree that this is an important outcome for those people living with COPD, we also highlight that exacerbations negatively impact on health status, rates of hospitalisation, readmission and disease progression and therefore should be considered with equal importance.[1] Severe exacerbations requiring hospitalisation have been shown to be independently associated with all-cause mortality in patients with COPD.[2] [1]GOLD report 2018 Report [2] Soler-Cataluna et al. Thorax, 2005; 60: 925-931	Thank you for your comment. The committee concluded that breathlessness was a key outcome, but that other outcomes, including the risk of exacerbations, were also of particular importance for these review questions. The summary of the committee discussions of the evidence also highlights that the committee concluded that it was important not to consider individual outcomes in isolation, but to consider the overall impact on quality of life, as estimated in the economic model.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Chiesi Ltd	Evidence review F	40	14	Triple therapy was considered outside the scope of the guideline. However, studies evidencing the efficacy and safety of triple therapy combinations are available. We suggest including the following studies for review, to allow for the place of triple therapy within the algorithm to be fairly and accurately assessed: • TRILOGY study: Singh et al. Lancet, 2016; 388(10048): 963-973 • TRINITY study: Vestbo et al. Lancet, 2017; 389(10082): 1919-1929 • TRIBUTE study: Papi et al. Lancet, 2018; 391(10125): 1076-1084 • IMPACT study: Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680 • FULFIL study: Lipson et al. Am J Respir Crit Care Med, 2017; 196(4):438-446	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs (including those you have cited) it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
Chiesi Ltd	Evidence review F	44	15	The guideline recommends offering triple therapy (LAMA+LABA+ICS) only to those who remain breathless or have exacerbations despite taking a LABA+ICS and who have asthmatic features/features suggesting steroid responsiveness. However, no additional recommendation is provided for those who still remain breathless or have exacerbations despite using a dual bronchodilator therapy (LABA+LAMA). There is evidence to support the use of triple therapy over and above a dual bronchodilator in providing additional exacerbation reduction and improved quality of life: The TRIBUTE study showed a significant 15% reduction in the rate of moderate-to-severe exacerbations (RR: 0.848, 95% CI 0.723-0.995, p=0.043) and an improvement in mean SGRQ total score (adjusted mean difference: -1.68, p≤0.001) with single inhaler triple	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs (including those you have cited) it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				therapy (beclometasone/formoterol/glycopyrronium) compared to a dual bronchodilator (indacaterol/glycopyrronium). It is worth noting that these results were found in patients without a current diagnosis of asthma, [1] thereby supporting the use of triple therapy in patients without asthmatic features. The IMPACT study showed similar beneficial effects with a 25% reduction in the rate of moderate-to-severe exacerbations (RR: 0.75, 95% CI 0.70 to 0.81, p<0.001) and an improvement in mean SGRQ total score (mean difference: -1.8, 95% CI -2.6 to -1.0, p<0.001) with single inhaler triple therapy (fluticasone furoate/umeclidinium/vilanterol) compared to a dual bronchodilator (umeclidinium/vilanterol). [2] We would therefore recommend considering the inclusion of a further step to triple therapy from a LABA+LAMA in those patients who remain breathless or have exacerbations. [1] Papi et al. Lancet, 2018; 391(10125): 1076-1084 [2] Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680	be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
Chiesi Ltd	Evidence review F	46	29	The committee have appraised the mortality benefit shown with an LABA+ICS compared with a LAMA+LABA. The committee considered the plausibility of this and decided that this was largely seen in one study only (Wedzicha et al, 2008). We encourage the committee to review other evidence which support the mortality benefit of inhaled corticosteroid-containing medications. Although narrowly missing its primary endpoint, the TORCH study[1] showed a signal towards a favourable benefit of inhaled corticosteroids compared to placebo (p=0.052). Whilst the IMPACT study showed that all-cause mortality was significantly lower with both the inhaled corticosteroid-containing arms compared with the LABA/LAMA arm (p=0.01 Triple therapy vs LABA/LAMA, and p=0.02 ICS/LABA vs LABA/LAMA).[2]	Thank you for your comment. There was a point estimate of mortality benefit with LABA/ICS compared to LAMA for both high and low risk groups, but the 95% CI of the low risk group crossed the line of no effect. The high risk group included 2 studies, Wedzicha 2008 and Pepin 2014, and here there was a reduction in the risk of mortality overall, but this was due to the large Wedzicha 2008 trial, as the Pepin 2014 study had a large confidence interval that crossed the line of no effect. Therefore, of the 4 included studies only Wedzicha 2008 showed a reduction in the risk of mortality with LABA/ICS compared to LAMA. The IMPACT study was published after the last search date for this review (March 2018). We are unable to include this

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				[1] Calverley PM et al. N Engl J Med, 2007; 356(8): 775-89. [2] Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680	trial in the analysis in this update of the guideline as we have not performed a systematic search for trials published after March 2018. However, if we look at the effects that adding this trial would have on the meta-analysis for mortality in the high risk group of people taking LAMA/LABA versus LABA/ICS, the RR (95% CI) would change from 1.00 (0.57, 1.76) to 1.34 (0.96, 1.87) and the pooled RR for both low and high risk groups would change from 1.03 (0.63, 1.68) to 1.32 (0.96, 1.80). This does not support the conclusion that there is a clear benefit in reduced mortality from taking LABA/ICS compared to LAMA/LABA. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
Chiesi Ltd	Evidence review F	47	32	The committee have agreed that it would be appropriate to revisit the place of triple therapy in a future guideline update, especially given the recent evidence on the effectiveness of fixed triple therapy. We support the proposal to evaluate this recent evidence, however given this evidence is all fully published (indeed fixed-triple therapy trials were available prior to the scoping of this guideline),	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				we encourage the committee to review the data in this update of the guideline, given its importance in determining the place of triple therapy in the COPD treatment pathway.	publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated.
Chiesi Ltd	Evidence review F	73	16	The committee have used an out-dated spelling of "beclomethasone" in the search strategy to identify relevant clinical trials for this evidence review. Please also note that the search term "beclometasone" should have been included in order to capture all relevant trials.	Thank you for your comment and for pointing this out. We will update this search term in future, but we are confident that no trials have been missed in the current review as a result of this issue.
Boehringer-Ingelheim Ltd	Evidence review F	300	n/a	It is stated for the Singh (2015a) study (OTEMTO) that there is an "unclear risk of bias: study states that it is double-blind, but no details are provided", and on the following page states that there is high and moderate risk of bias to SGRQ and TDI outcomes as a consequence. We would like to clarify any questions about the study blinding by providing the information directly from the Clinical Study Report: "Patients, investigators, and everyone involved in analysing or with an interest in this double-blind trial were to remain blinded with regard to the randomisation treatment assignments until after database lock. BI generated the randomisation schedule, and prepared and coded the medication in a blinded fashion. Study medication was assigned to the patients via the IRT (interactive response technology) system." "The ability to unblind was available to the investigator/deputy and to BI Global Pharmacovigilance via the IRT system. Unblinding was only be used in emergency situations when the investigator needed to know the identity of the study medication in order to provide appropriate medical treatment." No subjects were unblinded during the trial.	Thank you for your comments. We have incorporated this information into the LAMA monotherapy review and updated the risk of bias for OTEMTO 1 and 2 accordingly.
Pulmonx Corporation	Evidence review F - Forest	110	Forest plot risk	The graphic should be corrected to show results favouring EBV for the collateral ventilation negative patients (3.12.1) and favouring Usual Care for collateral ventilation positive patients (in 3.12.2).	Thank you for your comment. The axis on this forest plot has been changed to show results favouring EBV.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

	Plots; Endobronchial valves		Ratio – Improvement in FEV1		
Pulmonx Corporation	Evidence review F - Forest Plots; Endobronchial valves	114	Forest plot risk Ratio – Improvement in SGRQ by 4 points	The legend under the forest plot is reversed – it should favour EBV and not Usual care as stated	Thank you for your comment. The axis on this forest plot has been changed to show results favouring EBV.
NHS Central London CCG	Evidence review F - Inhaled therapies Evidence review F - Inhaled therapies	40 47-48	14 52, 1-5	Unfortunately, omitting triple therapy from the scope of the guideline update may well have undesirable consequences. Manufacturers of triple inhalers are marketing them intensively and inappropriate adoption of triple inhalers by prescribers is likely to waste a lot of NHS funds over the next few years. See comment below for an explanation of the mechanisms that will lead to waste. Irrespective of whether or not the guideline covers triple therapy and triple inhalers (long acting beta-2 agonist + long acting muscarinic antagonist + corticosteroid; LABA + LAMA + ICS), manufacturers of triple inhalers and 'opinion leaders' are likely to cite any recommendation by NICE to minimise the number of inhalers as an endorsement of triple inhalers. Adoption of triple inhalers by prescribers is likely to waste a lot of NHS funds over the next few years. For this reason, please omit any recommendation to minimise the number of inhalers. The rationale for the statement above about waste is as follows:	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

	Evidence review F - Inhaled therapies	47	19-21	Both marketed triple inhalers include drugs which will not come off patent for many years: • Umeclidinium 2029 • Glycopyrronium 2027 Therefore we will not see branded generic competition for many years, and we are unlikely to see large reductions from the current price of £540 per patient per year (all prices cited here were correct as of June 2018). Using triple inhalers will tie us to a high price for many years. Lower cost branded generic corticosteroid, LABA + corticosteroid, and tiotropium inhalers are available and we would expect competition to lead to further price reductions over the next few years. Beclometasone inhalers are not licensed for COPD, but beclometasone is a component of both Fostair and Trimbow which are licensed for COPD. Some will think it reasonable to prescribe triple therapy as: [LAMA + LABA] inhaler + beclometasone inhaler (price £395 + £108 = £503 p.a., i.e. less than the price of the triple inhalers). Some will want to only prescribe products that are licensed for treatment of COPD, e.g. Fluticasone/vilanterol (Relvar) inhaler + tiotropium (Braltus) inhaler (current price £268 + £314 = £582 p.a., but we would expect lower priced LABA + ICS and tiotropium inhalers in the next few years). If, based partly on any NICE recommendation to minimise the number of inhalers, triple inhalers are added to formularies and widely prescribed, increased waste of NHS money is also likely to occur via a second mechanism: triple inhalers are likely to be	The recommendation in 1.2.15 to 'minimise the number of inhalers and the number of different types of inhaler used by each person as far as possible' is not an endorsement of triple inhalers and, based on the current algorithm in the guideline, triple therapy is only recommended for the relatively small group of people who have been taking LABA/ICS.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				prescribed for many patients for whom NICE's guideline does not recommend triple therapy. In reality, most of the NHS does not have an effective way of preventing this spread if the inhalers are on formularies. Patients prescribed triple inhalers outside of NICE's recommendation may be exposed to an avoidable increased risk of pneumonia. An RCT showed no outcome benefit of giving triple therapy as a single inhaler rather than two inhalers: Vestbo J, Papi A et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. Lancet 2017; 389: 1919-29. Recommending LABA + LAMA as first line, together with a recommendation to minimise the number of inhalers, will undermine the savings potential that branded generic tiotropium inhalers and branded generic LABA inhalers will give the NHS. Marketed LABA + LAMA inhalers all include drugs with long remaining patent durations.	
Boehringer-Ingelheim Ltd	Evidence review F: inhaled therapies	8	3	Please be aware of a systematic literature review currently ongoing on the inhaled therapies in COPD (mono, dual and triple therapies). The protocol has been registered in PROSPERO and is under peer journal review.	Thank you for your comment. We have passed this information to our surveillance team to help inform subsequent updates of this guideline.
Boehringer-Ingelheim Ltd	Evidence review F: inhaled therapies	8	36	"This review only includes drugs and doses licenced in the USA and EU". It is not clear whether doses not available in the UK have been used in this analysis. If so, we would like to see sensitivity analyses performed to inform UK/EU practices.	Thank you for your comment. This review was carried out as a collaboration with the Cochrane Airways Group and all of the data extraction was carried out by their clinical expert. All doses licensed in the USA and EU were included in the analysis, but it was concluded that restricting to only doses currently in the UK would be highly unlikely to make a substantial difference to the results of the analysis.
Boehringer-Ingelheim Ltd	Evidence review F:	16	20	We observe that there is no comparison between LAMA+LABA and LABA+ICS for treatment switching. This transition is shown in the	Thank you for your comment. The model did incorporate switching between LAMA+LABA and LABA+ICS. The

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

	inhaled therapies			figure (p18, line 1). We would like to see this taken into account in the model as we feel clinicians would appreciate guidance in this area.	descriptions of treatment strategies that you refer to on page 16 are defined according to stepping-up decisions (i.e. what happens when a new treatment is added). This was because there was ambiguity in the stepping-up decision from monotherapy to dual therapy. For example, LABA could step up to LAMA+LABA or to LABA+ICS, therefore giving two mutually exclusive strategies for patients starting on a LABA. In all strategies, patients on LAMA+LABA could switch to a LABA+ICS, and vice versa.
Boehringer-Ingelheim Ltd	Evidence review F: inhaled therapies	16	30	We would like to see mapping following the new GOLD 2017 guidelines, including FEV_1, symptoms and exacerbation history.	Thank you for your comment. We agree that it would have been an interesting exercise to develop an economic model based on the GOLD A-D categories. We based the economic model structure on the GOLD 1-4 stages defined by FEV1 % predicted for the following reasons: (1) The majority of existing clinical evidence is reported in terms of GOLD defined by FEV1 % predicted. (2) The GOLD A-D stages relate to multiple factors (FEV1, risk of exacerbations, and breathlessness), which would make modelling transitions between these stages over time difficult. (3) In the evidence review on predicting outcomes using multidimensional severity assessments, the committee determined that the GOLD A-D categorisation was not as useful as the GOLD 1-4 system in predicting COPD outcomes.
Boehringer-Ingelheim Ltd	Evidence review F: inhaled therapies	18	1	We would like to see switching between LAMA+LABA and LABA+ICS included in this guideline.	Thank you for your comment. The guideline did not contain a review question on switching between LAMA+LABA and LABA+ICS and so no recommendations could be made on this topic. However, in all strategies in the economic model, patients on LAMA+LABA could switch to a LABA+ICS, and vice versa.
Boehringer-Ingelheim Ltd	Evidence review F:	20	11	The treatment switching between LAMA+LABA and LABA+ICS is not reported in the results sections.	Thank you for your comment. Switching between LAMA+LABA and LABA+ICS was permitted in the economic

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

	inhaled therapies				model. As this transition was permitted in all strategies, it did not constitute a mutually exclusive option. Therefore, results are not reported comparing a scenario in which switching is allowed between dual therapies to one in which it is not. We felt that it would be inappropriate to include such a comparison, as patients typically switch between treatments due to intolerability or adverse events, and the model was not set up to distinguish specific subgroups of patients for whom switching might be appropriate.
Boehringer-Ingelheim Ltd	Evidence review F: inhaled therapies	25	3	Typo LABAICS instead of LABA/ICS	Thank you for your comment. We have corrected this error.
Boehringer-Ingelheim Ltd	Evidence review H: Economic model report	General	General	The economic model developed for this clinical guideline has been done following a very high standard and the uncertainties have been handled very well. The report is well written and giving all the necessary details to understand in depth the work undertook by the guideline team.	Thank you for your comment. We welcome your support of the economic evaluation.
Boehringer-Ingelheim Ltd	Evidence review H: Economic model report	7	Comparators	The report states: “Accounting for this uncertainty in the number of possible treatment strategies provides a total of 6 mutually exclusive options”. It would have been very useful to see the switching option from LAMA+LABA and LABA+ICS	Thank you for your comment. Switching between LAMA+LABA and LABA+ICS was permitted in the economic model.
Boehringer-Ingelheim Ltd	Evidence review H: Economic model report	7	Model structure	“The model uses a Markov structure, with states based on GOLD severity stages defined by FEV1 percent predicted”. The updated GOLD 2017 Guidelines use FEV1, symptoms and exacerbations to grade COPD severity and it would have been interesting to include this.	Thank you for your comment. We agree that it would have been an interesting exercise to develop an economic model based on the GOLD A-D categories. We based the economic model structure on the GOLD 1-4 stages defined by FEV1 % predicted for the following reasons: (1) The majority of existing clinical evidence is reported in terms of GOLD defined by FEV1 % predicted. (2) The GOLD A-D stages relate to multiple factors (FEV1, risk of exacerbations, and breathlessness),

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					which would make modelling transitions between these stages over time difficult. (3) In the evidence review on predicting outcomes using multidimensional severity assessments, the committee determined that the GOLD A-D categorisation was not as useful as the GOLD 1-4 system in predicting COPD outcomes.
Boehringer-Ingelheim Ltd	Evidence review H: Economic model report	9	Incorporating treatment effects	Please be aware of a systematic literature review currently ongoing on the inhaled therapies in COPD (mono, dual and triple therapies). The protocol has been registered in PROSPERO and is under peer journal review.	Thank you for your comment. We have passed this information to our surveillance team to help inform subsequent updates of this guideline.
Boehringer-Ingelheim Ltd	Evidence review H: Economic model report	9	Figure 2	It is unclear whether the treatment switching between LAMA+LABA and LABA+ ICS has been taken into account in this model.	Thank you for your comment. Switching between LAMA+LABA and LABA+ICS was permitted in the economic model.
Boehringer-Ingelheim Ltd	Evidence review H: Economic model report	10	Uncertainty	The report states: "For base-case results, structural uncertainty in implementing treatment benefit was also addressed stochastically, using the methodology described by Bojke et al (2009), by randomly selecting 1 of the 5 treatment benefit scenarios for each probabilistic iteration." It is unclear whether the number of iterations is sufficient to stabilise the results in the different benefit scenarios. Further clarification would be welcomed.	Thank you for your comment. We have re-run the analyses which select stochastically between the treatment scenarios using 5,000, rather than 1,000 iterations. This did not affect the conclusions of the model.
Boehringer-Ingelheim Ltd	Evidence review H: Economic model report	14	Table 2	GOLD stages defined as FEV1% in mild, moderate, severe and very severe. It would be interesting to see the mapping done with the new GOLD A,B,C and D classifications.	Thank you for your comment. We agree that it would have been an interesting exercise to develop an economic model based on the GOLD A-D categories. We based the economic model structure on the GOLD 1-4 stages defined by FEV1 % predicted for the following reasons: (1) The majority of existing clinical evidence is reported in terms of GOLD defined by FEV1 % predicted. (2) The GOLD A-D stages relate to multiple factors (FEV1, risk of exacerbations, and breathlessness),

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					which would make modelling transitions between these stages over time difficult. (3) In the evidence review on predicting outcomes using multidimensional severity assessments, the committee determined that the GOLD A-D categorisation was not as useful as the GOLD 1-4 system in predicting COPD outcomes.
Boehringer-Ingelheim Ltd	Evidence review H: Economic model report	19	Drug costs	The report states: "We relaxed this assumption in a scenario analysis where 25% of patients on dual therapy were assumed to use 2 separate inhaler devices". We would be interested to know if this assumption has been validated by clinicians.	Thank you for your comment. The committee felt that the large majority of patients treated with dual therapy would use a single fixed-dose combination inhaler in practice. This is why the base case analysis makes the assumption that all patients use a single inhaler. The purpose of the sensitivity analysis was to explore whether using costs of two separate inhalers for some patients would materially affect results.
Boehringer-Ingelheim Ltd	Evidence review H: Economic model report	27	Stable utilities	The approach of the committee to reflect the differences in quality of life between the GOLD stages is pragmatic. Bringing the clinical expertise into the interpretation of the utility scores is welcome and will give a more practical sense to the results of this modelling exercise.	Thank you for your comment. We welcome your support of the methodology.
Boehringer-Ingelheim Ltd	Evidence review H: Economic model report	33	Table 23	The report states: "Since triple therapy was not included in the NMA, we obtained treatment effects for this regimen from alternative sources. Where possible, we took outcomes from a Cochrane review comparing triple therapy with LAMA monotherapy (Rojas-Reyes et al., 2016)" Please be aware of a systematic literature review currently ongoing on the inhaled therapies in COPD (mono, dual and triple therapies). The protocol has been registered in PROSPERO and is under peer journal review.	Thank you for your comment. We have passed this information on to the NICE surveillance team, to inform future decisions about updates of the guideline.
Boehringer-Ingelheim Ltd	Evidence review H: Economic model report	39	Treatment effect on switching and	The report states: "Contrastingly, treatment switching generally occurs due to adverse events or intolerance". There is no consideration given to the withdrawal of ICS in COPD patients that do not demonstrate ICS responsiveness or exhibit any 'asthmatic features'.	Thank you for your comment. The committee felt that treatment stepping-down occurs relatively infrequently in practice, so was not included in the model. Moreover, the economic model is based specifically on a population of patients with COPD, rather than with symptoms of both

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

			stepping up		COPD and asthma, as we did not identify any evidence on such patients.
Neurocare Europe Ltd	General	General	General	Clinical trial data presented in support of the above observations Home based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD) J A Neder, D Sword, S A Ward, E Mackay, L M Cochrane, C J Clark Thorax 2002;57:333–337 RESULTS: All patients were able to complete the NMES training programme successfully, even in the presence of exacerbations (n=4). Training was associated with significant improvements in muscle function, maximal and endurance exercise tolerance, and the dyspnoea domain of the CRDQ ($p<0.05$) Improvements in muscle performance and exercise capacity after NMES correlated well with a reduction in perception of leg effort corrected for exercise intensity ($p<0.01$) CONCLUSIONS: For severely disabled COPD patients with incapacitating dyspnoea, short term electrical stimulation of selected lower limb muscles involved in ambulation can improve muscle strength and endurance, whole body exercise tolerance, and breathlessness during activities of daily living. Respir Med. 2014 Apr;108(4):609-20. doi: 10.1016/j.rmed.2013.12.013. Epub 2014 Jan 2.Neuromuscular electrical stimulation improves clinical and physiological function in COPD patients. Vieira PJ[1], Chiappa AM[2], Cipriano G Jr[3], Umpierre D[1], Arena R[4], Chiappa GR[5]. RESULTS :Compared with the control group, NMES increased FEV1 and FEV1/FVC, 6-MWD and Tlim ($P < 0.01$) and reduced BDS and SGRQ ($P < 0.01$). Additionally, changes in the Tlim were positively correlated with respiratory improvements in FEV1 (rho =	Thank you for your comment. These articles do measure functional outcomes that were considered important by the committee. However, these fall within the exclusion criteria of trials lasting less than a 12 week duration. This time period was chosen by the committee to ensure that recommendations reflected the long-term, rather than acute, effects of interventions. Full details of the protocol for this review can be found in Appendix A of the self-management, education and telehealth evidence review.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				0.48, P < 0.01). Also, NMES reduced TNF-α and increased β-endorphin levels, compared with the control group (P < 0.001). *CONCLUSION:In summary, 8 weeks of NMES promotes reduction of the perceived sensation of dyspnea during exercise in patients with COPD. This finding is accompanied by improvements in FEV1, exercise tolerance and quality of life, and DH. Interestingly, these findings may be associated with enhanced vasodilatory function and a reduction in inflammatory responses*. Chest. 2013 Feb 1;143(2):485-93. Benefits of neuromuscular electrical stimulation prior to endurance training in patients with cystic fibrosis and severe pulmonary dysfunction.Vivodtzev I[1], Decorte N, Wuyam B, Gonnet N, Durieu I, Levy P, Cracowski JL, Cracowski C. *CONCLUSIONS:NMES training performed prior to endurance training is useful for strengthening peripheral muscles, which in turn may augment gains in body weight and quality of life, further reductions in ventilation requirements during exercise, and retard insulin resistance in patients with CF with severe pulmonary obstruction.* Chest. 2012 Mar;141(3):716-25. doi: 10.1378/chest.11-0839. Epub 2011 Nov 23.Functional and muscular effects of neuromuscular electrical stimulation in patients with severe COPD: a randomized clinical trial. Vivodtzev I[1], Debigaré R, Gagnon P, Mainguy V, Saey D, Dubé A, Paré MÈ, Bélanger M, Maltais F. CONCLUSIONS: In patients with severe COPD, NMES improved muscle CSA. This was associated with a more favorable muscle anabolic to catabolic balance. Improvement in walking distance after NMES training was associated with gains in muscle strength, reduced ventilation during walking, and the ability to tolerate higher stimulation intensity.	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				Tuberk Toraks. 2015;63(1):1-7.Comparison of the effects of neuromuscular electrical stimulation and endurance training in patients with severe chronic obstructive pulmonary disease.Kaymaz D[1], Ergün P, Demirci E, Demir N. RESULTS:After the PR program, walking distance and endurance time significantly increased in both groups (p< 0.001 for each), whereas the MRC scores of both groups significantly decreased (p< 0.001 for each). In the ET group, significant decreases were noted in all domains of SGRQ and HADS. In the NMES group, significant improvements were observed in the HADS scores and in all SGRQ domain except symptom domain. CONCLUSION:NMES can be used as an effective treatment strategy in PR programs for peripheral muscle training in patients with severe COPD. Int J Chron Obstruct Pulmon Dis. 2016 Jun 3;11:1189-97. doi: 10.2147/COPD.S105049. eCollection 2016.Home-based neuromuscular electrical stimulation improves exercise tolerance and health-related quality of life in patients with COPD. Coquart JB[1], Grosbois JM[2], Olivier C[3], Bart F[4], Castres I[1], Wallaert B[3] RESULTS :The study revealed that NMES significantly improved functional mobility (-18.8% in GNMES and -20.6% in GUEPE), exercise capacity (+20.8% in GNMES and +21.8% in GUEPE), depression (-15.8% in GNMES and -30.1% in GUEPE), and overall HRQoL (-7.0% in GNMES and -18.5% in GUEPE) in the patients with COPD, regardless of the group (GNMES or GUEPE) or severity of airflow obstruction. Moreover, no significant difference was observed between the groups with respect to these data (P>0.05).	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				CONCLUSION:Home-based PR including self-monitored NMES seems feasible and effective for severely disabled COPD patients with severe exercise intolerance. Effectiveness of Neuromuscular Electrical Stimulation on Auxiliary Respiratory Muscles in Patients with Chronic Obstructive Pulmonary Disease Treated in the Intensive Care Unit Dilek KOÇAN KURTOĞLU1 , Nurettin TAŞTEKİN1 , Murat BİRTANE1 , Erhan TABAKOĞLU2 , Necdet Abstract Objective: Chronic obstructive pulmonary disease is a major public health problem. In the present study, we aimed to investigate the possible effects of upper extremity exercises and neuromuscular electrical stimulation therapy applied to auxiliary respiratory muscles on arterial blood gases, blood pressure, heart rate values, and quality of life in patients with chronic obstructive pulmonary disease Results: There were statistically significant improvements in peak heart rate, breathing frequency per minute, and functional independency scores in the group where exercise and neuromuscular electrical stimulation had been concomitantly applied. Clin Respir J. 2015 Nov 24. doi: 10.1111/crj.12411. [Epub ahead of print]Efficacy of Neuromuscular Electrical Stimulation in Patients with COPD Followed in Intensive Care Unit. Akar O[1], Günay E[1], Ulasli SS[1], Ulasli AM[2], Kacar E[3], Sariaydin M[1], Solak Ö[2], Celik S[4], Ünlü M[1].	

				RESULTS: Lower extremity muscle-strength was significantly improved in Group-1 (from 3.00 to 5.00, P=0.014) and 2 (from 4.00 to 5.00, P=0.046). Upper extremity muscle strength was also significantly improved in all three groups (from 4.00 to 5.00 for all groups, P=0.038, P=0.046 and P=0.034, respectively). Duration of mobilization and discharge from the ICU were similar among groups. There was a significant decrease in serum IL-6 level in Group-1 and in serum IL-8 level in group-1&2 after rehabilitation. *CONCLUSION:This study indicates that pulmonary rehabilitation can prevent loss of muscle strength in ICU. Nevertheless, we consider that further studies with larger populations are needed S and/or active and passive muscle training in bedridden ICU patients who are mechanically ventilated.* Int J Chron Obstruct Pulmon Dis. 2016 Nov 28;11:2965-2975. eCollection 2016. Effectiveness of neuromuscular electrical stimulation for the rehabilitation of moderate-to-severe COPD: a meta-analysis. Chen RC[1], Li XY[1], Guan LL[1], Guo BP[1], Wu WL[1], Zhou ZQ[1], Huo YT[1], Chen X[2], Zhou LQ[1]. Results We extracted data from 276 patients. NMES contributed to statistically improved quadricep strength (standardized mean difference 1.12, 95% confidence interval [CI] 0.64-1.59, I^2=54%; P<0.00001) and exercise capacity, including longer exercise distance . Lancet Respir Med. 2016 Jan;4(1):27-36. doi: 10.1016/S2213-2600(15)00503-2. Epub 2015 Dec 15.Neuromuscular electrical stimulation to improve exercise capacity in patients with severe COPD: a randomised double-blind, placebo-controlled trial.Maddocks M[1], Nolan CM[2], Man WD[2], Polkey MI[3], Hart N[4], Gao W[5], Rafferty GF[6], Moxham J[6], Higginson IJ[5]. Findings :Change in 6MWT distance was greater in the active NMES group (mean 29·9 [95% CI 8·9 to 51·0]) compared with in the placebo group (-5·7 [-19·9 to 8·4]; mean difference at 6 weeks 35·7	

				m [95% CI 10·5 to 60·9]; p=0·005). Sensitivity analyses for complete-cases and adjustment for baseline values showed similar results. Interpretation : NMES improves functional exercise capacity in patients with severe COPD by enhancing quadriceps muscle mass and function. These data support the use of NMES in the management of patients unable to engage with conventional pulmonary rehabilitation. More work is needed to study how to maintain the effect. Conclusion :NMES appears an effectual means of enhancing quadricep strength and exercise capacity in moderate-to-severe COPD patients. Further research is demanded to clarify its effect on other outcomes and determine the optimal parameters for an NMES program. Thorax. 2014 Jun;69(6):525-31. doi: 10.1136/thoraxjnl-2013-204388. Epub 2014 Jan 7. Efficacy of lower-limb muscle training modalities in severely dyspnoeic individuals with COPD and quadriceps muscle weakness: results from the DICES trial. Sillen MJ[1], Franssen FM[1], Delbressine JM[1], Vaes AW[1], Wouters EF[2], Spruit MA[1]. *MEASUREMENTS AND MAIN RESULTS:* Groups were comparable at baseline. Quadriceps muscle strength increased after HF-NMES (+10.8 Newton-metre (Nm)) or strength training (+6.1 Nm; both p<0.01), but not after LF-NMES (+1.4 Nm; p=0.43). Quadriceps muscle endurance, exercise performance, lower-limb fat-free mass, exercise-induced symptoms of dyspnoea and fatigue improved significantly compared with baseline after HF-NMES, LF-NMES or strength training. The increase in quadriceps muscle strength and muscle endurance was greater after HF-NMES than after LF-NMES. Conclusions : HF-NMES is equally effective as strength training in severely dyspnoeic individuals with COPD and muscle weakness in	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				strengthening the quadriceps muscles and thus may be a good alternative in this particular group of patients. HF-NMES, LF-NMES and strength training were effective in improving exercise performance in severely dyspnoeic individuals with COPD and quadriceps weakness. Neuromuscular electrical stimulation (NMES) may reduce muscle atrophy in patients with severe chronic obstructive pulmonary disease (COPD), according to Canadian researchers.The results were reported at the ATS 2010 International Conference in New Orleans. "NMES improved quadriceps and calf muscle mass. Improvements in quadriceps muscle mass were positively correlated with changes in the level of proteins involved in muscle signalling pathway," said Dr. Vivodtzev. "These results suggested that NMES training would increase the anabolism to catabolism ratio in muscle proteins of COPD patients and prevent muscle-wasting."	
Chiesi Ltd	General	General	General	Question 1: Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why. Removal of ICS/LABA and Triple Therapy treatment options from people who do not display asthmatic features will significantly impact clinical practice and be challenging to implement. Many patients with a history of exacerbations require inhaled corticosteroids for the prevention of further exacerbations of COPD. An algorithm which does not suggest any further treatment therapy options for patients without asthmatic features on a LABA/LAMA will leave healthcare professionals struggling to adequately treat their patients. The recommendation to “explore further treatments options, such as surgery” seems a drastic and costly option for the majority of cases.	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm. The committee did not intend to place undue emphasis on surgery as a future treatment option, but were unable to include a long list of options due to space constraints. They intended that the guideline referred to at this stage.
Chiesi Ltd	General	General	General	Question 2: Would implementation of any of the draft recommendations have significant cost implications? Limiting the use of ICS-containing therapies to those with asthmatic features and not allowing frequent exacerbators to access these treatments could have serious cost implications in respect to treatment failure or hospitalisation due to exacerbations. With a shortfall of 5.9% for clinical staff equating to 50,000 clinical staff vacancies for the NHS, implementing measures likely to increase healthcare resource utilisation may not help this problem. [1] Furthermore, the recommendation of surgery as the next treatment option after use of a LABA/LAMA in those with no asthmatic features, would have large cost implications for the NHS if this was to be followed. We would recommend that this recommendation be revised, and replaced with a pharmacological escalation and de-escalation protocol. [1] The Nuffield Trust. The NHS workforce in numbers. 2017. Available from: https://www.nuffieldtrust.org.uk/resource/the-nhs-workforce-in-numbers [Accessed 25/07/18]	Thank you for your comment. We have passed this information on to our resource impact team. Results of the network meta-analysis of inhaled therapies and economic model indicate that LAMA+LABA produces a reduction in exacerbations compared to LABA+ICS, so the committee felt that recommending LAMA+LABA is likely to reduce, rather than increase, hospital costs. Recommendations regarding surgery relate to patients with an FEV1 of less than 50% and breathlessness that affects their quality of life despite optimal medical treatment. It is unlikely that treatment de-escalation would be viable option for such patients. The resource impact team have included costs of lung volume reduction procedures in their costing report and template, in order to help local budget holders plan any additional spend.
Chiesi Ltd	General	General	General	Question 3: What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)	Thank you for your comments. The topic of inhaler models and training was not within the scope of this update and, as a result, we were unable to change the previous recommendations. However, the committee concluded that it was important that patients have training in inhaler use to

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				In view of the numerous inhaler device types and the difficulty both patients and healthcare professionals have in using these correctly, additional training for both would be welcomed. The training of patients by healthcare professionals has been shown to be an effective means of improving inhaler technique. [1] Furthermore, stronger recommendation in the guideline to simplify treatment regimens through reducing the number of inhalers a patient uses would be a helpful step towards measures to improve adherence. [2] [1] Price D, Bosnic-Anticevich S & Briggs A. Respir Med, 2013;107:37–46. [2] Yu, AP et al. J Med Econ, 2011; 14(4): 486-96	ensure that they are able to use the devices correctly. They included a reference to this point in the recommendations at the end of the inhaled combination therapy section. They also acknowledged that suitable training of healthcare professionals is essential to achieve the goals of these recommendations. This is covered by the final recommendation in the inhalers section that was out of scope for this update. The recommendation covering the choice of drugs and inhalers includes a reference to minimising the number and types of inhalers in an attempt to improve treatment adherence.
Royal College of General Practitioners	General	General	General	Do you foresee any major issues for the implementation of this guideline in primary care? *Yes, the issue of triple therapy is not addressed.* Can you identify any important omissions in the recommendations? *1. Addressing triple therapy.* *2.re addressing recommendation to use fixed ratio in diagnosing obstructive airways disease.* *3. Lack of recognition of COPD phenotypes including asthma–COPD overlap syndrome (ACOS)* *4. Lack of treatment goals* *5. Lack of recognition of the Impact of comorbidities on COPD treatment decisions* *6. How to improve the limited adherence to COPD treatment guidelines particularly with the use of integrated decision support in*	Thank you for your comments. Comment 1 - NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm. Comment 2 - The topic of the use of spirometry in diagnosis of COPD is not within the scope of this update, and therefore

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				clinical systems in primary care to help GPs, nurses and pharmacists Do you think this guideline is significantly more or less useful for UK primary care than the GOLD guideline and if so why? *Less useful as it only addresses narrow areas of scope. GOLD looks at the whole picture* We would like to hear your views on these questions: 1. Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why. *Use of LABA/LAMA as initial bronchodilator therapy (cost)* What are the key issues or learning points for professional groups? 1. *Use of LABA/LAMA as first line re monotherapy.* 2. *Big challenge is the lack of advice re triple therapy.* 3. *Conflicting advice re use LLN v fixed ratio in diagnosis*.	changes could not be made to these recommendations. The committee were aware of ongoing discussions about using the lower limit of normal for COPD diagnosis. However, at the time of scoping this guideline update it was not thought that there was enough available evidence to make recommendations as part of this update. These comments will be passed to the NICE surveillance team, for discussion when future updates of the guideline are planned. Comment 3- Unfortunately the majority of trials examined in the inhaled therapy combinations review excluded people with asthma and COPD, which forced the committee to write a consensus recommendation to cover treatment of these people. The committee recognised the importance of determining the most effective inhaled bronchodilator for people with COPD and asthma and made a research recommendation to address the gap in the evidence. Comment 4- The committee noted this point, but concluded that in the absence of evidence it was not possible to be more specific about goals of treatment, other than that they are designed to reduce breathlessness and the risk of exacerbations. Comment 5- The committee recognised the importance of comorbidities in people with COPD. As a result, they included people with multimorbidities as a subgroup analysis in all of the systematic review protocols used for this update. However, the majority of the included trials did not recruit people with comorbidities or failed to report data for the participants with comorbidities separately, which prevented the committee from having sufficient evidence to make specific recommendations for these people. However, the committee did include a reference to optimising treatment for comorbidities before referral to a lung volume reduction

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					multidisciplinary team and as a potential contraindication for lung transplantation. In addition, the recommendation for factors associated with prognosis include multimorbidities and there is a new reference to the NICE guideline on multimorbidity at the beginning of the section of the guideline on managing stable COPD. Comorbidities are also mentioned in other parts of the guideline that were not within the scope of this update. Comment 6- This issue was not one contained within the scope of this update of the guideline, and therefore the committee were unable to make any comments on this point. *Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why?* The use of LABA/LAMA as initial bronchodilator therapy may require an increase in costs upfront, but the resource impact analysis suggests that these will likely be offset by a reduction in hospitalisations. *What are the key issues or learning points for professional groups?* Thank you for your comments. Please refer to the responses above.
British Thoracic Society	General	General	General	Q1: Inhaled therapies – this will require a change in practice for a wide range of clinicians. Changes to current therapy must be supported by clinical assessment (exclude features of asthma etc) and education on device use. This will be challenging to deliver at the required scale, but the potential savings are substantial. Restricting oxygen in smokers will encounter opposition, especially in centres currently conducting a thorough risk assessment supported by education. Q2: Seretide and Tiotropium are among the most expensive and most commonly prescribed long acting inhaled therapies (but not	Thank you for your comments. Q1 The committee are confident that the recommended treatments are the most clinically and cost-effective long acting therapies for people with COPD. Although the recommendations and algorithm represent a change in current practice, the long-acting therapies are already in current use. In addition, the committee do not intend that there will be wholesale switching of patients, rather that people starting long-term therapy for the first time will follow the new pathway. Only people whose symptoms are not controlled on their current therapy would be switched to the

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				the most effective). Triple therapy is often used in patients with milder disease. Switch to new agents in keeping with guidance will substantially reduce cost. Q3: Misdiagnosis remains a concern; patients on COPD registers require confirmation of diagnosis and assessment for features of asthma etc to correctly implement the guidance. Remote switching of patients is risky. Q4 – addressed above. Q5: Both guidelines should be consistent regarding which exacerbations require antibiotics, specifically in regard to sputum purulence. In contrast to the COPD guidance, the antimicrobial guideline recommends antibiotics in all severe (hospitalised) exacerbations and does not focus on sputum purulence/ viscosity in less severe exacerbations. Patients with severe infective exacerbations requiring hospitalisation are more likely to have pseudomonas. Those at high risk of death often show a short time to death (DECAF 5-6 median time to death among those not surviving to discharge = 2 days). Risk stratification to inform antibiotic choice is used in other conditions applying the pragmatic view that you may not get “a second bite at the cherry” in high risk patients.	new pathway. This should therefore not require a major investment of time in training people to use new devices. The committee decided that the benefits of giving long-term oxygen (LTOT) to current smokers were outweighed by the risks to these smokers and other people in their households of burns and fires. They recommended that people with COPD who smoke and could benefit from LTOT be offered help to stop smoking to enable them to access LTOT in the future. The committee were aware that these recommendations may prove controversial, but they concluded that they represented an appropriate course of action given the increased risks to smokers and their households. The committee thought that for people who smoke the risks were sufficiently high that simply conducting a risk assessment and providing education was not enough to mitigate the risks to these people and their households. Q2. Thank you for this information. The committee were aware of the variation in costs between different drugs and combinations of drugs. The weighted average cost was used in the economic analysis to determine the most cost-effective treatment. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm. Q3. The recommendations are not intended to result in the wholesale switching of people onto LAMA/LABA (or LABA/ICS). The committee envisaged that the recommendations would to apply for people with COPD who are starting long-acting therapies for the first time or those currently taking long-acting therapies who have uncontrolled symptoms. The committee have included a detailed description of the people they think would benefit from LABA/ICS rather than LAMA/LABA which can be used to prevent misdiagnosis. They have also included a recommendation to ensure that people whose symptoms are controlled on their current medication are not switched unnecessarily. Q5. Thank you for this information. The NICE antimicrobial prescribing guideline is expected to be published in December 2018. The recommendations in the COPD guideline have now been removed and replaced with a reference to these updated guidelines.
British Thoracic Society	General	General	General	Selection for provision of home ventilation following an exacerbation requiring acute ventilation: The HOT HMV trial has clearly defined the population who benefit (persistent hypercapnia two weeks after recovery and with PaCO2>7kPa – NNT to prevent one readmission or death = 6). JAMA 2017;317:2177-86.	Thank you for your comment. The current update of the COPD guideline focused on managing stable COPD and, as a result, risk stratification for people undergoing an exacerbation and treatment of people during/immediately following an exacerbation was out of scope.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				This guideline only examined risk stratification in stable state, but not acute exacerbations. DECAF offers excellent performance in the latter (Thorax 2012 & 2016 & National Audit recommendations 2015) and is simple to complete - indices routinely assessed. Patients at low risk are suitable for hospital at home or early supported discharge (more than doubling the proportion in previous models – particularly pertinent considering NHS demands). Early identification of those at high risk (who also show a short time to death) should inform provision and place of care. Home NIV post exacerbation by HOT HMV criteria (JAMA 2017) and hospital at home selected by low risk DECAF (Thorax 2018) are now supported by health economic assessments.	We have passed the information supplied and your suggestions for reviews of prognosis and the use of home ventilation in people with unstable COPD to our surveillance team to help inform their decisions for future updates of this guideline.
Teva UK	General	General	General	In this revision of the COPD guidelines, NICE have used an economic evaluation, supported by data from a meta-analysis of RCTs for single-agent vs dual-agent long-acting bronchodilator therapy, to demonstrate that a strategy in which all patients initiate therapy with a LAMA+LABA combination is cost-effective compared with starting on a LAMA and stepping up to dual therapy as needed. This approach is valuable for demonstrating that the additional cost associated with using a more expensive treatment can be justified in terms of the overall clinical gains, provided it is clear that there is a real improvement in HRQoL associated with the more expensive therapy. However, this approach does not address whether a less costly treatment which is marginally less efficacious may be more appropriate in a subgroup of patients with less severe disease. The subgroup analysis presented suggests this may be the case. Ideally, clinical data comparing the outcomes for the two strategies (LAMA to LAMA+LABA vs LAMA+LABA) are needed to assess the clinical benefits of either approach. However, such data are not available. Indeed, data comparing LAMA vs LAMA+LABA in patients with less severe disease are also lacking. Recommendations therefore need to take into account clinical experience and assess whether the data that have been published since the 2010 NICE	Thank you for your comment. The recommendations for long-acting bronchodilators relate to patients who remain breathless or have exacerbations despite using a short-acting bronchodilator. Therefore, the population offered a LAMA+LABA is, by definition, more akin to the high-risk subgroup in the economic model (since this group is defined as patients with 1 or more exacerbation in the year before trial entry), in which LAMA+LABA showed an even higher probability of being cost-effective than in the model base case (>90%). Consequently, it is very likely that LAMA+LABA is cost-effective for the population in whom it is recommended. Furthermore, LAMA+LABA still has the highest probability of being cost-effective in the low-risk subgroup for option A (the scenario which the committee found the most plausible), demonstrating that this treatment is still likely to be cost-effective in a population without a history of recent exacerbations. No randomised evidence currently exists comparing outcomes for patients switching through multiple lines of treatment. This was one of the reasons why economic modelling was conducted for this topic: to predict long-term

				guidelines warrant a change in clinical practice. Indeed, the clinical data that are available for LAMA vs LAMA+LABA, as identified in the systematic review and analysed in the meta-analysis presented by NICE, indicate that although some efficacy parameters show a statistically significant benefit for LAMA+LABA over LAMA monotherapy, there are no clinically meaningful differences in efficacy endpoints between the two treatments. These results thus suggest that LAMA monotherapy is likely to be a valuable initial therapy for some patients, as recommended in the 2018 GOLD guidelines. Clinical practice suggests that an individualised approach to the choice of therapy is preferable and this is supported by the 2018 GOLD guidelines. Inclusion of LAMA as a possible option for patients initiating therapy for COPD gives patients and their physicians this choice and will avoid the increase in treatment costs associated with starting all patients on combination therapy. Furthermore, concern has been expressed regarding the overtreatment of COPD through patients starting on LAMA+ICS and then moving to triple therapy. Initiating all patients on LAMA+LABA rather than LAMA alone also has the potential to lead to over treatment and is best avoided by considering initiating therapy on LAMA and escalating therapy only in patients with suboptimal symptom control or at increased risk of exacerbation. We thus recommend that LAMA monotherapy is included in the updated guidelines as an option for initiating therapy in appropriate patients. References 1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, managemeng and prevention of chronic obstructive pulmonary disease. 2018 Report. Available at: https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf Accessed July 2018.	health and cost outcomes using head-to-head comparisons of long-acting bronchodilators. In modelling multiple therapy lines, patients' exacerbation rate/TDI/SGRQ/FEV1 related to the treatment that they were currently receiving - e.g. patients starting on a LABA had an exacerbation rate associated with that treatment, but experienced a reduced exacerbation rate if they stepped up to LAMA+LABA. The committee indicated that this was a reasonable assumption to make. While pairwise comparisons of LAMA+LABA versus LAMA did not exceed minimally importance differences (MIDs) in efficacy outcomes, it should be noted that (1) these MIDs were established to compare active treatments with placebo, and thresholds were therefore set higher than they would be if comparing two active treatments (2) the economic analysis incorporated all relevant treatment outcomes from the network meta-analysis (whether or not they were statistically significant or exceeded an MID), and found that, given the balance of all competing factors, LAMA+LABA shows a high probability of providing health benefits at an acceptable additional cost. NICE guidance is not intended to replace clinical judgement, and we accept that patient populations are heterogeneous. However, the clinical and economic evidence on inhaled therapies indicates that LAMA+LABA is likely to be the optimal choice of long-acting bronchodilator for the majority patients who continue to remain breathless or exacerbate despite using a short-acting bronchodilator. Recommendations on further treatment are clear that escalation of treatment should be provided when there is a clinical need (patients still remain breathless or have exacerbations). Furthermore, results of the economic model showed that LAMA+LABA still remains cost-effective when triple therapy is included as a downstream option.

				2. Singh D, Barnes PJ, Stockley R *et al.* Pharmacological treatment of COPD: the devil is always in the detail. *Eur Respir J* 2018;51. 3. Thomas M, Halpin DM, Miravitlles M. When is dual bronchodilation indicated in COPD? *Int J Chron Obstruct Pulmon Dis* 2017;12:2291-2305. 4. Mak V. Treatment guidelines for COPD - Going for GOLD? *Primary Care Research Update* 2017;4 (2). 5. Brusselle G, Price D, Gruffydd-Jones K *et al.* The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. *Int J Chron Obstruct Pulmon Dis* 2015;10:2207-17. 6. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Clinical guideline 101. Published 23 June 2010. Available at: https://www.nice.org.uk/guidance/cg101 Accessed July 2018. 7. Price D, Ostrem A, Thomas M, Welte T. Dual bronchodilation in COPD: lung function and patient-reported outcomes - a review. *Int J Chron Obstruct Pulmon Dis* 2017;12:141-168. 8. Anzueto A, Miravitlles M. The Role of Fixed-Dose Dual Bronchodilator Therapy in Treating COPD. *Am J Med* 2018;131:608-622. 9. Cazzola M, MacNee W, Martinez FJ *et al.* Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008;31:416-69. 10. Witek TJ, Jr., Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. *Eur Respir J* 2003;21:267-72. 11. Schunemann HJ, Griffith L, Jaeschke R *et al.* Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. *J Clin Epidemiol* 2003;56:1170-6.	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				12. IQVIA. June 2018.	
Royal Pharmaceutical Society	General	General	General	The Royal Pharmaceutical Society is the professional body for pharmacists and pharmacy in Great Britain. As professionals in pharmaceutical care, pharmacists are well equipped to offer advice on management of chronic diseases. With an increasing number of pharmacist independent prescribers and those specialising in specific disease states such as chronic obstructive pulmonary disease (COPD), pharmacists are often directly involved in diagnosis and supporting patients to monitor their condition.	Thank you for your comments on the guideline.
UK Inhaler Group	General	General	General	In broad terms there has been insufficient recognition that choice of inhaler is an important part of COPD management, and as important as selection of drug. If a patient can't use an inhaler, or use it properly with the correct technique, then the choice of drug becomes irrelevant, as the patient will not get the benefit intended by the prescribing clinician. This is a blind spot both for clinicians treating patients, but also for organisations developing guidelines. Think of the device as the engine, and the drug as the oil. The engine needs the right oil to work effectively. The device is integral to the patient receiving the medication within it. Systematic review and analysis related to the inhaler device (not just the drug) is needed if treatment is to be optimised for patients.	Thank you for your comments. The topic of inhaler models and training was not within the scope of this update and, as a result, we were unable to change the previous recommendations. However, the committee concluded that it was important that patients have training in inhaler use to ensure that they are able to use the devices correctly. They included a reference to this point in recommendation1.2.16. They also acknowledged that suitable training of healthcare professionals is essential to achieve the goals of these recommendations. This is covered by recommendation 1.2.19 in the section that was out of scope for this update. We have passed the suggestion for a review of inhaler devices to our surveillance team to help inform their decisions for future updates of this guideline.
Association for Respiratory Nurse Specialists	General	General	General	1. Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why. The guidelines on management around prophylactic antibiotic prescribing may prove challenging to clinicians and difficult for patients to accept. The oxygen guidelines are clear in how to manage risk but again may not be acceptable to patients and relatives, some clinicians may	Thank you for your comments. The committee recommended the healthcare professional think about the use of prophylactic azithromycin for a defined subset of people who are experiencing frequent, prolonged or severe exacerbations resulting in hospitalisation. This was based, in part, on the evidence for a reduction of a third in the number of exacerbations per person per year in people with

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				also struggle with a harder line. Management around inhaled therapy and considered use of ICS should change / improve care for COPD patients offering appropriate symptomatic relief without increased unnecessary risk. It is also clear for clinicians 2. Would implementation of any of the draft recommendations have significant cost implications? Implementation of prophylactic antibiotics, oxygen prescribing and inhaled therapy will all have a significant impact on reducing cost from inappropriate prescribing and complications from side effects; alongside increased risk in patients with potential associated cost (fires, burns, trips and falls). 3. What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.) Examples of good practice are always very useful. The more robust oxygen prescribing guideline will assist clinicians when making difficult decisions, alongside the risk assessments completed. 4. The guideline recommends that long term oxygen therapy should not be offered to people who continue to smoke despite being offered smoking cessation advice and treatment, and referral to a specialist stop smoking service. This is because the risks to the individual and people they live with outweigh the potential benefits of long-term oxygen therapy. Do you believe that this recommendation is appropriate? We would welcome your comments on this issue Absolutely appropriate-all support should be towards smoking cessation. Supplementary oxygen is less effective when smoking. Burn and fire risks high. This supports clinicians to not prescribe oxygen in high risk patients therefore assisting in risk reduction and patient safety.	COPD treated with prophylactic antibiotics. To ensure that this treatment was restricted to the patients that would benefit most, whilst balancing the risk of antimicrobial resistance, they also included a number of conditions before prescription to ensure that all appropriate alternative treatments have been tried. They also acknowledged the lack of evidence for long-term safety and effectiveness of this intervention and envisaged that people taking prophylactic antibiotics would be monitored carefully. The committee noted that the issue of providing long-term oxygen to people who continue to smoke is a complex one on which opinions are still divided in both the clinical and patient communities. However, they decided to keep the recommendation to not offer long-term oxygen therapy if people continue to smoke as it was concluded that these recommendations were designed to prevent smokers from injury or harm, and not to deny them access to treatment. They concluded the risks from the use of long-term oxygen by people who smoke were sufficiently high that the risk-benefit balance was in favour of not using the treatment in this group. NICE has noted the number of stakeholders who have raised the issue of the length of steroid treatment as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence to justify updating this part of the guideline. However, with the recent publication of a Cochrane review it has now been agreed that it is appropriate for these recommendations to also be updated. A separate update of these recommendations has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				We propose to stand down recommendations 1.3.22 – 1.3.25 on antibiotics for the management of exacerbations. Instead the guideline will cross refer to the recommendations in the guideline on antimicrobial prescribing for acute exacerbations of COPD. Do you agree with this proposal? The clarity in the antimicrobial prescribing for acute exacerbations of COPD is welcomed but there may be some challenge from clinicians who need easy access to one document to treat patients. I do not believe it will be problematic and the advantage is a clear and robust prescribing policy. There could be some confusion in patients when the antibiotic course is recommended for 5 days and the oral corticosteroids for 7-14 days.	the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline and pathway.
Primary Care Respiratory Society	General	General	General	*Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why*. 1. Use of LABA/LAMA as initial bronchodilator therapy (cost, and major change in practice) Everyone is getting their head around GOLD strategy and now this says do something else. What do we do with all those who are doing just fine on LAMA alone? Recommendation is to use LABA/LAMAs to reduce exacerbations, which is not in keeping with the products' UK licences, even if it is supported by the evidence. 2. Validated spirometry - LLN vs fixed ratio debate 3. Reduced use of ICS in patients without features of asthma 4. Might require more clinic capacity for assessing people for lung reduction surgery as many people meet the referral criteria. But it may be that people have been under referring for a while and these guidelines might correct this and ensure more people receive appropriate intervention. Some considered that these guidelines are very little change from routine care.	Thank you for your comments. Comment 1- Thank you for your comments. The committee were aware of the GOLD recommendations but their decisions were made according to the NICE 2017 guideline manual and took into account the evidence provided. Although this may differ to the recommendations provided by GOLD the committee were confident that their recommendations were a reflection of the evidence they reviewed and their clinical judgement. They did, however, agree it was appropriate to add an additional recommendation to the guideline to make clear that people well controlled on monotherapy when the guideline publishes do not need to be switched to an alternative treatment until their symptoms are no longer well controlled. Comment 2 - The topic of the use of spirometry in diagnosis of COPD is not within the scope of this update, and therefore changes could not be made to these recommendations. The committee were aware of ongoing discussions about using the lower limit of normal for COPD diagnosis. However, at the time of scoping this guideline update it was not thought that

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					there was enough available evidence to make recommendations as part of this update. These comments will be passed to the NICE surveillance team, for discussion when future updates of the guideline are planned.
Primary Care Respiratory Society	General	General	General	*Would implementation of any of the draft recommendations have significant cost implications?* 1. Capacity in lung reduction clinics. More aggressive work up of those with severe disease for new tech lung volume surgery will add costs, 2. Palliative care inpatients capacity – such a small percentage die of lung disease in hospice care. Too many are dying in hospital. 3. Increased use of dual long acting bronchodilation therapy as first line treatment, and potential overuse of triple therapy. 4. Advice not to use telemedicine may reduce costs.	Thank you for your comments. We have passed this information onto the resource impact team, for consideration as part of the implementation support tools they provide.
Primary Care Respiratory Society	General	General	General	*What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)* 1. Practical resources and examples of good practice are always a very useful addition to support implementation. 2. Speak to lung reduction clinics and scope missing cohort.	Thank you for your comment. We have passed this information to our implementation team.
Primary Care Respiratory Society	General	General	General	*For the guideline:* *o Are there any recommendations that will be a significant change to practice or will be difficult to implement? If so, please give reasons why.* *o What are the key issues or learning points for professional groups?* 1. Use of LABA/LAMA as first line treatment. 2. The lack of advice about the role of triple therapy. 3. Conflicting advice re use Lower limit of normal (LLN) vs fixed ratio in diagnosis. 4. Referrals for macrolides	Thank you for your comment. Comment 1- The committee agree this recommendation would represent a change in practice in many areas, but concluded it was supported by both the clinical and economic evidence, and would lead to improved outcomes for COPD patients. Comment 2 - NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				5. The role of spirometry and the National certification register scheme 6. Lack of consideration of the breadth of settings in which care can be delivered – NICE needs to keep up to date better with the realities of the way services are being configured and delivered. It should not dictate where care is provided as this varies from area to area. These guidelines should look very different from those of 2004 if they are keeping abreast of the variety of ways in which care is being delivered. 7. Narrow thinking about patients which does not acknowledge the extent of co morbidity patients are living with. Pulmonary rehab is not just delivered in isolation to COPD patients. In reality, generic solutions to deconditioned patients with multi morbidities are being introduced all over the country.	insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm. Comment 3 - The topic of the use of spirometry in diagnosis of COPD is not within the scope of this update, and therefore changes could not be made to these recommendations. The committee were aware of ongoing discussions about using the lower limit of normal for COPD diagnosis. However, at the time of scoping this guideline update it was not thought that there was enough available evidence to make recommendations as part of this update. These comments will be passed to the NICE surveillance team, for discussion when future updates of the guideline are planned. Comment 4- The committee recommended the healthcare professional think about the use of prophylactic azithromycin for a defined subset of people who are experiencing frequent, prolonged or severe exacerbations resulting in hospitalisation. This was based, in part, on the evidence for a reduction of a third in the number of exacerbations per person per year in people with COPD treated with prophylactic antibiotics. To ensure that this treatment was restricted to the patients that would benefit most, whilst balancing the risk of antimicrobial resistance, they also included a number of conditions before prescription to ensure

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					that all appropriate alternative treatments have been tried. They also acknowledged the lack of evidence for long-term safety and effectiveness of this intervention and envisaged that people taking prophylactic antibiotics would be monitored carefully. Comment 5- Unfortunately spirometry was not within the scope of this update and, as a result the committee were unable to make any new recommendations concerning the training of healthcare professionals. We have passed this information onto surveillance to help inform decisions for future updates of this guideline. Comment 6- Thank you for this information. NICE methodology, as detailed in the guideline manual, limits updates to sections of the guideline where new evidence has been detected during the surveillance process. We have passed on your comments to help inform decisions for future updates of this guideline. Comment 7- The committee recognised the importance of comorbidities in people with COPD. As a result, they included people with multimorbidities as a subgroup analysis in all of the systematic review protocols used for this update. However, the majority of the included trials did not recruit people with comorbidities or failed to report data for the participants with comorbidities separately, which prevented the committee from having sufficient evidence to make specific recommendations for these people. However, the committee did include a reference to optimising treatment for comorbidities before referral to a lung volume reduction multidisciplinary team and as a potential contraindication for lung transplantation. In addition, the recommendation for factors associated with prognosis include multimorbidities and there is a new reference to the NICE guideline on

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					multimorbidity at the beginning of the section of the guideline on managing stable COPD. Comorbidities are also mentioned in other parts of the guideline that were not within the scope of this update.
Primary Care Respiratory Society	General	General	General	GOLD vs NICE – we asked our members whether this guideline would be more or less useful than GOLD for UK primary care. They replied – 1. Less useful as it does not address all aspects of COPD care - GOLD looks at the whole picture 2. Less useful as it has not adequately addressed the issue of when to use ICS combination or triple therapy. 3. Less useful - the fudge of 'features suggesting steroid responsiveness' is unhelpful 4. Less useful - What's missing is an algorithm such as the one developed by PCRS on treatment escalation or GOLD's ABCD approach as the wording in this document is very confusing and still suggests that triple therapy is acceptable for patients who remain breathless which is no different from the 2010 guidelines. The NICE 2018 algorithm does partly address this as it discusses ICS in the context of asthmatic tendencies but the wording does need to be clarified in the main document. https://www.pcrs-uk.org/sites/pcrs-uk.org/files/Gold%20article%20only_REV_March2018.pdf 5. More useful - The other sections (excluding the ICS issues) are useful and the dialogue around key recommendations very helpful. 6. More useful. Diagnostic recommendations useful in confirming AND excluding COPD- GOLD tends to assume they have COPD to start with. There is some real concern that lack of alignment between GOLD and NICE in some areas will create the same difficulties as having asthma guidelines from NICE and BTS/SIGN. If NICE is going to diverge from GOLD, it would be useful to say why.	Thank you for your comments. Comment 1. The committee were aware of the GOLD recommendations but their decisions were made according to the NICE 2017 guideline manual. NICE methodology limits updates to sections of the guideline where new evidence has been detected during the surveillance process and, as a result, it is inevitable that sections of the guidelines are updated infrequently. Comment 2- NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm. The clinical and economic evidence showed that the most effective treatment regimen was LABA+LAMA, but the committee concluded that it would be inappropriate to deny

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					people with asthmatic features/features suggesting steroid responsiveness treatment with ICS. They made the recommendation for LABA+ICS treatment of these people based on their clinical experience and the finding from the economic model that showed that dual therapy was more effective than monotherapy. Comment 3- The committee recognised that the term 'asthmatic features/features suggesting steroid responsiveness' was not ideal, but they include both terms to try to that people with COPD with asthma and without asthma, but who were thought to be steroid responsive, were given the opportunity to benefit from LABA+ICS. They defined the term to help the healthcare professional identify these people and included a research recommendation to help stimulate research into the characteristics of these people that could be used to tighten this definition further. Comment 4- As discussed above the section of the guideline relating to triple therapy was outside of the scope of this update and as a result, the triple therapy recommendation could not be altered. However, this section is going be updated and hopefully this will reduce any confusion. Comment 5 - we are glad that you find the other sections useful. Comment 6- we are glad that you find the diagnosis section useful. The committee were aware of the GOLD recommendations but their decisions were made according to the NICE 2017 guideline manual and took into account the evidence provided. Although this may differ to the recommendations provided by GOLD the committee were confident that their

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					recommendations were a reflection of the evidence they reviewed and their clinical judgement.
Primary Care Respiratory Society	General	General	General	It was noted by our commentators that in various areas, the recommendations were based on the opinions of the guideline committee due to insufficient evidence. Medication recommendations were based on just 5 studies across all classes 2010 – 2016, all pharma funded. This feels insufficient and lacking in rigour. In particular, we do not think that the evidence summary (evidence review F inhaled therapy) provides sufficient justification for the major and potentially costly change in practice for moving straight to LAMA/LABA combination in recommendation 1.2.11 There also appears to be little coverage of different models of care delivery. For example, is there any evidence for a 5 day follow up post exacerbation vs 14 day +/- telephone reviews	Thank you for your comment. Where there is an insufficient evidence base we do rely on the clinical expertise of the committee to inform the recommendations. This follows the process detailed in the NICE 2017 manual for developing guidelines The conclusion that LABA/LAMA is more clinically and cost-effective than LABA/ICS and monotherapy is based on the results of network meta-analyses and an economic model. Taking the results of the network meta-analyses as whole (see appendix N for summary tables), LAMA/LABA were more clinically effective than LABA/ICS and monotherapy for the average patient. Although the effects of LAMA/LABA do not exceed the MIDs for most outcomes the committee noted that MIDs were developed to assess whether an active treatment was superior to a placebo treatment, rather than to compare active treatments. As a result, use of these MIDs may underestimate the difference in effect between treatments. To overcome these issue, the committee concluded therefore that it was important not to consider these individual outcomes in isolation, but to consider the overall impact on quality of life, as estimated in the economic model. The results of this model showed that dual therapy was more effective than monotherapy and that LAMA/LABA was more cost-effective than LABA/ICS. Models of care delivery were not included in the scope of this update. We have passed your suggestion for a review of this topic onto the surveillance team to inform future updates of the guideline.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Primary Care Respiratory Society	General	General	General	Due to the NICE COPD guideline becoming so out of date, many healthcare professionals looking for guidance on managing COPD have been turning to GOLD strategy, which stays abreast of developments. NICE would do well to recognise this in their guideline, and to address the COPD phenotypes which may guide treatment of individual patients more accurately than previous guidelines. Indeed, in a recent survey of PCRS members, 65% of respondents used GOLD or a local variation of GOLD as their management pathway, with only 33% using NICE (PCRS-UK – data on file June 2017). NICE would do well to recognise this and ensure their guideline is up to date.	Thank you for your comment. We have passed this information onto surveillance to help inform their decisions to update the guideline in the future.
Primary Care Respiratory Society	General	General	General	At present there appears to be no signposting to excellent resources in the respiratory community – videos on inhaler technique, summary COPD guideline for primary care from PCRS, materials for patients, spirometry quality standards etc.	Thank you for your comment. Thank you for your comment. Unfortunately, we are unable to specifically refer to other sources of guidance unless they have been endorsed by NICE. If these tools are of particular use, the developer of the tools could submit them to NICE for endorsement using this web link.
Primary Care Respiratory Society	General	General	General	Note that READ codes in primary care are in the process of being switched over to SNOMED CT codes. Correct any references to READ codes.	Thank you for your comment. We have passed this information to our surveillance team to help them inform future updates and changes to the guideline.
AstraZeneca UK	General	General	General	1. National Institute for Health and Care Excellence. Medicines Optimisation: the Safe and Effective Use of Medicines to Enable the best Possible Outcomes. NICE guideline. March 2015. https://www.nice.org.uk/guidance/ng5 2. Medicines Optimisation: Helping patients to make the most of medicines. Good practice guidance for healthcare professionals in England. May 2013 https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Policy/helping-patients-make-the-most-of-their-medicines.pdf 3. Bafadhel M et al, Lancet Respir Med 2018; 6: 117–26 4. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic	Thank you for your comments. These references have been considered in relation to each of your associated comments.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				Obstructive Lung Disease (GOLD) 2018 Report, 2018. Available at http://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf Used under permission from Global Initiative for Chronic Obstructive Lung Disease 5. Pavord ID et al, Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD. Thorax 2016; 71(2): 118-25. 6. Watz H et al, Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. The Lancet Respiratory medicine 2016; 4(5): 390-8. 7. Vedel-Krogh et al, Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. Am J Respir Crit Care Med 2016; 193(9): 965-74. 8. Singh D et al, Eosinophilic inflammation in COPD: prevalence and clinical characteristics. Eur Respir J 2014; 44(6): 1697-700. 9. Cazzola M et al, A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. Pulm Pharmacol Ther 2007;20:556–561. 10. Aaron SD et al, Tiotropium in combination with placebo, salmeterol, or fluticasone– salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2007;146:545–555. 11. Perng DW et al, Additive benefits of tiotropium in COPD patients treated with long-acting b agonists and corticosteroids. Respirology 2006;11:598–602. 12. Singh D et al, Superiority of ‘‘triple’’ therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. Thorax 2008;63:592–598.#	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				13. Welte T et al, Efficacy and Tolerability of Budesonide/Formoterol Added to Tiotropium in Patients with Chronic Obstructive Pulmonary Disease, Am J Respir Crit Care Med Vol 180. pp 741–750, 2009 14. Jones P et al, The St George's respiratory questionnaire manual, version 2.1. London: St George's Hospital Medical School; 2003. 15. NICE, Roflumilast for treating chronic obstructive pulmonary disease, Technology appraisal guidance [TA461] Published date: 26 July 2017 https://www.nice.org.uk/guidance/ta461 16. Jones P et al, The St George's respiratory questionnaire manual, version 2.1. London: St George's Hospital Medical School; 2003	
NHS England	General	General	General	This guideline is a useful but partial update of two previous documents from 2004 and 2010. It would have been nice to see a fresh approach with a complete revision. Some of the retained recommendations appear dated. One obvious area of omission is the lack of reference to models of care. There is plenty of evidence around the benefits of the Chronic Care Model or integrated care and community delivery structures.(CLR)	Thank you for your comments. We have passed this information to our surveillance team to help inform future updates of the guideline.
NHS England	General	General	General	The guideline does not compare well with GOLD (expert based) guideline and seems old fashioned in comparison. Still too much emphasis on spirometry rather than risk and little reference to personalised or stratified approaches (nothing about eosinophilia, ACOS/ BCOS etc). Apart encouraging pulmonary rehabilitation and LVRS referrals I cannot see any unanticipated cost pressures. The straight to LABA/LAMA is unlikely to have much of a cost impact because most patients end up quickly on a combination inhaler quickly anyway.	Thank you for your comment. The committee for this update of the COPD guideline consisted of clinical experts and lay people with COPD. Based on NICE methodology, as detailed in the NICE 2017 manual, topics were selected for update based on the based on the presence of new evidence that was expected to change existing recommendations. As a result, the scope of this update was confined to the management of stable COPD and we were unable to update other parts of the guideline.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					We have passed your comments concerning the areas of the guideline that you think need updating onto surveillance to inform future updates of this guideline. We have passed your comment on cost to our resource impact team, who have produced a costing report and template to help local budget holders plan any additional spend resulting from the guideline.
Royal College of Physicians	General	General	General	The RCP is grateful for the opportunity to respond to the above consultation, In doing so we would like to endorse the response submitted by the British Thoracic Society (BTS). We have also liaised with NACAP (National Asthma and COPD Audit Programme) and would like to make the following comments.	Thank you for your comments on this guideline.
Royal College of Physicians	General	General	General	We welcome new guidelines as they are much needed. However in the guideline vacuum of the last 7 years GOLD has made a number of recommendations widely adopted in the UK which are very different from the old and the new NICE guidelines, namely the ABCD classification. We think the guidelines need to address this difference as it will cause huge confusion amongst clinicians.	Thank you for your comments. The committee were aware of the GOLD recommendations but their decisions were made according to the NICE 2017 guideline manual and took into account the evidence provided. Although this may differ to the recommendations provided by GOLD the committee were confident that their recommendations were a reflection of the evidence they reviewed and their clinical judgement.
Royal College of Physicians	General	General	General	We believe this is a lost opportunity to engage with the National Asthma and COPD Audit Programme (NACAP) and its QI aspirations by not recommending participation in audit as a key process in understanding care quality. Secondly in not mentioning the key national Best Practice Tariff (BPT) indicators around hospital admission.	Thank you for your comments. The committee were aware of NCAP and its aspirations but their decisions were made according to the NICE 2017 guideline manual and took into account the evidence provided. Although this may differ to the recommendations provided by GOLD the committee were confident that their recommendations were a reflection of the evidence they reviewed and their clinical judgement.
Royal College of Physicians	General	General	General	In terms of pharmacological management of stable COPD, the recommendations on treatment options seem to divide patients into two categories of asthma symptoms or no asthma symptoms. No reference is made to eosinophils or exacerbations in selecting ICS medications. This again may cause confusion given the current GOLD recommendations.	Thank you for your comment. In both cases, people with COPD are required to have breathlessness or exacerbations before starting long-acting therapy. The definition of people with asthmatic features/features suggesting steroid responsiveness was chosen to include people with asthma and others who could benefit from using ICS. This definition

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					includes consideration of a number of factors including a higher blood eosinophil count.
Royal College of Physicians	General	General	General	In summary we think it would be a mistake not to address the differences between these new recommendations and those of GOLD else we may risk a similar confusion to the NICE asthma vs BTS/SIGN asthma guidelines.'	Thank you for your comment. This NICE guideline was produced according to the 2017 NICE guideline manual, and the committee made recommendations based on the best available clinical and cost-effectiveness evidence presented to them. Whilst the NICE guideline may not align in all places with the GOLD guidance, we are confident that it represented an accurate interpretation of the available evidence.
NHS England	General-Question 1	General	General	Need clearer guidance on assessment in relation to GOLD and patients with different severity and targeting patient groups- e.g. recurrent exacerbators, advanced disease (CRG)	Thank you for your comment. We have passed these suggestions to our surveillance team to help inform their decisions for future updates of this guideline
NHS England	General-Question 2	General	General	Has the potential to reduce costs e.g. reduction of ICS but could have greater impact across the health economy if adapted as per response to 1. (CRG)	Thank you for your comment. We have passed this information to our resource impact team.
NHS England	General-Question 3	General	General	Practical guidance as per previously mentioned. (CRG)	Thank you for your comment.
NHS England	General-Question 4 and 5	General	General	Yes we agree with these two questions. (CRG)	Thank you for your comment.
Royal College of Anaesthetists	Guideline	General	General	It has been deemed that the majority of the proposed changes do not impact upon the anaesthetic speciality practice.	Thank you for comment.
KSS AHSN Patient Safety Collaborative	Guideline	General	General	Some people in our organisation were conflicted regarding the draft guidelines as they seemed, in essence, aligned with GOLD but the terminology is very unclear. The area addressing pharmacological management was felt to be very vague. There is concern that the different markers for reversibility to confirm a diagnosis of asthma (in other guidelines) remain confusing for primary care. It is unclear how the markers of eosinophil count can be utilised in primary care to support consideration of an asthmatic element as it isn't clear what is meant by higher eosinophil count.	Thank you for your comment. Unfortunately, the section of the guideline covering the differentiation between COPD and asthma was not in the scope of this update and, as a result, the committee were unable to change the recommendations apart from including a reference to the NICE asthma guideline. The committee discussed the inclusion of a threshold to define a higher eosinophil count, but concluded that based on the evidence available it was not possible to define a specific

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					threshold. In particular, they noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. However, the accompanying research recommendation to address which features predict inhaled corticosteroid responsiveness most accurately in people with COPD could provide information on this topic and help improve the definition of asthmatic features/features suggesting steroid responsiveness in future updates of the guideline.
Neurocare Europe Ltd	Guideline	General	General	The central question is "What are the most clinically and cost-effective therapies for managing complications (pulmonary hypertension and cor pulmonale) in people with stable chronic obstructive pulmonary disease (COPD)?" We have studied the main section of this consultation document carefully; in particular the table (page 6) which lists the interventions considered and are unsure as to whether it was your intention to deliberately exclude non pharmaceutical interventions since none appear to have been considered . However further reading suggests that the most important outcome measures (in measuring intervention effectiveness as demonstrated in clinical trials) are considered to be (page 18 line 24) Improvements in quality of life or functional outcomes such as the 6 minute walk test and these factors " were prioritised during discussions as these were agreed to be important outcomes for people with COPD" Also the committee noted that although most included studies measured pulmonary haemodynamic outcomes such as systolic pulmonary artery pressure (systolic PAP), mean pulmonary artery pressure (mPAP) and oxygen saturation, these outcomes were not likely to be important to people with COPD in the absence of functional improvements. If improvements in functional performance and HRQoL are considered to be the most important outcomes of effective therapy then we suggest that the committee consider the results of clinical trials carried out with COPD patients where the intervention has been Neuromuscular Electronic Muscle stimulation (NMES) since	Thank you for your comment. These articles do measure functional outcomes that were considered important by the committee. However, these fall within the exclusion criteria of trials lasting less than a 12 week duration. This time period was chosen by the committee to ensure that recommendations reflected the long-term, rather than acute, effects of interventions. The guideline does contain a research recommendation on treatment to manage pulmonary hypertension and cor pulmonale in people with COPD, and this is not limits to pharmacological treatments. Trials of NMES of at least a 12 week duration would be considered relevant to that research recommendation.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				many such trials demonstrate that statistically significant improvements in functional performance and HRQoL can be achieved with the use of this non-invasive ,safe and cost effective therapy. Although many of the (NMES) trials summarised below do include haemodynamic data the Researchers are primarily interested in the effect of NMES on muscle condition and strength and the translation of this into exercise capability, endurance and general improvements in functional performance and the resulting impact on HRQoL and we have highlighted in blue these comments from the Results and Conclusions sections of the Trials summarised. NMES devices vary considerably in their design and manufacture and in the strength and form of the output signal produced. In clinical trials the results obtained will be heavily dependent on output characteristics and on the treatment protocol used in terms of frequency and length of each treatment event We note that in your assessment of clinical trial quality that most trials are judged to be of low to moderate quality " The committee noted that the overall quality of evidence was poor "(Page 19 line 18) and as such Trial results and conclusions cannot be viewed as reliable predictors of possible real world outcomes. We have no means of assessing the quality of the trials which we have presented below but have no reason to suppose that they are likely to be in general of lower quality than the trials which the report summarises and should therefore merit consideration on at least an equal basis. We would be delighted to see a research recommendation that NMES be trialed in an NHS setting with COPD patients which thus far does not seem to have taken place	
British Dietetic Association	Guideline	General	General	It is disappointing that there appears to be no dietetic representation on the GDG with expertise in this field. Evidence on the role of diet and nutritional status in the trajectory of care for patients with COPD is increasingly being recognised. It is an area where patients feel	Thank you for your comment. No topics related to dietetics were included within the scope of this update of the guideline, and therefore it was concluded it was not necessary to have a dietitian on the guideline committee. If these topics are

				they can make a difference too and plays a role in self-management. Dietary needs are diverse and include malnutrition, obesity and weight management, managing CV risk, osteoporosis, Vitamin D, conservation of lean tissue in conjunction with resistance training should be considered as part of the holistic approach for patients with COPD from diagnosis, through pulmonary rehabilitation and into end of life care. Key systematic reviews and international guidance reflects this see: - Collins PF, Stratton RJ, Elia M. (2012) Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. American Journal of Clinical Nutrition 95(6): 1385–1395. - Collins PF, Elia M, Stratton RJ (2013) et al 2013 Nutritional support and functional capacity in chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respirology 18: 616-629. - Ferreira IM, Brooks D, Lacasse Y, Goldstein RS, White J. (20122005) Nutritional supplementation for stable chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews DOI: 10.1002/14651858.CD000998.pub3 - Schols AM, Ferreira IM, Franssen FM, et al., (2014) Nutritional support and therapy in COPD: a European Respiratory Society statement. European Respiratory Journal. DOI: 10.1183/09031936.00070914 Key elements of these reviews do not appear to have any prominence in this updated guidance. Perhaps they were not included in the scope but perhaps the content could be better reflected in the section on nutrition 1.2.98 and by incorporating the comments above in the guidance.	included in future updates of the guideline, then it is highly likely such representation would be present on the committee.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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Glaxo SmithKline	Guideline	General	General	Reference list: Hurst JR, et al. *N Engl J Med.* 2010;363:1128-1138 Lipson DA et al. *N Engl J Med*, 2018; 3;378(18):1671-1680 Papi A et al, *Lancet* 2018 S0140-6736(18)30206-X Suissa S, et al. *Thorax* 2012;67:957–963 Wedzicha JA et al. Respir Med. 2014; 108:1153–11624 Wedzicha JA, et al. *N Engl J Med*. 2016;374:2222–2234. Environmental Audit Committee 'UK Progress on reducing F-gas Emissions (HC 469). The Government's Response - 25 July 2018	Thank you for your comments. We have looked at these references in relation to the relevant comments in which they are referenced, and responses are provided in each comment.
University Hospitals Birmingham NHS Foundation Trust	Guideline	General	General	Some of this guideline will be 14 years old when published, which is too old, and there are notable sections which are out-dated including on iV aminophylline and doxapram – see below. Should we really be publishing a "new" guideline where some parts are this age. I appreciate that there is a huge amount of content in the COPD guideline, but perhaps it is too broad to keep up to date and should be divided into smaller focused guidelines which might be easier to keep up to date eg Diagnosing COPD; Managing stable COPD (excluding inhaler therapy); Inhaler therapy in COPD; Managing exacerbations of COPD? Inhaler therapy seems to be the area that evolves most quickly.	Thank you for your comments. The sections of this guideline that have been updated were selected because new evidence was identified which could potentially change current practice. The reasons behind the decisions on which topics were chosen for update can be seen in the final scope on the NICE website.
Novartis	Guideline	General	General	Box giving advice for ALL inhaled therapies could be moved higher on the page to reflect that this related to the use of all inhaled therapies, not just LABA/LAMA.	Thank you for your comment. The addition of the terms 'for ALL inhaled therapies' is intended to highlight this issue. The committee decided to leave this box in the same place as they concluded that the text makes this point clearly already.
Novartis	Guideline	General	General	There is no guidance on withdrawal of ICS containing therapies in patients who may not require them. There are a number of patients who may be on maintenance LABA/ICS or triple (LABA+LAMA+ICS) therapy despite not having asthmatic features or showing any benefit and it would be good for primary care practitioners to have guidance on how to switch to LABA/LAMA particularly as LABA/LAMA is the most cost effective regimen in the analyses.	Thank you for your comments. The topic of switching between inhaled therapies was not within the scope of this update and, as a result, we did not examine any evidence on this issue. We were also unable to look at ICS withdrawal or triple therapy in this update.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					We have passed the suggestion for the inclusion of guidance on treatment switching to our surveillance team to help inform their decisions for future updates of this guideline
Primary Care Respiratory Society	Guideline			We are not sure how the markers of eosinophil count can be utilised in primary care to support consideration of an asthmatic element as it isn't clear what is meant by higher eosinophil count, as there are many different variables. There is no point in mentioning eosinophil count without being clear about thresholds.	Thank you for your comment. The committee discussed the inclusion of a threshold to define a higher eosinophil count, but concluded that based on the evidence available it was not possible to define a specific threshold. In particular, they noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. However, the accompanying research recommendation to address which features predict inhaled corticosteroid responsiveness most accurately in people with COPD could provide information on this topic and help improve the definition of asthmatic features/features suggesting steroid responsiveness in future updates of the guideline.
Primary Care Respiratory Society	Guideline			Is there no algorithm for diagnosis? A visual would be helpful.	Thank you for your comment. The algorithm for diagnosis was not updated as this topic was not included in the scope of the update (apart from further investigations for initial assessment to confirm the diagnosis). The existing algorithm is located in section 5.2 of the 2010 update.
Primary Care Respiratory Society	Guideline	General	General	No treatment algorithm provided – if there was one in the draft guideline somewhere, none of our commentators found it. This needs to be prominent within the body of the recommendations– ideally in a format that can be printed out and put on a wall.	Thank you for your comment. There is an algorithm for the management of stable COPD that is being produced to accompany this update. It was available during consultation under the draft guidance consultation documents (please use this link).
Primary Care Respiratory Society	Guideline	General	General	At present there appears to be no signposting to excellent resources in the respiratory community – videos on inhaler technique, summary COPD guideline for primary care from PCRS, materials for patients, spirometry quality standards etc.	Thank you for your comment. Unfortunately, we are unable to specifically refer to other sources of guidance unless they have been endorsed by NICE. If these tools are of particular use, the developer of the tools could submit them to NICE for endorsement using this web link.
Boehringer-Ingelheim Ltd	Guideline	General	General	We note the following:	Thank you for your comment. The committee intended the definition of asthmatic features/features suggesting steroid responsiveness to cover both people with a secure diagnosis

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				• It is well recognised that prescription of ICS therapy frequently takes place outside with the recommendations of treatment guidelines (Chalmers et al. 2017 Primary Care Respiratory Medicine volume 27, Article number: 43) • As per comments made elsewhere in this response, there is potential for the reference to 'asthmatic features' to be misinterpreted with respect to individual patients (Kostikas et al. 2016 Int J Chron Obstruct Pulmon Dis. 11:1297-306)	of asthma and those who do not have asthma, but who are steroid responsive. The description of this term is intended to help clarify the people who are expected to be steroid responsive. However the committee were aware that there was a lack of evidence concerning the identifiable characteristics of these people and, as a result, they included a research recommendation on this point. They also included a research recommendation to help determine the most clinically and cost effective treatment for people with asthma and COPD as they recognised that these people are frequently excluded from trials of long-acting bronchodilators in people with COPD.
NHS England	Guideline		1.2.102 /3	The term "end-stage" is meaningless. The preferred term is "advanced disease (CLR)	Thank you for your comment. It was concluded that whilst 'advanced disease' is now commonly used terminology, the wording used in the guideline would be well understood by both patients and clinicians, and therefore did not need to be altered.
NHS England	Guideline	General	General	There is much benefit in this update and many good nuggets for use by clinicians – though we would suggest that the antibiotic use during an exacerbation is just part of this guidelines. For the generalist there are so many different guidelines and there is little need to add to this. (CRG)	Thank you for your comment. We have passed this suggestion to our antimicrobial prescribing team, for consideration alongside the guideline they are producing.
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	General	General	Question 4: We have major concerns about the recommendation not to supply long term oxygen therapy (LTOT) to continued smokers. We feel this cannot be justified ethically or in terms of evidence. There are of course risks associated with continued smoking and oxygen provision. However, no data is presented to quantitate the risks. It is acknowledged that individual risk-benefit analysis is needed for all subjects considered for LTOT. We believe that smoking should be a component of this assessment, but that a uniform policy is unethical. Part of the risk assessment will involve risk to others from fire hazard, but in most cases where hazardous	Thank you for your comment. The committee discussed this but decided that recommendation 1.2.56 means that patients will be offered appropriate advice and support to help them stop smoking so that they can receive oxygen therapy. This recommendation was not based on evidence about a lack of benefit of oxygen therapy for people who smoke but was instead designed to prevent smokers from injury or harm. Current evidence detailed in the evidence review suggests that smokers are at greater risk of adverse events associated

				treatment is offered, the principle is that the risk and ways to mitigate it are explained to the patient, who then consents to treatment in the light of this risk and benefit. There seems no reason a priori to treat oxygen differently, and to do so seems paternalistic and to contradict the principles of patient choice and involvement in therapeutic decisions. To simply require patients to cease smoking as a matter of policy even with assistance fails to take account the real difficulties in countering addiction. As noted, no evidence is presented in terms of risk benefit analysis to justify a more dogmatic approach. One can argue that smoking may mitigate the effect of oxygen therapy, but one can just as well argue that we should be more aggressive in treating continued smokers as their oxygen carrying capacity will be less for a given pO2; one could speculate that a higher target pO2 might be appropriate. In our own practice we discourage smoking, support quit attempts, but recognise that some will continue to smoke despite this. We then advise risk reduction by not smoking whilst using oxygen or for 20 minutes afterwards, and not in the same room where oxygen is delivered. This is supported by liaising with the fire service in routine fire safety checks for those prescribed LTOT, with on-going advice on annual review. This risk assessment must keep in mind subject's capacity and understanding, as well as potential risk to others in the event of fire, and sometimes we feel risk clearly does outweigh benefit and oxygen is not prescribed. However, I have attached what is now quite an old audit of survival of over 400 subjects in our service. Over 70 of these continued to smoke. There was no evidence of difference of survival in self-reported smokers and self-reported non-smokers suggesting the treatment was equally efficacious. Significant fire incidents have been very rare despite this large incidence of smokers. We believe that to routinely deny these patients the benefit of LTOT in the absence of demonstrable harm is clearly unethical as well as being unjustified on the basis of evidence presented. We would have great difficulty accepting this proposal if adopted. We feel that the correct recommendation is to strongly support quit attempts, and then to carry out an	with oxygen use than non-smokers. The committee also acknowledged that there are potential harms not just for the patient but also for other people, such as family and neighbours.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				individualised risk/benefit assessment that explicitly incorporates fire risks within this.	
NHS England	Guideline		1.1	No mention in this section about quality assured spirometry/ competency or registration (CLR)	Thank you for your comment. The topic of diagnosis was outside of the scope of this update (apart from further investigations for initial assessment to confirm the diagnosis). As a result, the committee were unable to make new recommendations about quality assuring spirometry.
NHS England	Guideline		1.1	The use of ERS reference values is now out of date and superseded by GLI. No mention of LLN (CLR)	Thank you for your comment and the information concerning GLI. We have incorporated this into the guideline in place of the older ERS reference.
NHS England	Guideline		1.1.20	Should this cross reference the recent NICE asthma guidelines? (CLR)	Thank you for your comment. There is a cross-reference to the asthma guideline in the previous recommendation.
NHS England	Guideline		1.2.10	Straight to LABA/LAMA after SABA may cause some raised eyebrows but has some merit (CLR)	Thank you for your comment and your support for this recommendation.
NHS England	Guideline		1.2.11	Recommendation is LAMA + LABA as first line treatment without offering single long acting bronchodilation. Justification given is that minimising the number of inhalers will be easier for people with COPD but this is first line treatment so this will be the first exposure to inhalers – it is 1 inhaler so confusion should not be an issue. Patient choice/side effects/symptoms/cost need to be considered in milder patients who may not require 2 medications. (CRG)	Thank you for your comment. It is envisaged that although LAMA+LABA will be the first line treatment for long- acting therapies, people with COPD will have been using short-acting devices before this point. Minimising the number or types of inhalers should reduce confusion, but LAMA+LABA was chosen as a first line treatment based on clinical and cost-effectiveness rather than this issue. The clinical evidence underlying this decision was divided at the whole trial level into study populations with low or high risk of exacerbations based on previous exacerbation history. In the low risk population, which should correspond to milder patients, LAMA+LABA was more effective than monotherapy based on the network meta-analysis across multiple outcomes similar to the high risk population and, as a result, the committee did not make separate recommendations for these people.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					The committee wrote recommendation 1.2.15 to address the issues of patient choice and cost for everyone with COPD.
NHS England	Guideline		1.2.119	This whole section needs to be clear about the differences between self-care, self-management training, agreed self-management plans, shared decision making and action plans for emergencies. I don't get the impression that the terminology is precise enough here. Where is the best place to provide self-management training? (CLR)	Thank you for your comment. The committee discussed this but decided that the terminology made a clear distinction between self-care, self-management, shared decision making and action plans. It was decided that the best place to provide self-management training could not be made more specific as there are a variety of places where this can be done.
NHS England	Guideline		1.2.13	The link for advice on managing COPD with asthma takes you to the NICE asthma guidelines. There is no advice here on managing people with COPD with asthma features as the text implies, it is a guideline for diagnosis and treatment of stable asthma, and does not offer clinicians advice on management of people with COPD and co-existing asthma (CRG)	Thank you for your comment. The majority of studies included in the clinical evidence base excluded people with COPD who had comorbid asthma and, as a result, this limited the recommendations that the committee could make on behalf of these people. The reference to the NICE asthma guideline was included because of the absence of evidence for this population. However, this has now been removed as the asthma guideline does not provide advice specifically on the treatment of asthma for people who have COPD. The committee recognised that the lack of clarity concerning the optimal treatment pathway for people with asthma and COPD was far from ideal and wrote a research recommendation to try to stimulate research into this issue.
NHS England	Guideline		1.2.14	This bit is vague. What are asthmatic features? Does it mean wheeze and eosinophilia? Patients with emphysema who remain breathless should not receive ICS/LABA (CLR)	Thank you for your comment. The committee defined asthmatic features/features suggesting steroid responsiveness as any previous, secure diagnosis of asthma or of atopy, a higher blood eosinophil count, substantial variation in FEV1 over time (at least 400 ml) or substantial diurnal variation in peak expiratory flow (at least 20%).
NHS England	Guideline		1.3.18	Why not include the recommendation here? (CLR)	Thank you for your comment. Unfortunately, with the exception of inhaled combination therapy, the topic of pharmacological management for COPD is not within the

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					scope of this update, and therefore changes could not be made to these recommendations.
NHS England	Guideline		1.3.22	I don't see the point in having a separate guideline for antibiotic treatment of exacerbations (CLR)	Thank you for your comment. This guideline was produced by a separate and different process within NICE to the main COPD guideline, and this is why it is presented as a separate guideline.
NHS England	Guideline		1.2.49	Why not include the recommendation in the guideline (CLR)	Thank you for your comment. This recommendation forms part of a separate guideline but the two are linked in the Stable COPD: Oral Therapy section of the NICE COPD pathway which is available on the NICE website. https://pathways.nice.org.uk/pathways/chronic-obstructive-pulmonary-disease
NHS England	Guideline		1.2.56	Agree. Do not offer oxygen to smokers (CLR)	Thank you for your comment and your support for this recommendation.
NHS England	Guideline		1.2.83	Repetition of pulmonary rehabilitation (CLR)	Thanks you for your comment. The committee agreed that this could be confusing and have re-worded recommendation 1.2.84 to make this clearer.
NHS England	Guideline		1.2.84	The MDT should include a thoracic surgeon (CLR)	Thank you for your comment. The topic of multidisciplinary management and specialists is not within the scope of this update, and therefore changes could not be made to these recommendations.
NHS England	Guideline		Table 6	I thought we had moved on from unhelpful repeated measurement of spirometry to assessment of exacerbation risk (GOLD) (CLR)	Thank you for your comment. The topic of follow-up of people with COPD in primary care is not within the scope of this update, and therefore changes could not be made to these recommendations.
NHS England	Guideline		Table 6	Summary of follow up in primary care. For those with mild/mod/severe disease there is no mention of screening for anxiety or depression – this is an omission as it is recognised that breathless people frequently suffer anxiety and depression which, if left unacknowledged and untreated, impacts further on breathlessness. For those with severe disease depression is mentioned but anxiety is omitted so should be added. (CRG)	Thank you for your comment. The topic of follow up of people with COPD in primary care is not within the scope of this update, and therefore changes could not be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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UK Clinical Pharmacy Association	Guideline	51-52	26-27 (p51) 1-2 (p52)	We wonder whether NICE should make a clear recommendation for one class of therapy (LABA + ICS) over any other when they are clear that there is an absence of evidence to make recommendations, and thus may be particularly contentious as there is a clear difference in opinion on appropriate therapy in groups of patients. Whilst we agree that patients with a history of COPD and asthma require an ICS, it may be argued that many of these patients should follow the NICE NG80 guideline pathway (or alternatively the BTS/SIGN asthma guidelines), which would recommend low dose ICS without LABA in patients uncontrolled on short-acting bronchodilator alone.	Thank you for your comment. The committee made the recommendation for LABA+ICS treatment of people with asthmatic features/features suggesting steroid responsiveness based on their clinical experience and the results of the economic model that showed that dual therapy was more effective than monotherapy. They did not recommend that the NICE asthma guideline was followed for these patients for several reasons: • steroid responsiveness is not confined to people who have asthma • people with asthma and COPD require treatment for their COPD in addition to their asthma.
NHS England	Guideline	1	7	Note we have reviewed and commented on the following sections: diagnosis and prognosis, inhaled combination therapies, prophylacti antibiotics, oxygen therapy, managing pulmonary hypertension and cor pulmonale, lung surgery and lung volume reduction procedures, education, self-management and telehealth monitoring for COPD (CRG)	Thank you for your comments on this guideline, which have been responded to where they appear in this table.
Association of Chartered Physiotherapists in Respiratory Care	Guideline	1.2.23		Some companies would advise cleaning hot soapy water weekly - air drip dry. Does this need to be monthly	Thank you for your comment. The topic of spacers to treat stable COPD is not within the scope of this update, and therefore changes could not be made to these recommendations.
Association of Chartered Physiotherapists in Respiratory Care	Guideline	1.2.26		Per and post lung function formal nebuliser assessment with benefits noted as per guideline- with consideration of no benefit.	Thank you for your comment.
Association of Chartered Physiotherapists in Respiratory Care	Guideline	1.2.56		Would suggest reconsider withholding oxygen for smokers. It can also be other members of household who smoke who pose risk too. Would suggest MDT risk assessment completed.	Thank you for your comment. The committee agreed that the presence of smokers in a house with someone with COPD could still constitute a fire risk but this could be mitigated by awareness of the risk. They therefore made a separate recommendation for people who live with people who smoke

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					(recommendation 1.2.55). This recommendation also details the importance of a structured risk assessment.
Association of Chartered Physiotherapists in Respiratory Care	Guideline	1.1.7		Can this include comment on lower limit of normal.	Thank you for your comment. The topic of the use of spirometry in diagnosis of COPD is not within the scope of this update, and therefore changes could not be made to these recommendations. The committee were aware of ongoing discussions about using the lower limit of normal for COPD diagnosis. However, at the time of scoping this guideline update it was not thought that there was enough available evidence to make recommendations as part of this update. These comments will be passed to the NICE surveillance team, for discussion when future updates of the guideline are planned.
Association of Chartered Physiotherapists in Respiratory Care	Guideline	1.2.63		Can there be more clarity for what constitutes exercise desaturation to avoid unnecessary appointments.	Thank you for your comment. This existing recommendation was amended following an evidence review on the use of ambulatory oxygen for breathlessness. The reference to dyspnoea (breathlessness) was removed and a recommendation was made to cover this (1.2.63), while the rest of the original recommendation remained out of scope of the review.
Association of Chartered Physiotherapists in Respiratory Care	Guideline	1.2.69		would expect more detail on prompt treatment of NIV - acidotic ABG to mask time for example as in RCP COPD audit door to mask 2 hours. also in section 1.3.34	Thank you for your comment. The topic of non-invasive ventilation for COPD exacerbations is not within the scope of this update, and therefore no changes could be made to these recommendations.
Association of Chartered Physiotherapists in Respiratory Care	Guideline	1.2.77		PR recommended for MCR 2 if would benefit. PR accredited scheme recommended.	Thank you for your comment. The topic of pulmonary rehabilitation is not within the scope of this update, and therefore no changes could be made to these recommendations.
Association of Chartered Physiotherapists	Guideline	1.2.78		Post discharge PR prompt following discharge- with target of within 4 weeks.	Thank you for your comment. The topic of pulmonary rehabilitation is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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in Respiratory Care					
Primary Care Respiratory Society	Guideline	4	4/7	The current wording of 'The diagnosis is suspected on the basis of symptoms and signs and supported by spirometry' is insufficient. This headline should guide health professionals how to make the diagnosis not just suspect it. Wording of the order of "A diagnosis of COPD is made on the basis of the presence of characteristic symptoms, examination and tests to exclude alternative pathology and the presence of obstructive spirometry, i.e. symptoms and spirometry alone are not sufficient. E.g symptoms of COPD plus obstructive spirometry could be lung cancer.'	Thank you for your comment. The topic of diagnosing COPD with the support of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations.
Royal College of General Practitioners	Guideline	4	3	The current wording of" The diagnosis is suspected on the basis of symptoms and signs and supported by spirometry "is insufficient. This headline should guide health professionals how to make the diagnosis not just suspect it. Wording of the order of "A diagnosis of COPD is of COPD is made on the basis of the presence of characteristic symptoms, examination and tests to exclude alternate pathology and the presence of obstructive spirometry. i.e. symptoms and spirometry alone are not sufficient. E.g. symptoms of COPD plus obstructive spirometry could be lung cancer.	Thank you for your comment. The topic of diagnosing COPD with the support of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations.
Association for Respiratory Technology and Physiology	Guideline	4	7	To be clear (and scientific) they should use units, for example "over 35 years"	Thank you for your comment. The topic of symptoms of COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Association for Respiratory Technology and Physiology	Guideline	4	16	Should really say "unexplained weight loss". Could also include family history	Thank you for your comment. The topic of symptoms of COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
British Dietetic Association	Guideline	4	16	States 'weight loss' but should say MUST ≥2, low BMI (<20 kg/m^2) or unintentional weight loss of 5-10% over last 3-6 months. Unintentional weight loss is very important clinically but can also be the first sign of an underlying pathology in COPD requiring investigation.	Thank you for your comment. The topic of symptoms of COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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Royal College of General Practitioners	Guideline	5	11	The Guideline recommends using spirometry but does not headline the criterion by which a diagnosis of obstruction is made. By inference (by citing what to do in the elderly/young when the ratio of FeV-1/FVC of < 0.7) this suggests the fixed ratio is recommended. It is disappointing that the issue of Lower limit of Normal v fixed ratio was not reinvestigated as many respiratory specialists recommend the ~LLN as a better cut off point to diagnose airways obstruction. If the fixed ratio of <0.7 is still recommended then state this clearly. Not everyone who reads the guideline will be a respiratory specialist. Guidelines from the Czech Republic, Italy, Poland and Sweden all specified a post-bronchodilator FEV_1/FVC ratio less than the lower limit of normal (LLN) (*i.e.* below the 5th percentile for age, sex and height). The Spanish guidelines use the fixed ratio as the criterion for diagnosis, except in patients aged <50 years and >70 years, for whom the LLN is recommended. http://erj.ersjournals.com/content/47/2/625	Thank you for your comment. The topic of diagnosing COPD with the support of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations. We have passed the information provided and the suggestion to update this section, in particular looking at the lower limit of normal v fixed ratio to our surveillance team to inform future updates of this guideline.
Association for Respiratory Nurse Specialists	Guideline	5	11	Change to say perform Quality Assured Spirometry.	Thank you for your comment. The topic of diagnosing COPD with the support of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	5	11	The Guideline recommends using spirometry for diagnosis but does not headline the criterion by which a diagnosis of obstruction is made. Citing what to do in the elderly/young when the ratio of FEV1/FVC of < 0.7 suggests the fixed ratio is recommended. It is disappointing that the issue of Lower limit of Normal (LLN) v fixed ratio was not re investigated as many respiratory specialists recommend the LLN as a better cut off point to diagnose airways obstruction. This has been a much debated area of controversy and it would be good for NICE to make its position clear. If the fixed ratio of <0.7 is still recommended then state this clearly, and explain why LLN was not chosen.	Thank you for your comment. The topic of diagnosing COPD with the support of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations. We have passed the information provided and the suggestion to update this section, in particular looking at the lower limit of normal v fixed ratio to our surveillance team to inform future updates of this guideline.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				Not everyone who reads the Guideline will be a respiratory specialist!	
Association for Respiratory Technology and Physiology	Guideline	5	13	Not sure what they mean by "exceptionally good" - be better to clarify - e.g. improvement in lung function/reduction in symptoms etc.	Thank you for your comment. The topic of diagnosing COPD with the support of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	5	15	It is suggested that spirometry is required to monitor disease progression. The BODE, DOSE and risk factors for COPD reviews all suggest that full spirometry is not required as the only indicator involved in measuring disease progression in the evidence is FEV1. (Jones RC, Donaldson GC, Chavannes NH, Kida K, Dickson-Spillmann M, Harding S, et al. Derivation and Validation of a Composite Index of Severity in Chronic Obstructive Pulmonary Disease. American Journal of Respiratory and Critical Care Medicine. 2009;180(12):1189-95. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnoea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350 (10):1005-12) – We would suggest that this should be clarified to just an FEV1 being required for monitoring COPD.	Thank you for your comment. The section on spirometry was out of scope of this update. However, the committee added the bullet point for the use of spirometry to measure disease progression to an existing recommendation based on the information from Table 6 of the guideline. The committee decided against specifying FEV1 and FVC instead of full spirometry to allow healthcare professionals to make this decision based on their expertise and the equipment available to them. The evidence review for the section on assessing severity and prognosis looked at the prognostic usefulness of various indices compared to FEV1 alone and concluded that that none of the existing indices were suitable and/or better at predicting outcome than FEV1 alone. This review did not look at the prognostic usefulness of spirometry or FEV1/FVC ratio or FVC. As a result, the committee only included FEV1 in the list of prognostic factors.
NHS England	Guideline	5	15	Note that it is suggested that spirometry is required to monitor disease progression. The BODE, DOSE and risk factors for COPD reviews all seem to suggest that full spirometry is not required which is difficult for many old people (and younger ones) as the only indicator involved in measuring disease progression in the evidence is FEV1 (Jones RC, Donaldson GC, Chavannes NH, Kida K, Dickson-Spillmann M, Harding S, et al. Derivation and Validation of a Composite Index of Severity in Chronic Obstructive Pulmonary	Thank you for your comment. The section on spirometry was out of scope of this update. However, the committee added the bullet point for the use of spirometry to measure disease progression to an existing recommendation based on the information from Table 6 of the guideline. The committee decided against specifying FEV1 and FVC instead of full spirometry to allow healthcare professionals to make this decision based on their expertise and the equipment available to them.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				Disease. American Journal of Respiratory and Critical Care Medicine. 2009;180(12):1189-95. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005-12) – would suggest that this should be clarified to just an FEV1? (CRG)	The evidence review for the section on assessing severity and prognosis looked at the prognostic usefulness of various indices compared to FEV1 alone and concluded that that none of the existing indices were suitable and/or better at predicting outcome than FEV1 alone. This review did not look at the prognostic usefulness of spirometry or FEV1/FVC ratio or FVC. As a result, the committee only included FEV1 in the list of prognostic factors.
Association for Respiratory Technology and Physiology	Guideline	5	18	Should really consider using LLN - lots of good evidence as you know about using this to reduce misdiagnosis. They suggest looking for alternate diagnosis, but patient could be normal/free from lung disease doesn't make sense here.	Thank you for your comment. The topic of diagnosing COPD with the support of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations. We have passed the information provided and the suggestion to update this section, in particular looking at the lower limit of normal v fixed ratio to our surveillance team to inform future updates of this guideline.
Association for Respiratory Nurse Specialists	Guideline	5	18	This recommendation may need to include what is 'typical symptoms of COPD' for clarity	Thank you for your comment. The topic of diagnosing COPD with the support of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations.
British Thoracic Society	Guideline	6	9-11	The guideline recommends use of reference values acknowledged to be "inapplicable" in Black and Asian populations. To ensure accurate assessment and diagnosis of patients regardless of race, reference values adjusted for race should be used (e.g. ERS GLI-2012).	Thank you for your comment and the information concerning GLI. We have incorporated this into the guideline in place of the older ERS reference.
Primary Care Respiratory Society	Guideline	6	5/6	'Any healthcare worker who has had appropriate training and has up-to-date skills.' HCPs are not required to undergo training. If they are able to demonstrate their competence when assessed and are accepted on the National register, then they are judged competent regardless of whether any training is undertaken.	Thank you for your comment. The topic of diagnosing COPD with the support of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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NHS England	Guideline	6	3	"All healthcare professionals who care for people with COPD should have access to spirometry and be competent in interpreting the results - difficult to monitor and police." The word "competent" needs defining. (PC)	Thank you for your comment. The topic of diagnosing COPD with the support of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	6	4	'and be competent in interpreting the results' Anyone diagnosing COPD needs to have skills to or have access to someone with skills to interpret spirometry, but it is not necessary for all HCPs to be competent in performing and/or interpreting spirometry.	Thank you for your comment. The topic of diagnosing COPD with the support of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations.
University Hospitals Birmingham NHS Foundation Trust	Guideline	6 6	Line 5 Line 9	Quality assured spirometry should be performed by an accredited/ certified spirometry practitioner Use GLI reference values for spirometry rather than 1993 ERS reference values. - Agree	Thank you for your comment. The topic of diagnosing COPD with the support of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations. Thank you for the information concerning GLI. We have incorporated this into the guideline in place of ERS reference values.
Primary Care Respiratory Society	Guideline	6	7	We are surprised that there is nothing here about the National ARTP spirometry register being a part of quality control. This is a missed opportunity to highlight the scheme which expects to raise the standard of respiratory diagnosis. https://www.pcc-cic.org.uk/sites/default/files/articles/attachments/improving_the_quality_of_diagnostic_spirometry_in_adults_the_national_register_of_certified_professionals_and_operators.pdf	Thank you for your comment. The topic of diagnosing COPD with the support of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations.
NHS England	Guideline	6	7	"Spirometry services should be supported by quality control processes." Again -difficult to monitor and assure in primary care. (PC)	Thank you for your comment. The topic of diagnosing COPD with the support of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations.
Association for Respiratory Technology and Physiology	Guideline	6	9	Recommending ERS 93 ref equations - May resp societies recommend GLI for spiro - this then helps with comment regarding ethnicity and age. As a minimum, they should be recommending a	Thank you for your comment and the information concerning GLI. We have incorporated this into the guideline in place of the older ERS reference.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				move to these equations, as more devices now have these equations loaded.	
Primary Care Respiratory Society	Guideline	6	9	"It is recommended that ERS 1993 reference values are used, but it is recognised that these values may lead to under-diagnosis in older people and are not applicable in black and Asian populations [2004]" Should that be over-diagnosis?	Thank you for your comment and the information concerning GLI. We have incorporated this into the guideline in place of the older ERS reference.
Primary Care Respiratory Society	Guideline	6	12	Consider adding a warning to the useful discussion of what to do with incidental abnormal CXR or CT scan findings. The warning that making a diagnostic entry of COPD in primary care record systems based solely on CXR abnormalities with no further diagnostic evaluation is an important contributor to over diagnosis of COPD. The same could be said about spirometry during acute admissions for chest infections without repeat spirometry and diagnostic evaluation at follow up after resolution of the acute episode. Overall there is a missed opportunity to spell out the diagnostic mistakes that lead to both under- and over-diagnosis of COPD.	Thank you for your comment. The committee concluded the issue around over-diagnosis of COPD based solely on imaging results was covered by the recommendation that these people should be referred for spirometry and a respiratory review, rather than a diagnosis being made based on the imaging results alone. The topic of how COPD should be diagnosed was not within the scope of this update of the guideline, and therefore it was not possible for the committee to make comments on how spirometry results during acute admissions should be interpreted.
Primary Care Respiratory Society	Guideline	6	13	It would be useful for NICE to provide guidance on how to manage this risk (increased risk of lung CA if have emphysema on CT scan)?	Thank you for your comment. Unfortunately, this guideline did not contain a review question on managing people with an increased risk of lung cancer, and therefore the committee were not able to make recommendations on this topic. However, we have passed this comment on to our surveillance team for consideration when future updates of the guideline are being planned.
NHS England	Guideline	6	13	Is there a reason why primary care mentioned here? (Increasingly reports suggest CT emphysema and most in primary care if the spirometry is normal would be uncertain how to manage that?) Agree regarding chest x-ray requiring spirometry but it is the clinician who arranges the test to ensure follow up takes place (according to GMC guidance).	Thank you for your comment. The committee concluded that in the majority of cases this review would take place in primary care, and that it was therefore appropriate to mention this in the recommendation.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				(CRG)	
KSS AHSN Patient Safety Collaborative	Guideline	6	16	This statement is vague. Many people have a small degree of emphysema on CT found incidentally. What are 'changes of chronic airways disease on CXR or CT'? Suggest re-wording along the lines of 'if new changes of emphysema, hyperinflation, or airway thickening are found incidentally on CXR or CT arrange clinical assessment in primary care to assess for symptoms, consider the need for spirometry. If significant symptoms consider referral to secondary care/specialist community teams.	Thank you for your comment. This recommendation was based on the high level of correlation between findings of emphysema on CT scan or CXR, and a subsequent spirometrically confirmed diagnosis of COPD. The committee believe the current wording of the recommendation accurately reflects the evidence identified within the guideline, and therefore no changes to this wording have been made.
KSS AHSN Patient Safety Collaborative	Guideline	6	23	In what way does 'being aware' of the increased risk of lung cancer in people with emphysema alter practice? If it doesn't then suggest omit.	Thank you for your comment. The committee noted that no evidence was identified in the guideline to suggest how these people should be managed differently; but concluded it was relevant to bring this risk to the attention of clinicians involved in treating these people.
NHS England	Guideline	6	23	Note the increase risk of lung cancer if emphysema on CT scan – is there therefore a recommendation on how to manage this risk (screening etc) (CRG)	Thank you for your comment. Unfortunately, this guideline did not contain a review question on managing people with an increased risk of lung cancer, and therefore the committee were not able to make recommendations on this topic. However, we have passed this comment on to our surveillance team for consideration when future updates of the guideline are being planned.
Association for Respiratory Technology and Physiology	Guideline	Table 6	37	Do you mean SpO2 rather than SaO2 (also, Table 7)	Thank you for your comment. Tables 6 and 7 were not included in the scope of this update and, as a result, we are unable to change the existing recommendations.
Primary Care Respiratory Society	Guideline	7	12	Please clarify why BMI is important as part of initial evaluation – and more so than say pulse for atrial fibrillation (another basic clinical examination) or QRISK3 for cardiac risk or indeed as both WHO and GOLD recommend and Alpha 1 antitrypsin deficiency. Seems very strange to have the BMI in this group – and something that many clinicians ask … why is this important over other areas? Such as anxiety too.	Thank you for your comment. The topic of further investigations for diagnosing people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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NHS England	Guideline	7	12	Please clarify why BMI is important as initial evaluation – and more so than say pulse for atrial fibrillation (another basic clinical examination) or QRISK3 for cardiac risk or indeed as both WHO and GOLD recommend and Alpha 1 antritripsin deficiency. Seems very strange to have the BMI in this group – and something that many clinicians ask … why is this important over other areas (anxiety too). (CRG)	Thank you for your comment. The topic of further investigations for diagnosing people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	8		Table 2 Please explain why you are recommending doing echo / ECG – but not a QRISK3, especially considering the commonest cause of death in people with COPD is cardiac disease and this will not be picked up by ECG / echo (though heart failure and persisting arrhythmia will)	Thank you for your comment. The additional investigations listed in Table 2 were part of the section on further investigation and were not in the scope of this update. We are therefore unable to add new test to the table, but could amend existing entries based on the evidence reviewed in other sections of the update. The table was amended with the deletion of pulse oximetry because this test was examined as part of the review of tests to confirm diagnosis of COPD. Other changes were made to the table to reflect evidence examined in the reviews of tests to confirm diagnosis of COPD and the review examining referral criteria for lung volume reduction procedures or to clarify the role of an existing assessment.
Thermo Fisher Scientific	Guideline	8	1	This inclusion criterion overlooks Procalcitonin. The test is routinely available and used in the UK as part of the diagnostic criteria for management aeCOPD presentations	Thank you for your comment. The use of antibiotics to treat exacerbations was out of the scope of this update as it was focused on the management of stable COPD. However, we have passed information on to the NICE Antimicrobial prescribing team as it is relevant for their guidance on the prescription of antibiotics during acute exacerbations
Royal Free London NHS Foundation Trust	Guideline	8	1	Please consider adding serum immunoglobulin assay to the Additional Investigations for people with frequent COPD exacerbations. We run a tertiary immunology service and see late diagnoses of primary immunodeficiency in people with COPD because the 'exacerbations' are considered normal in COPD. Serum immunoglobulin assay is readily available and cheap. It is	Thank you for your comment. The topic of further investigations for diagnosing people with COPD was not within the scope of this update, and therefore we are unable to add this test to table 2. We are also unable to add this test to table 5 for the same reason.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				practice changing because of the availability of immunoglobulin replacement for people with confirmed immunodeficiency. This latter intervention is life changing for patients, who on average have a seven year delay prior to diagnosis. The usual 'SPUR' criteria (test for immunodeficiency if infections are SEVERE, PERSISTENT, UNUSUAL or RECURRENT) applies here yet people with COPD are not being tested. An alternative location for this would be Table 5, Frequent Infections "Exclude bronchiectasis and immunodeficiency".	However, we have passed the information you provide to our surveillance team to help inform decisions regarding future updates of this guideline.
NHS England	Guideline	8	1	Seems strange to be doing echo / ecg – but not a QRISK3 especially considering the commonest cause of death in people with COPD is cardiac disease and this will not be picked up by ecg / echo (though heart failure and persisting arrhythmia will) (CRG)	Thank you for your comment. The topic of further investigations for diagnosing people with COPD was not within the scope of this update, and therefore we are unable to add this test to table 2. However, we have passed the information you provide to our surveillance team to help inform decisions regarding future updates of this guideline.
Royal College of General Practitioners	Guideline	8	6	Recommendation 1.18 states that reversibility testing is not routinely need in making a diagnosis of COPD. In practice a patient presents with symptoms which could be attributable to asthma or COPD. 1 in 7 patients (National COPD Audit Wales 2016) have features of asthma and COPD and reversibility testing helps tease out those people who might have this overlap and avoid the use of medication might be harmful e.g. propranolol Recommendation 1.21 acknowledges that finding a reversibility of 400ml suggests the presence of asthma i.e. acknowledges that finding reversibility is important.	Thank you for your comment. The topic of spirometry is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	8	6	Recommendation 1.18 states that reversibility testing is not routinely need in making a diagnosis of COPD. This was listed as one of the more disappointing aspects of the guideline by our commentators. There needs to be a more prominent recommendation for reversibility testing to distinguish pure COPD from COPD with features of asthma.	Thank you for your comment. The topic of reversibility testing is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				In practice a patient presents with symptoms which could be attributable to asthma or COPD. 1 in 7 patients (National COPD Audit Wales 2016) have features of asthma and COPD and reversibility testing helps tease out those people who might have this overlap and avoid the use of medication which might be harmful e.g propranolol. The guideline should make it clear that reversibility testing is an important part of the diagnostic assessment in order to help clarify the difference between COPD with and without features of asthma, since there is a clear implication that the distinction between COPD with and without features of asthma has an important bearing on treatment. One commentator expressed this as follows: 'concern that the different markers for reversibility to confirm a diagnosis of asthma remain confusing for primary care as from BTS Asthma guidelines - In adults with obstructive spirometry, an improvement in FEV1 of 12% or more in response to either β2 agonists or corticosteroid treatment trials, together with an increase in volume of 200 ml or more, is regarded as a positive test, although it does acknowledge some people with COPD can have significant reversibility - 400mls. Does this mean that people with COPD who have positive reversibility of 200mls and improvement of 12% in FEV1 are not considered to have an asthmatic element? '	
Boehringer-Ingelheim Ltd	Guideline	9	1.1.19 Table 3	BI strongly supports the highlighting of key differences between COPD and asthma, as has been present since 2004. However, given that the diagnosis of asthma is currently recommended as a fundamental point in the decision as to whether or not ICS are prescribed, it is critical to enable prescribers to be able to make a clear decision. We suggest cross reference to the NICE guideline for Diagnosing and Monitoring of Asthma to avoid any confusion in implementation.	Thank you for your comment. This recommendation already includes a reference to the NICE 2017 guideline for Diagnosing and Monitoring of Asthma.
Boehringer-Ingelheim Ltd	Guideline	9	16	The reference on the NICE guideline on asthma is [2004]. The clinical guideline 80 "Asthma: diagnosis, monitoring and chronic	Thank you for your comment, and this link has been updated in line with your suggestion.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				asthma management" was published in November 2017. We believe this reference should be cited instead as [2004, updated 2018] to reflect, and highlight the updated asthma guideline.	
Primary Care Respiratory Society	Guideline	10	1	Recommendation 1.1.21 acknowledges that finding a reversibility of 400ml suggests the presence of asthma, so acknowledges that finding reversibility is important. So the initial statement about the value of reversible spirometry should be corrected to be clear of its value for differential diagnosis.	Thank you for your comment. Unfortunately, reversibility testing was not within the scope of this update and, as a result, we are unable to change any of the recommendations in this section.
Primary Care Respiratory Society	Guideline	10	3	Though you say there is no change in this section, you do indicate that you have reviewed diagnosis (GOLD, GINA, NICE Asthma, BTS SIGN Asthma). All talk about significant change on FEV1 as 200mls and as far as we are aware, NICE COPD will be the only one talking about 400mls. We are aware this is relative but fear this may cause confusion amongst generalists and indeed many specialists.	Thank you for your comment. In this guideline, evidence was reviewed on diagnostic tests other than spirometry (such as CT scans and chest X-rays), and on indexes that may predict COPD outcomes (of which GOLD was one considered). Evidence was not reviewed on which diagnostic criteria to use for rather COPD or asthma, and therefore it was not possible to make changes to the recommendations in this section.
NHS England	Guideline	10	3	Though no change in this section you do indicate that you have reviewed diagnosis. (GOLD, GINA, NICE Asthma. BTS SIGN Asthma) all talk about significant change on FEV1 as 200mls and as far as we are aware NICE COPD will be the only one talking about 400mls. (We are aware this is relative but will cause confusion amongst generalists and indeed many specialists). (CRG)	Thank you for your comment. In this guideline, evidence was reviewed on diagnostic tests other than spirometry (such as CT scans and chest X-rays), and on indexes that may predict COPD outcomes (of which GOLD was one considered). Evidence was not reviewed on which diagnostic criteria to use for rather COPD or asthma, and therefore it was not possible to make changes to the recommendations in this section.
Royal College of General Practitioners	Guideline	10	18	The recommendation that a multidimensional index of severity is not routinely used. BODE is understandably rejected due to difficulty of being used in primary care. The DOSE index, p, was rejected since the median c statistic score was only 0.65 in spite of a high hazard score of 8.00 and its ease of use in primary care.	Thank you for your comment. The committee did note the discrimination of the DOSE index, and noted that in situations where other prognostic indices were not available, this may have performed well enough to be recommended. However, they concluded that none of the indices looked at (including DOSE) had properties that were sufficiently better than FEV1 alone as a measure of prognosis, and therefore it was not possible to recommend their use.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Primary Care Respiratory Society	Guideline	10	18	Take care the wording does not imply 'should use in unstable patient with COPD'. Many in primary care find DOSE (dyspnoea, (MRC) obstruction (FEV1) smoking status and exacerbation) as easy to use and if in keeping with validation, why is this not recommended? DOSE is not mentioned but is multidimensional and designed for primary care (We accept that BODE is not suitable for primary care –due to inclusion of 6MWT – but neither is this performed in most specialist environments (or reported on in discharge letters))	Thank you for your comment. This update of the guideline was confined to sections relating to people with stable COPD and this recommendation clearly states this. The committee did not agree that the recommendation could be misinterpreted to imply that since BODE was not suitable for prognosis in people with stable COPD it should be used in people with unstable COPD and so no changes have been made here. The committee examined the evidence for DOSE and decided against recommending it for the following reasons: • The median classification accuracy of the index was poor (c-statistic 0.62 for mortality), which was comparable to FEV1 alone. • Although the hazard ratio associated with being in the most severe classification group was associated with a large increase in mortality, this data came from a single study. • This index did not include other relevant prognostic factors such as previous hospitalisations. The reasons behind the committee's decisions are covered in more detail in the discussion section of the prognostic evidence review in Chapter D.
NHS England	Guideline	10	18	Does this mean should use in unstable patient with COPD. Many in primary care find DOSE (dyspnoea, (MRC) obstruction (FEV1) smoking status and exacerbation as both easy to explore and if in keeping with validation why is this not suggested? This is not mentioned but is multidimensional and designed for primary care (Note the rationale suggests BODE is not suitable for primary care – which it is not with the 6MWT – but neither is this performed in most specialist environments (or reported on in discharge letters) (CRG)	Thank you for your comment. This update of the guideline was confined to sections relating to people with stable COPD and this recommendation clearly states this. The committee did not agree that the recommendation could be misinterpreted to imply that since BODE was not suitable for prognosis in people with stable COPD it should be used in people with unstable COPD and so no changes have been made here. The committee examined the evidence for DOSE and decided against recommending it for the following reasons:

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					• The median classification accuracy of the index was poor (c-statistic 0.62 for mortality), which was comparable to FEV1 alone. • Although the hazard ratio associated with being in the most severe classification group was associated with a large increase in mortality, this data came from a single study. • This index did not include other relevant prognostic factors such as previous hospitalisations. The reasons behind the committee's decisions are covered in more detail in the discussion section of the prognostic evidence review in Chapter D.
Primary Care Respiratory Society	Guideline	10	20	Good list – and appears appropriate, but again no mention of FEV1/FVC ratio or FVC – so please comment on why full spirometry required rather than an accurate FEV1 on page 5 line 15 (as mentioned earlier)	Thank you for your comment. The section on spirometry was out of scope of this update. However, the committee added the bullet point for the use of spirometry to measure disease progression to an existing recommendation based on the information from Table 6 of the guideline. The committee decided against specifying FEV1 and FVC instead of full spirometry to allow healthcare professionals to make this decision based on their expertise and the equipment available to them. The list of factors included in the section on assessing severity and using prognostic factors was derived from an existing list of factors from the 2010 guideline with additions from the current committee. The evidence review for this section looked at the prognostic usefulness of prognostic indices compared to FEV1 alone and concluded that that none of the existing indices were suitable and/or better at predicting outcome than FEV1 alone. This review did not look at the prognostic usefulness of spirometry or FEV1/FVC ratio or FVC. As a result, the committee only included FEV1 in the list.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

NHS England	Guideline	10	20	Good list – and appears appropriate (again no mention of FEV1/FVC ratio or FVC – so comment on why full spirometry required rather than an accurate FEV1 on page 5 line 15 (see earlier) (CRG)	Thank you for your comment. The section on spirometry was out of scope of this update. However, the committee added the bullet point for the use of spirometry to measure disease progression to an existing recommendation based on the information from Table 6 of the guideline. The committee decided against specifying FEV1 and FVC instead of full spirometry to allow healthcare professionals to make this decision based on their expertise and the equipment available to them. The list of factors included in the section on assessing severity and using prognostic factors was derived from an existing list of factors from the 2010 guideline with additions from the current committee. The evidence review for this section looked at the prognostic usefulness of prognostic indices compared to FEV1 alone and concluded that that none of the existing indices were suitable and/or better at predicting outcome than FEV1 alone. This review did not look at the prognostic usefulness of spirometry or FEV1/FVC ratio or FVC. As a result, the committee only included FEV1 in the list.
Boehringer-Ingelheim Ltd	Guideline	10	25	With respect to breathlessness (MRC scale), it may be valuable to mention that there is another version of the scale, the modified MRC (mMRC) that is almost identical in language but scores between 0-4 rather than 1-5: this has the potential to cause confusion and potentially an under-recording of the patient's dyspnoea status.	Thank you for your comment. The committee decided not to include a reference to the differences between scoring the mMRC and MRC scales in the recommendation as this was concluded to be too much detail for the recommendation. However, we have included this information in the discussion section of the evidence review.
British Dietetic Association	Guideline	10	27	States 'low BMI' but should say MUST ≥2, low BMI (<20 kg/m^2) or unintentional weight loss of 5-10% over last 3-6 months	Thank you for your comment. The guideline did not review evidence on the relationship between malnutrition or weight and outcomes for people with COPD, and therefore it was not possible for the committee to make changes to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

UK Clinical Pharmacy Association	Guideline	11	2	CAT score needs to be defined as COPD Assessment Test, especially for the non-specialists are often not aware of what it is. It also probably needs to be higher up the list of factors that indicate severity of COPD disease.	Thank you for your comment - we have now added the full name of the CAT score to this recommendation. The committee were confident the order the factors in this list are presented was an appropriate one, and this has therefore not been changed.
Boehringer-Ingelheim Ltd	Guideline	11	2	BI strongly support the inclusion of 'symptom burden (for example CAT score)' as a factor for prognosis and treatment decisions. We would recommend that use of specific indicators such as MRC dyspnoea scale and CAT score be included in sections 1.2.10 and 1.2.15	Thank you for your comment. Thank you for your support of the recommendation on prognostic factors. However, the recommendations on measures to assess the effectiveness of bronchodilator therapy was not included within the scope of this update and we are unable to amend it. The committee decided against including specific indicators of symptom burden in the inhaled combination therapy recommendation because they agree that the healthcare professional would be able to decide how to measure these symptoms without further input from the committee.
Association for Respiratory Technology and Physiology	Guideline	11	10	Which criteria is this guideline recommending for assessing copd severity - should recommend, rather than list several criteria which give different answers. Again, fixed cut-off for FEV/FVC is not correct.	Thank you for your comment. The topic of assessing and classifying the severity of airflow obstruction is not within the scope of this update, and therefore no changes could be made to these recommendations.
Association for Respiratory Technology and Physiology	Guideline	11	12	Patients may not have symptoms in mild / early disease. If asymptomatic, surely it is not wise to not diagnose mild copd (e.g. label as normal) - surely a missed opportunity to start intervention (e.g. smoking cessation) and prevent disease progression.	Thank you for your comment. The topic of assessing and classifying the severity of airflow obstruction is not within the scope of this update, and therefore no changes could be made to these recommendations.
Boehringer-Ingelheim Ltd	Guideline	12	1	Please update to reference GOLD 2018.	Thank you for your comment. The assessment and classification of the severity of airflow obstruction is not within the scope of this update and, as a result, we are unable to amend this table. We have passed this information onto surveillance to help inform future updates of the guideline.
University Hospitals Birmingham	Guideline	12	Table 4	It's disappointing that there is no reference to lower limit of normal and the problems with the fixed 70% cut off to define airflow obstruction.	Thank you for your comment. The assessment and classification of the severity of airflow obstruction is not within

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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NHS Foundation Trust				Is it helpful to have several severity grading guidelines in? Should we not be recommending one?	scope of this update and, as a result, we are unable to amend this table. We have passed your comments onto surveillance to help inform future updates of the guideline.
Primary Care Respiratory Society	Guideline	12	Table 4	What is the purpose of this table? It indicates that there are different schemes for determining severity of airflow obstruction but does not guide about which one to use. And all but the NICE 2004 version are in agreement.	Thank you for your comment. The assessment and classification of the severity of airflow obstruction is not within the scope of this update and, as a result, we are unable to amend this table. We have passed your comments onto surveillance to help inform future updates of the guideline.
Boehringer-Ingelheim Ltd	Guideline	13	1.2	BI suggest that it may be useful to include a statement in section 1.2 'Managing stable COPD' relating to ensuring that the healthcare professional manages the patient's expectations: the patient may still become breathless and experience a mild fluctuation in symptoms from day to day, and importance should be placed on helping the patient to be able to expect these outcomes and self-manage appropriately.	Thank you for your comment. The committee noted this suggestion, but concluded that since this was not something addressed by any of the evidence reviewed in the guideline, it was not appropriate to make any recommendations around this point.
Royal Free London NHS Foundation Trust	Guideline	14	1	The focus on smoking cessation here and elsewhere is on tobacco smoke. There is no mention of other exposures and the need to reduce those too (marijuana and other illicit drugs, and occupation).	Thank you for your comments. The topic of illicit drugs and COPD is not within the scope of this guideline, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	14	2	It would be worth making a specific recommendation to ask about a history of cannabis smoking, since this is an important risk factor for COPD and the question is often not asked.	Thank you for your comments. The topic of cannabis smoking and COPD is not within the scope of this guideline, and therefore no changes could be made to these recommendations.
Royal Pharmaceutical Society	Guideline	14	14	Community Pharmacists are ideally placed as the first point of contact for patients, to ask patients if they smoke and offer advice to stop smoking. They do this as part of their consultation when handing out prescriptions and when undertaking medication reviews, especially patients whose medicines for health conditions are made worse by smoking or who have a smoking related illness.	Thank you for your comments. The topic of smoking cessation guidance for managing stable COPD is not within the scope of this guideline, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				Pharmacist and pharmacy staff can identify patients requesting OTC treatments or advice for NRT.	
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	14	16	We agree with the general scheme for the use of inhaled therapies. However, we note there is no guidance on 'stepping down' of inhalers. In particular, in clinical practice there are patients who have been given inhaled steroids, but in retrospect this seems to have been without good reason. Should the steroids be stopped? Other patients appear to have received inhaled steroids appropriated but they get possible complications (particularly pneumonia, perhaps recurrent bacterial bronchitis). Should the steroids be stopped? There is a paucity of evidence base, but there is some e.g. the WISDOM trial and CRYSTAL. Further, the GOLD guidelines in latest revision consider step down of therapy. This is a practical issue faced frequently by semi-specialist HCPs such as practice nurses conducting COPD reviews. Some guidance here using expert review and that evidence which is available would be valuable.	Thank you for your comment. The topics of switching between inhaled therapies, stepping down treatment and ICS withdrawal were not within the scope of this update and, as a result, we did not examine any evidence on this issue. We have passed your request for the inclusion of guidance on ICS withdrawal and treatment switching, and the information about the WISDOM and CRYSTAL trials, to our surveillance team to help inform their decisions for future updates of this guideline
Primary Care Respiratory Society	Guideline	14	17	In most medical conditions the object is to relieve symptoms over a prolonged period of time so that the patient is encouraged to be more active and for the condition to have less impact on their life. The results using LABA/LAMA are better than SABA on its own – apart from the cost – why are we not helping to relieve symptoms immediately and minimise the impact on our patients' lives?	Thank you for your comment. The topic of inhaled therapy using SABA is not within the scope of this update, and therefore no changes could be made to these recommendations.
NHS England	Guideline	14	17	In most of medical conditions the object is to relieve symptoms over a prolonged period of time so that the patient is encouraged to be more active and for the condition to have less impact on their life. We use twice daily NSAIDs often for rheumatoid arthritis, once daily treatment for blood pressure, long acting medications (rather than GTN) for angina. The results using LABA/LAMA are better than SABA on its own – apart from the cost – why are we not helping to relieve symptoms immediately and minimise the impact on our patients lives? (CRG)	Thank you for your comment. The topic of inhaled therapy using SABA is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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British Thoracic Society	Guideline	15	12-20	In patients with features suggestive of asthma (and those with proven co-existent asthma) we agree LAMA/LABA (without ICS) should not be used and that ICS/LABA is the dual therapy of choice. In patients without features of asthma but with higher blood eosinophils, the wording suggests that LAMA/LABA should not be used. Consistent with GOLD 2017, we consider LAMA/LABA an appropriate option in this subgroup – worth clarifying. Rationale: "features suggesting steroid responsiveness" appropriately includes blood eosinophils". Provided there are no features of asthma, RCT evidence supports use of LAMA/LABA in patients with COPD and higher eosinophil counts. FLAME excluded patients with asthma, and compared LAMA/LABA to LABA/ICS. LAMA/LABA was superior to LABA/ICS regardless of eosinophil status (i.e. including in patients with eosinophils > 2%). Differences in IMPACT may reflect inclusion of patients with previous Asthma, lack of a washout period, and greater enrichment for exacerbations (most patients were on ICS pre-randomisation). Allowing LAMA/LABA in these patients simplifies the pathway for non-specialists: a) LAMA - LAMA/LABA – LAMA/LABA/ICS; b) how the eosinophilic phenotype should be defined, both in terms of absolute count and whether based on single or repeated measures is subject to debate (perhaps wisely, we note that this is not specified in the guideline). We do agree that stable state eosinophils help identify steroid responsiveness.	Thank you for your comments. We are glad you agree with the use of LABA/ICS in people with COPD with asthmatic features/features suggesting steroid responsiveness. The committee's definition of asthmatic features/features suggesting steroid responsiveness was aimed at capturing the characteristics of the group of people who would benefit from treatment with a steroid. This included people with a secure diagnosis of asthma, but was also intended to cover people who do not have asthma, but are steroid responsive. The inclusion of other factors in the list, including a higher blood eosinophil count, was intended to help ensure that these people received LABA+ICS. The treatment pathway now begins with dual therapy (either LAMA+ LABA or LABA+ ICS) because dual therapy was more clinically and cost-effective than monotherapy in the economic model based on NMA analysis. The committee discussed the inclusion of a threshold to define a higher eosinophil count, but agreed that based on the evidence available it was not possible to define a specific threshold or to decide whether single or repeated measurement of eosinophils should be carried out. In particular, they noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. However, the accompanying research recommendation to address which features predict inhaled corticosteroid responsiveness most accurately in people with COPD could provide information on this topic and help improve the definition of asthmatic features/features suggesting steroid responsiveness in future updates of the guideline.
Boehringer-Ingelheim Ltd	Guideline	15	21-25	BI wish to highlight that initiating LABA+ICS on the basis of symptoms alone without exacerbations is in opposition of the	Thank you for your comment. The committee were confident, based on the large number of trials for these treatments

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				product licences for COPD for all available LABA/ICS combinations, which all require patients to have experienced a "history of repeated exacerbations" or who have an "exacerbation history" (Summary of Product Characteristics for Fostair 100/6, Seretide 500/50, AirFluSal Forspiro, Relvar Ellipta 92/22, Symbicort Turbohaler 200/6, DuoResp Spiromax). BI would welcome further comment within the guideline.	measuring a wide range of outcomes (including breathlessness, exacerbations and adverse events) for each of the treatment option, that the recommendations were an appropriate reflection of the clinical and economic evidence.
Primary Care Respiratory Society	Guideline	15	17/18/26	Consider wording – could imply that you should not use these treatments if they do not receive treatment for tobacco dependency, or don't have non-pharmacological treatment or vaccinations.	Thank you for your comment. We have amended the wording of this recommendation to include 'being offered' to ensure that people are not denied treatment if they do not receive treatment for tobacco dependency.
Boehringer-Ingelheim Ltd	Guideline	15	1	BI recommend that guidance is issued with respect to considering the dose of inhaled corticosteroid that is prescribed: there are a variety of different drugs, different salts and different particle sizes of ICS available in the combination inhalers with differing potencies: we would recommend that prescribers are aware of this and are directed towards inhaled steroid equivalence tables (eg. MIMS/BNF) that provide this information. There is some awareness of this in asthma where there are recommendations for low/medium/high doses of ICS at different stages, but none in COPD. We would also like to point out that licensed doses for ICS in asthma are different to COPD- we would recommend that the guideline highlights this. This may have an impact on considering side effects, including pneumonia, with ICS treatment.	Thank you for your comments. The use of ICS, apart from as a dual therapy in combination with LABA, is not within the scope of this update. As a result, we are unable to change the previous recommendations (apart from adding the MHRA link) or add new recommendations to this section. We have passed your request for the inclusion of guidance on ICS doses and drugs to our surveillance team to help inform their decisions for future updates of this guideline.
Boehringer-Ingelheim Ltd	Guideline	15	2	The guideline recommends that 'the risk of side effects (including pneumonia)' should be discussed with patients taking inhaled corticosteroids. - BI are pleased to see that NICE recommend a risk benefit analysis of ICS use in COPD. We would like to see this statement extended to include recent studies assessing the	Thank you for your comments. The use of ICS, apart from as a dual therapy in combination with LABA, is not within the scope of this update. As a result, we are unable to change the previous recommendations (apart from adding the MHRA link) or add new recommendations to this section. In addition, in the absence of an evidence review, we are unable to add additional warnings to this section.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				risks of ICS use in COPD so that clinicians can make an informed decision. - There are an increasing number of studies that investigate the metabolic effects of long term high dose inhaled corticosteroids. Recently, Price et al.(Price et al. 2016 Plos One 11(9)) demonstrated with a UK database study that statistically significant increases (0.16%) in HbA1c were observed in patients prescribed inhaled corticosteroid versus non inhaled corticosteroid therapies. Patients in the ICS cohort also had significantly more diabetes-related general practice visits per year and received more frequent glucose strip prescriptions, compared with those prescribed non-ICS therapies. Patients prescribed higher cumulative doses of ICS (>250 mg) had greater odds of increased HbA1c and/or receiving additional antidiabetic medication, and increased odds of being above the Quality and Outcomes Framework target for HbA1c levels, compared with those prescribed lower cumulative doses (≤125 mg). Further we would like to make the committee aware that there is also emerging evidence from a UK database study to suggest that the incidence of type II diabetes mellitus increases in a dose responsive manner with ICS exposure (soon to be published data). This observation has already been reported in Canada (Suissa et al. 2010. Amer Journ of Med 123:1001-1006). - BI are pleased that the risk of pneumonia with ICS has been highlighted. The risk of pneumonia with ICS has been observed in clinical trials (Calverley et al. 2007. N Engl J Med 356(8):775-89, Crim et al. 2009, Eur Respir J 34(3):641-7, Lipson et al. 2018, N Engl J Med 378(18):1671-1680) but we believe the issue may be greater than reported. One real world study, looking at patients who would have been ineligible for inclusion into	We have passed your request for the revision of guidance on ICS usage, based on the risks highlighted by the referenced studies, to our surveillance team to help inform their decisions for future updates of this guideline.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				the TORCH clinical trial, demonstrated a higher risk of hospitalisation and mortality in more vulnerable patients (Chalmers et al. 2018 Am J Respir Crit Care Med 189;2014:A3754). ICS use should be carefully balanced with risk (Singanayagam et al. 2010 QJM 103(6): 379-85). To highlight this, we would like to see a warning outlined in the algorithm to avoid inappropriate use of ICS.	
Chiesi Ltd	Guideline	15	3	In addition to the footnote referencing the MHRA, please also add reference to the European Medicine Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) review of pneumonia risk with inhaled corticosteroids. This review confirms the known increase risk of pneumonia in COPD patients treated with inhaled corticosteroids, but importantly that the benefits of inhaled corticosteroids continue to outweigh their risks.[1] [1] EMA/197713/2016. Available from: http://www.ema.europa.eu/ema [Accessed 12/07/18]	Thank you for your comment. The committee agreed that the link to the MHRA report was sufficient to cover this issue, particularly as the MHRA will have considered the EMA review as part of coming to their decision.
Royal College of General Practitioners	Guideline	15	4	The guideline's main omission is that of not addressing the role of triple therapy either separately or in a single inhaler. The GDG considered the role of adding LAMA to ICS/LABA but not the role of effectively adding ICS to LABA/LAMA. We appreciate that the question of triple therapy was not part of the scope and that the results of major studies may not have been available at the time of the evidence cut off timeline. However, the results of these studies have important. Unless the guideline addresses the role of triple therapy there is a major risk of over use of triple therapies with the potential for large impacts on NHS costs and patient health.	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
Primary Care Respiratory Society	Guideline	15	4	The biggest omission in this guideline in the view of our commentators is that of not addressing the role of triple therapy either separately or in a single inhaler. The GDG considered the role of adding LAMA to ICS/LABA but not the role of effectively adding ICS to LABA/LAMA. The clear implication of 1.2.11, 1.2.12 and 1.2.14 taken together is that triple therapy / inhaled corticosteroids should NOT generally be used in patients with COPD who do NOT have associated features of asthma. This should be clearly stated in a separate point 1.2.14a. It is now recognised, and the recommendations imply, that inhaled steroids have previously been overused incurring unnecessary costs and avoidable adverse effects, in patients with COPD without features of asthma. At present, the guideline could imply that all roads lead to treatment with ICS. This represents a clear change from previous practice and it should be clearly stated and a clear rationale given for the change. The economic evidence for the additional benefit of triple over dual therapy in patients with COPD who DO have features of asthma has been called into question and it would be worthwhile to provide an estimate of costs per QUALY for this, using current costs of these alternatives. Having had an out of date COPD guideline for many years, it seems perverse to issue a guideline that will already be out of date by the time of publication. We strongly recommend that triple therapy in single inhalers Trelegy and Trimbow are included in this guideline. NICE has already done the work to produce evidence reviews, so this just needs incorporating into the guideline, and the health economic work doing on it. NICE should not publish a guideline that is immediately out of date. We have evidence from our members that many have moved	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				towards GOLD to guide their COPD management, because the NICE guideline was so out of date. Indeed, in a recent survey of PCRS members, 65% of respondents used GOLD or a local variation of GOLD as their management pathway, with only 33% using NICE (PCRS-UK – data on file June 2017). NICE would do well to recognise this and ensure their guideline is up to date.	
AstraZeneca UK	Guideline	15	4	AstraZeneca supports the decision to recommend two different therapeutic approaches, LAMA/LABA and ICS/LABA, as first step after the reliever therapy, to different patient groups based on their asthma features and responsiveness to the inhaled steroids. This approach contributes to the implementation of a patient-centric and personalised care process as promoted by the NHS[1,2]. It ensures that the most appropriate choice of clinically and cost effective medicines (informed by the best available evidence base) are made that can best meet the needs of the patient[2]. Overall, this approach will help the improvement of health outcomes of COPD patients as well as a better use of the NHS resources. Of course, it is important to bear in mind that the COPD phenotype may vary over time, and therefore the "features suggesting steroid responsiveness" may change with time. This means that patients' characteristics should be periodically monitored *(potentially at yearly review or more frequently if they have had a history of asthma)* and that patients may move between groups over time. A review of existing patients should also be considered in order to guarantee that the right people are treated with the right medicines[2].	Thank you for your comments. We are glad that you agree with the committee's recommendations on the use of different dual therapies for different COPD populations. The committee agreed that patients' responses to medication, including steroid responsiveness, may change over time and that this might necessitate a corresponding change in inhaled therapy. However, they decided that the regular review of medication was covered in the summary of follow-up of people with COPD in primary care table and did not make a separate recommendation. The committee concluded that a recommendation was required to cover the treatment of existing patients. This recommendation is aimed at ensuring that people whose symptoms are controlled are not switched unnecessarily, but that when this ceases to be the case they treated according to the new pathway.
KSS AHSN Patient Safety Collaborative	Guideline	15	12	Many patients do very well with addition of single agent LAMA or LABA (particularly LAMA. The rationale for moving to LAMA + LABA is not understood. Of course if you study a large group of patients some will do better on dual therapy giving a significant	Thank you for your comment. From the network meta-analysis and economic model, the most clinically effective and cost-effective option was to begin treatment with a dual inhaled therapy. This means that for an average patient the

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				difference at the group level. But that doesn't mean that there are patients within the monotherapy group that are doing just as well. Clinicians do struggle when reputable bodies come out with clear cut differences re treatments (e.g. this would be very different recommendation from the current GOLD guidelines).	best treatment option was dual therapy. There are issues extrapolating this population level result to a single patient of course, and there will be some patients who would respond well to monotherapy, but on average a patient will be better off with dual therapy with LAMA/LABA rather than monotherapy. The committee included recommendation 1.2.13 which acknowledges that some patients will already have their symptoms under control with monotherapy and these people can continue on their existing treatment until their clinical needs change.
University Hospitals Birmingham NHS Foundation Trust	Guideline	15	Line 12	Whilst it is important to ensure that patients with asthma in addition to COPD receive inhaled steroids, the guideline as written excludes the use of inhaled steroids at all in patients with COPD and no asthmatic features. Whilst there are concerns about overuse of inhaled steroids in COPD, and potential side effects of ICS (notably pneumonias) this is out of keeping with other COPD guidelines including the GOLD guidelines. There is RCT evidence that combination ICS/LABA reduce exacerbation frequency in COPD, and rate of decline in quality of life. The recent triple inhaler studies on Trimbow and Trelegy (LABA/ICS/LAMA) which have recently been reviewed by NICE suggest that these combination inhalers appear to have a role in some patients with COPD. The evidence from these studies appears to confirm a role for LABA/ICS/LAMA combination treatment in patients with symptomatic COPD (CAT score >10), who are exacerbating. The Trimbow studies were performed in patients with FEV1<50%;Trelegy also included milder patients with FEV1 50-80%, but did not perform a subset analysis in this milder patient group. The GOLD guidelines seem to promote too wide a use of triple therapy, including any patients who remain symptomatic and continue to exacerbate despite dual bronchodilator therapy (GOLD D). My interpretation of the evidence base is that we should use inhaled steroids in patients with COPD, who have treatable asthmatic traits. We should avoid ICS use in other patients if we can, using LABA/LAMA combination inhaler therapy. In patients with FEV1<50% who continue to exacerbate despite dual	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				bronchodilator therapy, smoking cessation, immunisation and PR, there may be a role for triple therapy including ICS, but this should be carefully monitored and withdrawn if there are ICS-attributable side effects including, in particular, recurrent pneumonic episodes.	
UK Clinical Pharmacy Association	Guideline	15	12	NICE should recommend that patients requiring LAMA + LABA should ideally be offered a combination inhaler (cheaper to the NHS, more convenient for patients, may improve adherence whilst ensuring that one drug is not taken without the other).	Thank you for your comment. Unfortunately, the effectiveness of single versus combined inhaler devices was not included in the scope of this update and the committee are unable to make this recommendation as a result.
Primary Care Respiratory Society	Guideline	15	12	We do not think that the evidence summary (evidence review F inhaled therapy) provides sufficient justification for the major and potentially costly change in practice for moving straight to LAMA/LABA combination in recommendation 1.2.11. This seems to rest on network metanalaysis and a single piece of economic analysis. This seems to us to be very tenuous evidence for major change in practice. We do not believe the evidence supports this recommendation. We cite below the comparison on page 24 of evidence review F comparing LABA/LAMA with LAMA alone 1. LABA/LAMA versus LAMA Very low to moderate quality evidence from up to 26 RCTs with up 21,877 people found no meaningful difference in the change in FEV1, TDI or SGRQ score or the number of SGRQ responders at 3, 6 and 12 months; or in the numbers of people experiencing SAEs, COPD SAEs or dropouts due to adverse events in people offered LAMA/LABA compared to LAMA. Very low to high quality evidence from up to 24 RCTs with up 20,683 people could not differentiate people offered LAMA/LABA compared to LAMA with regards to the number of people	Thank you for your comment. The committee concluded that the evidence demonstrated benefits from LAMA/LABA combination therapy over monotherapy across a wide range of outcomes (in both low and high risk individuals), and although the magnitudes of these differences were not always clearly meaningful in isolation, the economic model synthesising the benefits across a range of outcomes demonstrated there were meaningful and cost-effective benefits to patients from starting with combination therapy. The committee did not agree that either network meta-analysis or economic evaluation represent tenuous evidence, but are in fact the best available tools to synthesise evidence across a range of interventions and outcomes. As in all NICE guidance, the committee noted these represent recommendations for the average patient, and there will always be individuals whose particular circumstances merit alternative treatment, but were confident the recommendations made would lead to improved health outcomes for people with COPD.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				experiencing moderate to severe or severe exacerbations, cardiac SAEs, pneumonia and all-cause mortality. Given this analysis why is a stepped approach starting with LAMA alone not recommended for patients with COPD without features of asthma? Is this a sledgehammer to crack a nut in milder patients? We do not accept the justification that minimising the number of inhalers will be easier for people with COPD because this is first line treatment so first exposure to inhalers.	
Primary Care Respiratory Society	Guideline	15	12	There doesn't seem to be much reference to the impact of LABA/LAMA in exacerbations and although latest evidence on exacerbations has been reviewed it doesn't appear to have been translated very clearly into the treatment guidelines.	Thank you for your comment. The results of the NMAs showed that, in people who had an exacerbation within the last year, there was a reduction in moderate to severe exacerbations with LAMA/LABA compared to LAB/ICS, LAMA or LABA monotherapy. The effects of these inhaled therapies on exacerbations and other outcomes were combined in an economic model, which showed that LAMA/LABA was the most clinically and cost-effective intervention. The committee used this information as the basis of their recommendation to offer LAMA/LABA as first line long-acting bronchodilator therapy to people without asthmatic features/features suggesting steroid responsiveness. This recommendation specifically mentions that the people who should be offered this treatment 'remain breathless or have exacerbations' despite a list of other interventions that fall earlier in the treatment pathway.
Primary Care Respiratory Society	Guideline	15	12	The reference (4) here seems to suggest that tiotropium is a problem. Does this mean that the other LAMA are okay? If important enough to reference, should this be added as a specific comment in the main body of text – especially as the commonest cause of death in people with COPD is cardiac disease	Thank you for your comment. The MHRA advice states that the risk of cardiovascular side effects should be taken into account when prescribing tiotropium to people with certain cardiac conditions. This should not be taken to automatically mean that other LAMAs are safe for these people as those with cardiac issues were excluded from many of trials included in the analysis.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Boehringer-Ingelheim Ltd	Guideline	15	12	BI recommend that the footnote about the cardiovascular safety of tiotropium delivered by the Respimat or the Handihaler is removed. The guideline references the MHRA published advice on the risk for people with certain cardiac conditions when taking tiotropium delivered via Respimat or Handihaler (2015) after suggesting offering LAMA+ LABA. This advice is following on from the TIOSPIR clinical trial, which assessed the safety and efficacy of tiotropium Handihaler versus tiotropium Respimat. The current wording could be misinterpreted that MHRA considered the risk:benefit of the two devices to be different. There was no significant difference in the risk of death from any cause between the two arms. Also, note that the clinical trials for all LAMAs, not just tiotropium Handihaler and tiotropium Respimat, excluded patients with certain cardiac co-morbidities. As a result, the summary of product characteristics for all the LAMAs cautions the use in patients with certain cardiac conditions.	Thank you for your comment. The committee does not agree that the current wording is open to misinterpretation. It clearly states that there is a risk for a certain group of people in taking tiotropium using either device. We recognise that the trials for other LAMAs also excluded people with cardiac problems and that this issue is not confined to tiotropium.
Boehringer-Ingelheim Ltd	Guideline	15	12	BI supports the rationale behind the recommendation to prescribe LAMA/LABA as a first line therapy for patients, particularly with the weight of evidence comparing LAMA/LABA therapy to LAMA monotherapy. However, we would wish for it to be acknowledged by the NICE guideline that the LAMA class itself has a strong evidence base for improving outcomes compared with short-acting therapy and placebo, demonstrating not only improvements in lung function, but also more valuable patient-orientated outcomes such as improvements in breathlessness, health-related quality of life, exercise tolerance and exacerbations (as reported in evidence review F). BI would like NICE to specifically acknowledge that there is a very extensive evidence base supporting the use of Spiriva (tiotropium) as a maintenance therapy for COPD.	Thank you for your comment. We are glad you agree with the committee's recommendations for first line dual therapy. The relative effectiveness of LAMA monotherapy compared to placebo is mentioned in the benefits and harms section of the review chapter already, but was not the focus of the review and so was not covered in detail. However, we are unable to comment on the effectiveness of LAMA monotherapy compared to short-acting therapy as this was not in the scope of the update and we did not review the evidence.
Boehringer-Ingelheim Ltd	Guideline	15	12	BI would recommend that the language of ‘offer/consider’ be made clearer to remove potential ambiguity in the prescribing choice. The	Thank you for your comment. The words 'offer' and 'consider' have been chosen to reflect the strength of the evidence

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				decision as to whether non-ICS containing or ICS-containing combinations are prescribed should be specifically based on whether patients meet the criteria regarding asthmatic features/steroid responsiveness. BI recommend that the wording is changed from either 'offer' or 'consider' to wording or an algorithm that more clearly denotes the appropriate patient cohorts that should receive these medicines..	underlying each recommendation and this is explained in the 'Making decisions using NICE guidelines' document that is referred to at the start of the guideline. These words are used consistently across updated NICE guidelines. The use of 'consider' for the LABA/ICS recommendation reflects the shortage of evidence for this recommendation and that, as a result, this was based on committee consensus. In addition the committee's use of 'asthmatic features/features suggesting steroid responsiveness' is already aimed at dividing the population into appropriate patient cohorts to receive the different medications.
NHS England	Guideline	15	12	The reference here seems to suggest that tiotropiium is a problem. Does this mean that the other LAMA are okay? Should this if important enough to add a reference too be added as a specific comment – especially as the commonest cause of death in people with COPD is cardiac disease. (CRG)	Thank you for your comment. The MHRA advice states that the risk of cardiovascular side effects should be taken into account when prescribing tiotropium to people with certain cardiac conditions. This should not be taken to automatically mean that other LAMAs are safe for these people as people with cardiac issues were excluded from many of trials included in the analysis.
KSS AHSN Patient Safety Collaborative	Guideline	15	14	Many patients with COPD have one of the features listed as 'asthmatic features etc. eg some eosinophila (no mention of level of eosinophilia is given). If PEFR is low to start with it is quite easy to have >20% variation as no minimal change is given. We are not aware of any robust evidence at this point in time to support the recommendation of LABA + ICS in this group and are concerned that this recommendation will lead to an excess of patients exposed to ICS with associated risks.	Thank you for your comment. The committee intended the definition of asthmatic features/features suggesting steroid responsiveness to cover both people with a secure diagnosis of asthma and those who do not have asthma, but who are steroid responsive. The description of this term is intended to help clarify the people who are expected to be steroid responsive. The committee discussed the inclusion of a threshold to define a higher eosinophil count, but concluded that based on the evidence available it was not possible to define a specific threshold or to decide whether single or repeated measurement of eosinophils should be carried out. In particular, they noted that the normal levels of eosinophils

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					vary within the population and that different thresholds are used by different centres. However the committee were aware that there was a lack of evidence concerning the identifiable characteristics of these people and, as a result, they included a research recommendation on this point. They also included a research recommendation to help determine the most clinically and cost effective treatment for people with asthma and COPD as they recognised that these people are frequently excluded from trials of long-acting bronchodilators.
Chiesi Ltd	Guideline	15	16	The guideline recommends offering a LABA+LAMA to patients who remain breathless or have exacerbations (despite treatment for tobacco dependence, optimised non-pharmacological management/ vaccinations and use of a short acting bronchodilator). It is inappropriate to recommend a LABA+LAMA for the prevention of exacerbations given that these agents do not hold a licence for this, especially without highlighting this to both patients and prescribers. Guidance issued by the MHRA advises prescribers to "be satisfied that such use would better serve the patient's needs than an appropriately licensed alternative before prescribing a medicine off-label"[1] Furthermore, regulators did not grant LABA+LAMA combination therapies a licence for prevention of exacerbations due to insufficient evidence to support this indication. [2-5] [1] MHRA. 2009. Off-label or unlicensed use of medicines: prescribers' responsibilities. Available from: https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities [Accessed 12/07/18] [2] Duaklir Genuair 340/12 micrograms inhalation power. Summary of Product Characteristics. Feb 2018. [3] Anoro Ellipta 55/22 micrograms inhalation powder. Summary of Product Characteristics. July 2017.	Thank you for your comments. The committee made these recommendations based on the results of a clinical and cost-effectiveness analysis. The economic model allowed consideration of the cumulative benefits of these interventions across a range of outcomes. The resulting recommendations reflect the combined benefits to the person with COPD, not just the effect on exacerbations. The committee also concluded that these medicines are already in common use for people with COPD, and prescribers should be familiar with the benefits and risks associated with using them.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				[4] Spiolto Respimat 2.5/2.5 micrograms, inhalation solution. Summary of Product Characteristics. March 2017. [5] Ultibro Breezhaler 85/43 micrograms, inhalation powder hard capsules. Summary of Product Characteristics. May 2018.	
UK Clinical Pharmacy Association	Guideline	15	16	We are concerned about the terminology "Remain breathless or have exacerbations". This is too vague a measure. It is not measurable in a consistent manner, so will lead to variation in practice. It also risks inappropriate treatment in mildest patients, such as those with only mild breathlessness (e.g. MRC 1 or 2) or infrequent exacerbations (e.g. 2 over a 5 year period) . Arguably CAT score may be a better measure of COPD health status and symptoms, as this is more holistic (containing measures of breathlessness, cough, exercise limitation, limitation of activities etc) than MRC, which focuses only on breathlessness and so is a very narrow assessment of patients' experience of COPD. Consider defining as symptomatic (CAT>/= 10 or breathless (MRC >/= 3); or have at least 2 exacerbations (or 1 hospital admission) per year. This will keep consistency in recommendations with GOLD, which is more commonly followed in the UK than the current NICE CG101 COPD guidelines (2010), as the GOLD guidelines are updated annually, and so have taken into account significant changes in published evidence in COPD since NICE last updated.	The committee discussed including additional information to assist prescribers to decide when a patient should transition from short-acting bronchodilator therapy to a long-acting maintenance therapy. They decided that the wording of the existing recommendations were sufficient for this as they already include the information to move the patient to a long-acting therapy if they remain breathless or have exacerbations despite using a short-acting bronchodilator. The committee concluded that this was sufficiently clear to ensure that healthcare professionals would not switch people whose symptoms could be controlled using short-acting bronchodilator to a long-acting therapy prematurely. As a result, they decided to leave the decision about timing to the discretion of the healthcare professional.
NHS England	Guideline	15	17	Does this mean that if they don't want treatment for tobacco dependency they will not be entitled to LAMA/LABA (CRG)	Thank you for your comment. We have amended the wording of this recommendation to include 'being offered' to ensure that people are not denied treatment if they do not receive treatment for tobacco dependency.
KSS AHSN Patient Safety Collaborative	Guideline	15	18	This line could lead to regular treatment being delayed until for example patients have been through a pulmonary rehabilitation programme	Thank you for your comment. This was not the intention of the committee and they have amended the recommendation to include the words 'being offered' before treatment for tobacco dependence to clarify this issue.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

NHS England	Guideline	15	18	Ditto – does the patient have to have optimised pulmonary rehab before starting LAMA/LABA (CRG)	Thank you for your comment. This was not the intention of the committee and they have amended the recommendation to include the words 'being offered' before treatment for tobacco dependence to clarify this issue.
UK Clinical Pharmacy Association	Guideline	15	21	NICE should recommend that patients requiring LABA + ICS should ideally be offered a combination inhaler (cheaper to the NHS, more convenient for patients, may improve adherence whilst ensuring that one drug is not taken without the other).	Thank you for your comments. The effectiveness of combined versus multiple single inhaler devices was not within the scope of this update and, as a result, we are unable to recommend one device over another. However, the recommendation to 'minimise the number of inhalers and the number of different types of inhaler used by each person as far as possible' is likely to have the desired effect of reducing the number of inhalers people are prescribed.
Primary Care Respiratory Society	Guideline	15	21	It is disappointing that NICE does not mention PR in 1.2.12 before progressing to ICS as well. This also differs from PCRS guidance where we recommend making sure this intervention is offered before changing or increasing treatment	Thank you for your comment. The wording 'optimised non-pharmacological management' is meant to include interventions such as pulmonary rehabilitation. This is made clear in the algorithm in the 'fundamentals of COPD care' box and we have added to the review chapter discussion to clarify this issue.
KSS AHSN Patient Safety Collaborative	Guideline	15	22	This line implies that spirometry diagnoses COPD which contradicts the diagnostic section and is an incorrect statement. Spirometry supports a clinical diagnosis of COPD. Suggest re-word	Thank you for your comment. The committee intended this wording to reflect the importance of spirometry in the diagnosis COPD, but agree that COPD is diagnosed on the basis of symptoms and signs and supported by spirometry. They decided against altering the wording of this recommendation because this issue is clearly covered in the section of the guideline that covers diagnosis of COPD.
UK Clinical Pharmacy Association	Guideline	15 51	23 14-19	We are concerned that the recommendation for COPD with asthma features (not withstanding a poor terminology – see next comment) in patients still 'breathless or exacerbating despite a short-acting bronchodilator , is not consistent with and contradicts the NICE asthma guidelines NG80 (2017), which states that patients uncontrolled on short-acting bronchodilator alone should receive a low dose ICS. If they are still uncontrolled, add in a leukotriene antagonist, and only then if still uncontrolled, add in a LABA. This	Thank you for your comment. The recommendations in this section differ from the asthma guideline because they are aimed at people with COPD and asthmatic features/features suggesting steroid responsiveness. This group includes people with COPD and asthma, but also includes people without asthma, who are steroid responsive. Due to exclusion of people with comorbid asthma from the majority of trials, there is a shortage of evidence for the most effective treatments for this group of people. As a result, the

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				will lead to inconsistent practice, cause confusion due to varying recommendations. We wonder why patients who are breathless or have exacerbations despite identical interventions are recommended to be offered different amounts of long-acting bronchodilators? This draft NICE guideline (p 51, lines 14-19) states that dual long-acting bronchodilator is more cost-effective than single agent, but if you have features suggesting steroid responsiveness, you get just one long-acting bronchodilator. This risks leaving this group of COPD patients sub-optimally treated for symptom and exacerbation control. For example, the FLAME study (Wedzicha JA et al. New Engl J Med 2016) specifically excluded patients with any history and patients with a high eosinophil count (>600/mm^3), but still demonstrated a significant reduction in exacerbations with LAMA+LABA compared to ICS/LABA.	committee made recommendations based on their clinical experience for this group and for people with steroid responsiveness. They also made 2 research recommendations to try to stimulate research into addressing the issues of which treatments are most effective for people with COPD and asthma and to try to determine which characteristics determine steroid responsiveness. The results of the clinical and cost-effectiveness analysis showed that dual therapy was more effective than monotherapy and that, of the dual therapy options, LAMA/LABA was the most effective. The committee's recommendation to consider LABA/ICS for people who have asthmatic features/features suggesting steroid responsiveness does not prevent these people from receiving LAMA on top of LABA/ICS should they remain breathless or continue to have exacerbations.
UK Clinical Pharmacy Association	Guideline	15	23	We are concerned about the terminology used here. Not all COPD patients who respond to ICS have asthma features. e.g. TORCH study (Calverley et al, New Engl J Med 2007) only 3.7% of patients had reversibility and patients with current diagnosis of asthma were excluded from the study. Consequently this recommendation of need for asthma features (which will likely be interpreted as meaning 'a diagnosis of asthma') alongside features suggesting steroid responsiveness goes against published evidence. It may be reasonable to state features suggestive of steroid responsiveness, and within this a concomitant diagnosis of asthma, but not of asthma specifically.	Thank you for your comment. The committee agreed with your comment that not all COPD patients who respond to ICS have asthma features. They chose the wording 'asthmatic features/features suggesting steroid responsiveness' to reflect this. The definition of this term includes a number of features that would suggest that a patient is steroid responsive and would benefit from LABA+ ICS. These include, but are not confined to, a diagnosis of asthma. The committee were confident that healthcare professionals would be able to understand the committee's intentions based on the definition provided. The committee acknowledged during their discussions (see discussion section of the review), that there was a shortage of evidence for the most effective treatments for people with asthma and COPD because these people were excluded from the majority of trials. They included research recommendations to investigate the most effective treatments

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					for these people and to determine in more detail which characteristics could be used to define steroid responsiveness.
UK Clinical Pharmacy Association	Guideline	15	25	Again, these measures of breathlessness and exacerbations need to be defined and measurable.	The committee discussed including additional information to assist prescribers to decide when a patient should transition from short-acting bronchodilator therapy to a long-acting maintenance therapy. They decided that the wording of the existing recommendations were sufficient for this as they already include the information to move the patient to a long-acting therapy if they remain breathless or have exacerbations despite using a short-acting bronchodilator. The committee concluded that this was sufficiently clear to ensure that healthcare professionals would not switch people whose symptoms could be controlled using short-acting bronchodilator to a long-acting therapy prematurely. As a result, they decided to leave the decision about timing to the discretion of the healthcare professional.
NHS England	Guideline	15	26	Similarly do they have to have been treated – think this needs rephrasing (CRG)	Thank you for your comment. We have amended the wording of this recommendation to include 'being offered' to ensure that people are not denied treatment until they have completed the bullet points (such as accepting treatment for tobacco dependency).
AstraZeneca UK	Guideline	15	14,23	See comments above (no 2) regarding the clarification between asthmatic features/ features suggesting steroid responsiveness and no asthmatic features/ features suggesting steroid responsiveness	Thank you for your comment. The committee intended the definition of asthmatic features/features suggesting steroid responsiveness to cover both people with a secure diagnosis of asthma and those who do not have asthma, but who are steroid responsive. The description of this term is intended to help clarify the people who are expected to be steroid responsive. However the committee were aware that there was a lack of evidence concerning the identifiable characteristics of these people and, as a result, they included a research recommendation on this point. They also included a research recommendation to help determine the most clinically and

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					cost effective treatment for people with asthma and COPD as they recognised that these people are frequently excluded from trials of long-acting bronchodilators.
KSS AHSN Patient Safety Collaborative	Guideline	15	22,23	This is confusing. We feel there are broadly 3 groups of patients: 1. Asthma (who may have some chronic airflow obstruction due to airway remodelling). These patients should be treated as per asthma guidelines. 2. COPD Should be treated as per COPD guidelines. 3. Patients who have features of both asthma and COPD (ACO). There is no evidence on how these patients should be treated and the guideline group need to consider how to deal with that fact.	Thank you for your comment. We agree that people with asthma should be treated according to the asthma guidelines and they are not covered by the recommendations in the COPD guideline. We also agree with point 2. The committee has recognised the shortage of evidence for the most effective treatments for people with COPD and asthma and has made several attempts to deal with this as follows: 1. The committee made a consensus recommendation to treat people with asthmatic features/features suggesting steroid responsiveness with LABA/ICS. This group of people is not confined to people with a diagnosis of asthma and COPD, but was deliberately made broader to cover other people who are steroid responsive, but do not have asthma. 2. The committee also made research recommendations to try to stimulate research on the most effective treatments for people with asthma and COPD, and to try to identify the characteristics of people (without a diagnosis of asthma) who would respond to steroids.
UK Clinical Pharmacy Association	Guideline	16	17-19	We support the recommendation that patients must receive the inhaler device that they have been trained to use, and we have advocated this for several years (see: Capstick T, Khachi H, Murphy A, d'Ancona G, Meynell H, Wilson P. Generic prescribing is not appropriate for inhaled drugs. *The Pharmaceutical Journal* 8 JAN 2015. https://www.pharmaceutical-journal.com/opinion/correspondence/generic-prescribing-is-not-appropriate-for-inhaled-drugs/20067456.article	Thank you for your comment. The committee noted this suggestion, but concluded that in the absence of specific evidence being identified looking at the issue of prescribing inhalers by brand, it was not appropriate to make a stronger recommendation than that currently included in the guideline, which they felt does highlight the importance of ensuring people receive inhalers they are confident and competent in using.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				However we would argue that this needs to be a stronger recommendation: Inhalers should be prescribed by brand name to ensure that patients receive inhalers that they have been trained to use (rather than using brand name as an example).	
UK Clinical Pharmacy Association	Guideline	16	13-14	This last statement (the drugs' potential to reduce exacerbations, and their side effects and cost.) is particularly relevant to the fact that this draft fails to recognise potential added benefit of LAMA+LABA+ICS to LABA+LAMA. We would strongly advise that NICE review the data from IMPACT (Lipson et al. New Engl J Med 2018; DOI: 10.1056/NEJMoa1713901) or TRIBUTE (Papi A et al. Lancet 2018; http://dx.doi.org/10.1016/S0140-6736(18)30206-X) as this provides evidence for additional benefits of LAMA+LABA+ICS above LABA-LAMA in patients with high levels of COPD symptoms and frequent COPD exacerbations. Failure to consider these data risks publication of a guideline that is not up to date with current evidence and may risk publishing sub-optimal recommendations. Without reviewing these data, we are concerned that this statement may not be completely correct.	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
UK Inhaler Group	Guideline	16	18/19	It is widely accepted that inhalers should be prescribed by brand in order to ensure that the patient receives the product the prescriber intended. This will avoid the risk of a patient receiving an inhaler they have never seen before at the point of dispensing. This recommendation could be worded more strongly as follows - 1.2.16 When prescribing ~~long-acting drugs~~ inhalers, ensure people receive inhalers they 18 have been trained to use *and which the prescriber intended for them, by specifying the brand of inhaler on prescriptions.* ~~(for example, by specifying the brand and 19 inhaler in prescriptions). [2018]~~ This is a central recommendation in UKIG's work.	Thank you for your comment. The committee noted this suggestion, but concluded that in the absence of specific evidence being identified looking at the issue of prescribing inhalers by brand, it was not appropriate to make a stronger recommendation than that currently included in the guideline, which they felt does highlight the importance of ensuring people receive inhalers they are confident and competent in using.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

UK Inhaler Group	Guideline	16	21/22	The importance of training is a key point. But it is not only patients who need training, but the clinicians themselves. There has been under-investment in training for prescribers and dispensers who manage and support respiratory patients. UKIG has produced standards for training of clinicians. See the UKIG Inhaler standards and competency document and please reference this in the guideline. https://www.respiratoryfutures.org.uk/media/69774/ukig-inhaler-standards-january-2017.pdf There are many videos showing inhaler technique, and UKIG is collaborating with Asthma UK to produce a definitive comprehensive set of videos which are due for launch this summer. We shall forward you the link when it becomes available.	Thank you for your comment. The section of the guideline covering inhaler training was not within the scope of this update and, as a result, the committee were unable to change or add to the previous recommendations. The committee included training for people with COPD in recommendation about the choice of drugs and inhalers (recommendations 1.2.15 and 1.2.16), but were unable to amend the inhalers section of the guideline to add any details about training of healthcare professionals.
KSS AHSN Patient Safety Collaborative	Guideline	16	1	This line could lead to regular treatment being delayed until for example patients have been through a pulmonary rehabilitation programme	Thank you for your comment. We have amended the wording of this recommendation to include 'being offered' to ensure that people are not denied treatment until they have completed the bullet points (such as attending a pulmonary rehabilitation programme or accepting treatment for tobacco dependency).
Primary Care Respiratory Society	Guideline	16	1.2.13	The link for advice on managing COPD with asthma takes you to the NICE asthma guidelines. There is no advice here on managing people with COPD with asthma features as the text implies. It is a guideline for diagnosis and treatment of stable asthma, not useful for COPD with asthma – this is a lazy and unhelpful link.	Thank you for your comment. The majority of studies included in the clinical evidence base excluded people with COPD who had comorbid asthma and, as a result, this limited the recommendations that the committee could make on behalf of these people. The committee made a consensus recommendation based on their clinical expertise (recommendation 1.2.12) and a research recommendation to try to identify the most effective inhaled therapies for people with COPD and asthma. The recommendation which pointed to the asthma guideline, was intended to clarify that people with COPD and asthma should have their asthma treated according to the asthma guidelines However, in the absence of evidence for this

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					population, it has now been decided that this should be removed.
Chiesi Ltd	Guideline	16	6	The guideline recommends offering triple therapy (LAMA+LABA+ICS) only to those who remain breathless or have exacerbations despite taking a LABA+ICS. However, no additional pharmacological recommendation is provided for those who still remain breathless or have exacerbations despite using a dual bronchodilator therapy (LABA+LAMA) or a single bronchodilator (e.g. LAMA). There is evidence to support the use of triple therapy over and above both a mono and dual bronchodilator in providing additional exacerbation reduction and improved quality of life: The TRINITY study showed a significant 20% reduction in the rate of moderate-to-severe exacerbations (RR: 0.80, 95% CI 0.69-0.92; p=0.0025) with single inhaler triple therapy (beclometasone/formoterol/glycopyrronium) than tiotropium alone, and more patients in the triple therapy group were responders in terms of the St. George's Respiratory Questionnaire (SGRQ) total score (decrease from baseline ≥4units) at both week 26 (OR: 1.32, p=0.0024) and week 52 (OR:1.33, p=0.0019).[1] The TRIBUTE study showed a significant 15% reduction in the rate of moderate-to-severe exacerbations (RR: 0.848, 95% CI 0.723-0.995, p=0.043) and an improvement in mean SGRQ total score (adjusted mean difference: -1.68, p≤0.001) with single inhaler triple therapy (beclometasone/formoterol/glycopyrronium) compared to a dual bronchodilator (indacaterol/glycopyrronium). It is worth noting that these results were found in patients without a current diagnosis of asthma, [2] thereby supporting the use of triple therapy in patients without asthmatic features. The IMPACT study showed similar beneficial effects with a 25% reduction in the rate of moderate-to-severe exacerbations (RR:	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				0.75, 95% CI 0.70 to 0.81, p<0.001) and an improvement in mean SGRQ total score (mean difference: -1.8, 95% CI -2.6 to -1.0, p<0.001) with single inhaler triple therapy (fluticasone furoate/umeclidinium/vilanterol) compared to a dual bronchodilator (umeclidinium/vilanterol). [3] The guideline suggests the only option for patients without asthmatic features currently uncontrolled on a LABA+LAMA are options such as surgery. Given this approach may not be necessary in the majority of patients, we would advocate allowing for pharmacological escalation and de-escalation of therapies where appropriate in the algorithm to include use of LABA+ICS and triple therapy before consideration of options such as surgery. [1] Vestbo et al. Lancet, 2017; 389(10082): 1919-1929 [2] Papi et al. Lancet, 2018; 391(10125): 1076-1084 [3] Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680	
UK Clinical Pharmacy Association	Guideline	16	6	We have serious concerns about the scope of this NICE guideline, which means that the draft guideline is already significantly out of date with proposed recommendations, and risks being irrelevant in practice. We would strongly advise that NICE review the data from IMPACT (Lipson et al. New Engl J Med 2018; DOI: 10.1056/NEJMoa1713901) or TRIBUTE (Papi A et al. Lancet 2018; http://dx.doi.org/10.1016/S0140-6736(18)30206-X) as this provides evidence for additional benefits of LAMA+LABA+ICS above LABA-LAMA in patients with high levels of COPD symptoms and frequent COPD exacerbations. Failure to consider these data risks publication of a guideline that is not up to date with current evidence and may risk publishing sub-optimal recommendations. Consequently this guideline does not provide advice for patients who are still symptomatic or exacerbate despite LABA+LAMA. This	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				is a major failing, leaves a significant cohort of patients without appropriate advice or recommendations to ensure optimal COPD management. (NB. TRIBUTE: only 13.5% had reversibility to SABA; IMPACT: only 18% with reversibility to salbutamol, so suggests you don't have to have features of asthma) NICE should recommend that patients requiring LAMA + LABA + ICS should ideally be offered a combination inhaler (cheaper to the NHS, more convenient for patients, may improve adherence whilst ensuring that one drug is not taken without the other).	
Primary Care Respiratory Society	Guideline	16	6	Does this mean that the person with no history of asthma or suggesting asthma should not be given ICS? This should be another bullet point if this is the view of the group – as current practice in specialist care in my experience and indeed speaking to several hundred generalists per year at least is to commence triple therapy if they are on dual bronchodilation or LABA/ICS if admitted.	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
AstraZeneca UK	Guideline	16	6	AstraZeneca would like to recommend that LAMA+LABA+ICS be available to both patients with asthmatic features/features suggesting steroid responsiveness who remain breathless on LABA	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				+ ICS and for those without asthmatic features/features suggesting steroid responsiveness who develop exacerbations despite taking LAMA+LABA. We believe all patients with COPD may benefit from the complimentary action of a LAMA, ICS and LABA in a triple combination, when symptoms worsen and when exacerbations are not controlled, despite a LABA+LAMA or an ICS+LABA therapy. COPD phenotype may vary over time, and previous non-exacerbators may develop more frequent exacerbations as their disease progresses. Therefore the "features suggesting steroid responsiveness" may change with time. One of the goals of COPD management is to achieve rapid, optimal control of symptoms, particularly in patients with more severe disease, in order to maintain physical function and quality of life. LAMA and LABA differ in bronchodilator action, providing additive improvements in markers of lung function and exercise capacity. The guideline draft recommends treatment initiation with LAMA + LABA for those without asthmatic features/features suggesting steroid responsiveness but provides no pathway to maintain this combined bronchodilator approach should the patient's phenotype change. Several studies have suggested that the LAMA, LABA and ICS components have complementary and additive actions in reducing exacerbation frequency[9-14]. These studies did not specifically include criteria for steroid responsiveness, and most have excluded those patients with a previous history of asthma. An increased effectiveness of the triple therapy compared to a double (LAMA/LABA or ICS/LABA) or mono therapy (LAMA or LABA) has been demonstrated in different studies[4,5,6,7,8,9]. For example, triple therapy with budesonide/formoterol added to tiotropium has shown marked better outcomes in various	this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.

				assessments at the clinic and at home in the morning compared with tiotropium alone[15]. For instance, prebronchodilator FEV1 improved with tiotropium combined with ICS/LABA over tiotropium alone[9,10] and tiotropium plus salmeterol[10]. Furthermore, morning FEV1 and peak expiratory flow measured at home (soon after the patient arose from bed) were significantly improved with budesonide/formoterol added to tiotropium compared with tiotropium alone[13]. The improvements in morning FEV1 reached a difference of 185 ml 5 minutes post-dose, which were greater than the clinic recordings[15]. In addition, improvements in daytime symptoms, night time awakenings, reliever use, and health-related quality of life were observed[15]. Approximately 50% of patients in the budesonide/ formoterol added to tiotropium arm improved their total SGRQ scores by more than four points compared with 40% in the tiotropium-alone group; this four-point difference has been shown to be clinically significant[16]. On top of that, a significant 62% reduction was seen in severe exacerbations when patients were treated with budesonide/formoterol added to tiotropium[15]. Two further recent studies demonstrated a superiority of the triple therapy compared to double therapy with LAMA/LABA or ICS/LABA in the reduction of exacerbations and better lung function and health-related quality of life[13,14]. In the study *Lipson DA et al*, triple therapy with fluticasone furoate, umeclidinium, and vilanterol resulted in a lower rate of moderate or severe COPD exacerbations than fluticasone furoate–vilanterol or umeclidinium–vilanterol. Triple therapy also resulted in a lower rate of hospitalization due to COPD than umeclidinium–vilanterol. Furthermore, *Papi A et al* demonstrated that the triple combination of extrafine beclometasone dipropionate, formoterol fumarate, and glycopyrronium in a single inhaler was associated with a significantly larger reduction in rate of moderate-to-severe COPD	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				exacerbations than the dual bronchodilator combination of indacaterol plus glycopyrronium over 52 weeks of treatment, without differences in adverse effects, particularly pneumonia. Both these studies did not include patients with an asthma diagnosis. AstraZeneca is currently undertaking Phase IIIB clinical trials of a single inhaler triple therapy combination inhaler containing budesonide, formoterol and glycopyrrolate. These studies include direct comparison to the LABA/LAMA and LABA/ICS dual therapy counter-parts, and regulatory approval is being sought, including step up to single inhaler triple therapy from both dual therapy approaches. It is apparent that COPD is a progressive disease and patients may change phenotype. For this reason, it is important that a patient's therapeutic options can change over time to allow for appropriate personalised care. Therefore, every patient should have the opportunity to benefit from a triple inhaled therapy if suitable.	
NHS England	Guideline	16	6	Does this mean that the person with no history of asthma or suggesting asthma should not be given ICS? (– as current practice in specialist care in our experience and indeed speaking to several hundred generalists per year at least is to commence triple therapy if they are on dual bronchodilation or LABA/ICS if admitted. (CRG)	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
UK Inhaler Group	Guideline	16	12	This guidance should be referenced: Choosing an appropriate inhaler device for the treatment of adults with asthma or COPD https://www.guidelines.co.uk/respiratory/inhaler-choice-guideline/252870.article We strongly recommend that this algorithm for selection of appropriate inhaler is included in this guideline.	Thank you for your comment. The choice of inhaler device is not within the scope of this update and, as a result the committee did not review the evidence and were unable to make specific recommendations on this topic. In addition, we are unable to specifically refer to other sources of guidance unless they have been endorsed by NICE. If, in your opinion, this tool is of particular use, the developer of the tool could submit it to NICE for endorsement using this web link.
Boehringer-Ingelheim Ltd	Guideline	16	12	Recommendations are given to assess a patients' preference and ability' however there is no mention of inspiratory effort/inspiratory capacity as an objective measure of ability to inhale therapy. Considering the evidence behind ability to inhale medication, there is scope to include an objective measure to aid clinical recommendations for appropriate medications for each patient (Ghosh et al. 2017 Journal of aerosol medicine and pulmonary drug delivery 30(6), Loh et al. 2017 Ann Am Thorac Soc 14(8): 1305-1311, Sharma et al. 2017 Journal of the COPD foundation 4(3))	Thank you for your comment. Unfortunately recommendations on how to use inhalers were out of scope of this update of the guideline and, as a result, the committee did not examine the evidence on the issue of measuring patient ability to inhale the drugs. However, as you noted, the committee concluded that this was an important issue and mentioned ability to use inhalers in the recommendation about the choice of drugs and inhalers. We have passed the information provided to our surveillance team to inform decisions concerning future updates of this guideline.
Royal Free London NHS Foundation Trust	Guideline	16	13	'Side effects' and 'cost' should be separate bullet points in the same list – these are currently bundled in alongside the potential to reduce exacerbations although they are not the same thing and should be considered separately in the risk-benefit analysis	Thank you for your comment. The recommendation referring to these factors have been separated in the recommendation as requested.
Chiesi Ltd	Guideline	16	15	We support the recommendation to minimise the number of inhalers and inhaler types used by patients. We suggest adding "in a combination inhaler" after each recommendation for specific inhaled therapies to reinforce the importance of reducing the inhaler burden.	Thank you for your comments. The use of combined versus single inhaler devices was not within the scope of this update and, as a result, we are unable to add the text on combined inhalers to the recommendations in this section.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				Studies have shown that patients using multiple inhalers were significantly less likely to persist with therapy or be adherent to treatment than those with a single inhaler. [1] [1] Yu, AP et al. J Med Econ, 2011; 14(4): 486-96	
UK Inhaler Group	Guideline	16	15	It is important to use inhalers appropriately not necessarily to *minimise the number* of inhalers a patient uses. If a patient is taught how to use their inhalers, it is not necessary to reduce the number they use. This message needs modifying to be accurate and helpful to clinicians. However, data does show that mixing different types of inhalers does cause worsening outcomes for patients, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5191843/	Thank you for your comment. The committee agreed that it was important that the patient is trained to use their inhaler(s) and they made a recommendation to reflect this. Although in theory, if a patient is taught how to use their inhalers then it is not necessary to reduce the number they use, the committee decided that, in practice, having multiple different types of device was more likely to result in worse outcomes for patients. The recommendation to minimise the number and types of inhalers reflects this.
Boehringer-Ingelheim Ltd	Guideline	16	15	The guideline recommends to 'minimise the number of inhalers and number of different type of inhaler used by each person as far as possible'. BI are strongly supportive of this recommendation. As there is currently not one device that covers the whole spectrum of inhaled therapies, we would like to see an extension of this recommendation to include keeping patients on inhalers that use the same inspiratory manoeuvre. i.e Quick and deep for dry powder inhalers or slow and steady for metered dose inhalers and soft mist inhalers. For most patients, a SAMA or SABA is their first prescribed inhaler, and so a 'slow and steady' inhaler technique would be the first inhaler device training received. BI recommends that patients should be kept on inhalers that require the same inspiratory technique to minimise confusion.	Thank you for your comment. Thank you for your support of this recommendation. The choice of inhaler device is not within the scope of this update. As a result, the committee did not review the evidence and were unable to make more specific recommendations on inhaler devices or inhaler technique.
NHS England	Guideline	16	17	"When prescribing long-acting drugs, ensure people receive inhalers they have been trained to use (for example, by specifying the brand and inhaler in prescriptions). [2018]." Could be exploited by pharma companies to promote their product? Community Pharmacists are often involved in the training of patients to use inhalers after they have been prescribed. (PC)	Thank you for your comment. The committee intended this recommendation to help highlight the importance of ensuring that people are able to use their inhalers to get the maximum benefit from their treatments. As you mention in your comment, community pharmacists are expected to play an important role in this process.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					The inclusion of a reference to cost in the recommendation concerning the choice of drug and inhaler is intended to make cost part of the decision making process alongside benefits to the patient.
Boehringer-Ingelheim Ltd	Guideline	16	18	The guideline recommends '...specifying the brand and inhaler in prescriptions'. BI are strongly supportive of this recommendation. There are an increasing number of generic inhalers available and these differ widely in the way they operate, their appearance, and delivery characteristics. We would also like to see recommendations about responsible prescribing of inhalers, in particular commenting that switching of inhalers should be based upon clinical decisions and not solely driven by costs. . Should substitution of a generic for a branded be appropriate, safeguards are required to ensure that patients receive adequate training and are willing to use the new device. Additional monitoring is also required to ensure disease control is not compromised. Non-compliance rates are already high among patients with COPD- increasing the risk of poor adherence without consultation is likely to add to these problems.	Thank you for your comment. The committee noted this suggestion, but concluded that in the absence of specific evidence being identified looking at the issue of prescribing inhalers by brand, it was not appropriate to make a stronger recommendation than that currently included in the guideline, which they felt does highlight the importance of ensuring people receive inhalers they are confident and competent in using.
Teva UK	Guideline	15, section 1.2.11 and p51	12-20 and lines 13–19	We are concerned regarding the recommendation to initiate COPD therapy with LAMA+LABA for all patients who do not have asthmatic features and remain breathless or have exacerbations despite using short-acting bronchodilators. Our concerns are based on the points listed below. Clinical evidence does not support initiation on combination therapy as opposed to starting on LAMA and moving to LAMA+LABA if the clinical improvement is not sufficient • There is no clinical evidence suggesting that initiating therapy with LAMA+LABA is associated with significantly better treatment outcomes compared with initiating therapy with a LAMA and moving to a combination in patients with persistent symptoms or who experience exacerbations	Thank you for your comment. The committee agreed that the evidence demonstrated benefits from LAMA/LABA combination therapy over monotherapy across a wide range of outcomes (in both low and high risk individuals), and although the magnitudes of these differences were not always clearly meaningful in isolation, the economic model synthesising the benefits across a range of outcomes demonstrated there were meaningful and cost-effective benefits to patients from starting with combination therapy.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				• Clinical evidence comparing the efficacy and safety of LAMA+LABA vs LAMA relates to clinical trials involving patients with moderate-to-severe disease; there are no data for patients with less severe disease • Evidence for the clinical benefits of LAMA+LABA over LAMA are more conclusive for the clinical endpoint, FEV1, than for the more clinically meaningful patient reported outcome (PRO) endpoints such as SGRQ score/response rate The NICE draft recommendations disagree with the 2018 GOLD guidelines • The 2018 GOLD guidelines[1] recommend an individualized approach to pharmacological therapy, reflecting the heterogeneity of patients with COPD. This is further discussed in a recent editorial which makes recommendations for reviewing treatment in patients already on COPD treatment and discusses the need to be able to escalate and de-escalate therapy based on symptoms and the risk of exacerbations.[2] For this to be feasible, a number of different treatment options need to be available for consideration at treatment initiation and for patients already on therapy. Recommending all patients start on LAMA+LABA removes the ability to offer a personalized approach to management of COPD. • The 2018 GOLD guidelines recommend a step-up approach to the management of patients with stage A-C disease, escalating therapy from monotherapy to dual therapy in patients with persistent symptoms or further exacerbations. Initiation with dual therapy is only recommended for patients with stage D disease. This approach is further endorsed in a recent review, Thomas et al,[3] which discusses criteria that might be helpful for identifying patients for whom escalation would be helpful,	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				e.g. the patient's symptomatic response, decreased exercise capacity, increased need for rescue medication, and occurrence of exacerbation. • Approximately two-thirds (65%) of UK primary care respiratory physicians use the GOLD guidelines (or locally developed guidelines based on the GOLD recommendations), according to a recent survey, with the remaining third using the NICE guidelines.[4] Consensus between the NICE guidelines and the GOLD guidelines is likely to facilitate uptake of both guidelines. In contrast, if the recommendations of the two guidelines diverge considerably, this is likely to lead to confusion regarding the management of COPD in England and significant differences between different practices. Concerns regarding over treatment, polypharmacy and safety • There has been some concern regarding over treatment of COPD.[3] A UK study found that a third of patients were being prescribed triple therapy, including 19%, 28% and 37% of GOLD A, B and C patients, respectively, in whom such therapy would generally be considered inappropriate.[5] The authors suggest this reflects inappropriate initiation of therapy with LABA+ICS. Starting all patients on LAMA+LABA may similarly result in over treatment. • Many COPD patients are elderly and have a range of co-morbidities. Thus, polypharmacy should be avoided where possible because of the potential for interactions with other agents. For example, concomitant administration of LABA and diuretics (loop diuretics and thiazides), xanthine-derivatives or steroids can lead to hypokalaemia, while concomitant administration of drugs known to prolong QTc-interval (e.g. certain antiarrhythmics, certain antihistamines, monoamine oxidase inhibitors and tricyclic	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				antidepressants) may increase the risk of ventricular arrhythmias • LABA can adversely affect cardiac function (manifest, for example, as increases in pulse rate, blood pressure and QTc-interval prolongation) and thus impact on cardiovascular disease. Caution is recommended when using LABA in patients with cardiovascular disorders, patients with convulsive disorders or thyrotoxicosis. In addition, increases in blood glucose levels are observed in some patients, which necessitates caution when prescribing a LABA for patients with diabetes. Thus, for some patients, avoiding the use of a LABA is advantageous. We therefore suggest that: • Consistent with the 2010 NICE guidelines,[6] the previous GOLD guidelines and the 2018 GOLD guidelines, the 2018 NICE guidelines should recommend treatment is initiated using an individualized approach at a level considered relevant to the level of severity of the condition and/or symptoms and is escalated as deemed necessary. Based on clinical considerations, the NICE guidelines should include long-acting bronchodilator monotherapy as an option for initiation of therapy in patients whose symptoms are not controlled on short-acting bronchodilator therapy.	
Boehringer-Ingelheim Ltd	Guideline	17	2	BI note that the guidance relating to inhalers has not changed since 2004. BI would strongly recommend strengthening 1.2.19 and 1.2.20 relating to patient training on their device: patients often have their devices switched and no further training is given on the new device, based on the presumption that the device is either considered 'easy to use' or is similar enough to the previous device. However, this has resulted in incidences of inhaler misuse and potential patient safety issues when the patient has not been properly trained following an inhaler switch (see "Braltus	Thank you for your comment. The committee agreed with the importance of inhaler technique, and with ensure that appropriate training and support is given to people, both when new inhalers are initiated, and at follow-up appointments. The recommendations you refer to are were not included within the scope of this update of the guideline, and therefore it was not possible to make changes to them. However, it was concluded the recommendations were clear that people should be trained to use all inhalers they are

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				(tiotropium): risk of inhalation of capsule if placed in the mouthpiece of the inhaler", MHRA Drug Safety Update, May 2018)	prescribed, and their use should be regularly monitored. It was also noted that this point was included in the quality standard for COPD (QS10), specifically in statement 2: "People with chronic obstructive pulmonary disease (COPD) who are prescribed an inhaler have their inhaler technique assessed when starting treatment and then regularly during treatment."
Boehringer-Ingelheim Ltd	Guideline	17	4	BI would be keen to see point 1.2.18 elaborated upon further with the rationale why an inhaler may not be suitable for a particular patient (e.g. poor inspiratory effort, dexterity issues) and provide guidance as to what may be more suitable (e.g. a soft mist inhaler or pMDI with spacer rather than a DPI if inspiratory effort is an issue, a non-capsule-based inhaler if dexterity is an issue).	Thank you for your comments. The topic of suitability for inhaler use is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	17	11	Actuation of the inhaler into the spacer, and breathing are two distinct steps. This should be emphasised.	Thank you for your comments. The topic of spacers is not within the scope of this update, and therefore no changes could be made to these recommendations.
Association for Respiratory Technology and Physiology	Guideline	17	14	Typo "metered", not "metred"	Thank you for your comments. This typo has been amended.
Primary Care Respiratory Society	Guideline	17	14	Spacers MDI with spacer is a very effective way for patients to use high dose bronchodilators during exacerbations of COPD. This is a very important and underused therapeutic intervention. It should be mentioned here, with advice that every person with COPD who has exacerbations should have a SABA MDI and spacer and should be taught how to use it for increasing their dose of SABA during exacerbations. This advice should be reiterated in the self-management section p 34	Thank you for your comments. The topic of spacers is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

University Hospitals Birmingham NHS Foundation Trust	Guideline	18	Line 3	Prescription of nebulised medication should follow a formal nebuliser assessment documenting benefit in one of the categories as stated in this guideline	Thank you for your comments. The topic of prescription of nebulised medication is not within the scope of this update, and therefore no changes could be made to these recommendations.
UK Clinical Pharmacy Association	Guideline	20	15-16	(i) We would advise that there is a need to specify ruling out Mycobacterial infections, to avoid resistance, particularly for non-tubercuolous mycobacterial infections, where inducing macrolide resistance could be a significant adverse event (ii) What's the evidence for contraindicating *Pseudomonas aeruginosa* infection for azithromycin? Azithromycin is commonly prescribed for patients colonised with *Pseudomonas aeruginosa.*	Thank you for your comments. The committee agreed that ruling out mycobacterial infections was important, and this has been added to the recommendations. The wording has also been offered to clarify that *Pseudomonas aeruginosa* is not being mentioned as contraindicating azithromycin, but rather is something that should be investigated as it would require different treatment to a standard infective exacerbation of COPD.
UK Clinical Pharmacy Association	Guideline	20	1	We wonder whether the terminology is sufficiently accurate. Azithromycin is usually prescribed for COPD patients for it's immunomodulatory, antiinflammatory, and antibacterial effects, rather than purely as 'proiphylactic antibiotic'	Thank you for your comment. The committee felt the wording of the recommendation was sufficiently clear, but did note that since azithromycin may have benefits for reasons other than solely its antibacterial effects, it was not necessarily true that other antibiotics (such as doxycycline) would be equally effective, and therefore the recommendation on doxycycline has been deleted from the guideline.
NHS England	Guideline	20	1	This section is clear – and we would commend it (though line 20 might suggest that should have specialist input) (CRG)	Thank you for your comment and your support for these recommendations.
Royal College of Anaesthetists	Guideline	20 61	2 9	Generally the evidence to support the use of prophylactic antibiotics is deemed to be weak and the consultation acknowledges that the long term implications are unknown. There is concern about how this recommendation is monitored. While criteria for use are explicit, mission creep could be inevitable and the policy could be ignored, particularly in hard pressed general practice. The drug regime is cheap though.	Thank you for your comment. The committee felt the short-term evidence on the use of prophylactic antibiotics was strong, but agreed the lack of long-term data reduced confidence in the findings overall. In light of this, they concluded that the overall strength of the recommendation should be reduced from 'offer' to 'consider' to reflect this uncertainty.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

NHS England	Guideline	20	2	"Offer azithromycin (usually 250 mg 3 times a week) to people with COPD" - please clarify if this should be a primary care or secondary care decision to prescribe prophylactic Abs (PC)	Thank you for your comment. The committee concluded that both specialists and sufficiently skilled GPs would be able to initiate prophylactic antibiotics, and therefore it was not appropriate to be more specific in the recommendation. However, they did agree that there may be GPs who feel a person may benefit from prophylaxis, but are not confident to initiate treatment without specialist advice, and therefore added an additional recommendation to note that specialist input should be sought in these cases.
Association for Respiratory Nurse Specialists	Guideline	20	4	This recommendation will be a challenging change in practice because traditionally prophylactic antibiotics have not been withheld from smokers although it is recognised the effectiveness is diminished.	Thank you for your comment. The committee concluded that due to the evidence of reduced effectiveness of prophylactic antibiotics in people who continue to smoke, the benefits of treatment did not outweigh the harms (both side effects and risk of antibiotic resistance) in this population, and therefore it was not appropriate to make a positive recommendation in this group.
Royal Free London NHS Foundation Trust	Guideline	20	15	There will be some patients who experience frequent hospitalised exacerbations but never produce sufficient sputum for analysis. It is not completely clear whether azithromycin should ONLY be given to sputum producers. We also strongly argue that argue that review by a respiratory specialist should be mandatory in any patient for whom azithromycin is considered, to ensure that other therapy has been optimised and other diagnoses appropriately excluded.	Thank you for your comment. The committee concluded that on the basis of the available evidence, it was only possible to recommend prophylactic antibiotics to people who produce sputum for analysis, and noted that in the small number of patients where this was not possible, an individualised judgement would be needed from the clinician. The committee concluded that both specialists and sufficiently skilled GPs would be able to initiate prophylactic antibiotics, and therefore it was not appropriate to be more specific in the recommendation. However, they did agree that there may be GPs who feel a person may benefit from prophylaxis, but are not confident to initiate treatment without specialist advice, and therefore added an additional recommendation to note that specialist input should be sought in these cases.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

KSS AHSN Patient Safety Collaborative	Guideline	20	15	Suggest include AAFB culture in sputum assessment pre Azithromycin to avoid risk of treating NTM with monotherapy which ay lead to resistance	Thank you for your comment. The committee agreed with the importance of including mycobacteria as part of this assessment, and this has been added to the recommendation.
Association for Respiratory Nurse Specialists	Guideline	20	15	Should the recommendation include the need for Acid Fast Bacilli screening also?	Thank you for your comment. The committee agreed with the importance of including mycobacteria as part of this assessment, and this has been added to the recommendation.
Royal Free London NHS Foundation Trust	Guideline	20	16	Macrolides are an important treatment for non-Tuberculous Mycobacteria (NTM). Starting prophylactic macrolide without confirming absence of NTM risks development of resistant infection. Excluding NTM requires specific testing.	Thank you for your comment. The committee agreed with the importance of including mycobacteria as part of this assessment, and this has been added to the recommendation.
Barking & Dagenham, Havering & Redbridge CCG	Guideline	20	16	There is a lack of clarity re anti-pseudomonal choices - levo/moxifloxacin cited in some studies in Evidence Review E. Will it be useful to highlight these as choices with sputum cultures suggestive as this is colonising? Suspected infective organism. Cost of levo/moxi vx cipro also an issue? If considered the durations of antibiotic courses seem too short - some patients do not respond to one week only. Higher dose therapy with respect to penicillins (amox) may also be needed depending on clinical picture of those suggested.	Thank you for your comment. This section of the guideline only considers the issue of antibiotic prophylaxis for people with COPD, and not choice of anti-pseudomonal antibiotic. As such, it was not possible for the committee to include recommendations on this topic in this section of the guideline.
Association for Respiratory Nurse Specialists	Guideline	20	19	This recommendation will be challenging in practice as patients are not routinely offered a CT scan before commencing prophylactic antibiotics, is this what the algorithm is implying?	Thank you for your comment. The committee agreed that it was not appropriate to commence antibiotic prophylaxis without a CT scan having been conducted. However, they concluded this does not mean a new scan will necessarily need to be conducted, as the results of a sufficiently recent scan on file would also be adequate. The committee felt that the majority of patients eligible for prophylactic antibiotics would have received a CT scan already. This is because prophylactic antibiotics are only recommended in patients with abnormally frequent or severe exacerbations, most of whom will have undergone extensive diagnostic tests. Therefore, it is unlikely that this recommendation will produce a substantial increase in the number of CT scans performed.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

UK Clinical Pharmacy Association	Guideline	20	20	We would recommend that azithromycin should be specialist use only rather than routine care from non specialists.	Thank you for your comment. The committee concluded that both specialists and sufficiently skilled GPs would be able to initiate prophylactic antibiotics, and therefore it was not appropriate to be more specific in the recommendation. However, they did agree that there may be GPs who feel a person may benefit from prophylaxis, but are not confident to initiate treatment without specialist advice, and therefore added an additional recommendation to note that specialist input should be sought in these cases.
British Society for Antimicrobial Chemotherapy	Guideline	21	1	1.2.45 states doxycycline is a suitable alternative prophylactic agent to azithromycin in COPD. Using any agent this way carries the risk of resistance developing but long term azithromycin is beneficial via immune-modulatory effects rather than just antibacterial action. We are not confident that doxycycline's antibacterial action would be beneficial enough when used prophylactically to offset the threat increased resistance poses. We note that the evidence base for long term prophylaxis is limited and that these questions around best use are themselves included in this guidelines "recommended areas for research"	Thank you for your comment. The committee concluded that since azithromycin may have benefits for reasons other than solely its antibacterial effects, it was not necessarily true that other antibiotics (such as doxycycline) would be equally effective, and therefore the recommendation on doxycycline has been deleted from the guideline.
KSS AHSN Patient Safety Collaborative	Guideline	21	9	There needs to be some guidance on whether the prophylactic antibiotic should be stopped or continued when another antibiotic is started as part of the exacerbation plan.	Thank you for your comment. The committee discussed this issue and agreed that, in the majority of cases, there was no reason to discontinue prophylactic antibiotics when someone is treated for an acute exacerbation. A recommendation stating this has now been added to the guideline.
Royal Free London NHS Foundation Trust	Guideline	21	11	Suggest including a specific recommendation that if antibiotics are commenced for an intercurrent infection then any prophylactic antibiotics are stopped for the duration of the exacerbation treatment.	Thank you for your comment. The committee discussed this issue and agreed that, in the majority of cases, there was no reason to discontinue prophylactic antibiotics when someone is treated for an acute exacerbation. A recommendation stating this has now been added to the guideline.
Primary Care Respiratory Society	Guideline	21	20	All assessments should be made by a HOSAR team (Home oxygen service assessment and review)	Thank you for your comment. The committee discussed this but concluded that the specific team that carries out an assessment will vary between local regions. As a result, it

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					was decided not to include specific details of these teams as part of the recommendation.
UK Clinical Pharmacy Association	Guideline	22	22-23	We would advise adding in the fire risk with paraffin-based creams and ointments (e.g. MHRA https://www.gov.uk/drug-safety-update/paraffin-based-skin-emollients-on-dressings-or-clothing-fire-risk)	Thank you for your comment. The committee discussed this and concluded that the use of paraffin raised in the MHRA alert is an important consideration when assessing for the use of long-term oxygen therapy. However, the committee decided that this would be included within the risk assessment and therefore didn't need to be mentioned specifically, in particular as the MHRA alert itself does not directly relate to the use of oxygen therapy.
Royal College of General Practitioners	Guideline	22	1	Recommendation 1.2.51 states that referral for oxygen assessment should be made if resting oxygen saturation on air <=92%. BTS Guidelines recommend that this should be done on 2 occasions (3 weeks) in a stable state. Unless this is added there is a danger that there will be an over referral for oxygen assessment.	Thank you for your comments. Unfortunately only the recommendations on who should have treatment with long term oxygen therapy formed part of this review. Assessment of long-term oxygen therapy based on oxygen saturation was not within the scope of this update - more details can be seen in the COPD scope on the NICE website.
Primary Care Respiratory Society	Guideline	22	1	Recommendation 1.2.51 states that referral for oxygen assessment should be made if resting oxygen SATS on air <=92%. BTS Guidelines recommend that this should be done on 2 occasions (3 weeks) in a stable state. Unless this is added there is a danger that there will be an over –referral for oxygen assessment.	Thank you for your comments. Unfortunately only the recommendations on who should have treatment with long term oxygen therapy formed part of this review. Assessment of long-term oxygen therapy based on oxygen saturation was not within the scope of this update - more details can be seen in the COPD scope on the NICE website.
NHS England	Guideline	22	1	"oxygen saturations of 92% or less breathing air." - does this refer to pulse oximetry or blood gases? (PC)	Thank you for your comments. Unfortunately only the recommendations on who should have treatment with long term oxygen therapy formed part of this review. Assessment of long-term oxygen therapy based on oxygen saturation was not within the scope of this update - more details can be seen in the COPD scope on the NICE website.
University Hospitals Birmingham NHS Foundation Trust	Guideline	22	Line 4	Should we state 'blood gas measurements' rather than ABG so that capillary blood gases can be used as is in many places. With correct training and technique results are directly comparable to ABG	Thank you for your comments. Unfortunately only the recommendations on who should have treatment with long term oxygen therapy formed part of this review. Assessment of long-term oxygen therapy based on oxygen saturation was not within the scope of this update but we will send you

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					comments to the NICE surveillance team. More details can be seen in the COPD scope on the NICE website.
Association for Respiratory Nurse Specialists	Guideline	22	4	The algorithm seems to imply that only arterial samples should be used to measure blood gasses in oxygen assessment; would Capillary blood gas samples be adequate?	Thank you for your comments. Unfortunately only the recommendations on who should have treatment with long term oxygen therapy formed part of this review. Assessment of long-term oxygen therapy based on oxygen saturation was not within the scope of this update but we will send you comments to the NICE surveillance team. More details can be seen in the COPD scope on the NICE website.
Primary Care Respiratory Society	Guideline	22	8	We would suggest putting the non-smoking in bold.	Thank you for your comment. It is not within the NICE formatting style to put this section of the recommendation in bold. However, we believe that the recommendation is written clearly enough that this will not be misunderstood.
NHS England	Guideline	22	8	We would suggest putting the non smoking in bold. (CRG)	Thank you for your comment. It is not within the NICE formatting style to put this section of the recommendation in bold. However, we believe that the recommendation is written clearly enough that this will not be misunderstood.
Royal Free London NHS Foundation Trust	Guideline	22	13	Suggest changing '…one of the following…' to '… one OR MORE of the following…'	Thank you for your comment. We have noted your suggestion and updated the wording of the recommendation to 'one or more' to avoid any misunderstanding.
KSS AHSN Patient Safety Collaborative	Guideline	22	23	Suggest add consider the increased risk of burns and fire (for both the person with COPD and people living with them in the presence of smokers) when paraffin-based emollients are also being used by the person with COPD and the people living with them, in line with recent MHRA advice	Thank you for your comment. The committee discussed this and agreed that the use of paraffin raised in the MHRA alert is an important consideration when assessing for the use of long-term oxygen therapy. However, the committee decided that this would be included within the risk assessment and therefore didn't need to be mentioned specifically, in particular as the MHRA alert itself does not directly relate to the use of oxygen therapy.
KSS AHSN Patient Safety Collaborative	Guideline	23	3	The KSS oxygen network debated this question long and hard and agreed at a network meeting in July 2016 that "pursuing careful risk assessment of individuals with use of appropriate screening tools is preferred to a blanket ban on home oxygen for smokers"	Thank you for your comment. The committee discussed this and agreed that smokers should be offered help to quit, as detailed in the guideline. They also noted that the issue of providing long-term oxygen to people who continue to smoke is a complex one on which opinions are still divided in both

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				The consensus was that, providing smokers have been properly supported to quit and offered appropriate therapies, AND have had a robust risk assessment (not just the IHORM), they should not be denied home oxygen. Of note the 2015 BTS Home oxygen guidelines do not prohibit oxygen in smokers provided that a clear risk assessment has been carried out. It is not logical to recommend oxygen to people who live with others who smoke, while denying it to those who smoke themselves (with appropriate risk assessment). Though two of our members stated 'I welcome the guidance on no LTOT in current smokers.' The guidelines however are slightly ambiguous and potentially contradictory: B13 "base the decision on whether long-term oxygen is suitable on the results of the structured risk assessment" and B15 "do not offer long-term oxygen therapy to people who continue to smoke despite being offered smoking cessation advice and treatment, and referral to specialist stop smoking services". The latter does not specify the time frame that one would try quit therapy for and so the possible implication from B13 is that it may be deemed safe to start oxygen therapy for a while, based on risk assessment, but not for longer term. This will leave clinicians confused as could be interpreted as possibly considering offering it initially (as recommended with smoking cessation advice and treatment, and referral to stop smoking services), but then no clear guidance at what point they deem the patient not compliant with that and (if installed) need to remove it. So these recommendations need careful consideration of the order in which they are laid out and absolute clarity on the issue of offering oxygen (at any point at all) to a person who is currently a smoker or living with one. Similarly, absolute clarity around the stance when the patient	the clinical and patient communities. However, they decided to keep the recommendation to not offer long-term oxygen therapy if people continue to smoke as it was concluded that these recommendations were designed to prevent smokers from injury or harm, and not to deny them access to treatment. They concluded the risks from the use of long-term oxygen by people who smoke were sufficiently high that the risk-benefit balance was in favour of not using the treatment in this group.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				requiring oxygen lives with a smoker needs complete clarity so that there is no confusion whatsoever for the clinician and patient can be shown the wording so they have no "wiggle room".	
University Hospitals Birmingham NHS Foundation Trust	Guideline	23	Line 3	The MRC and NOT trials included smokers and the mortality benefits were obtained in a group which included smokers and ex smokers. No sub-set analysis was performed, so we don't know that the mortality benefits were confined to ex smokers. Should we deprive current smokers this life-saving treatment?? This is a really difficult area which we all struggle with, but I think a blanket recommendation that no smokers receive oxygen therapy is difficult. We don't deny cardiac or peripheral arterial surgery to current smokers or indeed lung cancer surgery. Given that the long term survival benefits of LTOT take a considerable time to kick in perhaps we should be saying that appropriately risk assessed patients (risks to themselves and/or others) who have shown significant and sustained attempts to quit smoking over a 6 month period *may* be suitable for LTOT prescription after discussion in a respiratory MDT?? Ambulatory oxygen is much easier because there is no mortality benefit, so I think that a blanket ban on current smokers is reasonable. What about e-cigarette smokers – should they be subject to the same restrictions on LTOT?? Prescribing oxygen to smokers should be considered on a case by base basis (BTS guidelines 2015). CO monitoring should be performed where possible in patients who continue to smoke.	Thank you for your comment. The committee discussed this and agreed that smokers should be offered help to quit, as detailed in the guideline. They also noted that the issue of providing long-term oxygen to people who continue to smoke is a complex one on which opinions are still divided in both the clinical and patient communities. However, they decided to keep the recommendation to not offer long-term oxygen therapy if people continue to smoke as it was concluded that these recommendations were designed to prevent smokers from injury or harm, and not to deny them access to treatment. They concluded the risks from the use of long-term oxygen by people who smoke were sufficiently high that the risk-benefit balance was in favour of not using the treatment in this group, even though they did agree that there was no evidence the clinical benefits of treatment were lower in people who smoke. The committee also discussed the use of e-cigarettes but concluded that these were already included as part of the risk assessment recommendation (recommendation 1.2.55), as it was not clear that e-cigarettes produce the same level of risk as normal cigarettes.
Association for Respiratory Nurse Specialists	Guideline	23	3	Absolutely appropriate-all support should be towards smoking cessation. Supplementary oxygen is less effective when smoking. Burn and fire risks high. This supports clinicians to not prescribe oxygen in high risk patients therefore assisting in risk reduction and patient safety.	Thank you for your comment and support for this guideline.
Royal Free London NHS Foundation Trust	Guideline	23	7	The language here around oxygen use 15 hours "per day" risks misinterpretation of the important overnight period. It would be better to say "per 24 hours".	Thank you for your comment. The committee concluded that the specialists who will be advising patients on oxygen therapy will be aware of this information and this does not need to be stated specifically in the recommendation.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

KSS AHSN Patient Safety Collaborative	Guideline	23	7	Suggest add 'Advise people that there is increased survival benefit over a minimum of 15 hours with longer use of oxygen. (Many clinicians are unaware of the results of the NOTT trial)	Thank you for your comment. The recommendation for a minimum of 15 hours was made because of the benefits of using oxygen for this time period. The committee concluded they would expect that all healthcare professionals would tell patients about the benefits and risks of a treatment and so do not believe that this needs to be stated specifically in the recommendation.
Pulmonx Corporation	Guideline	24	General	We agree with and support the recommendations as formulated.	Thank you for your comment and your support for this guideline.
University Hospitals Birmingham NHS Foundation Trust	Guideline	26	10	Pulmonary rehab is such a key part of COPD management this section needs to reference the BTS PR guidelines/quality standards and that programmes should be accredited.	Thank you for your comment. Unfortunately, pulmonary rehabilitation was not within the scope of this update of the guideline, and therefore it was not possible for changes to be made to the recommendations in this section.
Primary Care Respiratory Society	Guideline	26	10	The importance of Pulmonary Rehab is not stated strongly enough. Nor is the need for it to be repeated in a patient's lifetime. Given the life span of many people with COPD - 15 years post diagnosis to death - you will need to attend multiple times as the physical effects are not sustained for that period, and the disease management is changing so people require more regular education. The guidelines suggest only one referral – and do not specify that it should be attended within a clinically significant period. Yet the door is open for an escalation in pharmacological treatments i.e. page 20 – frequent oral antibiotics	Thank you for your comments. The topic of pulmonary rehabilitation is not within the scope of this update, and therefore no changes could be made to these recommendations.
British Dietetic Association	Guideline	26	14	According to British Thoracic Society (BTS) guidelines "a referral to pulmonary rehabilitation provides an ideal opportunity for anthropometrical and nutritional assessment to take place, thus providing an opportunity to identify individuals at greatest risk of malnutrition, enabling a referral to specialised dietetic primary or secondary care services". "Patients with a body mass index (BMI) in the underweight or obese range should be considered for specific dietetic support". Corresponding with British Thoracic Society	Thank you for your comments. The topic of pulmonary rehabilitation is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				Guidelines. (2013). - https://www.brit-thoracic.org.uk/document-library/clinical-information/pulmonary-rehabilitation/bts-guideline-for-pulmonary-rehabilitation/ - accessed 16.3.18	
British Dietetic Association	Guideline	27	4	The draft states that the rehabilitation programme should include nutrtion. Patients should ideally be screened for nutritional risk prior to commencing pulmonary rehabilitation as patients at risk may be less likely to complete the programme. Those that do complete might be classified as a non-responder. In some individuals the aim may be to increase fat-free mass; this will not occur unless adequate energy is provided and protein at a level of 1.2. - 1.5g/kg body weight /day. In those whom are obese and at CV risk the aim may be to encourage weight loss, but this may compromise lean tissue (muscle mass), low muscle mass is a predictor of morbidity and mortality. Specialist dietary advice may be required for both undernourished individuals who have MUST score greater than or equal to 2, low BMI < 20 kg/m2 and obese individuals where the aim may to reduce weight but preserve lean tissue. There is evidence that nutritional support provided to malnourished COPD patients participating in pulmonary rehabilitation, enhances the response to treatment: https://www.ncbi.nlm.nih.gov/pubmed/22513295 https://www.ncbi.nlm.nih.gov/pubmed/23432923	Thank you for your comments. The topic of pulmonary rehabilitation is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	27	15	It appears in the evidence review that the QALY data makes LVRS and endobronchial valves very expensive interventions – should the cost implication be explicit in the summary? Were the group confident that the QALY costs are worthy of implementation?	Thank you for your comment. Cost considerations are not generally included in short guideline recommendations themselves. However, the potential for additional resource use associated with these recommendations is discussed in the 'how the recommendations might affect practice' section. In addition, the resource impact team have included costs of lung volume reduction procedures in their costing report and template, in order to help local budget holders plan any additional spend. The committee discussed the cost-effectiveness of lung volume reduction procedures at length, as captured in

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					Evidence Review G. While published economic analyses reported a relatively high ICER for LVRS, these studies were conducted from the perspective of US and Canadian healthcare systems. The committee indicated that the ICER is likely to be substantially lower in NHS settings for the following reasons: (1) The number of days hospital stay following surgery is, on average, considerably lower in the UK compared to the hospital stays reported in the economic literature. For example, 31.1/23.3 days for Canada/US versus 10.5 days in the UK. (2) The cost of a day's hospital stay is substantially higher in the US: ~$1,880 versus ~£222 in the NHS. (3) Published economic analyses use short time horizons, which are likely to underestimate the QALY gain associated with LVRS. (4) US analyses make very conservative assumptions in extrapolating survival to a 10 year time horizon, which is, again, likely to underestimate QALYs. (5) Evaluations which conducted subgroup analyses found that LVRS is substantially more cost-effective in patients with predominantly upper-lobe emphysema and those with a low exercise capacity. Since one of the key functions of lung volume reduction multidisciplinary teams is to assess patients' capacity to benefit from surgery, it is likely LVRS will result in greater health benefits for patients selected through this process, compared to the average patient in the published economic analyses. For endobronchial valves, the identified published analysis was conducted from the perspective of the German healthcare system, and was judged by the committee to be

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					broadly comparable to the NHS. The reported ICER indicates that endobronchial valve treatment is of borderline cost-effectiveness (£21,900 per QALY). However, the committee again indicated that the ICER is likely to be lower in reality, due to the short time horizon of the analysis, and because it is likely that multidisciplinary teams would select patients with the highest capacity to benefit.
NHS England	Guideline	27	15	It appears in the evidence review that the QALY data makes LVRS and endobronchial valves very expensive interventions – should the cost implication be explicit in the summary? Where the group confident that the QALY costs are worthy of implementation? (CRG)	Thank you for your comment. Cost considerations are not generally included in short guideline recommendations themselves. However, the potential for additional resource use associated with these recommendations is discussed in the 'how the recommendations might affect practice' section. In addition, the resource impact team have included costs of lung volume reduction procedures in their costing report and template, in order to help local budget holders plan any additional spend. The committee discussed the cost-effectiveness of lung volume reduction procedures at length, as captured in Evidence Review G. While published economic analyses reported a relatively high ICER for LVRS, these studies were conducted from the perspective of US and Canadian healthcare systems. The committee indicated that the ICER is likely to be substantially lower in NHS settings for the following reasons: (1) The number of days hospital stay following surgery is, on average, considerably lower in the UK compared to the hospital stays reported in the economic literature. For example, 31.1/23.3 days for Canada/US versus 10.5 days in the UK. (2) The cost of a day's hospital stay is substantially higher in the US: ~$1,880 versus ~£222 in the NHS.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					(3) Published economic analyses use short time horizons, which are likely to underestimate the QALY gain associated with LVRS. (4) US analyses make very conservative assumptions in extrapolating survival to a 10 year time horizon, which is, again, likely to underestimate QALYs. (5) Evaluations which conducted subgroup analyses found that LVRS is substantially more cost-effective in patients with predominantly upper-lobe emphysema and those with a low exercise capacity. Since one of the key functions of lung volume reduction multidisciplinary teams is to assess patients' capacity to benefit from surgery, it is likely LVRS will result in greater health benefits for patients selected through this process, compared to the average patient in the published economic analyses. For endobronchial valves, the identified published analysis was conducted from the perspective of the German healthcare system, and was judged by the committee to be broadly comparable to the NHS. The reported ICER indicates that endobronchial valve treatment is of borderline cost-effectiveness (£21,900 per QALY). However, the committee again indicated that the ICER is likely to be lower in reality, due to the short time horizon of the analysis, and because it is likely that multidisciplinary teams would select patients with the highest capacity to benefit.
Royal Free London NHS Foundation Trust	Guideline	27	18	Assessing people for VRS at the end of PR is challenging because the tests necessary to do this, and expertise around VRS lie in secondary care whereas most PR is delivered in community settings. This will therefore be challenging in practice.	Thank you for your comment. Although the assessment for VRS would be offered at the end of pulmonary rehabilitation, the recommendations don't require the assessment to take place in a community setting. Recommendation 1.2.84 is suggesting that the healthcare provider should offer the patient a respiratory review which would then be referred to the appropriate specialist team.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Primary Care Respiratory Society	Guideline	27	25	The group could consider adding in another bullet point – 'non-enhanced CT scan that suggests emphysema' (as per specialist review) as if this is not present the patient will not progress – and CT scan is available for most generalists to organise now (probably around 40% of GPs have open access).	Thank you for your comment. The use of non-enhanced CT scans is included in recommendation 1.2.85 as part of the criteria to refer from the respiratory review to a lung multidisciplinary team.
NHS England	Guideline	27	25	Could the group consider adding in non-enhanced CT scan that suggests emphysema (as per specialist review) as if this is not present the patient will not progress – and CT scan is available for most generalists to organise now (probably around 40% of GPs have open access). (CRG)	Thank you for your comment. The use of non-enhanced CT scans is included in recommendation 1.2.85 as part of the criteria to refer from the respiratory review to a lung multidisciplinary team.
Royal Pharmaceutical Society	Guideline	27	29	With an increasing role of specialist and consultant pharmacists, pharmacists play a vital role on the management of chronic conditions such as COPD. It is important to remember that pharmacist are experts in medicines and therefore are not only able to support patients in managing COPD, but discussing inhaler techniques and devices that better support patient's condition. We would recommend alongside nurse specialist having a pharmacist specialist in a multidisciplinary team.	Thank you for your comment. The topic of multidisciplinary management and specialists is not within the scope of this update, and therefore no changes could be made to these recommendations.
British Thoracic Society	Guideline	28	1-2	Lung volume reduction surgery and valves: suggest include hyperinflation threshold for referral (RV >180%) and minimum lung function for procedural safety (FEV1 > 15%; DLCO > 20%) for clarity / to better inform pre-referral assessment (minor point).	Thank you for your comment. The committee discussed this but concluded that the multidisciplinary team would be responsible for the assessment of hyperinflation and aware of the thresholds required for this.
Association for Respiratory Technology and Physiology	Guideline	28	1	What are patients had hyperinflation measured by techniques such as helium dilution/nitrogen washout, in addition to Plethysmography? - All techniques should be included - if values are raised this suggests hyperinflation. The paper should also consider simpler ways such as comparing VC and FVC to determine dynamic compression. Paper does not mention important parameters like VC and FEV1/VC	Thank you for your comment. The committee discussed this and agreed that there are a number of ways that hyperinflation can be measured. However, they concluded that these would be used in addition to plethysmography and so this was considered the most important to include in the recommendation.
British Dietetic Association	Guideline	28	23	Refer to dietitian for nutritional optimisation prior to surgery if MUST ≥2, low BMI (<20 kg/m^2) or unintentional weight loss of 5-10% over last 3-6 months	Thank you for your comment. Unfortunately this did not form part of the evidence review that was presented to the committee and so a recommendation could not be made on this.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

MAP BioPharma Ltd	Guideline	29	1-4	The updated COPD guideline will be published shortly before the final recommendation from NICE is published for CSL Behring's human alpha1-proteinase inhibitor under the Highly Specialised Technology (HST) programme. In the light of this forthcoming HST guidance, it would be appropriate for the guideline to state explicitly that the NHS should take into account technology recommendations from NICE in relation to the use of alpha-1 proteinase inhibitors as opposed to the current wording which suggests a no commissioning position.	Thank you for your comment. Unfortunately, we are unable to include a reference to HST guidance prior to its publication. However, we have passed this information to our surveillance team to ensure that the impact on the guideline is considered following publication of the HST (currently scheduled for February 2019).
Primary Care Respiratory Society	Guideline	29	9	Suggest add 'spirometry for FEV1' (this point has been made previously). This is because many undertake repeat poor quality spirometry without interpreting and keeping this to FEV1 will enable it to be interpreted and acted on.	Thank you for your comment. The topic of spirometry in multidisciplinary management is not within the scope of this update, and therefore no changes could be made to these recommendations.
NHS England	Guideline	29	9	Suggest add spirometry for FEV1 (this point has been made previously) this is because many undertake repeat poor quality spirometry without interpreting and keeping this to FEV1 so that this can be interpreted and acted on. (CRG)	Thank you for your comment. The topic of spirometry in multidisciplinary management is not within the scope of this update, and therefore no changes could be made to these recommendations.
British Dietetic Association	Guideline	29	16	States 'dietary issues' but add MUST ≥2, low BMI (<20 kg/m^2) or unintentional weight loss of 5-10% over last 3-6 months or advice for intentional weight loss if BMI over 30kg/m^2	Thank you for your comment. The topic of dietary issues in multidisciplinary management is not within the scope of this update, and therefore no changes could be made to these recommendations.
NHS England	Guideline	30	2	"active cycle of breathing techniques. [2004, amended 2018]" this is not clear - what does this mean? (PC)	Thank you for your comment. "Active cycle of breathing techniques" is the name for a specific active breathing technique designed to clear sputum from the lungs. We are confident this is a term that will be familiar to physiotherapists working with people with COPD.
British Dietetic Association	Guideline	30	9	Also, if people are malnourished as they are more likely to have depression	Thank you for your comment. The topic of depression in COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
British Dietetic Association	Guideline	30	16	Calculating BMI alone is a poor marker of nutritional risk in COPD patients. This is partly due to population changes; the average weight of COPD cohorts is >25kg/m^2 (overweight). There is evidence that the lowest risks (mortality, hospitalisation, length of	Thank you for your comment. The topic of nutritional factors in COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				hospital stay) in COPD is actually observed between a BMI between 25-30kg/m^2. It is now widely acknowledged that amongst the various respiratory phenotypes that exist under the COPD umbrella, there are also identifiable nutritional phenotypes characterised by malnutrition, sarcopenia, cachexia or a combination. Importantly, these nutritional phenotypes, associated with poorer prognosis can be present across all BMI categories. Lastly, one of the strongest predictors for poor outcomes in COPD is clinically relevant unintentional weight loss over the previous 3 (>5%) to 6 (>10%) months. There are validated nutritional screening tools that include BMI and unintentional weight loss components. Suggested recommendation: routinely screen for malnutrition risk in all COPD patients using a validated screening tool (e.g. Malnutrition Universal Screening Tool, MUST). Those patients identified as at risk of malnutrition should be referred to a dietitian for more comprehensive nutritional assessment.	
British Dietetic Association	Guideline	30	17	The footnote relating to this recommendation states that "The NICE guideline on obesity states that a healthy range is 18.5 to 24.9 kg/m2, but this range may not be appropriate for people with COPD". This BMI range is definitely not appropriate for people with COPD. The ERS/ATS, BODE index and certain screening tools have recommended a BMI cut-off of <21kg/m2 in older people (>65yrs) and those with chronic wasting diseases such as COPD.	Thank you for your comment. Unfortunately, the section of the guideline on nutritional factors was not included in the scope of this update of the guideline, and therefore it was not possible for the committee to make changes to these recommendations.
British Dietetic Association	Guideline	30	18	MUST ≥2, low BMI (<20 kg/m^2) or unintentional weight loss of 5-10% over last 3-6 months	Thank you for your comment. The topic of nutritional status or obesity and COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
British Dietetic Association	Guideline	30	20	States low BMI but should be Low BMI <20kg/m^2	Thank you for your comment. The topic of nutritional status or obesity and COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
British Dietetic Association	Guideline	30	23	From experience, we have often found that busy Respiratory Doctors and Respiratory Nurses rarely follow hyperlinks from one NICE guideline to another. Therefore, the nutritional management	Thank you for your comment. The topic of nutrition support for COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				content in the COPD guidelines should contain enough direction to ensure all COPD patients receive evidenced based nutritional care.	
Royal Pharmaceutical Society	Guideline	30	23	More pharmacies have become healthy living pharmacies and taken a prominent role in providing patients with diet and lifestyle advice. Healthy Living Pharmacies have health champions who can promote wellbeing and health improvement.	Thank you for your comment. The topic of nutrition support for COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
British Dietetic Association	Guideline	30	20,21& 22	This could link to the pulmonary rehabilitation section and the suggested evidence showing the additional benefits of nutritional support alongside exercise? This recommendation does not suggest referring to a dietitian, not mentioning referral to a dietitian can result in unsafe breaks or delays in nutritional care. Suggested recommendation: People identified as at nutritional risk should be referred to a dietitian (rather than receive dietetic advice). High energy and high protein diets including nutritional supplements have been shown to improve nutritional intake, nutritional status and functional capacity. We would suggest linking to the Managing Malnutrition in COPD practical guide for healthcare professionals which can be found: https://www.malnutritionpathway.co.uk/copd	Thank you for your comment. The topic of nutrition support for COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Abbott Nutrition	Guideline	30	20,21,22	If the BMI is low or weight loss is more than 10% in 3-6 months patients should also be given high protein high energy nutritional supplements to increase their total calorific and protein intake and be encouraged to take exercise to augment the effects of nutritional supplementation. There is evidence that weight loss is also a significant factor in disease progression and should be monitored as well as BMI. Weight loss of more than 10% in 3-6 months indicates a risk of malnutrition ('MUST' guidelines) regardless of age. Body weight BMI and muscle mass independently predict mortality and length of hospital stay in people with COPD. If the BMI is low or weight loss is more than 10% in 3-6 months patients should also be given high protein high energy nutritional	Thank you for your comment. The topic of nutrition support for COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				supplements to increase their total calorific and protein intake and be encouraged to take exercise to augment the effects of nutritional supplementation. MUST - British Association for Parenteral and Enteral Nutrition. Malnutrition universal screening tool. Bapen.org.uk Ezzell I and Jensen GL "Malnutrition in chronic obstructive Pulmonary disease" *The American Journal of clinical nutrition 2000;72:1415-1416* Steer j, Norman E, Gibson GJ et al "Comparison of indices of nutritional status in the prediction of in-hospital mortality and early readmission of patients with acute exacerbations of COPD" *Thorax 2010 ;65:A127(p117)* Hoong JM Ferguson M Hukins C et al "Economic and operational burden associated with malnutrition in chronic obstructive pulmonary disease" *Clinical Nutrition 2017;36:1105-1109*	
Abbott Nutrition	Guideline	30	20,21,22	If there is evidence of Malnutrition (BMI <20kg/m^2 or weight loss of >10% in 3-6 months or BMI<18.5Kg/m^2 and 5% weight loss and patient has limited mobility or is house bound consider using a nutritional supplement with additional Vitamin D_3. There is evidence that vitamin D deficiency is common in people with COPD leading to muscle wasting and osteoporosis. Martineau AR, James WY et al	Thank you for your comment. The topic of nutrition support for COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				"Vitamin D3 supplementation in patients with Chronic Obstructive pulmonary disease: A Multicentre double blind randomised controlled trial " *Lancet Respiratory Medicine Vol 13 issue 2 P120-130 2015* Persson LJ, Aanerud M, Hiemstra PS, et al. "Chronic obstructive pulmonary disease is associated with low levels of vitamin D". PLoS One*. 2012;7(6):e38934.* Daisuke Inoue, Reiko Watanabe, Ryo Okazaki "COPD and osteoporosis: links, risks, and treatment challenges" https://doi.org/10.2147/COPD.S79638 29 March 2016 Volume 2016:11(1) Pages 637—648 John Bottrell, RRT "Links Between COPD and Osteoporosis" *COPD.net July 26, 2017* Ferguson GT, Calverley P "Prevalence and Progression of Osteoporosis in Patients With COPD: Results From the Towards a Revolution in COPD Health Study" Chest Volume 136, Issue 6, December 2009, Pages 1456-1465	
Abbott Nutrition	Guideline	30	20,21,22	There is evidence that individuals with chronic conditions like COPD require 1.2-1.5g/kg/day of protein to prevent sarcopenia/ muscle weakness and loss of FFM. If there are signs of muscle weakness / wasting in malnourished COPD patients a high protein nutritional supplement should be chosen (more than 20% energy from Protein)	Thank you for your comment. The topic of nutrition support for COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				Schols AMWJ "Nutritional and metabolic modulation in chronic obstructive pulmonary disease management" *European respiratory Journal 2003;22:81s-86s* Deutz N, Bauer JM, Barazzoni R et al "Protein intake and exercise for optimal muscle function with aging. Recommendations from the ESPEN Expert Group." *Clinical Nutrition 2014;33:929-36* Hsieh MJ, et al. Nutritional supplementation in patients with chronic obstructive pulmonary disease. *J Formos Med Assoc. 2016;115:595–601.* Vermeeren MAP, et al. Effects of an acute exacerbation on nutritional and metabolic profile of patients with COPD *Eur Respir J. 1997;10:2264–9.*	
British Dietetic Association	Guideline	31	1-2	We do not feel this suggestion makes clinical sense as a 5kg weight loss in a 45kg COPD patient should be managed very differently than a 5kg weight loss in a 115kg patient. Both exceed the arbitrary 3kg. Suggested recommendation: Pay attention to unintentional weight changes in older people, particularly if the change in weight is more than 5% in 3 months or more than 10% in 6 months [Refer to section on nutritional screening].	Thank you for your comment. The topic of nutrition support for COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	31	3	Would the group consider adding in a phrase that highlights the need to address pain and other symptoms in people with end stage COPD? – as these can be commonly ignored and the advice here is primarily about the lung symptoms. Gore JM, Brophy CJ, Greenstone MA. How well do we care for patients with end stage chronic obstructive pulmonary disease	Thank you for your comment. The topic of palliative care for COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				(COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. Thorax. 2000;55(12):1000-6	
NHS England	Guideline	31	3	Would the group consider adding in a phrase that highlights the need to address pain and other symptoms in people with end stage COPD – as these can be commonly ignored and the advise is primarily about the lung symptoms. Gore JM, Brophy CJ, Greenstone MA. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. Thorax. 2000;55(12):1000-6 (CRG)	Thank you for your comment. The topic of palliative care for COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	31	4	In the summary, it would be worth adding low dose opiates (as generalists often try to manage this in the same way as pain.)	Thank you for your comment. The topic of palliative care for COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
NHS England	Guideline	31	4	In the summary would be worth adding low does opiates (as generalists often try to manage this in the same way as happens with pain. (CRG)	Thank you for your comment. The topic of palliative care for COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Royal Free London NHS Foundation Trust	Guideline	31	7	Regarding palliative oxygen, this is recommended in people with breathlessness WHO ARE HYPOXIC – there is considerable over-use of oxygen in non-hypoxic palliative care and this risks additional clinically unnecessary and costly prescription.	Thank you for your comment. The topic of palliative care for COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	33	3	It is important to have information for people with COPD – that highlights common co-morbidities (e.g. osteoporosis / heart disease / anxiety / depression) which can trigger patients to seek appropriate help – we suggest this is added.	Thank you for your comment. The committee discussed this and agreed that it was important to highlight some of the common comorbidities. This is now included as an extra bullet point at the end of recommendation 1.2.118, which says 'other long term conditions that are common in people with COPD (for example hypertension, heart disease, anxiety, depression)'.
NHS England	Guideline	33	3	We think it would be important to have information in people with COPD – that highlights common co-morbidities (eg osteoporosis / heart disease / anxiety / depression) which can trigger patients to seek appropriate help – could this be added please? (CRG)	Thank you for your comment. The committee discussed this and agreed that it was important to highlight some of the common comorbidities. This is now included as an extra bullet point at the end of recommendation 1.2.118, which says 'other long term conditions that are common in people

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					with COPD (for example hypertension, heart disease, anxiety, depression,)'.
UK Inhaler Group	Guideline	33	10	Covering inhaler technique under a section headed 'information' is underselling the importance of teaching, demonstrating, observing the patient and rechecking inhaler technique until the patient can demonstrate that they can use the device systematically. This needs to be presented as an active part of prescribing and review, which is undertaken systematically, not as a more passive 'giving of information'.	Thank you for your comment. Inhaler use is also covered in the inhaled therapies section of the guideline which includes basing the choice of inhalers on the person's ability to use the inhalers.
UK Inhaler Group	Guideline	33	10	What metrics do you suggest for ensuring information is given, inhaler technique taught, and adherence with medicines monitored? What documentation should there be to ensure that these take place?	Thank you for your comment. Inhaler use is also covered in the inhaled therapies section of the guideline which includes basing the choice of inhalers on the person's ability to use the inhalers.
Royal Free London NHS Foundation Trust	Guideline	33	22	There is considerably more evidence linking gastro-oesophageal reflux than indoor/outdoor pollution to exacerbation risk, it is not clear how this list was generated.	Thank you for your comment. Evidence was identified on gastro-oesophageal reflux (and is presented alongside the rest of the data in Evidence Review E). The committee concluded, however, that there was insufficient evidence in order for gastro-oesophageal reflux to be included on this list of factors.
KSS AHSN Patient Safety Collaborative	Guideline	34	5	This is rather vague advice and may lead to overuse of oral steroids. Suggest use the wording on definition of an exacerbation on page 37. Many COPD patients have symptoms which significantly affect their ADLs, the symptoms can increase temporarily but are not necessarily an exacerbation.	Thank you for your comment. The committee discussed this and decided that the overuse of steroids is covered in recommendation 1.2.124. This states that steroid and antibiotic use should be discussed at all review appointments, and the reasons behind anyone using more than 3 courses per year will be investigated.
NHS England	Guideline	34	5	Even more important to ensure the patient is treated holistically rather than just managing the lung (see 34/5) (CRG)	Thank you for your comment. The committee agreed that holistic treatment of the patient is important. They have added extra information into recommendation 1.2.118 which highlights that patients should also be informed about other common conditions associated with COPD including issues such as heart disease as well as anxiety and depression.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Primary Care Respiratory Society	Guideline	34	9	Please clarify what is a short course (GOLD suggests 5-7 days now); older NICE guidance was 7-14 days; clinicians need to know (Also worth highlighting the length in most research is in people within an in-patient environment as quite a few clinicians seem to think a much longer course is required if they have been in hospital.)	Thank you for your comment. NICE has noted the number of stakeholders who have raised the issue of the length of steroid treatment as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence to justify updating this part of the guideline. However, with the recent publication of a Cochrane review it has now been agreed that it is appropriate for these recommendations to also be updated. A separate update of these recommendations has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline and pathway.
NHS England	Guideline	34	9	Please clarify what is a short course (GOLD suggests 5-7d now) older NICE guidance was 7-14d; colleagues do want to know (also worth highlighting the length in most research is in people within an in-patient environment as quite a few clinicians seem to think a much longer course is required if they have been in hospital. (CRG)	Thank you for your comment. NICE has noted the number of stakeholders who have raised the issue of the length of steroid treatment as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was concluded there was insufficient new evidence to justify updating this part of the guideline. However, with the recent publication of a Cochrane review it has now been agreed that it is appropriate for these recommendations to also be updated. A separate update of these recommendations has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline and pathway.
Royal Free London NHS	Guideline	34	10	There is a divergence between the proposed antibiotic guideline for community treated exacerbations (generally more restrictive in use	Thank you for your comment. The NICE antimicrobial prescribing guideline for COPD is expected to be published in

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Foundation Trust				of antibiotics, reflecting poor evidence of efficacy and risk of resistance) and the recommendation for people to have rescue packs at home. There is also divergence in relation to how to guide use of antibiotics which in the OCPD guideline (but not the new antibiotic guideline) remains around change in sputum (page 35, line 7).	December 2018. The recommendations in the COPD guideline have now been removed and replaced with a reference to these updated guidelines.
KSS AHSN Patient Safety Collaborative	Guideline	34	12	The greater clarity on who is appropriate for rescue packs is welcomed	Thank you for your comment and your support for this recommendation.
Primary Care Respiratory Society	Guideline	34	12	Many patients believe they understand and are confident about when and how to take these medicines, and the associated benefits and harms and they know to tell their healthcare professional when they have used the 14 medication, and to ask for replacements. But we hear of people using 10 plus courses or back to back courses on repeat. From a patient safety perspective it would be sensible that 1. People are reviewed after an exacerbation requiring antibiotics or steroids 2. Prednisolone and antibiotics are not added to repeat prescription lists.	Thank you for your comment. The committee discussed this and decided that this issue is covered in recommendation 1.2.122. This states that patients should tell their healthcare professional when they have used their medication and to ask for replacements. As a result, patients should not be able to receive more steroids or antibiotics without a review of their use from their healthcare professional.
NHS England	Guideline	34	12	Many patients believe they know they understand and are confident about when and how to take these medicines, and the associated benefits and harms **and** they know to tell their healthcare professional when they have used the 14 medication, and to ask for replacements. But we hear across boundaries of people using 10 plus courses or back to back courses on repeat. From a patient safety perspective it would be sensible that 1. People are reviewed after an exacerbation requiring antibiotics or steroids 2. Prednisolone and antibiotics are not added to repeat prescription lists. (CRG)	Thank you for your comment. The committee discussed this and decided that this issue is covered in recommendation 1.2.122. This states that patients should tell their healthcare professional when they have used their medication and to ask for replacements. As a result, patients should not be able to receive more steroids or antibiotics without a review of their use from their healthcare professional.
NHS England	Guideline	34	16	Would recommend that this is included in the body of the guideline rather yet another guideline to refer to. (CRG)	Thank you for your comment. This guideline was produced by a separate and different process within NICE to the main

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					COPD guideline, and this is why it is presented as a separate guideline.
Primary Care Respiratory Society	Guideline	35	5	The guidance has always been vague here – and the commonest question is 'How long if their increased breathlessness interferes with activities of daily living?' Please provide advice here - is it 30 minutes? – one day? or like most of the exacerbation research – increased symptoms for 48 hours?	Thank you for your comment. The committee discussed this but decided they couldn't currently provide further advice as there is no clear evidence for the duration of an exacerbation and they concluded that symptoms are often relative to each individual patient.
NHS England	Guideline	35	5	The guidance has always been vague here – and the commonest question is how long if their increased breathlessness interferes with activities of daily living – can you provide advise here is it 30 minutes – one day or like most of the exacerbation research – increased symptoms for 48 hours? (CRG)	Thank you for your comment. The committee discussed this but decided they couldn't currently provide further advice as there is no clear evidence for the duration of an exacerbation and they concluded that symptoms are often relative to each individual patient.
Primary Care Respiratory Society	Guideline	35	10	This seems rather clumsy – most people would be frightened if they were more breathless. Perhaps discuss with patient if they would like to engage in talking therapies that can reduce the impact of their breathlessness.	Thank you for your comment. The committee discussed this but decided to keep the description of frightened in the recommendation. The best terminology to use for this was widely discussed during the making of the recommendations but it was decided that adding further descriptions might reduce the meaning of the description. Talking therapies could form part of the self-management plan.
NHS England	Guideline	35	10	This seems rather clumsy – most people would be frightened if they were more breathless. Perhaps discuss with patient if they would like to engage in talking therapies that can reduce the impact of their breathlessness. (CRG)	Thank you for your comment. The committee discussed this but decided to keep the description of frightened in the recommendation. The best terminology to use for this was widely discussed during the making of the recommendations but it was decided that adding further descriptions might reduce the meaning of the description. Talking therapies could form part of the self-management plan.
NHS England	Guideline	35	10	"Ask people with COPD if they experience breathlessness they find frightening. If they do, consider adding a cognitive behavioural component to their self-management plan to help them manage anxiety and cope with breathlessness. [2018]" - This will have resource implications for commissioning MH services (PC)	Thank you for your comment. We have changed this recommendation to 'consider including a cognitive behavioural component within their self-management plan' to clarify that this should be incorporated as part of the self-management plan and not in addition to it. The CBT component could be drawn from a range of interventions and so will not have the same resource implications for MH

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					services as if full CBT was recommended for the whole group.
KSS AHSN Patient Safety Collaborative	Guideline	35	11	The cognitive behavioural component is welcome, it would be helpful to signpost people to various modes available via the NHS	Thank you for your comment and your support for the guideline.
KSS AHSN Patient Safety Collaborative	Guideline	35	16	Suggest add' Explain that if admitted it is very likely that their hospital doctors will have a discussion around escalation of treatment/ceiling of care and it would be wise to have consider this in advance	Thank you for your comment. The committee discussed this and agreed that this should be included in the recommendation. The recommendation is now 'For people at risk of hospitalisation, explain to them and their family members or carers (as appropriate) what to expect if this happens (including non-invasive ventilation and discussions on future treatment preferences, including ceilings of care and resuscitation).' The committee decided that this gave patients the opportunity to discuss future treatment prior to hospitalisation.
KSS AHSN Patient Safety Collaborative	Guideline	35	18	This statement is welcome	Thank you for your comment and your support for the guideline.
Primary Care Respiratory Society	Guideline	36	22-24	1.2.134 For most people with stable severe COPD regular hospital review is not necessary, but there should be locally agreed mechanisms to allow rapid access to hospital assessment when needed The above point we commend as good care. However, "hospital assessment" should be replaced with 'specialist assessment' because it could be delivered by an integrated respiratory team/consultant in the community, rather than delivered in an acute hospital. In the absence of a specialist team or community based consultant, patients might be required to access hospital. But the notion that specialist care/assessment has to be delivered in the hospital is	Thank you for your comment. The topic of follow-up for people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				outdated and unhelpful at a time when more specialist care is being provided in the community than ever before. Often a Respiratory review service is not commissioned. If the patients are not 'threatening immediate admission', they cannot access review. This means they often deteriorate until they do require acute care. Commissioning a review service/ outreach/ community specialist team would enable admissions to be avoided and improves patients' experience and reduces unnecessary travel by the individual.	
NHS England	Guideline	36	4	1.2.131 "If time permits, optimise the medical management of people with COPD before surgery. This might include a course of pulmonary rehabilitation. [2004]". This could have unintended consequences of delaying surgery when rehab has not been adequately commissioned.	Thank you for your comment. The topic of medical management for people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	36	7	Use of the term 'Follow up' is not helpful here. 'Monitoring' is more appropriate language as 'follow up' tends to be used to refer to post-exacerbation/ hospitalisation.	Thank you for your comment. The topic of follow-up/monitoring of people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
NHS England	Guideline	36	20	Suggest add into the annual review in table 6 – assessment of co-morbidities if this is their annual clinical review (both management of established co-morbidity and assessment for other likely co-morbidities) (CRG)	Thank you for your comment. The topic of follow-up of people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Royal Free London NHS Foundation Trust	Guideline	36	22	Some of the 2004 language is very out of date for current practice in which multi-professional teams are working across primary, community and secondary care. So the comment here on 'hospital' refers to a building. What is important is that each patient can see the team member(s) they need to see, and access the investigations they need to access.	Thank you for your comment. The language in the old recommendations was updated as much as possible without risking changing the meaning of the recommendations. In some situations, it was felt to not be possible to modernise the language without altering the meaning of the recommendation, but we are confident the meaning of the recommendations will be clear to those using them.
British Dietetic Association	Guideline	37	1	"person with COPD's nutritional state" – we would suggest changing this to "person with COPD's nutritional **risk**"	Thank you for your comment. The topic of follow-up of people with COPD is not within the scope of this update, and

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					therefore no changes could be made to these recommendations.
British Dietetic Association	Guideline	37	1	"calculate BMI" – as previously mentioned, calculating BMI alone is a poor marker of nutritional risk in COPD patients and therefore we would suggest this recommendation: "Nutritional screening should be conducted at least twice per year using a validated screening tool (MUST)."	Thank you for your comment. The topic of follow-up of people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
NHS England	Guideline	37	1	Why are people measuring FVC ? Is there any evidence for this (either as a way of picking up other problems – which usually present in other ways much earlier) (CRG)	Thank you for your comment. The topic of follow-up of people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
UK Inhaler Group	Guideline	37	Table 6	Inhaler technique needs to be checked at every respiratory related encounter with the patient – not just once or twice a year. See NICE guideline NG80 for asthma *1.5.5 Ensure that a person with asthma can use their inhaler device:* • *at any asthma review, either routine or unscheduled* • *whenever a new type of device is supplied.* As COPD patients usually are deteriorating over time, it is even more important to check that they are getting benefit from their medicine. The NICE guideline for asthma is also more specific about checking the patient can use inhalers. We can see no reason why this advice should not be as clearly worded and explicit for COPD. *1.14.7 Observe and give advice on the person's inhaler technique:* • *at every consultation relating to an asthma attack, in all care settings* • *when there is deterioration in asthma control* • *when the inhaler device is changed*	Thank you for your comment. The topic of follow-up of people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				• *at every annual review* • *if the person asks for it to be checked.*	
Primary Care Respiratory Society	Guideline	37	Table 6	Summary of follow up/monitoring in primary care. For those with mild/mod/severe disease there is no mention of screening for anxiety or depression – there should be. For those with severe disease, depression is mentioned but anxiety is omitted.	Thank you for your comment. The topic of follow-up of people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	37	Table 6	Suggest add into the annual review in table 6 – assessment of co-morbidities if this is their annual clinical review (both management of established co-morbidity and assessment for other likely co-morbidities)	Thank you for your comment. The topic of follow-up of people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	37	Table 6	Annual measurement of FEV1 And FVC is recommended. This implies a need for full spirometry at every COPD review. This has major logistic implications for primary care, particularly given the introduction of requirements for quality assured spirometry and a possible reduction in practices offering this. The evidence supporting a need for annual spirometry in COPD review is weak. A recommendation for annual FEV1 is more feasible since this can be done using microspirometry	Thank you for your comment. The topic of follow-up of people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Boehringer-Ingelheim Ltd	Guideline	37	Table 6	BI strongly agrees with the NICE recommendation that patients with COPD are reviewed either at least annually, or bi-annually. We believe that the “effects of each drug treatment” acknowledges that all therapies should be reviewed, in particular “inhaled corticosteroid use”. Reasons for this include fluctuation in “ICS responsiveness”, including potential variation in exacerbations over the previous year(s) and variation in blood eosinophil count, as well as the known side effects of ICS, including pneumonia and diabetes (please see comment 10). Furthermore, in “measurements to make”, we suggest NICE include blood eosinophil count. “Higher blood eosinophil count” is suggested as a measurement in the algorithm that may warrant ICS use, but blood eosinophil count may vary over time and	Thank you for your comment and support for the recommendation. The topic of follow-up of people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				within the context of the patient's current situation (E.g. infections, OCS use etc).	
Association for Respiratory Nurse Specialists	Guideline	38	3	There is evidence that the use of DECAF (MRC Dyspnoea, Eosinophilia, Consolidation & Atrial Fibrillation)scores are useful in helping to assess the risk of patients with exacerbation of COPD and suitability for home from hospital treatment, should this be included / advocated	Thank you for your comment. Although the use of DECAF was in the protocol the committee decided that it did not meet the criteria for this section of the update which focused on prognosis in a person with stable COPD. As DECAF was designed for use only in a hospital where patients would more likely have exacerbations of COPD than stable COPD the committee decided it would not be a suitable test to include in this update, which focused solely on prognosis in people with stable COPD.
Primary Care Respiratory Society	Guideline	38	3	• Assessing the need for hospital treatment This table is useful for supporting a clinician to make a risk assessment re the stability of the patient, however can encourage hospitalisation in a number of patients who could be support by a hospital at home/admission avoidance/rapid response service. Throughout the guidance there is a lack of advice or promotion of these intense community services. Such services have ballooned since 2004, with the a drive for more healthcare to be provided in the community. So the proposal that complex COPD patients must be managed in hospital is misleading. Many of these domains can be managed successfully at home with comprehensive planning and monitoring.	Thank you for your comment. The topic of assessing the need for hospital treatment in people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	**39**	5-17	With the exception of chest x ray all the tests below can be performed in the home. With point of care testing some of these results can be immediate. The 'tone' of the NICE guidance can guide the assessing health care professional/GP to refer patients to hospital more than may be necessary. There does appear to be a bias here towards pointing patients to an acute hospital when many areas have community based services. NICE needs to be careful not to dictate where care is provided.	Thank you for your comment. The topic of people referred to hospital with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Society for Acute Medicine	Guideline	39	27-29	We are disappointed that this does not include the DECAF score as an aid to selecting who could be treated at home by these teams. There is increasing evidence that the decaf score predicts outcome in this condition (better than any other) and this is a missed opportunity	Thank you for your comment. Although the use of DECAF was in the protocol, the committee decided that the evidence identified for it did not meet the criteria for this section of the update which focused on prognosis in a person with stable COPD. As DECAF was designed for use only in a hospital where patients would more likely have exacerbations of COPD than stable COPD the committee decided it would not be a suitable test to include in this update, which focused solely on prognosis in people with stable COPD.
Thermo Fisher Scientific	Guideline	39	6	This inclusion criterion overlooks the point that in some UK centres, the standard of care would include performing a BRAHMS Procalcitonin test on patients presenting with aeCOPD. This can differentiate bacterial infection from inflammation, and aid antimicrobial stewardship decisions.	Thank you for your comment. The topic of people referred to hospital with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Society for Acute Medicine	Guideline	39	8	Is it really recommended to do an arterial gas in all those presenting to hospital? - surely would be better t osay all those with oxygen saturations <94% (on any concentration of inhaled oxygen) – Arterial stabs are painful and not risk free	Thank you for your comment. The topic of people referred to hospital with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
UK Inhaler Group	Guideline	40	14-16	There is another area for research here. We need to know how the patient engages with their inhaler device – about their ability to inhale appropriately. In the absence of such research, we suggest that if a drug and an inhaler are effective for a patient during an exacerbation – keep them on it until after they have got home and are stable. Only seek to make changes once they have stabilised after an exacerbation.	Thank you for your comment. Unfortunately this topic is not within the scope of this update of the guideline, and therefore it was not possible for the committee to make recommendations on this topic.
UK Inhaler Group	Guideline	40	9/10	It is important to specify MDIs in this context. A dry powder inhaler will be insufficient to deliver an appropriate dose when a patient is exacerbating. This also presents an important opportunity to check inhaler technique and to address it when the patient is no longer exacerbating.	Thank you for your comment. Unfortunately this topic is not within the scope of this update of the guideline, and therefore it was not possible for the committee to make recommendations on this topic.
UK Inhaler Group	Guideline	40	12	There is an important area for research here. It is not just about the patient's 'ability to use their device'. It is also about ensuring that the patient's lungs are able to receive the drug in the device used, and	Thank you for your comment. Unfortunately this topic is not within the scope of this update of the guideline, and therefore

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				therefore about appropriate selection of device. It is about the capability of the lungs, and their lung energy.	it was not possible for the committee to make recommendations on this topic.
University Hospitals Birmingham NHS Foundation Trust	Guideline	41	Line 19-23	This is at odds with the new antibiotic guideline on AECOPD, which states that most patients should have antibiotics for their acute exacerbations. I agree that antibiotics should be reserved for patients with purulent sputum as per the 2004 guideline and retained in the 2018 guideline.	Thank you for your comment. The NICE antimicrobial prescribing guideline is expected to be published in December 2018. The recommendations in the COPD guideline have now been removed and replaced with a reference to these updated guidelines.
Association for Respiratory Nurse Specialists	Guideline	41	18-19	There is some concern this could cause confusion as a separate document. Clinicians need to find information easily consideration may be had to include the antimicrobial prescribing guideline as an appendix or in main body.	Thank you for your comment. The original guidelines on antibiotic use have been removed from the document to prevent confusion. These have been replaced with a link to the updated antimicrobial prescribing guideline so that it can be easily accessed by clinicians.
Royal Free London NHS Foundation Trust	Guideline	41	5	New guidance on antibiotics states 5/7, using steroids for “7-14” is more challenging to prescribe (many people currently give the same course duration of antibiotic and of steroid, often 5/7).	Thank you for your comment. NICE has noted the number of stakeholders who have raised the issue of the length of steroid treatment as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence to justify updating this part of the guideline. However, with the recent publication of a Cochrane review it has now been agreed that it is appropriate for these recommendations to also be updated. A separate update of these recommendations has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline and pathway.
Primary Care Respiratory Society	Guideline	41	11	Many generalists ask how many is ‘frequent’? Should this refer people to osteoporosis guidelines?	Thank you for your comment. Unfortunately this topic is not within the scope of this update of the guideline, and therefore it was not possible for the committee to make changes to the recommendations on this topic.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

NHS England	Guideline	41	11	Many generalists ask how many is frequent? Should it refer to osteoporosis guidelines (CRG)	Thank you for your comment. Unfortunately this topic is not within the scope of this update of the guideline, and therefore it was not possible for the committee to make changes to the recommendations on this topic.
Thermo Fisher Scientific	Guideline	41	18	This comment implies that practice hasn't moved on since the 2004 guidelines, again to reiterate the point above centres are routinely using biomarkers to aid stewardship decisions.	Thank you for your comment. The committee acknowledged this as a relevant issue, but since the use of biomarkers to guide treatment of exacerbations was not within the scope of this update of the guideline, they were not able to make recommendations on this topic.
Thermo Fisher Scientific	Guideline	41	21	BRAHMS Procalcitonin can be used in the criteria for excluding the need for antibiotics.	Thank you for your comment. The committee acknowledged this as a relevant issue, but since the use of biomarkers to guide treatment of exacerbations was not within the scope of this update of the guideline, they were not able to make recommendations on this topic.
British Thoracic Society	Guideline	41	25	We appreciate that responses were not requested for grey areas. However urge the committee to revise the guidance on the duration of acute courses of prednisolone (currently 7-14 days); 5 days is sufficient in most cases and will minimise harm.	Thank you for your comment. NICE has noted the number of stakeholders who have raised the issue of the length of steroid treatment as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was concluded there was insufficient new evidence to justify updating this part of the guideline. However, with the recent publication of a Cochrane review it has now been agreed that it is appropriate for these recommendations to also be updated. A separate update of these recommendations has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline and pathway.
Association for Respiratory Technology and Physiology	Guideline	42	27	Should say PCO2" rather than "pCO2".....or to fit with rest of paper "PaCO2"	Thank you for your comment. This has been amended as you suggest to match the rest of the guideline.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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University Hospitals Birmingham NHS Foundation Trust	Guideline	42	8, 17 and 20	There is little evidence of benefit of theophyllines and aminophyliine in management of AECOPDs – Cochrane review and in my opinion this section needs to be up-dated – it is 14 years old. Likewise the use of Doxapram has been superseded by NIV. Reference needs to be made to the emergency oxygen guidelines with target sats of 88-92 pre ABG, and 94-98 post ABG, unless previous ventilation or raised CO2, in which case 88-92%, and the importance of prompt and appropriate oxygen prescribing – reference BTS COPD care bundle pilot.	Thank you for your comment. Unfortunately, with the exception of inhaled combination therapy, the topic of pharmacological management for COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
University Hospitals Birmingham NHS Foundation Trust	Guideline	43	5	Need to reference BTS hypercapnic respiratory failure guidelines, NCEPOD report and door to mask time for NIV of 2 hours. This is a life saving treatment and needs more prominence	Thank you for your comment. The topic of non-invasive ventilation for COPD exacerbations is not within the scope of this update, and therefore no changes could be made to these recommendations. Your comments have been passed onto the NICE surveillance team.
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	43	5	The criteria for domiciliary non-invasive ventilation are dealt with exceptionally briefly, but this is an area where there has been considerable change in clinical practice since the previous guidelines. This has significant cost and organisational implications, and framework recommendations/evidence review would be useful in guiding commissioning and provision of services.	Thank you for your comment. The topic of non-invasive ventilation for COPD exacerbations is not within the scope of this update, and therefore no changes could be made to these recommendations.
Association for Respiratory Nurse Specialists	Guideline	44	14	This recommendation will be a challenging change in practice because spirometry may not be accessible for all and it is unclear what the rationale for performing spirometry prior to discharge would be.	Thank you for your comment. The topic of discharge planning for patients with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	44	14	Discharge planning • 1.3.45 Measure spirometry in all people before discharge. FEV1 results do not guide specific interventions and spirometry should be performed for baseline in the 'well' patient, 6 weeks post exacerbation rather than at the point of the exacerbation. Very few hospitals perform spirometry pre-discharge in a patient who has had	Thank you for your comment. The topic of discharge planning for patients with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				an exacerbation. If it is a new diagnosis, then this has usually been made clinically, not using spirometry.	
NHS England	Guideline	44	14	Is there any point in leaving this in? We have never seen a discharge summary with spirometry figures in – nor do my patients tell me they have a test? If they are in hospital they will often with more rapid discharge feel too weak to do spirometry. Indeed new diagnoses on discharge summaries are usually made clinically rather than with spirometry. (CRG)	Thank you for your comment. The topic of discharge planning for patients with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
University Hospitals Birmingham NHS Foundation Trust	Guideline	44	15	Is it really still appropriate or indeed practical to recommend measuring spiro in all people admitted with an AECOPD? Can we reference the National COPD Audit, and state that all patients should have a spirometry result available in their notes during an admission, and that if there isn't one or its not been performed (in the last 5 years??) then spiro should be performed before discharge?	Thank you for your comment. The topic of non-invasive ventilation for COPD exacerbations is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	44	15	• 1.3.46 Re-establish people on their optimal maintenance bronchodilator therapy before discharge. It is not a prerequisite to discharge from hospital if the patient is discharged to a service with nebulised SABA before switching to LAMA. Also maintenance bronchodilation might include no SABA whereas most people discharged from hospital will be taking routine SABA and weaning off at home.	Thank you for your comment. The topic of discharge planning for patients with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.
Primary Care Respiratory Society	Guideline	44	24	The reference to follow up after discharge is very light touch. High quality and timely follow up is essential to avoid readmission and to restore control in the patient post exacerbation. The BTS discharge bundle should be considered for all severe patients. Follow up features as Quality Statement 8 in NICE's Quality standard. It deserves far more focus than it is currently given	Thank you for your comment. The topic of discharge planning for patients with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				in the guideline. These are the most vulnerable patients and those most likely to have repeat exacerbations. https://thorax.bmj.com/content/early/2015/07/21/thoraxjnl-2015-206833?papetoc=&utm_source=trendmd&utm_medium=cpc&utm_campaign=thorax&utm_content=consumer&utm_term=0-A In addition to hospital discharge bundles, if the patient is managed at home by specialist or high-level monitoring e.g. they must not be excluded from follow up/review processes. If patients are treated at home in specialist services and not admitted to hospital this may under-represent the clinical burden posed by the disease and therefore assessing severity of disease based on setting in which care is received might misguide professionals from escalating care.	
UK Clinical Pharmacy Association	Guideline	45	6-7	There is no consensus or evidence to state what a higher blood eosinophil count indicates definite inhaled corticosteroid response, and evidence is limited to post hoc analyses. Stating 'a higher eosinophil count' is very arbitrary, and we are aware of some centres in the UK using cut-offs of 150/mm^3, 300/mm^3, 400/mm^3, or higher. This guideline will not reduce variation in practice across the UK.	Thank you for your comment. The committee discussed the inclusion of a threshold to define a higher eosinophil count, but concluded that based on the evidence available it was not possible to define a specific threshold. In particular, they noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. However, the accompanying research recommendation to address which features predict inhaled corticosteroid responsiveness most accurately in people with COPD could provide information on this topic and help improve the definition of asthmatic features/features suggesting steroid responsiveness in future updates of the guideline.
Chiesi Ltd	Guideline	45	5	A higher blood eosinophil count is listed as a feature suggesting steroid responsiveness. We support the update of the guideline to move to a more precision-medicine approach, however, recent evidence from leading authorities in this area, propose that	Thank you for your comment. The committee discussed the inclusion of a threshold to define a higher eosinophil count, but concluded that based on the evidence available it was not possible to define a specific threshold. In particular, they

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				response to inhaled corticosteroids is on a continuous scale according to blood eosinophil concentration. This means that it is not only those with higher blood eosinophils who will benefit; a patient with an intermediate blood eosinophil level will achieve an intermediate, and probably worthwhile response to inhaled corticosteroids. [1] What is meant by a *higher blood eosinophil count* is not defined for clinicians. Given that there is much debate on defining the optimal threshold for separation of high and low blood eosinophil counts,[2] reflecting the above evidence by Singh et al in your definition of *asthmatic features/features suggesting steroid responsiveness,* may be more useful to clinicians. [1] Singh et al. Am J Respir Crit Care Med, 2017; 196(9): 1098-1100 [2] Rabe et al. Eur Respir J, 2017; 50: 1702165	noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. However, the accompanying research recommendation to address which features predict inhaled corticosteroid responsiveness most accurately in people with COPD could provide information on this topic and help improve the definition of asthmatic features/features suggesting steroid responsiveness in future updates of the guideline.
Chiesi Ltd	Guideline & Guideline	45 & 8	5 & 5	A substantial variation in Forced Expiratory Volume in one second (FEV_1) over time is listed as a feature suggesting asthmatic features/steroid responsiveness. Whilst we do not disagree that this feature is suggestive of asthma, earlier comments within the guideline regarding reversibility testing (section 1.1.18) are contradictory to this point. Section 1.1.18 suggests that reversibility testing is not necessary as part of the diagnostic process or to plan initial therapy with bronchodilators or inhaled corticosteroids. However, the updated algorithm proposed in this guideline suggests the clinician must identify whether or not the patient has asthmatic features prior to selecting an initial therapy- with reversibility testing a method of determining this.	Thank you for your comment. The section on reversibility testing was not within the scope of this update and, as a result, the committee was unable to change this recommendation. However, the committee noted that the recommendation refers to the use of reversibility testing to plan initial bronchodilator therapy and that as they would expect this to be a short-acting bronchodilator this recommendation is still relevant. However, the recommendation does refer to 'most people' which implies that in some cases it will be appropriate to carry out routine spirometric reversibility testing. The committee envisage that the healthcare professional will be able to determine whether this is necessary and will not be confused by the differences between the 2 recommendations.
Novartis	Guideline	45	5	The definition of Asthmatic features / features suggesting steroid responsiveness could benefit from some clarifications:	Thank you for your comment. The committee discussed the inclusion of a threshold to define a higher eosinophil count,

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				• Definite cut offs are given for FEV1 and Peak flow. In our opinion '… a higher blood eosinophil count' is unclear without a definite cut-off level or comparator. Published studies support a cut-off level of ≥300 blood eosinophils/µL.[1,2,3] 1. Watz et al. Lancet Respir Med. 2016 May;4(5):390-8 2. Roche et al. Am J Respir Crit Care Med. 2017 May 1;195(9):1189-1197 3. Chapman et al. Am J Respir Crit Care Med. 2018 May 20. doi: 10.1164/rccm.201803-0405OC. • '… substantial variation in FEV1 over time (at least 400 ml)' - As far as we are aware, this is not a commonly used, or studied, measure in COPD or asthmatic patients and may not be necessarily related to steroid responsiveness. Some relevant references would provide some clarity and support for this recommendation.	but concluded that based on the evidence available it was not possible to define a specific threshold. In particular, they noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. However, the accompanying research recommendation to address which features predict inhaled corticosteroid responsiveness most accurately in people with COPD could provide information on this topic and help improve the definition of asthmatic features/features suggesting steroid responsiveness in future updates of the guideline. The variation of 400 ml in FEV1 has been used elsewhere in the COPD guideline, such as reversibility testing. The committee were confident that this variation was greater than any natural variations that could be expected and therefore an appropriate cut-off point to use when defining asthmatic features and features suggesting steroid responsiveness.
Boehringer-Ingelheim Ltd	Guideline	45	5	BI recommends that the wording is changed to 'ICS responsiveness'. It is unclear whether in 'Asthmatic features/features suggesting steroid responsiveness', that 'a higher blood eosinophil count' is considered to be an asthmatic feature in COPD, or a feature suggesting steroid responsiveness in COPD. If it is considered an 'asthmatic feature', it should be implemented into the asthma diagnosis section 1.1.21.	Thank you for your comment. The committee have decided to keep the existing wording because they think that this provides more information to the healthcare professional than just using the term ''ICS responsiveness'. The committee intended the definition of asthmatic features/features suggesting steroid responsiveness to cover both people with a secure diagnosis of asthma and those who do not have asthma, but who are steroid responsive. A higher eosinophil count was included to help identify the latter group of people and it was therefore unnecessary to amend the asthma diagnosis section. In addition, the asthma diagnosis section was not within the scope of this update.
Boehringer-Ingelheim Ltd	Guideline	45	6	NICE defines the term 'Asthmatic features' as 'features suggesting steroid responsiveness' in this context, including any previous secure diagnosis of asthma or atopy, a higher blood eosinophil	Thank you for your comment. The committee recognised that in some cases, asthma may have been incorrectly diagnosed and they chose to state that a 'secure diagnosis of asthma' was required to prompt the healthcare professional to think

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				count, substantial variation in FEV1 over time (at least 400mL) or substantial diurnal variation in peak expiratory flow (at least 20%)'. - Historically, there has been a difficulty in differential diagnosis between COPD and asthma: we would not consider it sufficient for there to be a diagnosis on the patient record that may well have been made a long time ago or by a different healthcare professional, instead we would urge that patients with a historical diagnosis of asthma who are diagnosed with COPD have their asthma re-reviewed to either confirm or rule out the original diagnosis. In a very recent study, looking at quantifying concomitant diagnosis of asthma and COPD in the UK (Nissen et al. 2018, British Journal of General Practice, Accepted for publication), asthma diagnosis was shown to be over-recorded in COPD patients. More than half (52.5%) of validated COPD patients had ever received a diagnostic asthma read code. However, when considering additional evidence to support a diagnosis of asthma, concurrent asthma was only likely in 14.5% of validated COPD patients. - We recommend removing the term 'Asthmatic features' from the guideline as we believe this adds to the uncertainty between asthma and COPD diagnosis, and will ultimately result in many patients inappropriately treated with ICS/LABA/LAMA. Instead, we propose that ICS should be considered for patients already on LAMA/LABA, who exhibit 'ICS responsiveness'. This could include blood eosinophils ≥300cells/μL plus increased moderate/severe COPD exacerbations.	about their confidence in the diagnosis as part of the decision making process. The committee have decided to keep the existing wording because they think that this provides more information to the healthcare professional than just using the term ''ICS responsiveness'. They were unable to look at the evidence for triple therapy as this was not within the scope of this update and as a result, the existing triple therapy recommendation was retained. However, this topic will be updated in the near future and the committee will be able to examine which groups of people will benefit from this treatment.
Boehringer-Ingelheim Ltd	Guideline	45	6	The definition of the term 'Asthmatic features/features suggesting steroid responsiveness' includes a higher blood eosinophil count. The guideline suggests patients with a higher eosinophil level could be treated with LABA/ICS rather than LAMA/LABA first line.	Thank you for your comment. 1) The committee discussed the inclusion of a threshold to define a higher eosinophil count, but concluded that based on

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				1) Higher eosinophil level. There is no further guidance about what the definition of 'higher blood eosinophil count' is and this could therefore be open to interpretation. Blood eosinophils may be higher in COPD than in the general population and may also be higher during infection or exacerbations of COPD. The median blood eosinophil count was 180 cells/µl in a real world cohort (Vedel-Krogh et al. 2016 Am J Respir Crit Care Med 193(9): 965-74), a finding also replicated in the FLAME study (Wedzicha et al. 2016 N Engl J Med 374(23): 2222-34). This is important to keep in mind when determining an ICS-responsive level, or "higher" blood eosinophil count in COPD. **2)** Stability of eosinophils. There is currently no recommendation about how many blood eosinophil counts should be taken. There is paucity of data in the literature regarding the repeatability/stability of blood eosinophils in COPD patients. Fluctuation of blood eosinophil levels in COPD has been reported (Singh et al 2014, Eur Respir J 44(6): 1697-700) in a *post-hoc* analysis of the 3 year ECLIPSE study. Blood eosinophilia (defined by 2% cut-off) was persistently "high" at all visits in 37% of patients, persistently "low" in 14% and 49% of patients had blood eosinophil counts that oscillated above and below 2%. Another study using data from two COPD patient cohorts and cut off of 300 cells/µl also showed similar results, where 44% oscillated above and below (Casanova, Eur Respir J 50(5)). It would be useful to include repeated measures of blood eosinophil counts and not base decisions on a single, historical reading, where most patients may have a "higher blood eosinophil" at some point over time, depending on the cut-off level	the evidence available it was not possible to define a specific threshold. In particular, they noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. However, the accompanying research recommendation to address which features predict inhaled corticosteroid responsiveness most accurately in people with COPD could provide information on this topic and help improve the definition of asthmatic features/features suggesting steroid responsiveness in future updates of the guideline. 2) The committee were also unable to include any details about how many blood eosinophil counts should be taken as they did not review the evidence for repeated measures versus single measures. 3) Thank you for your support for the inclusion of eosinophils as a biomarker for ICS responsiveness. As discussed above, the committee were unable to specify a threshold, but they did envisage that higher eosinophil levels would be taken into account with other factors included in the definition before a decision was made to begin treatment with LABA+ ICS. In addition, the committee explicitly recognised the shortage of evidence to determine which people will exhibit steroid responsiveness. They included a research recommendation to address which features predict inhaled corticosteroid responsiveness most accurately in people with COPD in the hope that this could provide information on this topic and help ensure that LABA+ICS is prescribed to the specific people who are able to gain benefit from the ICS component. The committee was unable assess the effectiveness of the addition of ICS to LAMA+ LABA as triple therapy was not in the scope of this update and no evidence for triple therapy

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				used. One real world study recommended a minimum of two blood eosinophil counts to determine the eosinophilic status of COPD patients, and that these should be interpreted in context (Hamad et al. Eur Respir J 2018; 51: 1702177). Finally, a recent UK database study showed that among a total of 5,871 patients with at least three eosinophil measurements during follow-up, for patients whose first measurement was in the ≥ 300 cells/μL threshold, the proportion that remained ≥ 300 cells/μL was lower than 68% (Landis et al. 2017 COPD 14(4): 382-388). It would be useful to include repeated measures of blood eosinophil counts and not base decisions on a single, historical reading. We recommend that blood eosinophils are measured at least during each recommend annual (or bi-annual) review, if this is to be included as a biomarker for ICS treatment. It is also important to note that blood eosinophil counts should be taken in context e.g. during exacerbations, effect by ICS/OCS usage, etc. **3)** Evidence base for eosinophil as biomarker: BI are supportive of the inclusion of eosinophils as a biomarker for ICS responsiveness. However, we would like to highlight, that to our knowledge, there is currently no evidence to support the use of LABA/ICS over LAMA/LABA in patients with raised eosinophil levels. There are post-hoc analyses that suggest: - Patients with higher blood eosinophils experienced reduced exacerbations when treated with LABA/ICS vs. LABA monotherapy. A cut off of 2% blood eosinophils was	versus dual therapy was examined. However, the triple therapy recommendations are due to be updated in the near future and the committee will be able to look at the characteristics of people who show benefit with triple therapy versus dual therapy with LAMA+ LABA in this trials. 4) Thank you for this information. As discussed above, the committee were unable to specify a threshold for higher eosinophil counts. However, they envisaged that the majority of people with COPD would be offered LAMA+LABA rather than LABA+ICS as a first line long-acting inhaled therapy. The committee was unable to alter the existing triple therapy recommendation as triple therapy was not in the scope of this update. However, they will be able to examine the evidence for triple therapy versus dual therapy soon. The committee agree with the stakeholder that patients should be stratified appropriately in order to reduce the inappropriate long term use of ICS. In addition, this will ensure that people with COPD receive the most clinical and cost-effective inhaled therapy based on the analysis carried out in this update (LAMA+LABA), unless they are steroid responsive in which case LABA+ICS should be considered.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				used, but further analysis demonstrated that in patients treated with LABA alone, exacerbation rates increased progressively with increasing eosinophil count percentage category. This effect was driven by the patients with the higher blood eosinophil counts (Pascoe et al. 2016 Lancet Respir Med 3(6): 435-42) - Higher blood eosinophil counts, together with frequent exacerbations, may identify patients who could experience an incremental reduction in exacerbation risk when receiving ICS on top of LAMA/LABA. Data from the WISDOM and SUNSET study suggest that a blood eosinophil count of greater than or equal to 4% or 300 cells/μL could be a predictive biomarker of inhaled corticosteroid efficacy. There was no difference in exacerbation rates in patients with ≤ 150 cells/μL or 2% blood eosinophils (Magnussen et al. 2014 N Engl J Med 371(14): 1285-94, Calverley et al. 2017 Am J Respir Crit Care Med 196(9): 1219-1221, Watz et al 2016 Lancet Respir Med 4(5): 390-8, Chapman et al. 2018. Am J Respir Crit Care Med 198(3): 329-339). - It is important to note that in a prospective evaluation of FLAME, comparing LABA/ICS and LAMA/LABA, LABA/ICS did not show superiority over LAMA/LABA in reducing exacerbations in any of the analysed eosinophil thresholds (Wedzicha et al. 2016 N Engl J Med 374(23): 2222-34). - BI recommend eosinophils are used as a biomarker for ICS responsiveness in patients already on a LAMA/LABA, as opposed to being used as a biomarker when choosing between LAMA/LABA and LABA/ICS. As per the evidence base, we would encourage a cut off of 300 cells/μL or 4% with at least one exacerbation in the previous year. - We support ICS as a consideration for patients who may be 'ICS responsive', rather than offering to all patients with	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				high blood eosinophils. There is increasing discussion about 'treatable traits' (Agusti et al. 2016 Eur Respir J 47(2): 410-9) and 'exacerbation phenotypes' (Bafadhel et al. 2011 AmJ Respir Care Med 184(6): 662-71). If the eosinophils are not driving the symptoms and exacerbations, ICS is unlikely to be effective. **4)** Eosinophil cut off of 150 cells/µL vs. 300 cells/µL. There is no blood eosinophil cut off currently included in the recommendations. We recommend ICS to be considered if a patient has blood eosinophils ≥ 4% or 300 cells/µL,as opposed to 150 cells/µL or 2%, to ensure we maintain a risk benefit analysis of ICS. - BI acknowledges that some COPD patients will have ICS-responsive disease but fundamentally COPD is a neutrophilic airway disease, whereby ICS may have detrimental effects. - We believe that if a low cut off value of 150 cells/µL were used, the risk benefit analyses would not be in favour of ICS treatment. The risks associated with ICS, such as; adrenal suppression, increased incidence of diabetes, poorer control of type 2 diabetes, osteoporosis and pneumonia (Suissa et al. 2013Thorax 68(11): 1029-36, Suissa et al. 2009 Eur Respir J 34(1): 13-6) will be present, potentially without efficacy for COPD outcomes (as described above). It is estimated that approximately two thirds of the COPD population have blood eosinophils above 150 cells/µL (Mullerova et al. 2017. ERS International Congress, poster number PA3584) or ≥2% (Vedel-Krogh et al. 2016 Am J Respir Crti Care Med 193(9): 965-74). This could mean that if "asthmatic features" is interpreted as patients with blood eosinophils above 2% or 150 cells/µL at some point in history then the majority of COPD patients would be eligible for ICS.	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				Furthermore, "person still breathless" could mean short escalation to triple therapy. ICS are already overused in the UK COPD population (White et al. 2013 PloS One 8(10)), and we believe this lack of clarity will further perpetuate the problem. - A "higher eosinophil" cut-off commonly put forward in GSK studies is 150 cells/µl at screening or 300 cells/µl in the past twelve months; however, the anti-eosinophilic drug, mepolizumab, was recently reviewed by the PADAC of the US FDA. The committee considered that there was not substantial evidence of the efficacy when using this cut-off of "high" blood eosinophil levels. The FDA queried whether or not 150cells/µl was actually the right cut off point for this population (https://www.gsk.com/en-gb/media/press-releases/gsk-reports-on-outcome-of-the-fda-advisory-committee-on-mepolizumab-for-the-treatment-of-copd-patients-on-maximum-inhaled-therapy, https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM614138.pdf) - In contrast, using an eosinophil cut-off level of 300cells/µl (or 4%) derived from *post-hoc* analyses of randomised controlled trials (WISDOM, SUNSET, FORWARD), approximately 20% of the COPD population may be eligible for ICS use (Magnussen et al. 2014 N Engl J Med 371(14)). Patients would need to be assessed on an individual basis, but the evidence suggests that the risk benefit analysis is more likely to be in favour of ICS. We believe it is imperative for NICE to include a threshold for "higher eosinophil count" of ≥ 300cells/µL, plus an exacerbation history, with reference to the current clinical and real world evidences, to ensure that the guidance is not misinterpreted.	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				Patients should be stratified appropriately in order to reduce the inappropriate long term use of ICS.	
Royal Free London NHS Foundation Trust	Guideline	45	7	'higher' eosinophil count is not adequately defined. This should include a cut-off to be of any practical use.	Thank you for your comment. The committee discussed the inclusion of a threshold to define a higher eosinophil count, but concluded that based on the evidence available it was not possible to define a specific threshold. In particular, they noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. However, the accompanying research recommendation to address which features predict inhaled corticosteroid responsiveness most accurately in people with COPD could provide information on this topic and help improve the definition of asthmatic features/features suggesting steroid responsiveness in future updates of the guideline.
Boehringer-Ingelheim Ltd	Guideline	45	7	NICE defines the term 'Asthmatic features' as 'features suggesting steroid responsiveness' in this context, including any previous secure diagnosis of asthma or atopy, a higher blood eosinophil count, substantial variation in FEV1 over time (at least 400mL) or substantial diurnal variation in peak expiratory flow (at least 20%)'. BI recommend that the definition of variation in FEV_1 should include a relevant timeframe that can be implemented in a usual care setting. Evidence suggests that COPD reviews would be an ideal setting; however, more research is needed in variation in lung function as measured in a usual care setting. A patient with COPD could be expected to lose 400mL of lung function over a 10 year period, which will become apparent in a patient's case history. Indeed, it may be important to further emphasise the 'over 400 ml': in clinical studies with LAMA/LABA combinations, we have seen improvements in peak FEV_1 that approach and exceed 300 ml vs placebo and may also be considered a large response by clinicians.	Thank you for your comment. The committee intended the definition of asthmatic features/features suggesting steroid responsiveness to cover both people with a secure diagnosis of asthma and those who do not have asthma, but who are steroid responsive. The description of this term is intended to help clarify the people who are expected to be steroid responsive. The committee decided that it was not possible for them to recommend a relevant time frame for defining the variation in FEV1 based on the evidence available, however, they did envisage that the change in FEV1 would be over a much shorter time frame than a period of years. They included a research recommendation to help determine the characteristics of people with COPD who are steroid responsive to help address some of the uncertainty surrounding their definition of this group of people.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				(Singh, D. et al. 2015 RespirMed 109(10): 1312-9(OTEMTO), Bateman, E. et al, 2013 Eur Respir J 42(6): 1484-94(SHINE)).	
Boehringer-Ingelheim Ltd	Guideline	45	8	NICE defines the term 'Asthmatic features' as 'features suggesting steroid responsiveness' in this context, including any previous secure diagnosis of asthma or atopy, a higher blood eosinophil count, substantial variation in FEV1 over time (at least 400mL) or substantial diurnal variation in peak expiratory flow (at least 20%)'. BI recommend that the definition of substantial diurnal variation in peak expiratory flow should include relevant timeframes also reflecting feasibility of monitoring changes.	Thank you for your comment. The committee intended the definition of asthmatic features/features suggesting steroid responsiveness to cover both people with a secure diagnosis of asthma and those who do not have asthma, but who are steroid responsive. The description of this term is intended to help clarify the people who are expected to be steroid responsive. The committee decided that it was not possible for them to recommend a relevant time frame for defining the variation in peak expiratory flow based on the evidence available. However, they included a research recommendation to help determine the characteristics of people with COPD who are steroid responsive to help address some of the uncertainty surrounding their definition of this group of people.
Primary Care Respiratory Society	Guideline	45	24	Did the large study that was stopped early due to excess mortality in the early rehab group published in the BMJ not answer this? Is it ethical? Greening NJ, Williams JEA, Hussain SF, Harvey-Dunstan TC, Bankart MJ, Chaplin EJ, et al. An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. British Medical Journal. 2014;349	The committee were aware of the findings of this trial, but concluded that the research recommendation should stand. They noted that the people in the early rehabilitation group received an exercise intervention but, as noted by the authors of the study itself, this intervention was not the same as pulmonary rehabilitation in content or duration. As such, the committee decided that the existing trial did not address this question and so the research recommendation was still relevant.
NHS England	Guideline	45	24	We thought the large study that was stopped early due to excess mortality in the early rehab group published in the BMJ answered this? Is it ethical? Greening NJ, Williams JEA, Hussain SF, Harvey-Dunstan TC, Bankart MJ, Chaplin EJ, et al. An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of	The committee were aware of the findings of this trial, but concluded that the research recommendation should stand. They noted that the people in the early rehabilitation group received an exercise intervention but, as noted by the authors of the study itself, this intervention was not the same as pulmonary rehabilitation in content or duration. As such,

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				chronic respiratory disease: randomised controlled trial. British Medical Journal. 2014;349 (CRG)	the committee decided that the existing trial did not address this question and so the research recommendation was still relevant.
AstraZeneca UK	Guideline	45	5,6,7,8	AstraZeneca does not consider the way in which the criteria for asthmatic features and responsiveness to steroids are presented to be clear. In addition, we believe that a specific value for the higher blood eosinophil count should be indicated within these criteria. Therefore, we suggest the following wording: Asthmatic features/features suggesting steroid responsiveness – The patient must have at least one of the below features: • any previous, secure diagnosis of asthma or of atopy, • or a higher blood eosinophil count (eosinophil count > 0.10 x 10^9 cells/L and upwards), • or a substantial variation in FEV1 over time (at least 400 ml) • or substantial diurnal variation in peak expiratory flow (at least 20%). Rationale for changed wording: We believe that each of the above features indicates responsiveness to steroids and allows clinicians to identify which of the two groups a patient belongs to. It is important to consider that these features are not fixed and can vary over time, so a patient *not responsive* to steroids could become *responsive* over time. This suggestion is based on the premise that the diagnosis of asthma and potential inhaled cortico-steroid (ICS) responsiveness are not mutually interchangeable. In fact, the blood eosinophil count can predict responsiveness to steroids whether or not the patient has typical asthma characteristics or an asthma diagnosis. The identification of COPD patients who are most likely to respond to ICS is extremely important to ensure that the right drug is given to	Thank you for your comment. The committee discussed the inclusion of a threshold to define a higher eosinophil count, but concluded that based on the evidence available it was not possible to define a specific threshold or to decide whether single or repeated measurement of eosinophils should be carried out. In particular, they noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. The other bullets listed are identical to the ones already included in the existing definition. The committee agreed that patients' responses to medication, including steroid responsiveness, may change over time and that this might necessitate a corresponding change in inhaled therapy. However, they decided that the regular review of medication was covered in the summary of follow-up of people with COPD in primary care table and did not make a separate recommendation. The committee agreed with this point and the wording of the existing definition is intended to include both people with a secure diagnosis of asthma and those without this, but who are steroid responsive. Thank you for this information. The committee agreed that it was important to be able to identify people who are steroid responsive to ensure that they receive the most effective medication for them. They wrote a research recommendation to address which features predict inhaled corticosteroid responsiveness most accurately in people with COPD

				the right patients[2] and to contribute to personalised approaches to care[3]. Rationale for the specific value for EOS count (> 0.10 x 10^9 cells/L and upwards) The peripheral blood eosinophil count has been suggested to help identify those patients who will experience fewer exacerbations when taking an ICS containing therapy[3]. Therefore, we want to highlight this characteristic as particularly important for the identification of patients, who are responsive to steroids. In the study by Bafadhel et al, the treatment effect of an ICS/LABA (budesonide/formoterol 200/6 µg) vs a LABA (formoterol 6µg) alone, was analysed and compared to the blood eosinophil count as a continuous variable[3]. The post hoc analysis showed that the eosinophil count at randomisation predicted the exacerbation rate reduction treatment effect difference between ICS/LABA and LABA in a non-linear fashion, and was significant from a minimum eosinophil count of 0.10 x 10^9 cells/L and upward[3]. In addition, the relationship varied depending on the clinical outcome examined[3]. A significant difference in mean FEV1 of 32 mL occurred with ICS/LABA vs LABA at a blood eosinophil count of 0.22 x 10^9 cells/L, and a clinically important treatment difference in mean FEV1 of ≥50 mL was seen at eosinophil counts >0.27 x 10^9 cells/L[3]. Significant improvements in QoL (SGRQ change >4) were only observed in patients with higher eosinophil counts[3]. On the basis of this data, although the benefits in outcomes increase when patients with progressively higher blood eosinophil counts are treated with ICA/LABA vs LABA, significant improvements have been observed in patients with a blood eosinophil counts > 0.10 x 10^9 cells/L[3].	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				The role of a high blood eosinophil count in the responsiveness to steroids and in the exacerbations frequency is supported by the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines as well[4]. GOLD is suggesting that the treatment effect of ICS/LABA versus LABA on exacerbations is greater in patients with higher blood eosinophil counts. These findings suggest that blood eosinophil counts can be 1) a biomarker of exacerbation risk in patients with a history of exacerbations and 2) can predict the effects of ICS on exacerbation prevention. Moreover, the post-hoc analysis of two clinical trials has reported that the effects of ICS on exacerbation prevention are associated with blood eosinophil counts[5,6]. In addition, one large COPD cohort study showed an association between higher blood eosinophil counts and increased exacerbation frequency[7], although this was not observed in a different cohort[8]. Differences between studies may be related to different previous exacerbation histories and ICS use.	
Primary Care Respiratory Society	Guideline	46	10	Our understanding is that this has been fairly well analysed already with the work producing BODE and DOSE. DOSE is suitable for primary care use – and indeed was developed in the UK. The DOSE index has been shown to be better than its component items in primary care in UK and in International studies. (Jones R. AJRCCM 2009 180: 1189–1195) It has been shown to be better than its component items and predicting mortality. (Sundh Primary Care Respiratory Journal volume 21, pages 295–301 (2012) Jones RC, Donaldson GC, Chavannes NH, Kida K, Dickson-Spillmann M, Harding S, et al. Derivation and Validation of a Composite Index of Severity in Chronic Obstructive Pulmonary Disease: The DOSE Index. Am J Respir Crit Care Med. 2009;180(12):1189-95 . Celli B, Cote C, Marin J, CCasanova, Oca MMd, Mendez R, et al. The bodymass index, airflow obstruction, dyspnea, and exercise	Thank you for your comment. The committee did note the discrimination of the DOSE and BODE indices, and noted that in situations where other prognostic indices were not available, this may have performed well enough to be recommended. However, they concluded that none of the indices looked at (including BODE DOSE) had properties that were sufficiently better than FEV1 alone as a measure of prognosis, and therefore it was not appropriate to recommend their use.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:1005	
NHS England	Guideline	46	10	We thought this has been fairly well analysed already with the work producing BODE and DOSE. DOSE is suitable for primary care use – and indeed was developed in the UK Jones RC, Donaldson GC, Chavannes NH, Kida K, Dickson-Spillmann M, Harding S, et al. Derivation and Validation of a Composite Index of Severity in Chronic Obstructive Pulmonary Disease: The DOSE Index. Am J Respir Crit Care Med. 2009;180(12):1189-95. Celli B, Cote C, Marin J, CCasanova, Oca MMd, Mendez R, et al. The bodymass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:1005. (CRG)	Thank you for your comment. The committee did note the discrimination of the DOSE and BODE indices, and noted that in situations where other prognostic indices were not available, this may have performed well enough to be recommended. However, they concluded that none of the indices looked at (including BODE DOSE) had properties that were sufficiently better than FEV1 alone as a measure of prognosis, and therefore it was not appropriate to recommend their use.
UK Clinical Pharmacy Association	Guideline	46	28	Corticosteroids is spelt incorrectly	Thank you for pointing this out – this has now been corrected.
Chiesi Ltd	Guideline	47	1	The guideline suggests that there is lack of evidence concerning treatments for the subgroup of patients with COPD who also have asthma. The IMPACT trial[1] compared single inhaler triple therapy (fluticasone furoate/umeclidinium/vilanterol) with both an ICS/LABA (fluticasone furoate/vilanterol) and a LAMA/LABA (umeclidinium/vilanterol). This trial does not reference the exclusion of asthma patients. The IMPACT study showed beneficial effects in exacerbation reduction, improvement in mean SGRQ total score and improvement from baseline in trough FEV_1 with single inhaler triple	Thank you for your comment. The majority of trials included in the inhaled therapy combinations review excluded people with COPD and comorbid asthma. The IMPACT trial was not included in the evidence review as it was published after the last search date for this review (March 2018). NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				therapy compared to the both the dual bronchodilator and the ICS/LABA. [1] [1] Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680	appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
Chiesi Ltd	Guideline	47	21	We agree that people with COPD commonly experience exacerbations which have a negative impact on their quality of life and which are linked to worse disease progression. It is for this reason that the place of ICS-containing therapies should be re-considered within the treatment algorithm. Limiting these therapies to those with asthmatic features only and not allowing frequent exacerbators to access these treatments could have serious cost implications for the NHS in respect to their treatment failure or hospitalisation. A strong evidence base from recent studies supports the efficacy and safety of triple therapy over and above both single and double therapy for the reduction of exacerbations: <u>Triple therapy versus LAMA:</u> • TRINITY study: Vestbo et al. Lancet, 2017; 389(10082): 1919-1929 <u>Triple therapy versus ICS/LABA:</u> • TRILOGY study: Singh et al. Lancet, 2016; 388(10048): 963-973 • IMPACT study: Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680 • FULFIL study: Lipson et al. Am J Respir Crit Care Med, 2017; 196(4):438-446 <u>Triple therapy versus LABA/LAMA:</u>	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs (including those you cite) it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				• TRIBUTE study: Papi et al. Lancet, 2018; 391(10125): 1076-1084 • IMPACT study: Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680	
Chiesi Ltd	Guideline	48	8	*Inhaled therapy: triple therapy* has been suggested as an area for future research. The question has been posed whether triple therapy improves outcomes when compared with single or double therapy. A strong evidence base already exists from recent studies to answer this question, and prove the efficacy and safety of single inhaler triple therapy against both single and double therapy: <u>Triple therapy versus LAMA:</u> • TRINITY study: Vestbo et al. Lancet, 2017; 389(10082): 1919-1929 <u>Triple therapy versus ICS/LABA:</u> • TRILOGY study: Singh et al. Lancet, 2016; 388(10048): 963-973 • IMPACT study: Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680 • FULFIL study: Lipson et al. Am J Respir Crit Care Med, 2017; 196(4):438-446 <u>Triple therapy versus LABA/LAMA:</u> • TRIBUTE study: Papi et al. Lancet, 2018; 391(10125): 1076-1084 • IMPACT study: Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680 These studies should be included in the evidence base and taken into consideration when recommending management pathways for inhaled therapy for COPD patients. The proposed update to the treatment algorithm has been made without considering the entirety of the evidence available.	Thank you for your comments. NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs (including those you cite) it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

NHS England	Guideline	49	8-10	If cxr is so accurate as suggested why can the diagnosis not be made on a chest xray – this may confuse clinicians. (My experience on cxr reporting suggestive of COPD over the last 5 years from 4 hospitals – n=42 – 70% had normal spirometry (10% mild, 12% moderate, 2% severe obstruction). Similarly, increasingly we find people with normal spirometry but CT evidence of emphysema – suggest this is rephrased. The evidence base seems to be relying on a computerised system for assessing on Cxr which I am not sure is being used widely hence should this be specified. (CRG)	Thank you for your comment. The committee intended these recommendations to cover situations where incidental CT scans or chest X-rays indicate the potential signs of COPD or emphysema. They did not recommend that diagnosis be based on these findings alone because there will be people who show these signs, but lack any symptoms and have normal spirometry results. The committee concluded that it is important to avoid diagnosing people with COPD until they show symptoms and have abnormal spirometry as, once diagnosed, they may be started on unnecessary medication otherwise. In addition, if a primary care respiratory review is undertaken, this may enable the patient to make lifestyle changes, such as stopping smoking, which could improve their prognosis. The section of the guideline covering diagnosis was outside of the scope of this update, apart from this review question, and as a result, the committee could not make/amend any recommendations. However, the committee agreed that CT scans or chest X-rays were not viable options for primary diagnosis of COPD due to cost and availability issues. They also recognised that the evidence for chest X –rays involved computerised systems that aren't widely available in clinical practice, but concluded that a radiologist would be able to detect the signs of emphysema or signs of chronic airways disease and could respond appropriately.
NHS England	Guideline	50	10	"There may be a small number of additional referrals for spirometry, but this is expected to have a minimal resource impact." - any small impact could be significant in a primary care workforce struggling with workload, recruitment & retention issues.	Thank you for your comment. We have passed this information on to our resource impact team, for consideration as part of the work they will be producing alongside the guideline.
Chiesi Ltd	Guideline &	51	13	It is stated that the committee have recommended LAMA+LABA over other dual combinations because its provides the greatest benefit to overall quality of life, better on many individual outcomes	Thank you for your comments. As stated, evidence review F provides a pair-wise analysis of LABA/LAMA versus LABA/ICS. In the description of the results of this analysis,

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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	Evidence F	23	17	(e.g. moderate-to-severe exacerbations) and is the most cost-effective option. Evidence review F provides a pair-wise analysis of LABA/LAMA versus LABA/ICS. In this analysis: • It is stated that there is no meaningful difference in Transition Dyspnoea Index (TDI) score or quality of life measured by SGRQ • The evidence was conflicting with regards to FEV_1 • It is stated that the evidence was not able to differentiate between the treatments with regards to severe exacerbations There is no mention at all of moderate-to-severe exacerbations, so conclusions on this point should not have been drawn. The evidence summarised in the pair-wise analysis of LABA/LAMA versus LABA/ICS does not support the recommendations made on inhaled combination therapy in the guideline. Furthermore, studies examining the place of ICS+LABA+LAMA have not been included in this review, despite a large body of evidence currently available to support their place in the COPD treatment pathway: <u>Triple therapy versus LAMA:</u> • TRINITY study: Vestbo et al. Lancet, 2017; 389(10082): 1919-1929 <u>Triple therapy versus ICS/LABA:</u> • TRILOGY study: Singh et al. Lancet, 2016; 388(10048): 963-973 • IMPACT study: Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680	moderate to severe exacerbations are mentioned in the following evidence statement: very low to high quality evidence from up to 9 RCTs with up to 8,796 people found no meaningful difference in the change in FEV1 at 12 months; TDI score at 3 and 6 months; SGRQ score at 3, 6 and 12 months; the numbers of SGRQ responders at 3 and 12 months; or in the numbers of people experiencing moderate to severe exacerbations and SAEs in people offered LAMA/LABA compared to LABA/ICS. The conclusion that LABA/LAMA is more clinically and cost-effective than LABA/ICS is based on the results of the network meta-analyses conducted, and an economic model that combined the effects of each treatment across the multiple outcome domains to examine overall quality of life. From the network meta-analysis of moderate to severe exacerbations, in people with a previous exacerbation in the last year (high risk group) LABA/LAMA showed improvements compared to LABA/ICS, but these were less than the minimal important difference used for RR of 0.8 and 1.25. The committee noted that the minimal important difference for RRs was defined based on statistical measures rather than by reference to clinical trials of this outcome and that the minimal important differences were developed to assess whether an active treatment was superior to a placebo treatment, rather than to compare active treatments. As a result, use of these minimal important differences may underestimate the difference in effect between treatments. To overcome these issue, the committee concluded therefore that it was important not to consider these individual outcomes in isolation, but to consider the overall impact on quality of life, as estimated in the economic model. The results of this model showed that dual therapy was more effective than monotherapy and that LAMA/LABA was more cost-effective than LABA/ICS.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				• FULFIL study: Lipson et al. Am J Respir Crit Care Med, 2017; 196(4):438-446 <u>Triple therapy versus LABA/LAMA:</u> • TRIBUTE study: Papi et al. Lancet, 2018; 391(10125): 1076-1084 • IMPACT study: Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680	NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
Primary Care Respiratory Society	Guideline	51	20	In later rationale section it's mentioned that no LAMA is superior in efficacy – should it therefore clarify the MHRA reference on cardiac disease in terms of side effects? Also did the group have views on the LABA used – as this is not clear	Thank you for your comment. The MHRA advice states that the risk of cardiovascular side effects should be taken into account when prescribing tiotropium to people with certain cardiac conditions. This should not be taken to automatically mean that other LAMAs are safer for this group of people, but that there is no MHRA advice pertaining to the other LAMAs with regards to people at risk of cardiac events. The summary of product characteristics for all of available LAMAs contain warnings about prescribing these drugs for use in patients with certain cardiac conditions. The committee did not examine the evidence for the comparative effectiveness of LABAs as this was not within the scope of this update. As a result, the committee is unable to recommend one LABA over another.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

NHS England	Guideline	51	20	Mentioned that no LAMA is superior – should it therefore clarify the MHRA reference on cardiac disease. Also did the group have views on the LABA used – as this is not clear. (CRG)	Thank you for your comment. The MHRA advice states that the risk of cardiovascular side effects should be taken into account when prescribing tiotropium to people with certain cardiac conditions. This should not be taken to automatically mean that other LAMAs are safer for this group of people, but that there is no MHRA advice pertaining to the other LAMAs with regards to people at risk of cardiac events. The summary of product characteristics for all of available LAMAs contain warnings about prescribing these drugs for use in patients with certain cardiac conditions. The committee did not examine the evidence for the comparative effectiveness of LABAs as this was not within the scope of this update. As a result, the committee is unable to recommend one LABA over another.
Chiesi Ltd	Guideline	51	26	The guideline states that most trials specifically excluded people with both COPD and asthma, so there was no direct evidence for this group. The IMPACT trial[1] compared single inhaler triple therapy (fluticasone furoate/umeclidinium/vilanterol) with both an ICS/LABA (fluticasone furoate/vilanterol) and a LAMA/LABA (umeclidinium/vilanterol). This trial does not reference the exclusion of asthma patients. The IMPACT study showed beneficial effects in exacerbation reduction, improvement in mean SGRQ total score and improvement from baseline in trough FEV_1 with single inhaler triple therapy compared to the both the dual bronchodilator and the ICS/LABA. [1] [1] Lipson et al. N Engl J Med, 2018; 378(18): 1671-1680	Thank you for your comment. The majority of trials included in the inhaled therapy combinations review excluded people with COPD and comorbid asthma. The IMPACT trial was not included in the evidence review as it was published after the last search date for this review (March 2018). NICE has noted the number of stakeholders who have raised the issue of triple therapy as an important one to consider within the guideline. At the time this update to the guideline was scoped, it was agreed there was insufficient new evidence on triple therapy to justify updating this part of the guideline. However, with the recent publication of a number of large new RCTs it has now been agreed that it is appropriate for the triple therapy part of the guideline to also be updated. A separate update of the triple therapy recommendations in the guideline has therefore been commissioned and is currently underway. The new recommendations from this update do not currently appear in the guideline, but a

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

					separate public consultation on those recommendations will be conducted, after which they will be incorporated in to the guideline, pathway and treatment algorithm.
Teva UK	Guideline	51	13–19	These statements concern the comparison of the following two treatment strategies: LAMA to LAMA+LABA – start treatment on LAMA, and step up to LAMA+LABA if required LAMA+LABA combination – start treatment on LAMA+LABA without first prescribing a monotherapy The CEA considers three options: • A in which treatment-specific differences in adverse events and mortality are excluded • B in which treatment-specific differences in adverse events but not mortality are included • C in which treatment-specific differences in adverse events and mortality are included This approach was used because of uncertainty regarding the impact of treatment on AEs and mortality. We have concerns with these three conclusions, as discussed below. "LAMA+LABA provides the greatest benefit to overall quality of life" This statement is based on the results of the CEA which showed the gain in QALY for LAMA+LABA vs LAMA to LAMA+LABA was 0.08 in the base case option A and ranged between 0.073 and 0.11 for the overall population (options A–C), 0.09 to 0.13 in the high-risk population and from –0.03 to 0.07 in the low-risk population. This suggests that the benefit in terms in QALY is greater in patients with high-risk disease, as would be expected, and that low-risk patients may not experience a greater HRQoL benefit with LAMA+LABA, especially when effects on AEs and mortality are included.	Thank you for your comment. To address your points in order: *"This suggests that the benefit in terms in QALY is greater in patients with high-risk disease, as would be expected, and that low-risk patients may not experience a greater HRQoL benefit with LAMA+LABA…"* – Results of the economic model showed that LAMA+LABA has a higher probability of being cost-effective in the high-risk population. However, LAMA+LABA still has the highest probability of being cost effective in the low-risk subgroup for option A (the scenario which the committee found the most plausible). Moreover, the recommendation for LAMA+LABA relates to patients who remain breathless or have exacerbations despite using a short-acting bronchodilator. Therefore, the population offered a LAMA+LABA is, by definition, more akin to the high-risk population (since this group is defined as patients with 1 or more exacerbations in the year before trial entry), so it is likely that LAMA+LABA is more cost-effective than in the model base case. *"A further consideration is the choice of utilities and disutilities used in the model. Utilities for GOLD stages were derived from mapping from the SGRQ to EQ-5D using data from a study of COPD patients in primary care, i.e. not from studies of the interventions of interest"* – The NICE Methods Manual states that mapping of utilities can be undertaken when suitable EQ-5D data are not available. As a rule, we preferred to use observational sources to inform baseline and natural history model inputs, since these relate to patients in

				A further consideration is the choice of utilities and disutilities used in the model. Utilities for GOLD stages were derived from mapping from the SGRQ to EQ-5D using data from a study of COPD patients in primary care, i.e. not from studies of the interventions of interest. Values ranged from 0.55 to 0.78. Utilities from a second study were used in a sensitivity analysis but were considered by the NICE committee not to reflect the differences in HRQoL between GOLD stages. The range of these values was from 0.65–0.91, thus showing considerable variation in the values that could be used in the model. QALY gains in the overall population using the second set of utilities resulted in a slightly lower gain for option A in the overall population (0.069 vs 0.08). The model included disutilities for exacerbations and selected acute AEs. These were taken from a range of different sources. Disutilities for exacerbations were taken from a health preference study. In the model patients move between health states corresponding to different GOLD stages, defined by the decline in FEV1 over time. In the first cycle patients could move to a less severe GOLD stage, reflecting the effects of treatment. The distribution of FEV1 scores at baseline is therefore relevant to progression through the model. This was based on data from the THIN registry, having a mean FEV1 of 69.3%. However, this is higher than the score of approximately 50% for the patient populations involved in most RCTs of LAMA+LABA combinations.[7] This mismatch between the model baseline inputs and the clinical evidence further calls into doubt the HRQoL benefit reported for the analysis. Thus, the analysis suggests that there is not a clear HRQoL advantage for LAMA+LABA over LAMA to LAMA+LABA and there is likely to be considerable uncertainty in the QALY gain given the diverse sources of utilities and that none of the values are specific for the treatments or treatment strategies of interest.	a real-world setting, whereas data from randomised trials may lack generalisability. *"Utilities from a second study were used in a sensitivity analysis but were considered by the NICE committee not to reflect the differences in HRQoL between GOLD stages. The range of these values was from 0.65–0.91, thus showing considerable variation in the values that could be used in the model."* – As you say, there were some differences between the possible baseline utility datasets, which was the reason for conducting a sensitivity analysis using the Rutten van Mölken (2006) values. The committee were reassured by the fact that the choice of utility set had only a very small impact on the ICER of LAMA+LABA. *"Disutilities for exacerbations were taken from a health preference study."* – Exacerbation disutilities were taken from a health preference study which used the time-trade off method. Since this is the method used to value the EQ-5D UK dataset it was deemed to be appropriate. *"This was based on data from the THIN registry, having a mean FEV1 of 69.3%. However, this is higher than the score of approximately 50% for the patient populations involved in most RCTs of LAMA+LABA combinations."* – As previously discussed, we preferred observational sources to inform baseline and natural history data, as they are more reflective of patients in the real world. THIN data on FEV1 % predicted at baseline were collected at the point where a patient where each patient was first prescribed a long-acting bronchodilator. Therefore, these data are, by definition, relevant to the population of interest. *"LAMA+LABA is better than other inhaled treatments for many individual outcomes (such as reducing the risk of*

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

				LAMA+LABA is better than other inhaled treatments for many individual outcomes (such as reducing the risk of moderate to severe exacerbations) No data from the economic model are presented for rates of exacerbations or other clinical outcomes for different treatment strategies and it is unclear from the description of the model if the model produced such outputs. Therefore, it is unclear whether this statement is supported by the results of the CEA. The only evidence for a difference in individual clinical outcomes is from the meta-analysis. However, this is for the individual treatments (i.e. for the comparison of LAMA vs LAMA+LABA) not for the relevant treatment strategies (i.e. LAMA+LABA vs LAMA to LAMA+LABA), and the meta-analysis did not show significant differences for the incidence of at least one moderate to severe exacerbation, or at least one severe exacerbation. Thus, it is unclear whether there is any evidence to support this statement. "LAMA+LABA is the most cost-effective option" The probability of being cost-effective is based on the difference in QALY gain (0.08) and the cost difference of £271 (base case option A) but the estimated difference in QALY gain is likely to be an over estimate and the estimated cost difference is likely to be underestimated. As discussed above, there are uncertainties in the calculation of the difference in QALY gain between LAMA+LABA and the LAMA to LAMA+LABA strategy. The evidence presented suggests that the benefit is likely to be less, and possibly minimal, in the low-risk group. The cost difference for the LAMA+LABA vs LAMA to LAMA+LABA strategies is likely to be an underestimate. Firstly, this reflects the fact that the difference in the drug acquisition costs for LAMA+LABA vs LAMA is likely to be more than the difference per cycle of £10.56	*moderate to severe exacerbations)".* This statement relates to the clinical evidence from the network meta-analysis rather than to outcomes of the economic model, which indicate that LAMA+LABA has a high probability of being the best treatment across a number of outcomes. *"No data from the economic model are presented for rates of exacerbations or other clinical outcomes for different treatment strategies and it is unclear from the description of the model if the model produced such outputs."* – Exacerbation rates for each treatment are presented in the full model report. These rates are simply a function of baseline exacerbation rate (dependent on GOLD stage) and relative exacerbation rates taken from the clinical review, and therefore show a favourable exacerbation rate for LAMA+LABA. *"The only evidence for a difference in individual clinical outcomes is from the meta-analysis. However, this is for the individual treatments (i.e. for the comparison of LAMA vs LAMA+LABA) not for the relevant treatment strategies (i.e. LAMA+LABA vs LAMA to LAMA+LABA)"* – No randomised evidence exists comparing outcomes for patients switching through multiple lines of treatment. This was one of the reasons why economic modelling was conducted for this topic: to predict long-term health and cost outcomes using head-to-head comparisons of long-acting bronchodilators. In modelling multiple therapy lines, patients' exacerbation rate/TDI/SGRQ/FEV1 related to the treatment that they were currently receiving - e.g. patients starting on a LABA had an exacerbation rate associated with that treatment, but experienced a reduced exacerbation rate if they stepped up to LAMA+LABA. The committee indicated that this was a realistic assumption according to their clinical experience.

				used in the model. The values used in the model are based on the market shares for LAMA and LABA agents from Prescription Cost Analysis (PCA) data for January 2018; however, these do not reflect the current market positions for these drugs, which continue to evolve throughout 2018. Data from IQVIA, which are available up to June 2018, illustrate that the following changes have occurred: the market shares for lower cost LAMAs have increased (Braltus, £25.80 per pack, has increased by 2.81%, to a market share of 28.75%; Spiriva Respimat, £23.00 per pack, has increased by 1.48%, to a market share of 15.08% and Incruse Ellipta, £27.50 per pack, has increased by 0.8%, to a market share of 14.67%); and further the market share of the most costly LAMAs have decreased (Spiriva HandiHaler Refill pack, £33.50 has decreased by 4.13%, to a market share of 22.53%; and Spiriva HandiHaler Starter pack, £34.87 per pack, has decreased by 0.97%, to a market share of 5.06%). These changes in relative market shares will be reflected in later PCA data. This trend is expected to continue and will reduce the average price of LAMA per cycle and hence the cost difference between LAMA and LAMA+LABA.[12] Secondly, the model assumes that the LAMA+LABA strategy will reduce treatment costs for exacerbations but there is no conclusive evidence for this. There are no clinical data regarding the rates of exacerbations for patients treated with either strategy. Instead, the model includes a baseline rate of exacerbations per cycle according to GOLD stage taken from a natural history study, and exacerbation rates in subsequent cycles were determined based on data from a network meta-analysis comparing data from clinical trials for LAMA+LABA vs LAMA. However, the modelled incidence of exacerbations for the two treatment strategies are not reported, and the meta-analysis (which only compared LAMA+LABA vs LAMA not LAMA+LABA vs LAMA to LAMA+LABA) showed no significant difference in the number of patients with ≥1 severe exacerbation. Given that the difference in QALY gain presented in the analysis is likely to be an overestimate and the cost difference is likely to be	*"…the meta-analysis did not show significant differences for the incidence of at least one moderate to severe exacerbation, or at least one severe exacerbation"* – Not all of the pairwise comparisons for LAMA+LABA versus LAMA were statistically significant at the 5% level, but many were (the majority of outcomes for FEV1, SGRQ and TDI). Significant and non-significant outcomes all fed into the economic analysis, which found that, on balance, LAMA+LABA is likely to be the most cost-effective strategy. *"the estimated difference in QALY gain is likely to be an over estimate and the estimated cost difference is likely to be underestimated."* – As discussed, we believe that, if anything, results of the economic model underestimate, rather than overestimate, the cost effectiveness of LAMA+LABA, since the patient population in real life is likely to be more akin to the high-risk subgroup. *"the difference in the drug acquisition costs for LAMA+LABA vs LAMA is likely to be more than the difference per cycle of £10.56 used in the model. The values used in the model are based on the market shares for LAMA and LABA agents from Prescription Cost Analysis (PCA) data for January 2018; however, these do not reflect the current market positions for these drugs"* – The sensitivity analysis in which the cost of the cheapest product is used for every regimen uses a cost of £23 per pack (Spiriva Respimat) for the cost of LAMA, while the cost of LAMA+LABA remains unchanged (since all inhalers have the same price). Results show that LAMA+LABA still has the highest probability of being cost-effective by a considerable margin, and demonstrates that the relative market share of different LAMA products does not affect conclusions.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				underestimated, the ICERs for LAMA+LABA vs LAMA to LAMA+LABA reported in the NICE analysis are likely to be underestimates of the additional cost to benefit ratio for these two approaches. The base case included three options differing in whether treatment-specific differences in AEs and mortality were included. Inclusion of AEs decreased the QALY gain and increased costs, resulting in a higher ICER. Inclusion of AEs and mortality increased both the QALY gain and costs and resulted in a higher ICER. Thus, inclusion of the impact of treatment on mortality and AEs (as is clinically relevant), increases the ICER in the high-risk group, making the LAMA+LABA strategy less favourable, while in the low-risk group, LAMA+LABA is dominated by LAMA to LAMA+LABA. This further suggests that LAMA+LABA is unlikely to offer a substantial economic benefit over the LAMA to LAMA+LABA strategy. We therefore suggest • There is insufficient evidence to conclusively state that the LAMA+LABA strategy is associated with: 1) better HRQoL outcomes or 2) a lower risk of severe exacerbations compared with the LAMA to LAMA+LABA strategy • The additional drug acquisition costs associated with the LAMA+LABA vs LAMA to LAMA+LABA, as used in the economic evaluation, are likely to be an underestimate. Furthermore, it is unclear that these will be partially offset by reductions in costs for treatment of exacerbations. • Therefore, the ICERs presented for LAMA+LABA vs LAMA to LAMA+LABA are likely to be an underestimate • The economic evaluation suggests that LAMA to LAMA+LABA is the least costly option and may well be associated with a similar HRQoL benefit as for LAMA+LABA; hence LAMA+LABA may not be cost-effective compared with LAMA to LAMA+LABA.	*"the model assumes that the LAMA+LABA strategy will reduce treatment costs for exacerbations but there is no conclusive evidence for this. There are no clinical data regarding the rates of exacerbations for patients treated with either strategy."* – As previously stated, evidence from the network meta-analysis shows that LAMA+LABA has a high probability of being the best treatment for the majority of exacerbation outcomes. Therefore, it is logical that this strategy reduces exacerbation treatment costs. *"The base case included three options differing in whether treatment-specific differences in AEs and mortality were included. Inclusion of AEs decreased the QALY gain and increased costs, resulting in a higher ICER. Inclusion of AEs and mortality increased both the QALY gain and costs and resulted in a higher ICER."* Due to the very wide confidence intervals associated with estimates of treatment effects on adverse events and mortality, the committee found option A (treatment effects on adverse events and mortality excluded) to be the most plausible scenario. ***"in the low-risk group, LAMA+LABA is dominated by LAMA to LAMA+LABA"*** – In the low-risk group, when treatment effects on adverse events and mortality are included, LAMA+LABA is dominated by the strategy of LABA -to- LAMA+LABA, not by LAMA -to- LAMA+LABA. This is due to the point estimate for treatment effect on mortality favouring LABA. The committee expressed the view that this finding was not clinically plausible, and was likely a chance finding.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				If the HRQoL gain is similar for both treatments, then LAMA to LAMA+LABA may be a preferable option, being less costly. • Treatment decisions should take into account clinical factors such as the severity of symptoms and the frequency of exacerbations. The economic evaluation considered patients with low vs high risk of exacerbation in a subgroup analysis (using treatment effect outcomes from the network meta-analysis and baseline exacerbation rate according to risk status) and found that LAMA+LABA had a lower probability of being cost-effective, and a higher ICER, in low-risk patients. This suggests LAMA to LAMA+LABA may be the preferable option for low-risk patients and should be included in the guidelines as an option for such patients.	
UK Clinical Pharmacy Association	Guideline	52	14-15	We disagree with the assertion made. The recommendation for LABA+ICS is NOT in line with current practice: 1. Most UK Practice follows the GOLD 2018 guidelines rather than the current NICE guidelines (2010), as the GOLD guidelines are updated annually, and so have taken into account significant changes in published evidence in COPD since NICE last updated. Therefore current practice needs to be acknowledged as being based on GOLD 2018, and not NICE 2010. 2. Many UK specialists would recommend LAMA or LAMA+LABA first line for COPD patients who are symptomatic (CAT>/=10) or breathless (MRC >/=3) whether or not they have at least 2 exacerbations in 12 months, irrespective of features of steroid responsiveness. 3. If patient has a concomitant diagnosis of asthma alongside COPD, then the use of LABA+ICS in patients still breathless or exacerbate despite short-acting bronchodilator IS NOT in line	Thank you for your comment. The clinical and economic evidence agreed that the most effective treatment regimen was LABA+LAMA, but the committee concluded that it would be inappropriate to deny people with asthmatic features/features suggesting steroid responsiveness treatment with ICS. They made the recommendation for LABA+ICS treatment of these people based on their clinical experience and the finding from the economic model that showed that dual therapy was more effective than monotherapy. They did not recommend that the NICE asthma guideline was followed for these patients for several reasons: • steroid responsiveness is not confined to people who have asthma • people with asthma and COPD require treatment for their COPD in addition to their asthma. The committee also wrote a research recommendation to try to stimulate research to determine the most clinically and

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				with either the BTS/SIGN asthma guidelines (2016), or the NICE NG80 asthma guidelines (2017). Both guidelines would recommend a low dose ICS in patients uncontrolled despite SABA alone.	cost effective inhaled therapy for people with COPD and asthma.
Chiesi Ltd	Guideline	52	5	The guideline suggests that there is no evidence on how to predict steroid responsiveness in people with COPD. This statement is incorrect given the large amount of clinical research currently published and on-going around use of biomarkers such as eosinophils to guide treatment decisions for those with COPD.	Thank you for your comment. The committee agreed that evidence did exist looking at features predicting steroid responsiveness in people with COPD. However, they also noted that no RCTs exist looking at differential response to treatments in people with particular features predicting steroid responsiveness.
Chiesi Ltd	Guideline	52	8	We agree that the recommendation on use of LAMA+LABA dual therapy is likely to increase the number of people with COPD prescribed this treatment. However, there is no consideration of the adverse effect of switching those patients controlled on therapies incorporating an ICS to a LAMA+LABA. The withdrawal of ICS has the potential to lead to an increase in exacerbations which in turn has a knock on effect to healthcare ultilisation and the cost of treating the acute exacerbation. The SUNSET study examined the effects of withdrawing ICS from patients treated with long-term triple therapy and stepping them down to a LAMA+LABA combination. The de-escalation from triple therapy led to a statistically significant reduction in lung function. Patients with higher eosinophils ≥300 cells/μL presented a greater lung function loss and higher exacerbation risk.[1] [1] Chapman KR et al. Am J Respir Crit Care Med, 2018. Doi: 10.1164/rccm.201803-04505OC	Thank you for your comments. The topic of switching between inhaled therapies was not within the scope of this update and, as a result, we did not examine any evidence on this issue. We were also unable to look at ICS withdrawal in this update. The committee did not intend that people currently taking inhaled therapies who have controlled symptoms should be switched to LAMA/LABA or LABA/ICS based on these recommendations. The recommendations are intended to apply to people beginning long-acting therapy. We have passed the suggestion for the inclusion of guidance on treatment switching and ICS withdrawal and the information about the SUNSET study onto NICE's surveillance team to help inform their decisions for future updates of this guideline.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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NHS England	Guideline	52	24	Oral prophylactic antibiotic therapy. The strict criteria for identifying patients who might benefit need careful explanation to a primary care audience. Many GPs follow headlines from guidance. The unintended consequence is that most patients with COPD end up on prophylactic antibiotics due to one or two exacerbations. The second unintended consequence is to have increased microbial resistance to antibiotics.	Thank you for your comment. The committee noted the importance of the criteria for prophylactic antibiotics being as clear as possible, to ensure that antibiotics are not overused. The committee were confident that people reading the recommendations in the guideline would see the intent was to ensure prophylactic antibiotics are restricted to those people who are not controlled through other pharmacological and non-pharmacological methods.
British Dietetic Association	Guideline	68	_	We feel it would be helpful to change “low BMI” throughout to “low BMI <20/kg/m^2”	Thank you for your comment. The committee did not review any evidence on how a low BMI should be defined for people with COPD as part of this update, and therefore it was not possible to modify the recommendations as you suggest.
British Dietetic Association	Guideline	68	1	‘Frailty’, please consider and include how the clinician would assess this.	Thank you for your comment. The committee did not review any evidence on how frailty should be defined for people with COPD as part of this update, and therefore it was not possible to modify the recommendations as you suggest.
Carterknowle and Dore Surgery	Guideline	71	1 (Table 6 – bottom)	The recommendation for annual FVC monitoring in COPD means we must do spirometry for each patient rather than just the FEV1 required for severity. This has a significant time cost as spirometry takes 20 minutes to perform whereas FEV1 is just a couple of minutes. I could find no evidence for doing FVC after diagnosis as part of monitoring. I understand that this is to look for patients who may have a restrictive lung disease, which is uncommon in primary care. I propose using FEV1 only for annual reviews in primary care. A patient would have spirometry if they have symptoms that do not fit, progression of FEV1, are uncontrolled (i.e. do not respond to a first time change in treatment) or every 5 years (a loss of 500 ml or more over 5 years will select out those patients with rapidly progressing disease who may need specialist referral and investigation. This is based on GOLD 2017 guidelines). At our practice we have a relatively low COPD prevalence of 1.3% but this for us means 26 hours of nurse time that we can invest elsewhere. With an estimated UK prevalence of 1.2million this could be 360,000 hours in the UK.	Thank you for your comment. The topic of follow-up of people with COPD is not within the scope of this update, and therefore no changes could be made to these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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KSS AHSN Patient Safety Collaborative	Guideline (Research Q	48	8	As the guideline doesn't recommend single agent bronchodilator therapy why is this a research question? Suggest change guideline and keep this as a research question)	Thank you for your comment. This research recommendation was from the 2010 guideline. Post-consultation, the committee have agreed to delete this recommendation as it is no longer relevant to compare monotherapy with triple therapy based on the new pathway presented in this update. In addition, the committee are aware of several existing trials comparing dual and triple therapy and NICE will be reviewing this evidence as part of a separate update of the triple therapy section in the very near future.
KSS AHSN Patient Safety Collaborative	Guideline (Research Qs)	47	9	How is 'corticosteroid responsiveness defined?	Thank you for your comment. The committee concluded that responsiveness to corticosteroids in this research recommendation is defined by improvements in a number of outcomes including exacerbations, quality of life, airway obstruction and breathlessness. They also noted the importance of measuring adverse events, such as pneumonia and any serious adverse events.
Glaxo SmithKline	Guideline and Algorithm	Gener al	Genera l	*Suggested revision* GSK request that NICE take into account the government stated aims with regard to reducing fluorinated gas emissions by encouraging physicians to use dry powdered inhalers over metered dose inhalers when this is in the best interest of patient care. The government has set out its intention to reduce fluorinated gas emissions in an Environmental Audit Committee report on 'UK progress in reducing F-gas emissions'. Acknowledging that only around 26% of currently prescribed inhalers have a low global warming potential (GWP), the report states that 'The Government agrees that GWP inhalers should be promoted within the NHS. Whilst propellant based metered dose inhalers (MDIs) are in some cases the only appropriate delivery	Thank you for your comments. The consideration of inhaler device is not within scope of this update and, as a result, the committee did not examine the relative effectiveness of different types of devices and are unable to include the suggested recommendation. This will not impact any other initiatives that NICE is undertaking/has undertaken to provide information about the relative environmental impacts of inhalers to patients and prescribers. We have passed your comments onto surveillance to help inform future updates of the guideline.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				mechanism, dry powder inhalers (DPIs) are equally effective for many patients.' The report goes on to say that NICE is working with the NHS and the Public Health England Sustainable Development Unit (SDU) to provide information about the relative environmental impacts of inhalers to patients and those prescribing inhalers, enabling patients to make an informed choice when they are offered a prescription. The SDU is consulting clinicians, specialists and industry manufacturers to assess the potential to increase the proportion of low GWP inhalers and publishes an annual sustainability 'Health check' scorecard which includes the proportion of MDIs and DPIs prescribed. Building on patient choice and appropriate clinical judgement – which of course should remain integral when prescribing inhalers – we request that NICE raise awareness of the importance of GWP inhalers in the core guidance and algorithm.	
ResMed UK	Guideline and Economic Model	General	General	Home NIV in COPD is a topic that should be considered for the next update, with particular focus on the following: Clinical and cost effectiveness of treating stable COPD Clinical and cost effectiveness of treating post-acute COPD This is based on the following publications: Murphy PB et al., 2017, JAMA Brueggenjuergen B et al., 2018, ajrccm-conference Gu Q et al., 2018. ajrccm-conference.	Thank you for your comment. We have passed this information on to our surveillance team, for consideration in future updates of the guideline.
British Thoracic Society	Guideline and evidence review	23	18-19	We agree ambulatory oxygen is primarily of benefit to patients who meet criteria for LTOT, regularly leave their home and are prepared to use ambulatory oxygen in this setting. In patients who do not meet criteria for LTOT the evidence is weak, but in trials and clinical practice a small proportion of patients show more substantial benefit than others. We suggest ambulatory	Thank you for your comments. The recommendation to not offer ambulatory oxygen therapy was based on the management of breathlessness alone. This decision was made based on the available evidence which did not show a clinically meaningful improvement in breathlessness following the use of ambulatory oxygen therapy. The committee did acknowledge that ambulatory oxygen therapy may be

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				oxygen should be allowed if patients who show an improvement in exercise tolerance and breathlessness following a walk test with and without oxygen, +/- a third placebo walk test with nasal cannulae connected to a cylinder but no oxygen (current practice for many centres).	beneficial under other circumstances, such as during exercise. However, this was beyond the scope of this review.
British Thoracic Society	Guideline inc rationale and evidence review. (Question 4)	23 55	3-5 7+	We strongly disagree with this statement, and urge the committee to not prohibit (and preferably fully support) LTOT in patients who continue to smoke despite appropriate advice and support provided: 1) They meet criteria for LTOT. 2) They are offered full support from smoking cessation services, and importance of cessation emphasised. 3) They have been informed of the risks of smoking (and use of other naked flames) in the vicinity of oxygen therapy and receive written safety instructions. 4) Oxygen is removed if concern arises that the risks outweigh benefits: i.e. they must continue to use oxygen appropriately and conform to safety advice. 5) They sign a form confirming acceptance of the above points (ensuring benefit, minimising and responding to risk). We do not agree that the risks of providing oxygen to smokers outweigh the benefits in correctly selected and well-informed patients. In particular we do not agree with the view that smokers "… will be smoking in close proximity to the oxygen…" if existing advice is followed. We highlight: - A substantial proportion of participants in RCTs supporting use of LTOT were current smokers (MRC = 43%, NOTTS=38%). There is no evidence that smokers did not benefit. - Burns in oxygen users are rare, fatalities exceptionally rare and a review of a wide range of medical and non-medical literature sources internationally found no incidents of third party injury (Lingford et al Annals of Burns and Fire Disasters 2006;19:99-100). Events = 86 (54 smokers),	Thank you for your comments about risk of burns associated with home oxygen use. Although Lingford et al (2006) did not report on third party injuries, the number of patients who were admitted to hospital with home oxygen burns was higher for smokers than non-smokers. The authors stated that "patients who smoke whilst on home oxygen expose themselves to a significant and avoidable burn injury risk". This reflects the concerns of the committee which led to its recommendations. The Lacasse article discusses the difficulties surrounding providing home oxygen therapy to smokers and suggests that physicians can only refuse home oxygen therapy if there is a threat to the patient's health and safety. As you mention in your comment, the authors suggested that it may be medically justifiable not to prescribe home oxygen if there is good reason to believe that the patient will smoke while on oxygen. These conclusions further reflect the concerns of the committee that led to its recommendations regarding home oxygen use for people who smoke.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				predominantly superficial “flash” burn. Full thickness = 7; skin graft = 2; inhalation injury = 21, fatality = 9. No third party injuries. To reduce risk they recommended use of fire retardant cannula (now implemented) and, most importantly, to warn and educate patients and their families. Oxygen does not burn or explode – you need fuel and an ignition source. Many other approved therapies confer much greater risk. - BTS oxygen guidelines and other international guidelines/ standards similarly recommend that patients, family and other care-givers must be warned not to smoke near oxygen. In general, major accidents associated with oxygen therapy are rare and can be avoided by good patient and family training along with common sense. - Some countries have restricted oxygen to non-smokers – in Denmark patients must confirm they do not smoke (signed). Ringbaek conducted surveys from other information sources – over 20% of patients on LTOT smoked. Compared to encouraging open disclosure and providing appropriate education, “banning” oxygen in smokers potentially increases risk. - Although deaths are very rare; two cases in Quebec triggered a review (Lascasse Thorax 2006;61:374-5). Legal advice was obtained: o The physician must ensure oxygen therapy is indicated. o The patient has a duty to disclose their smoking status. o The physician should inform patient about the fire hazards and ensure that s/he agrees to comply with the rules of safety. Written safety instructions should be provided. o The patient should sign a form in which they acknowledge the fire hazards of home oxygen therapy and consent to receive it.	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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				The legal team concluded that in smokers: "Withholding or withdrawing oxygen therapy may therefore be considered as a violation of charters of rights in force in most developed countries." The exception is "If it is felt that the patient will not comply with the safety procedures and especially if there is good reason to believe that the patient will smoke while on oxygen, then it is medically justifiable not to prescribe it." Examples of practice: the model of care in Northumbria Healthcare reflects the above guidance. Please note that risk assessments are part of routine practice. BOC will not supply oxygen unless a risk assessment has been completed (forms available on request). The fire service is informed of new oxygen installations and may conduct a separate risk assessment.	
Carterknowle and Dore Surgery	Question 5 in comments form	General	General	Your website isn't very user friendly and when I have a patient sat in front of me it makes your guidelines impossible to refer to. Please minimise the use of refer to 'X'.	Thank you for your comment. NICE guidelines are designed to be self-contained documents, but unfortunately it is impossible to remove all references to other guidance, especially those that refer to other relevant guidelines in their entirety. However, we do endeavour to keep these to a minimum to reduce disruptions to the user and include links to enable easy access to the additional documents. NICE Pathways can be used as a way of seeing all relevant guidance in one place.
British Thoracic Society	Research	45	24	This was addressed in a large negative UK RCT (Greening).	The committee were aware of the findings of this trial, but concluded that the research recommendation should stand. They noted that the people in the early rehabilitation group received an exercise intervention but, as noted by the authors of the study itself, this intervention was not the same as pulmonary rehabilitation in content or duration. As such, the committee decided that the existing trial did not address

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (Dec 2018)

Consultation on draft guideline - Stakeholder comments table
09/07/2018 – 06/08/2018

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					this question and so the research recommendation was still relevant.