Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Association of Respiratory Nurse Specialists	Guideline	General	General	The updates are sensible, which are clear about treatment and rationale and also consistent with GOLD approach.	Thank you for your comment.
Association of Respiratory Nurse Specialists	Guideline	General	General	In 1.2.14, 1.215 & 1.2 16 does to need to be more specific on how impact on activities of daily living, and those that have symptoms that interfere with ADL's is measured I.e use of CAT scoring?	Thank you for your comment. In response to stakeholder comments the committee have added a specific recommendation for a clinical review prior to escalation to triple therapy to ensure the symptoms and exacerbations are due to COPD and not potentially treatable about co-morbidities and that any other non-pharmacological treatment options, have been optimised or offered where relevant. They envisaged that this review would involve a discussion with the person with COPD and that this would be the best way of determining how breathlessness and other key symptoms are impacting their quality of life on a day to day basis. They agreed that tools such as CAT could be used, but this should not be at the expense of a discussion with the person with COPD. We have added this point to the rationale to make this clearer for healthcare professionals.
Association of Respiratory Nurse Specialists	Guideline	General	General	In terms of oral corticosteroid use it does not discuss use and duration in those with overlapping asthma? who may benefit from a longer duration of Steroid, however, if its purely COPD exacerbation then its clear.	Thank you for your comment. The committee decided that there was no evidence in the review that could provide a basis for giving people with COPD and overlapping asthma an extended course of treatment. However, based on their clinical experience there would not be any necessary changes in treatment for people with COPD and overlapping asthma compared to COPD only for treatment of a COPD exacerbation. They therefore agree that it was unnecessary to add any additional detail for

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					people with COPD and asthma to this recommendation. They noted in the discussion section that people with COPD and asthma should be treated as detailed in asthma guidelines if they have an asthma exacerbation.
AstraZeneca	Algorithm	General	General	AstraZeneca does not consider the way in which the criteria for "asthmatic features/features suggesting responsiveness to steroids" are presented to be clear - as it is not clear that only one of these criteria is required for a patient to be eligible for treatment on the right-hand side of the algorithm. We ask that the top box on the right-hand side of the algorithm is changed from: "Asthmatic features/ features suggesting steroid responsiveness[a]" to "Any of the asthmatic features/features suggesting steroid responsiveness[a]" for clarity. We also ask that footnote "a" specifically states: "The patient must have at least one of the below features." (Please see proposed algorithm figure 1 below) Rationale for this request: COPD patients with Asthmatic symptoms have a more severe disease compared to COPD or Asthma symptom patients alone. This is true when a range of clinical indicators are used (pulmonary function, respiratory symptoms, exacerbation rates [up to	Thank you for your comment. The committee decided that the list of asthmatic features was clear enough regarding the point that any one feature is required and decided this part of the algorithm should remain the same.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				four times higher], overall health, QoL and disability). These patients also require greater use of healthcare. This means that clarity of the criteria to ensure that all such patients are identified in a timely way is critical to ensure that patients with asthmatic features receive appropriate treatment at the earliest opportunity.	
AstraZeneca	Algorithm	Guideline	Guideline	AstraZeneca welcomes the fact that the new treatment algorithm now recommends that triple therapy (LAMA+LABA+ICS) be available to both patients with asthmatic features/features suggesting steroid responsiveness who are still limited by symptoms or have exacerbations despite treatment with LABA + ICS; and also for those without asthmatic features/features suggesting steroid responsiveness, who are still limited by symptoms or have exacerbations despite treatment with 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/or when exacerbations are not controlled, despite a LABA+LAMA or an ICS+LABA therapy. For clarification and alignment with GOLD on certain topics, as specified below, we propose	Thank you for your comment and for supporting these recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				minor changes to the algorithm, which are shown in Figure 1 below.	
AstraZeneca	Algorithm Footnote "a"	General	General	To align with the 2019 GOLD guideline, we ask that a specific eosinophil threshold in line with that included in GOLD for ICS+LABA treatment is added, so that footnote "a" is changed to: "Asthmatic features/features suggesting steroid responsiveness – The patient must have at least one of the below features: • any previous, secure diagnosis of asthma or atopy, • a higher blood eosinophil count (eosinophil count ≥300 OR eosinophil count ≥100 AND ≥2 exacerbations/1 hospitalisation) • a substantial variation in FEV1 over time (at least 400 ml) • substantial diurnal variation in peak expiratory flow (at least 20%)." We believe a specific eosinophil threshold is needed to ensure that non-specialists have sufficient guidance to implement the "higher blood eosinophil count" criterion in footnote "a". (Please see proposed algorithm figure 1 below)	Thank you for your comment. Dual therapy was not within the scope of this update and therefore we are unable to make changes to the definition at this time. This topic was updated in 2018 following the methods outline in the NICE guideline manual based on the highest quality evidence available and committee input.
AstraZeneca	Guideline algorithm	16	20-24	Statement 1.2.16: We do not agree that a 3-month trial period of triple inhaled therapy (LAMA+LABA+ICS) is in line with current best practice in the NHS by which clinicians consider stepping-up therapy for patients failing on triple	Thank you for your comment. Stepping down or de-escalation from long term triple therapy use was not within the scope of this update and the committee were therefore unable to make any recommendations on this topic. The committee agreed that the important consideration was whether the person with COPD

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				therapy. We recognise that de-escalation of the ICS component should be considered in the case of adverse events, which is also stated in the GOLD 2019 guideline. We ask that statement 1.2.16 is changed to: "In people with COPD who are taking LAMA+LABA and who have symptoms that continue to interfere with activities of daily living, consider LAMA+LABA+ICS. Should adverse events occur, consider de-escalation of ICS". In the algorithm, we ask that the box "Consider three month trial of LAMA+LABA+ICS. Revert if no improvement" is changed to: "Consider LAMA+LABA+ICS". We ask that a new box is added as the next step following this in the algorithm stating: "Consider de-escalation of ICS if adverse events AND explore further treatment options if needed (see guideline)". (Please see proposed algorithm figure 1 below)	and symptoms that affect their quality of life showed improvement of these symptoms when taking triple therapy and that if this was not the case that they should stop taking triple therapy and revert to taking LAMA/LABA. The absence of adverse events at that point in time would not be reason enough for them to remain on triple therapy. They expected that the healthcare professional would take adverse events into account when determining the success of the trial period particularly as these would be expected to adversely affect a person with COPD's quality of life. They therefore declined to make the suggested changes. The committee were unable to make any changes to the algorithm concerning de-escalation as this was out of scope, but there is a box at the bottom that refers to other treatment options in the full guideline for people who are still limited by breathlessness or frequent exacerbations.
AstraZeneca	Guideline algorithm	16	16-19	We ask that statement 1.2.15 is changed to: "In people with COPD who are taking LAMA+LABA, offer LAMA+LABA+ICS if: □ they have a severe exacerbation (requiring hospitalisation) or □ they have 2 moderate exacerbations within a year."	Thank you for your comment. As you note, the IMPACT trial compared both LAMA/LABA and LABA/ICS to triple therapy within the same trial and the study level quality of the evidence (risk of bias) was the same for both comparisons. However, other studies were included in the meta-analysis for both comparisons and the GRADE quality rating is determined for each outcome across all pooled studies.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				We do not consider it appropriate to specify "consider LAMA+LABA+ICS" in statement 1.2.15 and "offer LAMA+LABA+ICS" in statement 1.2.14 when the IMPACT study found triple therapy with a LAMA+LABA+ICS to result in a lower rate of moderate or severe COPD exacerbations and better lung function and health-related quality of life compared to dual therapy with either a LABA+LAMA or an ICS+LABA. (i.e the evidence for stepping up to triple therapy from either a LABA+LAMA or from an LABA+ICS is from the same trial, and hence it is the same level of evidence warranting use of the word "offer" on both sides of the algorithm). Algorithm: To reflect this, we ask that the "consider" box on the right-hand side of the bottom of the algorithm is deleted. (Please see proposed algorithm figure 1 below)	The committee's decision to make a weaker 'consider' recommendation for triple therapy for people who are taking LAMA/ LABA and have the specified number and type of exacerbations was based on a discussion of the balance of benefits and harms and the quality of the evidence across multiple outcomes. The committee agreed that although triple therapy showed some benefits over LAMA+LABA, there was also evidence of a potential harm, in particular, an increased risk of pneumonia. In comparison, for there was no increase in pneumonia in people taking triple therapy compared to LABA/ICS and there were beneficial effects on exacerbations. The committee therefore agreed that it was appropriate to make a stronger recommendation to for triple therapy for people taking LABA/ICS compared to those taking LAMA/LABA.
Barking & Dagenham, Havering & Redbridge Clinical Commissioning Groups	Algorithm	Guideline	Guideline	The algorithm states '*Start inhaled therapy only if all the above interventions have been offered (if appropriate) , and inhaled therapies are needed to relieve breathlessness or reduce exacerbations'*. This is not in line with the guidelines which make no such condition. Also this is not in line with the Evidence Review F – inhaled therapies. This evidence review on page 42, 2nd paragraph, states half way down, that '*The committee did not intend that the list of other*	Thank you for your comment. Evidence review F on dual therapy was from the 2018 update and therefore we are unable to answer comments regarding this review. However, regarding the algorithm the committee did not intend the list of COPD care fundamentals to act as a barrier to other treatment. Instead they wanted to make sure that people with COPD were given access to these treatments and plans (if appropriate). As it stands the algorithm only says that these treatments should have been offered, it does not specify that they must have been accepted or completed prior to treatment with an inhaled therapy.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				treatments , for example tobacco dependence and optimised non-pharmacological management , would act as a barrier to prevent people from accessing long-term treatments. Instead they agreed that it was important for the healthcare professional to ensure that people had been given access to these other interventions , where relevant , because they are beneficial for people with COPD, but that the recommendation was not to imply that people should be denied ling-term therapies while they waited for /undertook them.	
Barking & Dagenham, Havering & Redbridge Clinical Commissioning Groups	Guideline	16	11-24	There are a number of patients who currently have ICS+LABA and a LAMA separately. The guidelines should make it clear that before putting patients on a single triple therapy inhaler , an individualised assessment should made in line with the guidance of the benefits of each of drug types.	Thank you for your comment. The 2018 update of the guideline included a recommendation covering factors to be taken into account when choosing inhalers and included a statement to "Minimise the number of inhalers and the number of different types of inhaler used by each person as far as possible." The committee agreed that this recommendation should also apply to the choice of triple therapy devices. The committee deliberately did not specify that people should be prescribed single device for triple therapy because they could think of cases where multiple devices may be better suited to the needs of the person with COPD or specific circumstances, such as a 3 month trial. (Their discussion is detailed in the rationale and the evidence review discussion.) The guideline also contains sections on follow up of people with COPD and the committee did not make recommendation on reviewing prescribed treatments as they are already covered by

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					existing recommendation in this section. Table 6 contains a review of the effects of each drug treatment that should occur at least annually. The algorithm also makes this intention clear and states "Review medication and assess inhaler technique and adherence regularly for all inhaled therapies."
Barking & Dagenham, Havering & Redbridge Clinical Commissioning Groups	Guideline	16	11-15	We are concerned that this recommendation will lead to a significant number of patients being placed on triple therapy with extra costs and side effects that come with this. There are a significant number of patients who are on ICS/LABA who do not have not been assessed for 'asthmatic features/features suggesting steroid responsiveness'. They have also never been tried on a LABA+LAMA. Hence the guidelines need to stress that consideration should be given to an assessment of these features and a trial of LABA+LAMA considered, without the ICS. If the LAMA+LABA is successful then as explained in the guidance, this combination has the advantage of less side effects, in particular a lower risk of pneumonia.	Thank you for your comment. The resource impact assessment for these recommendations suggests that resource impact will be minimal because: the current proportion of people taking LAMA+ICS is low and even if they all switched this would therefore have limited resource impact; the recommendation to escalate treatment for people taking LAMA+LABA is a weaker "consider" recommendation; and the use of triple therapy is already widespread**.** It is therefore assumed the recommendations will not significantly change the current number of people already being offered triple therapy. Switching between dual therapies was not within the scope of this update and therefore we are unable to make changes to this section of the inhaled therapy recommendations. The guideline already includes a section on follow up and in table 6 the healthcare professional is expected to review the effects of each drug treatment at least annually. However, the committee have included a new recommendation at the end of the triple therapy recommendations to review and write down the reason for continuing ICS use at least annually. They have

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					also added a recommendation for an initial clinical review prior to escalating to triple therapy, which includes ensuring people's non-pharmacological care is optimised, and that any symptoms or exacerbation are caused by COPD and not another co-morbidity. In addition, the algorithm states "Review medication and assess inhaler technique and adherence regularly for all inhaled therapies".
Barking & Dagenham, Havering & Redbridge Clinical Commissioning Groups	Guideline	16	16-19	We are concerned that this recommendation will lead to a significant number of patients being placed on triple therapy with all the extra costs and side effects that come with this. 'Moderate' exacerbation has been identified with in the guidance as '*the person has a sustained worsening of respiratory status that required treatment with systemic corticosteroids and/or antibiotics'.* Unfortunately on many occasions in practice, oral corticosteroids and antibiotic are issued without a comprehensive assessment of the worsening of symptoms. Hence significant number of patients will be offered triple therapy. The guidance needs to be more explicit in stating that the exacerbations have to be assessed carefully before triple therapy is offered	Thank you for your comment. The committee has taken stakeholder comments into account and made a specific recommendation to conduct a clinical review before commencing triple therapy. The committee envisaged that this would take the form of a discussion to enable the healthcare professional to investigate the severity of the exacerbations and symptoms and help them determine whether they could have an alternative pathology (e.g. heart failure or anxiety). However, they did not specifically state that the exacerbations have to be assessed carefully before triple therapy is offered.
Barking & Dagenham, Havering & Redbridge Clinical	Guideline	16	24	Line 24 – '*If symptoms do not improve, switch back to LAMA+LABA'* should equally apply to recommendation 1.2.15. If within 6-12 months, the exacerbations are not reduced, then why take the extra risks of side effects including pneumonia.	Thank you for your comment. The committee agreed that based on evidence in people taking LABA + LAMA compared to triple therapy with continued exacerbations, the benefits of reduced exacerbations outweighed the risks of pneumonia and an immediate switch could be justified without a trial period. They also agreed that it would be difficult to have a short trial period

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Commissioning Groups					for exacerbations in practice due to their sporadic nature meaning none might occur in the trial period. Longer treatment periods of 6-12 months as you suggest would require stepping down of treatment and this topic was not within the scope of this update.
Boehringer Ingelheim Ltd	Algorithm	General	General	In the NICE 2010 guideline, in the inhaled therapy treatment algorithm the arrows are either straight or with a dotted line to denote whether therapy should be offered or considered. These terms are clearly presented for all of the treatment options. However, for clarity and consistency, as well as considering the approach taken by the 2010 version of the guideline, the arrow leading back from triple to LAMA/LABA should be solid rather than dotted.	Thank you for your comment. The algorithm was updated in 2018 and the current version clearly states 'offer' or 'consider' rather than relying on line style. However, the committee has taken your comment into account and have updated the algorithm arrows to solid lines in all cases to reduce misunderstanding.
Boehringer Ingelheim Ltd	Algorithm	General	General	BI welcome the inclusion of the statement 'be aware of an increased risk of side effects (including pneumonia) in people who take ICS'. It is important to ensure that healthcare professionals keep this in mind when escalating treatment to include ICS, particularly in line with statements 1.2.15 and 1.2.16 when the patient has already been prescribed LAMA/LABA and is stepping up treatment. When the patient has stepped up to triple and there is no visible benefit to the patient, the fact that there is an increased risk of side effects alongside the increased cost means that there is potentially a negative impact	Thank you for your comment. We are glad that you agree with the inclusion of pneumonia as an important side effect of ICS use for clinicians to be aware of. The committee divided people taking LAMA/LABA in to 2 groups based on whether they experience exacerbations (1 severe or 2 moderate in a year) or symptoms that adversely impact their quality of life in the absence of this level of exacerbations. They agreed that for the former groups the evidence of benefit was clearer and recommended escalation to triple therapy. However, the committee have included a new recommendation to document and review the reason for continuing ICS use this to try to ensure that people do not continue to take ICS unnecessarily.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				of retaining patients on triple therapy when no benefit is observed. In addition, BI would like to ensure that 'pneumonia' does not become effectively an all-encompassing term for used for 'steroid side effects' – as often it is the key side effect mentioned. Whilst BI recognise the valuable nature and the risk/benefit balance with regards to inhaled corticosteroids, for those patients for whom ICS are not necessary the systemic adverse events, including not just pneumonia but also osteopenia, increased risk of diabetes and adrenal suppression (and its associated effects) are all important to highlight.	For people with symptoms that adversely impact their quality of life in the absence of this level of exacerbations, the committee recommended a 3 month trial of triple therapy with a clinical review at the end, where step-down back to LABA + LAMA is the default unless symptom improvement is seen. The committee agree that this should address concerns around overmedication of ICS and help ensure that no-one is on triple therapy unnecessarily. The committee acknowledge that there are other side effects that occur as a result of ICS treatment, but pneumonia was identified as a particularly important side effect, it was specified as part of the review protocol and there was evidence for this outcome. It was included in the rationale, committee discussions and algorithm on this basis. In addition, the guideline already includes a recommendation highlighting that ICS has side effects and this recommendation was out of scope of this update so the committee was unable to make any changes to it.
Boehringer Ingelheim Ltd	Algorithm/ General	General	General	Overall, BI have concerns relating to the escalation of LAMA/LABA therapy to include ICS in patients who are neither considered as having asthmatic features or steroid responsive, particularly in the light of conflicting evidence with respect to the benefit that triple therapy is able to provide. BI are keen to ensure that criteria are put in place to determine whether a patient should move from LAMA/LABA to triple therapy, either for exacerbations or symptoms, in order to prevent unnecessary escalation from	Thank you for your comment. The committee agreed that improvements in quality of life scores in people with COPD in the KRONOS trial (that did not report recent exacerbations as part of the inclusion criteria) suggested that there may still be some benefits in the use of triple therapy for people with less severe COPD symptoms. The committee recommended that a 3 month trial of triple therapy be consider for these people. The committee decided to retain this recommendation following discussion of stakeholder comments, but they included an additional recommendation focusing on the clinical review that

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				LAMA/LABA therapy to triple therapy. BI are equally concerned by the lack of clarity around the proposal for a 3 month trial for triple therapy, both with regards to the criteria against which success is measured but also the risk that a 3 month review period may be difficult to implement, with the ultimate result of patients not having their therapy reviewed further and being inappropriately retained on triple therapy.	should precede the decision to escalate treatment. This includes requirements for the clinician to revisit and optimise non-pharmacological management of COPD, treatment of tobacco dependence and vaccinations where appropriate and to remind the clinician that there may be alternative causes of the symptoms besides COPD. The committee also improved the recommendation for the 3 month trial to make it clear that there should be another clinical review at this point where reversion to LABA + LAMA is the default unless symptom improvement is seen. They added more detail about this review process to the discussion section of the evidence review. They also added another new recommendation that the reason for ICS use be recorded and reviewed to help ensure that people are not taking ICS unnecessarily.
Boehringer Ingelheim Ltd	Algorithm/ General	General	General	BI strongly agree with the inclusion of optimising inhaler training and technique in 'fundamentals of COPD care' in the algorithm, particularly as this is highlighted as a key focus in the NHS England Long Term Plan. We would recommend that prescribers are reminded to perform this with the patient at each stage before any change of inhaler is initiated, as poor response to therapy may be related to poor inhaler technique or treatment adherence by the patient.	Thank you for your comment and support for this recommendation. The committee agreed that this is an important point and have redesigned the algorithm to make it clearer that that inhaler technique and adherence should be assessed regularly and that inhaled therapies should only be started when people meet certain criteria including have been trained to use inhalers and they can demonstrate satisfactory technique.
Boehringer Ingelheim Ltd	Evidence Review Economic	General	General	BI would like to highlight the high quality of the economic model and the clarity of the associated report.	Thank you for your comment.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	model report				
Boehringer Ingelheim Ltd	Evidence Review Economic model report	6	22	The economic model is based on FEV_1, despite COPD patients being now defined by GOLD stages A,B,C,D (based upon symptoms) rather than 1,2,3,4 (as per the GOLD 2013 guidelines where severity was based solely on lung function).	Thank you for your comment. It would have been an interesting exercise to develop an economic model based on the GOLD A-D categories. However, 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 2018 update to the guideline an evidence review on predicting outcomes using multidimensional severity assessments was undertaken, in which 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 Economic model report	7 18	6 6-11	There is a lack of consistency between the assumptions in the economic model which doesn't allow for a step down from triple therapy and the clinical guideline which recommends trial of triple therapy in certain patients. Please see comment 12 above	Thank you for your comment. The committee made the recommendation to trial triple therapy in patients without asthmatic features because, in their experience, people with COPD exhibit heterogeneity in their response to ICS. Therefore, the objective of trialling triple therapy is to distinguish patients who respond well to treatment from those who do not. The economic model was informed by overall mean treatment effects on exacerbations, FEV1, SGRQ, and TDI from the clinical review. Based on this evidence, it would not have been possible to adequately model treatment "responders" and "non-responders" and, by extension, to satisfactorily model stepping down from triple therapy.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Boehringer Ingelheim Ltd	Evidence Review Economic model report	17	Table 7	Table 7 summarises the treatment effects used in the model, however it is difficult to identify the results from the evidence review document and the ones estimated through indirect comparisons. Cross-referencing the results with the evidence review charts would be helpful.	Thank you for your comment. Values in Table 7 are all taken directly from the clinical review. Text has been added to indicate the specific location of these data in the evidence review chapter.
Boehringer Ingelheim Ltd	Evidence Review Economic model report	17-18	17-23; 1-5	The indirect comparison methodology used to inform the absolute exacerbation rates, transition probabilities, quality of life scores, adverse event rates, and mortality rates for LAMA+LABA is mentioned, but not explained completely clearly. Patients receiving monotherapy, dual or triple therapy have different disease severity, medication history and profile; basing the treatment effects on one monotherapy would therefore raise some concerns of the applicability of those results, and it is uncertain how the methodology takes this into account. A reference to the methodology would be helpful to follow the assumptions and calculations undertaken by the modelling group.	Thank you for your comment. A worked example describing how values for LAMA+LABA were calculated has been added for clarification. Absolute exacerbation rates, FEV1, SGRQ and TDI were relevant to the population of interest, since they are determined by characteristics of the cohort at baseline. These characteristics were obtained for people who specifically met the criteria for the decision problem (patients who continued to exacerbate or remained breathless despite treatment with dual therapy). Adverse event rates originally reflected patients treated with LABA monotherapy. However, a treatment effect for LABA+ICS versus LABA was applied to these to produce adverse event rates associated with LABA+ICS, to which treatment effects for triple therapy and LAMA+LABA were applied to produce absolute adverse event rates for all comparators.
Boehringer Ingelheim Ltd	Evidence Review Economic model report	33	11-15	BI appreciates the discussion on the strengths and limitations of the model, especially regarding the lack of data available for subgroup analysis for COPD patients with/without asthmatic features. However, this is not reflected in the algorithm of the guideline. As discussed in comment 9, a clarification on the wording "offer/consider" help the reader interpret the	Thank you for your comment. The recommendation to *offer* triple therapy to patients whose symptoms are not adequately managed by LABA+ICS reflects the clear clinical benefit of adding a LAMA to LABA+ICS. The weaker recommendations to *consider* triple therapy/a trial of triple therapy in patients on a LAMA+LABA was made because a) the clinical benefits of adding an ICS to LAMA+LABA are less pronounced than those of adding a LAMA to LABA+ICS, b) ICS is associated with an

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				algorithm more accurately, and in line with the committee's intentions	increased incidence of pneumonia, and c) the committee indicated that patients do not have a uniform capacity to benefit from ICS. "Offer" and "consider" terminology is common across all NICE guidelines, and information on the meaning of these terms is available before the recommendations on the online version of the guideline.
Boehringer Ingelheim Ltd	Guideline	General	General	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. **1)** INSTEAD showed that patients with moderate COPD and a low risk of exacerbations can be switched from a LABA/ICS to LABA without symptom	Thank you for your comment. The topic of ICS withdrawal is not within the scope of this update and, as a result, we are unable to change the previous recommendations or add new recommendations to this section of the guideline. However, in response to stakeholder comments the committee made a recommendation to document the reason for continuing ICS use in clinical records and review at least annually with the aim of ensuring that people with COPD do not take ICS unnecessarily. We will pass the information about the INSTEAD, OPTIMO, WISDOM, DACCORD and SUNSET trials and the PCRS steroid step-down plan to our surveillance team to help inform subsequent updates of this guideline.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				deterioration or an increase in exacerbation risk (Rossi et al. 2014. Eur Respir J 44(6): 1548-56) **2)** 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) **3)** 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). **4)** 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 (Chapman et al. 2018. Am J Respir Crit Care Med 198(3): 329-339) **5)** 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	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				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". In this context, it may be useful to consider pre-existing guidance that has been put forward with respect to stepping down ICS, such as guidance from the Primary Care Respiratory Society who have laid out a comprehensive steroid step-down plan, factoring in patient phenotypes and current ICS dose.	
Boehringer Ingelheim Ltd	Guideline	15	22	BI would be keen to see guidance 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	Thank you for your comment. Looking at the dose of ICS doses in inhaled therapies was not within the scope of the systematic reviews that support this update and therefore we are unable to recommend specific doses. However, the committee were aware of the points you raise and they are covered briefly in the discussion section of the triple therapy review as they formed

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				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.	part of a general conversation about formulations during the committee meeting. The section on ICS was not within the scope of this update and as a result, the committee were unable to add any recommendations to this part of the guideline.
Boehringer Ingelheim Ltd	Guideline	16	General	BI would recommend that the specific definition of 'offer/consider' be made clearer in the guideline and on the algorithm itself to assist prescribers with understanding the strength of the evidence upon which the guideline is based. Including the statement from the website "For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain." alongside the treatment recommendations in both the guideline and the algorithm would be useful. During discussion with HCPs BI have noted that there is little differentiation between what 'offer' and 'consider' mean – they are generally perceived to have equal weighting despite the NICE definitions.	Thank you for your comment. "Offer" and "consider" terminology is common across all NICE guidelines, and, as you have noted, information on the meaning of these terms is available before the recommendations on the online version of the guideline. The committee agreed it would be useful to have this information within the algorithm but this was not possible due to space constraints and other information taking precedence.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Boehringer Ingelheim Ltd	Guideline	16	11	BI maintains strong support of 1.2.14 with respect to the escalation of patients who are appropriately receiving ICS/LABA who continue to experience symptoms to the addition of a LAMA.	Thank you for your comment and support of this recommendation.
Boehringer Ingelheim Ltd	Guideline	16	16	1.2.15 There is insufficient critical evidence to suggest that there is a benefit in prescribing inhaled corticosteroids to those patients who have initially been classified as not being steroid responders. It may be useful to consider an approach using eosinophil cutoffs at different stages (in a similar way to how the GOLD 2019 update has approached this) for the initial decision of 'features suggesting steroid responsiveness'; GOLD has considered that a count of >300 cells/microlitre would be the cutoff point, and then if the patient is on LAMA/LABA a count of >100 cells/microlitre would be the threshold for whether triple therapy treatment may be appropriate for exacerbations. It would also be useful to suggest a trial period for triple in this instance too. Presently there is no route to revert back to LAMA/LABA in the event that triple therapy provides no additional benefit to the patient. An analysis by Suissa et al Eur Respir J 2018; 52: 1801848) suggests that there will be some exacerbating patients that don't respond to ICS. In order to assess efficacy with	Thank you for your comment. The evidence from the included clinical trials showed that triple therapy resulted in a reduction in dropouts due to severe adverse events in comparison to LAMA+LABA. It also resulted in a reduction in the rate of severe exacerbations per person per year and an increase in SGRQ responders at 12 months. The committee therefore agreed that for people with 2 moderate or 1 severe exacerbation the benefits outweighed the harms and they recommended triple therapy for these people. They decided against including a trial period for these people because there was more evidence of benefit from triple therapy than for people taking LAMA/LABA with symptoms who did not meet the exacerbation criteria. The committee had considered the use of eosinophil counts during the 2018 update that focused on LAMA monotherapy and dual inhaled therapy, but, based on the evidence included in these reviews, they agreed not to make a specific reference to eosinophil cut offs and included a general reference to a higher blood eosinophil count in the definition of asthmatic features/ features suggesting steroid responsiveness. These

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				respect to exacerbation control, it is likely that the trial period would need to be for longer than 3 months – between 6 and 12 months may be more appropriate, to coincide with an annual or twice yearly review. The IMPACT and TRIBUTE studies are the two studies being used to support the 3 month trial of triple therapy in patients who remain limited by symptoms on LAMA/LABA therapy (through demonstrating improvements in SGRQ response over 12 months). The Suissa analysis shows that both studies demonstrate an exacerbation 'surge' in the month following randomisation, which the paper considers may be a result of two specific factors: the inclusion of patients with past asthma (although patients with current asthma were excluded) and the withdrawal of ICS in patients for whom ICS are indicated. Importantly, the rate of exacerbations is comparable with LAMA/LABA for the subsequent 11 months of the trials. Suissa et al consider that this pattern of 'depletion of susceptibles' suggests there is a subset of patients who would benefit from triple therapy compared to LAMA/LABA, whilst the remaining patients benefit equally from LAMA/LABA. Whilst further investigation is required, this analysis highlights the increased	recommendations were out of scope in this update and the committee were therefore unable to make any changes to them. The committee examined the evidence for eosinophil count thresholds in relation to triple therapy and concluded that, based on the evidence available within the included studies in this review, it was not possible to define a specific threshold or to decide whether single or repeated measurement of eosinophils should be carried out. They noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. KRONOS and IMPACT presented data for exacerbations with an eosinophil threshold of 150 cells/ ul. This review was carried out based on the highest quality evidence available using the methodology in the NICE guideline manual. It only examined RCT evidence comparing dual to triple therapy. Since the Suissa study was not an RCTs, it was not included in our evidence base. We also did not search for or review additional evidence for the use of eosinophil counts to determine treatment options because this topic was not in scope. We will pass your comment about the need for better definitions of asthmatic features and features suggesting steroid responsiveness to assist prescribers in decision making to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				need for better phenotyping of patients and not a uniform approach to trialling all patients on triple therapy. Indeed, what this analysis may also suggest is that patients may not demonstrate any improvement when they start a trial of triple therapy but it is actually the subsequent withdrawal of ICS – and increase in exacerbation rate - that could demonstrate that triple therapy is the most appropriate treatment: this provides further need for better definitions of asthmatic features and features suggesting steroid responsiveness to assist prescribers in making this decision.	
Boehringer Ingelheim Ltd	Guideline	16	20	1.2.16 Given the current evidence, BI believes that the 3 month trial for triple should be removed from the guideline. There is conflicting evidence as to the benefit of initiating ICS therapy for patients taking LAMA/LABA therapy who remain symptomatic. Evidence Review I has predominantly used the IMPACT and TRIBUTE studies to support the 3 month trial of ICS for these patients, however there is some conflicting evidence of the benefit of triple over LAMA/LABA with respect to symptom control. The DACCORD study (Buhl R. et al, Int J COPD 2018: 13; 2557-2568) not only demonstrated a significant reduction in exacerbations with	Thank you for your comment. This review only examined RCT evidence and the DACCORD/Suissa studies were not RCTs, thus were not included. Recommendations are only made based on included evidence. The committee decided to retain this recommendation following discussion of stakeholder comments. However, they amended the recommendation for the 3 month trial to make it clear that there should be another clinical review at this point where reversion to LABA + LAMA is the default unless symptom improvement is seen. They also added another new recommendation that the reason for ICS use be recorded and reviewed to help ensure that people are not taking ICS unnecessarily.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				LAMA/LABA compared to triple therapy, but also had a greater improvement from baseline in COPD Assessment Test (CAT) total score over 1 year. Whilst the Suissa et al analysis was specifically examining the pattern of exacerbations in the study, it could rightly be considered that a raised level of exacerbations within the first month of treatment will have an influence on patients' perceptions of their own health-related quality of life, as reflected within the SGRQ score. Certainly, the evidence currently used to make the recommendation is heavily weighted by the IMPACT study, a study which included severe, exacerbating patients and therefore may not be representative of the guidance that is being put forward here in terms of symptomatic but non-exacerbating patients.	
Boehringer Ingelheim Ltd	Guideline	16	20	1.2.16 Patients at all stages of COPD will often continue to be limited by their symptoms in spite of having their treatment optimised due to the nature of the disease. As such, there needs to be an improved definition of 'person still limited by symptoms' to prevent all patients at the LAMA/LABA stage being potentially inappropriately escalated to triple therapy.	Thank you for your comment. The committee have added in the recommendation for the 3 month trial of triple therapy that "if symptoms have not improved, stop LAMA + LABA + ICS and switch back to LAMA + LABA" to clarify that continuation of limiting symptoms without improvement does not lead to escalation to triple therapy.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Boehringer Ingelheim Ltd	Guideline	16	20	1.2.16 Given the current evidence, BI believes that the 3 month trial for triple should be removed from the guideline. Currently there is no guidance for assessing the effectiveness of a 3 month trial of triple therapy having escalated from LAMA/LABA therapy. It is a concern that without specific guidance to provide the rationale for de-escalation following a trial, there is potential that patients will remain indefinitely on triple therapy without having shown any benefit of introducing the inhaled corticosteroid. BI would welcome guidance based around a well-recognised symptom or health status scale, for example MRC dyspnoea scale or the COPD Assessment Test (CAT), which are both practical to administer in a consultation with a patient but also are able to demonstrate meaningful improvements in patients' symptom control	Thank you for your comment. The committee decided to retain this recommendation following discussion of stakeholder comments. However, they amended the recommendation for the 3 month trial to make it clear that there should be another clinical review at this point where reversion to LABA + LAMA is the default unless symptom improvement is seen. They also added another new recommendation that the reason for ICS use be recorded and reviewed to help ensure that people are not taking ICS unnecessarily. The committee have also added a specific recommendation for a clinical review before escalation to triple therapy and have provided some information about the expected format of this review in the rationale that accompanies the recommendation and the evidence review discussion. Namely that it would involve a conversation with the person with COPD about their symptoms rather than relying solely on objective tools, such as the CAT score. The committee also noted that it was important to explicitly ask the person with COPD if taking the drug had improved their COPD symptoms in the 3 month review.
Boehringer Ingelheim Ltd	Guideline	16	20	1.2.16 Given the current evidence, BI believes that the 3 month trial for triple should be removed from the guideline. Even though the proposed recommendation is for a relatively short 3 month trial, there needs to be a rationale for prescribing ICS in patients who were originally considered to have disease that was not steroid responsive. GOLD have	Thank you for your comment. The committee made the recommendation to trial triple therapy in patients taking LAMA/LABA because, in their experience, people with COPD exhibit heterogeneity in their response to ICS. Therefore, the objective of trialling triple therapy is to distinguish patients who respond well to treatment from those who do not. In practice, not everyone who is steroid responsive will have been identified

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				addressed this issue for exacerbations by providing a lower eosinophil cut off (for exacerbating patients progressing from LAMA/LABA to triple therapy) – it may be useful for NICE to provide more specific direction as patients receiving LAMA/LABA therapy will, due to their disease, naturally have periods when symptoms worsen (as would also occur on triple therapy). It is important both from a clinical and cost perspective that this step is managed very carefully, so as to prevent the mass changeover of patients from LAMA/LABA to triple therapy – a look at how patients have been treated in asthma, which should be considering both escalation and de-escalation of therapy according to the BTS guidance, suggests that in practice very few patients have their treatment de-escalated.	correctly at the dual therapy stage and so some people taking LAMA/LABA will show improvements on triple therapy. The committee examined the evidence for eosinophil count thresholds in relation to triple therapy and concluded that, based on the evidence available within the included studies in this review, it was not possible to define a specific threshold for escalation to triple therapy. They noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. KRONOS and IMPACT presented data for exacerbations with an eosinophil threshold of 150 cells/ ul, while GOLD recommends a completely different threshold. The committee were unable to make recommendations on stepping down from long term treatment with triple therapy as this was not within the scope of this update. However, they have amended the recommendation for the 3 month trial to make it clear that there should be another clinical review at this point where reversion to LABA + LAMA is the default unless symptom improvement is seen. They also added another new recommendation that the reason for ICS use be recorded and reviewed to help ensure that people are not taking ICS unnecessarily.
Boehringer Ingelheim Ltd	Guideline	16	24	Guidance may also be useful in relation to 1.2.16: healthcare professionals may be confused as to whether they need to taper the ICS dose or immediately discontinue ICS if the 3 month trial is not successful: additional recommendations as to	Thank you for your comment. The committee have added in the recommendation for the 3 month trial of triple therapy that "if symptoms have not improved, stop LAMA + LABA + ICS and switch back to LAMA + LABA" to clarify this is an immediate discontinuation.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				how these patients should be taken off steroids would be valuable.	
Boehringer Ingelheim Ltd	Guideline	38	Table 6	BI strongly agrees with the NICE recommendation that patients with COPD are reviewed either at least annually, or 6 monthly. In light of the recommendation of 1.2.16 that patients taking LAMA+LABA who continue to experience symptoms consider a trial of LAMA+LABA+ICS, BI would recommend the inclusion in table 6 that a patient who has been prescribed LAMA+LABA+ICS in this way receives a 3 month review, and recommendations of specific criteria are made to assess whether the inclusion of ICS has had a positive/negative/no impact on the patient. However, with this consideration in mind, the difficulty of the implementation of the 3 month trial needs to be considered: if NICE do not provide any recommendation on the 3 month review, it is unlikely that patients will return for review for at least 6, if not 12 months.	Thank you for your comment. We are glad you agree with the recommendations in table 6. Follow-up of people with COPD was not within the scope of this update and therefore we are unable to make changes to this table. However, the committee have strengthened the wording of this triple therapy trial recommendation to stress that this is meant to last for 3 months only and that triple therapy should be stopped and the person switched back to LAMA+LABA if symptoms have not improved. They have also added a specific recommendation for a clinical review before escalation to triple therapy and have provided some information about the expected format of this review in the rationale that accompanies the recommendation and the evidence review discussion. Namely that it would involve a conversation with the person with COPD about their symptoms rather than relying solely on objective tools, such as the CAT score. The committee noted that it was important to explicitly ask the person with COPD if taking the drug had improved their COPD symptoms in the 3 month review.
Chiesi Ltd	Algorithm	General	General	Chiesi is concerned about the inclusion of '*b*' in the pharmacological algorithm on any reference to ICS which directs to the footnote *'Be aware of an increased risk of side effects (including pneumonia) in people who take ICS'* as this is not a balanced statement.	Thank you for your comment. Whilst the committee acknowledges that the benefits of ICS use outweigh the risks (shown by its inclusion in the recommendations), they agreed that specific side effects like pneumonia should still be highlighted in the guideline and accompanying algorithm. Pneumonia was identified as an adverse event of particular

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				The 2016 EMA PRAC recommendation states that the benefit of ICS outweighs the risk (associated with potential side effects, including pneumonia) in the treatment of COPD.[1] Without reference to this recommendation, the footnote could discourage the use of ICS in appropriate patients by misleading clinicians who are not COPD specialists, as the full balanced context is not presented. Furthermore, on the algorithm there is no footnote/reference to an increased risk of side effects with the other classes of medications. However, every drug included on the algorithm has an effect (therapeutic) and an associated side effect profile (e.g. the cardiovascular side effect profile associated with LAMA/LABAs[2] due to the binding of LAMAs to the cardiac M2 receptors). To avoid potential medication bias, we recommend removing this unbalanced statement from the algorithm. [1]EMA, PRAC recommendation (https://www.ema.europa.eu/documents/press-release/prac-reviews-known-risk-pneumonia-inhaled-corticosteroids-chronic-obstructive-	importance at the scoping stage and measured as its own specific outcome in the review, thus its prominence in the evidence review, guideline and algorithm. In addition, in the meta-analysis the risk of pneumonia was reduced in people taking LAMA+LABA compared to those taking LAMA+LABA+ICS (RR 0.65 [0.50.0.84]).

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				pulmonary-disease_en.pdf) (Accessed February 2019) [2]EMA Assessment (https://www.ema.europa.eu/documents/assessment-report/bevespi-aerosphere-epar-public-assessment-report_en.pdf) (Accessed February 2019)	
Chiesi Ltd	Algorithm	General	General	The guideline recommendation of LAMA/LABAs for *'persons limited by symptoms or has exacerbations despite treatment'* is concerning as LAMA/LABAs are not indicated for the prevention of exacerbations. There is specific regulatory guidance from the European Medicines Agency[3] on how a pharmacological intervention should demonstrate a reduction in exacerbations. An important element is assessing the outcome of moderate or severe exacerbations, as these two sub-categories of exacerbation have been shown to be clinically relevant. For a pharmacological intervention to gain a licence for exacerbation risk reduction, it must be able to demonstrate that its supporting clinical trials successfully meet the EMA requirements. Therefore considering this and the fact that regulators subsequently did not grant LAMA/LABA combination therapies with a licence	Thank you for your comment. Dual therapy was not within the scope of this update and therefore we are unable to make changes to this area. This recommendation was updated in the 2018 review of the COPD guideline.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				for prevention of exacerbations (due to insufficient evidence to support this indication) means they shouldn't be recommended for 'persons with exacerbations' in a guideline. This direction to clinicians to subsequently prescribe off-label without highlighting this fact could have safety implications for patients and potential medico legal consequences for prescribers. Subsequently, this impact on practice should be noted in this section of the evidence review and the MHRA guidance[4], which 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", should be added. The wealth and weight of historical data available with regard to ICS/LABA combinations, and now with fixed triple therapy (included in this review) which shows a superiority in reducing moderate to severe exacerbations in COPD patients, means this off license recommendation isn't necessary as these licensed therapies can be offered as an indicated alternative, thus ensuring patients are receiving an evidence based approach to their COPD treatment. [3]European Medicines Agency. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pa	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				ges/regulation/general/general_content_000426.jsp&mid=WC0b01ac0580034cf6 (Accessed February 2019) [4]MHRA. 2009. Off-label or unlicensed use of medicines: prescribers' responsibilities. Available from: (https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-useof-medicines-prescribers-responsibilities) (Accessed 12/02/19])	
Chiesi Ltd	Evidence Review C Economic Report	General	General	Chiesi welcome the opportunity to comment and review the economic report to address the specific review question for triple therapy. Chiesi would like to acknowledge the work of the committee for prioritising an interim update to the COPD guidelines to include triple therapy following the publication of clinical evidence since the initial scope was commissioned. Chiesi acknowledge the complexity faced by the committee to incorporate the revised GOLD A-D classification in the updated model and understand the decision to base the model on GOLD 1-4 classification. Chiesi agree with the decision to *'use the CPRD data in the model base case, since it reflects the population of interest in a real-world setting'* and the further sensitivity analyses for different scenarios, which demonstrates that triple therapy remains cost effective.	Thank you for your comment. We appreciate your support of the economic model methodology.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

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	Evidence Review C Economic Report	14	Cost Table	The cost per pack for Fluticasone Propionate (AirFluSal Forspirio_Inh 500/50mcg) reads £40.92). MIMS cost per pack for 30 days treatment is £29.97[8] [8]MIMS Online. Available at: www.mims.co.uk (Accessed February 2019)	Thank you for your comment. The cost of £29.97 for AirFluSal Forspiro was used in the economic model. The table has been amended to reflect this.
Chiesi Ltd	Evidence Review C Economic Report	32	8- 9	Can the committee clarify the cost differential between triple therapy and LABA+ICS? '...triple therapy costs an additional £16 per 30 days of treatment versus LABA+ICS'	Thank you for your comment. The cost of triple therapy per 30 days is £44.50. The cost of LABA+ICS per 30 days is £28.46 (calculated by weighting the cost per 30 days for each LABA+ICS inhaler by the number of times prescribed according to PCA data). The cost difference between the two is £16.04 per 30 days. This additional detail has been added to the discussion.
Chiesi Ltd	Evidence Review C Economic Report	32	27-28	Chiesi would like to clarify that the cost of triple therapy for 30 days treatment is £44.50[8], incorrectly typed on this line as £45.50. [8]MIMS Online. Available at: www.mims.co.uk (Accessed February 2019)	Thank you for your comment. This has been amended.
Chiesi Ltd	Evidence Review C Economic Report	33	12-15	Chiesi would support the opportunity for future analysis evaluating subpopulations of interest when further clinical evidence is available.	Thank you for your comment.
Chiesi Ltd	Evidence Review I Triple therapy	27	14	The statement that '*people who switched from LAMA/LABA to triple therapy were more likely to get pneumonia*' is potentially misleading as it does not account for molecular differences between the triple therapies. On *page 31, line 51*	Thank you for your comment. As you note, the committee discussion highlights that different triple therapy inhalers use different doses of ICS and that the different formulations of ICS may differ in their potency. However, ICS dosage and formulation was outside the scope of this review and therefore

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				through to page 32, lines 1 & 2, NICE correctly state the potentially increased risk of pneumonia '*in more potent ICS formulations (namely fluticasone propionate and fluticasone furoate)'*. An observation demonstrated in the IMPACT[5] study, as patients taking the fixed triple therapy, Trelegy (which contains the more potent fluticasone furoate ICS formulation), had a significant increase in pneumonia compared to patients taking LAMA/LABA. Conversely however, in the TRIBUTE[6] study, patients taking the fixed triple therapy, Trimbow (which contains the extrafine formulation of beclometasone dipropionate as its ICS formulation) **had no increase in pneumonia** compared to patients taking LAMA/LABA. Additionally, in the TRINITY[7] study (excluded from this review) there was no significantly increased pneumonia signal between Trimbow and a LAMA. Furthermore, in *Appendix F, page 85, figure 7 & page 86, figure 1 & 2*, the *Pneumonia forest plots,* produced from the systematic review, show the clear difference of the pneumonia signals demonstrated in each trial. These plots highlight the distinct, statistically significant, pneumonia signal with the fluticasone furoate (IMPACT) containing triple therapy, whereas the budesonide (KRONOS) and beclometasone	we are unable to make changes to the inhaled corticosteroid section of the guideline or recommend particular formulations by name. We have added the following text to the discussion section based on your comment: "The committee agreed that it was important that clinicians were aware of the differences in ICS dose between inhalers and triple therapy formulations because they would ideally prescribe the lowest dose of ICS that adequately controls a person's symptoms." .

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				dipropionate (TRIBUTE) containing triple therapies do not show a statistically significant pneumonia signal. Chiesi would like to see these evidenced differences taken into account in the guideline and the algorithm, so clinicians are aware of the different profiles of the fixed triple therapies available (as highlighted in this review) in order to make appropriate evidence based choices. [5] IMPACT study Lipson et al. N Engl J Med 2018; 378: 1671-80 [6] TRIBUTE study: Papi et al. Lancet, 2018;391(10125): 1076-1084 [7] TRINITY study: Vestbo et al. Lancet, 2017; 389(10082):1919-1929	
Chiesi Ltd	Evidence Review I Triple therapy	27	34	Chiesi welcome the statement regarding choosing an inhaler device based on '*cost and minimising the number of inhalers*'. We would recommend that this be linked specifically to fixed triple therapy. On *page 27, line 39* it is noted there is '*a widespread current use of triple therapy*', and we understand there is currently no 'open' triple combination of an ICS/LABA plus a LAMA that is less expensive than the fixed triple inhalers available[8].	Thank you for your comment. Current guidance already specifies that, in general, the number of inhalers should be minimised as far as possible. For this reason, the committee felt that it would be unnecessary to explicitly recommend that triple therapy is provided as a single inhaler. In addition, the committee agreed that it may be appropriate to provide triple therapy as 2 separate inhalers in some instances - such as when trialling triple therapy for patients stepping up from dual therapy, so that they can easily revert to their original treatment if triple therapy is not tolerated. As a result, they did not want to specify that the triple therapy should be administered using a single inhaler, although it is more cost-effective, but rather leave

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				While Chiesi appreciate the TRINITY[9] study has not been included in this review, (excluded due to the research question), this study provides the committee with clinical evidence (in a double dummy study) demonstrating that the fixed triple inhaler, Trimbow, was non-inferior to an 'open' triple combination of a LABA/ICS and a LAMA. Chiesi would like to make the committee aware of this evidence in order to support a recommendation to minimise the number of inhalers when specifically prescribing triple therapy (due to the reasons highlighted above with regard cost, non-inferiority in clinical outcomes as well as the potential benefits associated with minimising the number of inhalers for a patient). [8]MIMS Online. Available at: www.mims.co.uk (Accessed February 2019) [9] TRINITY study: Vestbo et al. Lancet, 2017; 389(10082): 1919-1929	this decision to clinician discretion with the general recommendation to minimise inhaler numbers as a guide. Thank you for the information about TRINITY, but as you note we are unable to include evidence that does not meet the inclusion criteria for this review and therefore the committee are unable to make recommendations based on the findings of the TRINITY trial.
Chiesi Ltd	Guideline	15	1-3 (Point 1.2.9)	The statement *'side effects (pneumonia)'* is potentially misleading. Please refer to our previous comment, *comment number 1*, highlighting the clear evidence that the benefit of ICS outweigh the risk in COPD patients (a statement by the EMA).[10]	Thank you for your comment. The section on inhaled corticosteroids was not within the scope of this update and therefore we are unable to make changes to this recommendation. However, the committee have recommended LABA/ICS (in the 2018 update) and triple therapy (in this update) for people with COPD who meet certain criteria on the basis that for these people the balance of benefits outweighs

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				Therefore, we suggest this full context should always be provided by the addition of the line '*that the benefits of inhaled corticosteroids continue to outweigh the risks'* in the guideline, otherwise it may mislead clinicians prescribing decisions to the potential detriment of their patients. We appreciate that the provision of this full context isn't possible on an algorithm and hence the previous comment in this matrix (*comment number 1*) to remove the *'b'* footnote for the reasons previously outlined. NICE could however include the statement, written to include the full context as outlined above, in the main body of the guideline. [10]EMA, PRAC recommendation (https://www.ema.europa.eu/documents/press-release/prac-reviews-known-risk-pneumonia-inhaled-corticosteroids-chronic-obstructive-pulmonary-disease_en.pdf)	the potential harms and as a result the committee decided against making any changes to the algorithm. Their deliberations are covered in the discussion sections of evidence review I (triple therapy) and review F (inhaled therapies). Please refer to the reviews here.
Chiesi Ltd	Guideline	16	11-19 (Point 1.2.14& 15)	In the guideline, triple therapy has been restricted for patients who have had '*one severe or 2 moderate exacerbations'* despite a wealth of evidence from the TRILOGY and TRIBUTE studies (included in review) showing a significant benefit of triple therapy in patients who had at	Thank you for your comment. The committee decided to set the exacerbation requirement as 1 severe (requiring hospitalisation) or 2 moderate based on the inclusion criteria reported in some of the studies and using their own clinical experience on what was likely to be appropriate in a wider clinical setting. The discussion section of the evidence review now makes it clear that the inclusion criteria in the trials varied with some studies

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				least one moderate or severe exacerbation in the previous 12 months. In the interests of providing balanced evidence based recommendations, Chiesi would welcome acknowledgment that fixed triple therapy (Trimbow) should be an option for patients who have had one moderate or severe exacerbation. Therefore, the recommendation for triple therapy should be expanded to reflect the patient populations included in these reviewed studies, and to reflect the licensed indication[11]. [11]Trimbow SPC (Available at: https://www.medicines.org.uk/emc/product/761/smpc) (Accessed February 2019)	including patients who had at least one moderate or severe exacerbation in the previous 12 months while it was 2 moderate or 1 severe exacerbation in the last 12 months in the IMPACT and FULFIL trials. The committee agreed not to recommend single or multiple inhaler courses specifically as there were some circumstances (for example, trialling a new combination of therapies) where having separate inhalers would be more useful. However, there is an existing recommendation to minimise the number of inhalers.
GlaxoSmithKline	Evidence Review: ITT	24	21 to 23	Regarding the comparison between triple therapy and LAMA+LABA therapy, NICE state that "*high quality evidence from up to 4 studies with up to 9,310 people found no meaningful difference in the rate of moderate to severe exacerbations per patient per year*". The IMPACT study (n>10,000) demonstrated a greater reduction in moderate to severe exacerbations, improvement in health-related quality of life (HRQoL) and lung function (FEV_1) in the triple therapy arm compared to the	Thank you for your comment. NICE evidence statements are generated based on all available evidence for each outcome. The number of people presented with the sample size is the total sample size across all studies for each outcome. The meta-analyses showed no meaningful difference in the rate of moderate to severe exacerbations per patient per year. The definition of no meaningful difference is based upon results not exceeding MIDs for clinical significance for these outcomes, as opposed to statistical significance. Please refer to the methods section in appendix B of the triple therapy review for an explanation of the categories used for our evidence statements.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				LAMA+LABA arm (25% exacerbation reduction p<0.001). FEV_1 – forced expiratory volume	
GlaxoSmithKline	Evidence Review: ITT	24 25	26 to 29 21 to 24	NICE state that "*low to moderate quality evidence from up to 4 studies with up to 9,310 people could not differentiate mortality, the number of people experiencing moderate to severe or severe exacerbations, the number of COPD or cardiac serious adverse events or TDI scores at 12 months for people offered triple therapy compared to LAMA+LABA*". NICE state that "*very low to moderate quality evidence from up to 9 studies with up to 13,252 people could not differentiate mortality, serious adverse events, COPD serious adverse events, pneumonia or the number of SGRQ responders at 3 months for people offered triple therapy compared to LABA+ICS*". The IMPACT study addressed the difference in serious adverse events and exacerbation rates when comparing triple therapy with dual therapy. Mortality was not a primary endpoint for the trial, but it was a pre-specified endpoint for the study.	Thank you for your comment. NICE evidence statements are generated based on all available evidence for each outcome. The number of people presented with the sample size is the total sample size across all studies for each outcome. The results from the meta-analyses could not differentiate the effects of the interventions for the outcomes listed. Please refer to the methods section in appendix B of the triple therapy review for an explanation of the categories used for our evidence statements.
GlaxoSmithKline	Evidence Review: ITT	25	18	Regarding the comparison between triple therapy and ICS+LABA, NICE state that "*very low to high quality evidence from up to 5 studies with up to*	Thank you for your comment. NICE evidence statements are generated based on all available evidence for each outcome. The number of people presented with the sample size is the

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				10,605 people found no meaningful difference in the rate of moderate to severe exacerbations per patient per year". The IMPACT study (n>10,000) demonstrated a greater reduction in moderate to severe exacerbations, improvement in HRQoL and lung function (FEV_1) in the triple therapy arm compared to the ICS+LABA arm (15% exacerbation reduction p<0.001).	total sample size across all studies for each outcome. The meta-analyses showed no meaningful difference in the rate of moderate to severe exacerbations per patient per year. The definition of no meaningful difference is based upon results not exceeding minimal clinically important differences (MIDs) for clinical significance for these outcomes, as opposed to statistical significance. The MIDs were identified through the Core Outcome Measures in Effectiveness Trials (COMET) data base and using committee input. Please refer to the methods section in appendix B of the triple therapy review for an explanation of the categories used for our evidence statements and for details about the MIDs used in this review.
GlaxoSmithKline	Evidence Review: ITT	28	31	NICE state that "*for comparisons between triple therapy and LAMA+LABA the evidence ranged from low- to high-quality and no studies were based in the UK*". The IMPACT study had 15 sites based in the UK, with 147 patients participating in the trial (GSK, Data on file).	Thank you for your comment. We have amended this statement to acknowledge that the IMPACT trial did include a small number of participants from the UK.
GlaxoSmithKline	Evidence Review: ITT	31 32	49 to 51 1 to 3	NICE state that "*it was however raised that some of the doses that will be prescribed to people may be higher than those used in some of the studies or involve more potent formulations of ICS (namely fluticasone propionate and fluticasone furoate), potentially further increasing the risk of*	Thank you for your comment. As you note, the committee discussion highlights that "different triple therapy inhalers use different doses of ICS and that some of the doses that will be prescribed to people may be higher than those used in some of the studies or involve more potent formulations of ICS…"

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				pneumonia. The committee therefore agreed that the increased risk of pneumonia due to the addition of ICS". There is no clinical evidence to support the above statement. We would question the rationale for citing these two molecules specifically, especially given that the risk of pneumonia is recognised as a class effect (European Medicines Agency – Pharmacovigilance Risk Assessment Committee, 2016). GSK are specifically concerned that an indirect inference is made that the effect is specific to these molecules. The Summary of Product Characteristics (SmPC) for fluticasone furoate / vilanterol (92 / 22mcg) states "there is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products". (European Medicines Agency, 2016, PRAC reviews known risk of pneumonia with inhaled corticosteroids for chronic obstructive pulmonary disease, https://www.ema.europa.eu/en/documents/press-release/prac-reviews-known-risk-pneumonia-inhaled-corticosteroids-chronic-obstructive-	Based on your comment, we have removed the reference to specific formulations of ICS. We have added the following text to the discussion section based on other stakeholder comments: "The committee agreed that it was important that clinicians were aware of the differences in ICS dose between inhalers and triple therapy formulations because they would ideally prescribe the lowest dose of ICS that adequately controls a person's symptoms."

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				pulmonary-disease_en.pdf, date accessed; 28 February 2019) (Electronic Medicines Compendium (eMC), 2019, Summary of Product Characteristics - Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed, https://www.medicines.org.uk/emc/product/5226/smpc, date accessed 4 March 2019)	
GlaxoSmithKline	Evidence Review: ITT	33	48	NICE state that "the evidence shows that addition of an ICS produces less clinical benefit than addition of a LAMA for patients on dual therapy". The IMPACT study (n>10,000) demonstrated a 25% reduction in the annual rate of moderate / severe exacerbations in the triple therapy group versus the LAMA+LABA group (p<0.001). This was a greater reduction than was seen when comparing the triple therapy cohort with ICS+LABA arm (15% reduction in moderate / severe exacerbations p<0.001).	Thank you for your comment. NICE take into account all available and applicable evidence for each outcome. The results of the meta-analysis will not always reflect the results of one clinical trial, and the threshold for clinical significance is not identical to the threshold for statistical significance. In addition, the committee took into account the differing balance of benefits associated with triple therapy compared LAMA/LABA or LABA/ICS across multiple outcomes when making their recommendations and this statement.
Kings College Hospital NHS Foundation Trust	Guideline	8 and 9	1.1.18 and 1.1.19	It would be very helpful if this opportunity is taken to clarify the dissonance between recommendations in NICE for the diagnosis of asthma and COPD in terms of spirometry criteria. This is critically important now because of the NHS Long Term plan's focus on accurate and early diagnosis of respiratory disease and the	Thank you for your comment. Diagnosing asthma and COPD was not within the scope of this update and therefore we are unable to make changes to this area. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				national push towards networked models with diagnostic spirometry hubs. Our current guidelines are not fit for purpose in terms of supporting accurate diagnosis and indeed promote variation in care because the same spirometry result could be interpreted or reported differently by different people depending on which guideline they follow. Firstly, in the real world, if a new patient with respiratory symptoms is being worked up for a diagnosis of possible airways disease, surely it is necessary to perform spirometry with reversibility and assess both results before making a diagnosis? The statement that reversibility testing is "not necessary" in COPD but that the diagnosis must be made on post-BD results is confusing to most people, especially a primary care audience. How can the degree of reversibility be known, and a diagnosis of asthma be excluded, unless both tests are done? Secondly, we are now asking clinicians to apply two different sets of diagnostic criteria when differentiating asthma versus COPD. NICE asthma guidance states that >200ml/12% reversibility is significant, whereas the COPD guideline still refers to 400ml or more as significant. So, for example, in the scenario where	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				a 45 y/o man with a primary care diagnosis of asthma age 7 and a 30 pack year hx of smoking has obstructive post-BD spirometry but 300ml/20% reversibility, should this be reported as consistent with COPD alone, or with asthma/COPD overlap? Clearly in specialist hands this patient would also have FENO, an eosinophil count and possibly cross sectional imaging for clarification, but most patients will not see a specialist. Our national guidelines need to support the provision of sensible reports for patients seen in a primary care diagnostic hub. These questions are also really important because treatment with ICS/LABA is now recommended for any patient with asthma/COPD overlap and we need to make sure that the right patients are going to be prescribed these high cost medications with potential for significant harm in the wrong setting. With Respiratory as a national priority for the first time in a generation, we should take this opportunity to make sure, as a respiratory community, that our national guidance is sensible, consistent and fit for purpose.	

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
KSS AHSN Patient Safety Collaborative	Guideline	16	11-19	We would suggest including a line reminding that smoking cessation should be re-addressed prior to considering stepping up inhaled therapy	Thank you for your comment. The committee agreed with your comment that that smoking cessation should be re-addressed prior to considering stepping up inhaled therapy and they have included an additional recommendation for a clinical review at this point that includes consideration of whether the person's non-pharmacological COPD management has been optimised and they have used or been offered treatment for tobacco dependence if they smoke. This is also highlighted in the algorithm where smoking cessation (treating tobacco dependence) is included in the treatment algorithm as the first point in 'the fundamentals of COPD care', alongside a statement that this should be revisited at every review.
KSS AHSN Patient Safety Collaborative	Guideline	42	3	There is a recent trial showing non-inferiority of prednisolone for 5 days. Would the committee consider recommending a 5 day course as standard?	Thank you for your comment. Based on stakeholder comments, the NICE guideline updates team conducted further subgroup analyses and the committee agreed to recommended oral corticosteroid courses of 5 days, because the evidence showed no benefit from taking corticosteroids for more than 5 days and shorter courses of 5 days are routinely used in clinical practice already.
NHS Central London CCG	Evidence review – triple therapy	23	6	This figure is incorrect if the lowest current prices of LABA/ICS and tiotropium inhalers are used.	Thank you for your comment. The price used for LABA+ICS reflects current prescribing patterns, rather than the cost of the cheapest product. We also conducted sensitivity analyses in which the cheapest product was used for every regimen (see Table 6 and Table 10), which showed that triple therapy still remains cost effective under these circumstances.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
NHS Central London CCG	Evidence review – triple therapy	24	2-3	See our comment 1. The costs do not reflect the price of the lowest priced LABA/ICS and tiotropium inhalers, and it is highly likely that prices of LABA/ICS and tiotropium inhalers will fall in the next few years whereas the prices of the triple inhalers are unlikely to fall substantially for many years as they each include a drug with a long remaining patent life.	Thank you for your comment. The price used for LABA+ICS reflects current prescribing patterns, rather than the cost of the cheapest product. We also conducted sensitivity analyses in which the cheapest product was used for every regimen (see Table 6 and Table 10), which showed that triple therapy still remains cost effective under these circumstances. Economic analyses do not typically account for future variation in drug prices, since changes in acquisition costs are unpredictable. If prices change substantially in future, there may be precedent to reassess cost effectiveness. However, the low ICER of triple therapy versus LABA+ICS indicates that the cost of the latter would have to fall quite substantially for triple therapy to no longer be considered cost effective.
NHS Central London CCG	Evidence review – triple therapy	27	29-30	The conclusion that using a single inhaler device is more cost effective appears not to be based on using the lowest priced LABA/ICS and tiotropium inhalers. The conclusion may well be incorrect because of this.	Thank you for your comment. The price used for LABA+ICS reflects current prescribing patterns, rather than the cost of the cheapest product. We also conducted sensitivity analyses in which the cheapest product was used for every regimen (see Table 6 and Table 10), which showed that triple therapy still remains cost effective under these circumstances.
NHS Central London CCG	Evidence review – triple therapy	33	41-43	The ICER figure has not been based on using the lowest priced LABA/ICS and tiotropium inhalers.	Thank you for your comment. The price used for LABA+ICS reflects current prescribing patterns, rather than the cost of the cheapest product. We also conducted sensitivity analyses in which the cheapest product was used for every regimen (see Table 6 and Table 10), which showed that triple therapy still remains cost effective under these circumstances.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
NHS Central London CCG	Evidence Review Economic report	32 (and probably others)	28	The costs per 30 days overstate the price of using two inhalers. Fobumix DPI 160/4.5mcg 120 dose (2bd)+ Spiriva Respimat 2.5 mcg (2od): £44.50 Trelegy & Trimbow (triple drug inhalers) cost £44.50. Fobumix is a generic Symbicort. This overstatement of the price of using two inhalers is important because (1) both marketed triple inhalers include drugs with long remaining patent lives, so that their prices are unlikely to fall for many years, and (2) there is already worthwhile price competition between 'generic' LABA + ICS inhalers and we can expect prices to continue to fall. Tiotropium is also off patent and at least one generic product is already available – again, it is reasonable to hope and expect that the price of inhaled tiotropium will fall in the next few years. In a few years time it is highly likely that the triple inhalers will be more expensive than separate LABA/ICS and tiotropium inhalers.	Thank you for your comment. It should be noted that the committee did not explicitly recommend that triple therapy should always be provided as a single inhaler, as there may be some instances where it is more appropriate to prescribe two separate inhalers. We have added text to the committee discussion to make it explicit that one of the grounds on which they declined to make a prescriptive recommendation in favour of single-inhaler therapy was because they feared it would have the effect of diminishing price competition. However, economic analyses do not typically account for future variation in drug prices. In this case, the cost per cycle of triple therapy delivered as 2 separate inhalers was based on current prescribing patterns of LABA+ICS and LAMA inhalers (rather than the cost of the cheapest devices), which is also common practice.
NHS Central London CCG	Evidence Review Economic report	33	44-45	It needn't produce a substantial increase in ICERs if the lowest priced LABA/ICS and tiotropium inhalers are used. See our comment 1.	Thank you for your comment. The price used for LABA+ICS reflects current prescribing patterns, rather than the cost of the cheapest product. We also conducted sensitivity analyses in which the cheapest product was used for every regimen (see Table 6 and Table 10), which showed that triple therapy still remains cost effective under these circumstances.
NHS Central London CCG	Guideline	53	20-29	It seems reasonable for the committee not to make a recommendation in favour of single or multiple inhaler devices. However, as per our	Thank you for your comment. The cost per cycle of triple therapy delivered as 2 separate inhalers was based on current

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				comments above, the economic modelling seems not to have used the prices of the lowest priced LABA/ICS and tiotropium inhalers, so that (lines 23-24) it is probably not correct to conclude that using a single inhaler device is more cost effective. Please can that comment be omitted? Importantly, implementation of the committee's reasonable decision not to make a recommendation in favour of single or multiple inhaler devices is likely to be hampered by the presentation of section 1.2.17 (page 16 line 25 to page 17 line 3). The manufacturers of the triple inhalers (which include drugs that will not come off patent for many years, so that their price is unlikely to fall) are likely to emphasise the recommendation to 'minimise the number of inhalers…..as far as possible'. It would be useful if a sentence could be added as a new section below 1.2.17: "When LABA + LAMA + ICS is used, there is no recommendation in favour of either single or multiple inhaler devices."	prescribing patterns of LABA+ICS and LAMA inhalers, rather than the cost of the cheapest devices. The committee were not able to make any changes to the recommendation on minimising the number of inhaler devices because the recommendation was out of scope of this update. They agreed that because the recommendation already included cost as part of the decision making process that it was unnecessary to make any additional recommendations on the choice of device types specifically for triple therapy.
NHS England	Guideline	General	General	We welcome the 2019 update which is a minor but important modification of the 2018 guideline. The update covers advice on triple inhaled therapy and short course prednisolone. This advice coincides with the availability of triple inhaler combinations .It is compatible with the	Thank you for your comment and this information.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				respiratory ambitions in the Long Term Plan. (MM)	
NHS England	Guideline	General	General	The guidance largely remains unchanged, only a few aspects have been updated in the light of latest evidence. On the overall impact of adoption of the guidance and resource implications: • Adoption of the latest recommendations is fairly widespread. • There might be financial implications for the recommended triple therapy inhalers which are new and expensive. Guideline authors acknowledge this observation and it is their opinion that the cost will be offset by reduced number of exacerbations and possible hospital admissions. • Introduction of steroid inhalers in some cases may increase risk of chest infections so might increase use of antibiotics or hospital admissions, but again improvement in the quality of life and general reduction in exacerbations is expected to help improve quality outcomes. • Broadly speaking there are no additional funding or workforce requirements to	Thank you for your comment and the information about implementation.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				consider in order to implement new/updated recommendations for management of COPD.	
NHS England	Guideline	1.2.13-16	General	These are sensible and pragmatic suggestions to consider when moving from LAMA/LABA or ICS/LABA to triple therapy. Reducing the total number of inhalers by using a single triple combination inhaler is likely to improve compliance and reduce the risk of poor inhaler technique. Although not considered in the guideline, this advice will also fit with the environmental sustainability policy which aims impact MDI greenhouse gas emissions by reducing total inhaler usage.	Thank you for your comment and support of the triple therapy guidance.
NHS England	Guideline	1.3.16	General	Sensible advice about limiting steroid course to seven days will limit harm from prolonged steroid usage.	Thank you for your comment and support of the new guidance.
NHS England	Guideline	6	3 section 1.1.8	'All health care professionals (HCPs) should have access to spirometry and be competent in interpretation'. GPs and primary care professionals are increasingly moving to be part of MDTs and could not possibly be skilled in everything. I would suggest that all HCPs should have access and that appropriate members of the MDT are skilled at interpreting spirometry.	Thank you for your comment. Spirometry and diagnosing COPD was not within the scope of this update and therefore we are unable to make changes to this area.
NHS North of England Commissioni	Guideline	General	General	Within the new NICE guidance https://www.nice.org.uk/guidance/ng115 there is a lack of advice on what to do with COPD	Thank you for your comment. Stepping down for people already on long-term triple therapy was not within the scope of this update and therefore we are unable to make recommendations

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
ng Support Unit				patients who have ended up on triple therapy but may not need to be there. The published guidance does state: The evidence on triple therapy (LAMA+LABA+ICS) is being reviewed as part of the 2019 update to this guideline. This update is expected to publish in June 2019. In advance of that the respiratory academy have published a reasonably helpful tool https://respiratoryacademy.co.uk/resources/stepping-down-ics-therapy-in-copd-2/ but it would be good to have something endorsed by NICE. The committee do not appear to be looking specifically at protocols for stepping down treatment. I note that in the draft 2019 update the committee have included a draft recommendation to consider conducting an initial 3-month trial of triple therapy to determine if it is effective or not in patients who have symptoms that continue to interfere with activities of daily living. The recommendation also states if symptoms do not improve (….within this 3-month trial), to switch back to LAMA+LABA. This doesn`t cover the large numbers of existing patients who may already be established on triple therapy unnecessarily and how to safely approach a step away from the steroid. That would be helpful.	on this topic. However, in response to stakeholder comments the committee made a recommendation to document the reason for continuing ICS use in clinical records and review at least annually with the aim of ensuring that people with COPD do not take ICS unnecessarily. NICE routinely produce baseline assessment and resource impact tools. To encourage the development of other practical support tools, we run an endorsement scheme aimed at encouraging our partners to develop these in alignment with NICE recommendations. Eligible tools are assessed and if successful, will be endorsed by NICE and featured on the NICE website alongside the relevant guideline. Please visit the above link to start the endorsement process.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Primary Care Respiratory Society UK	Algorithm	Guideline	Guideline	We feel it would be preferable to divide the left hand portion of the algorithm into separate 'breathlessness' and 'exacerbations' pathways. In its current form, prominence is given to patients with COPD with asthmatic features over the majority of COPD patients. The PCRS algorithm at least gives equal prominence to the 3 groups. (See Fig 5 in attached article https://www.pcrs-uk.org/sites/pcrs-uk.org/files/Gold%20article%20only_REV_March2018.pdf) We are in the process of updating this article in light of updated COPD guidelines from NICE and GOLD, and will continue to recommend the PCRS algorithm for primary and community based healthcare practitioners. It is disappointing that once again, similar to the 2010 guidance, that all paths lead to triple therapy and that is what will happen.	Thank you for your comment. The committee reviewed the algorithm and agreed that the "Inhaled therapies" section of the algorithm should be clearly split into 3 separate pathways: LAMA + LABA with limiting symptoms, LAMA + LABA with continued exacerbations, and LABA + ICS, with each of these making up a third of the space to represent the three different patient groups and the three corresponding recommendations. The committee have added a recommendation for a clinical review before people are escalated to triple therapy and this review is intended to ensure that people are not escalated unnecessarily. The recommendation includes reference to determining whether any exacerbations or symptoms are due to COPD and not a comorbidity that could be treated and reviewing whether non-pharmacological management is optimal and whether smoking cessation treatment has been offered if relevant. The committee also included a 3 month review of people who are escalated to triple therapy from LAMA/LABA on the basis of symptoms (and not exacerbations) and made it clear that these people should be stepped down to dual therapy if they do not show benefit within 3 months. Finally, the committee added a recommendation for the clinician to document the reason for continuing ICS use and review at least annually to try to ensure that people are not exposed to the potential harms of taking ICS unnecessarily.
Primary Care Respiratory Society UK	Guideline	16	20-24	We are concerned that this recommendation offering triple therapy to breathless patients (for which there is limited evidence) will allow many patients to progress to triple therapy as they have	Thank you for your comment. Based on stakeholder concerns and to account for the relative uncertainty in this recommendation compared to patients on LABA + ICS or LAMA + LAMA with continued exacerbations, the committee has made

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				chronic symptoms. However, it may be unrealistic to expect a switch back to LAMA+LABA at 3 months if improvement as it will be very difficult to determine a meaningful improvement. In the real world, this will mean that many patients will remain on triple therapy with the inherent risks. In reality, this appears to the same recommendation as the 2010 guidance which has resulted in many patients being on unnecessary triple therapy. It is disappointing that there is no consensus with GOLD for breathless patients as this will cause confusion for practitioners as to which guideline to follow.	changes to the recommendations to include an initial clinical review before commencing triple therapy, and to stress the importance of the review at the end of the three month trial period, where step-down back to LABA + LAMA is the default unless symptom improvement (including breathlessness) is seen. The committee envisage that this should help ensure no-one is left on triple therapy unnecessarily at this stage. In addition, they have made a new recommendation about reviewing and recording the reason for continuing ICS use to try to reduce the numbers of people who remain on ICS unnecessarily. This review was carried about based on the highest quality evidence available using the methodology in the NICE guideline manual, and we are unable to comment on how other guidelines conduct their reviews or make their recommendations.
Primary Care Respiratory Society UK	Guideline	42	3	It is disappointing that there is a lack of consensus about the use of oral corticosteroids between NICE and GOLD, as this may cause confusion. GOLD recommends 40 mg prednisolone daily for 5 days: NICE recommends 30mg daily up to 7 days. How are non-specialist clinicians to decide between which one of these is optimal? Perhaps an additional comment that clinicians need to decide on what is most appropriate for the individual patient in front of them would help to bridge this difference. GOLD recommendation on OCS dose and duration may be appropriate	Thank you for your comment. Based on stakeholder comments, the NICE guideline updates team conducted further subgroup analyses and the committee agreed to recommended oral corticosteroid courses of 5 days, because the evidence showed no benefit from taking corticosteroids for more than 5 days and shorter courses of 5 days are routinely used in clinical practice already. The oral corticosteroid dose was not within the scope of this update and therefore we are unable to make changes to the

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				for some patients, which NICE may be more appropriate for others.	specified dose. This was retained from the previous recommendation based on a 2004 evidence review. This review was updated following the methods outline in the NICE guideline manual based on the highest quality evidence available and we are unable to comment on how other guidelines conduct their reviews or amend our recommendations to match theirs. The recommendations in this guideline and in other NICE guidelines are not expected to replace clinician judgement and it is expected that clinicians will decide on the most appropriate treatment for the individual patient in front of them taking the recommendations and other considerations into account.
Teva UK Ltd	Guideline	General	General	In general we agree with the additional inclusion of information around triple therapy and look forward to receiving the advanced copy of the final guideline to review for any substantive errors 2 weeks before publication as indicated.	Thank you for your comment.
The British Thoracic Society	Algorithm	General	General	This is the front facing document likely to displayed and used in GP surgeries, perhaps without reference to the full guideline. It is therefore the most important document reviewed. Fundamentals The algorithm indicates Pulmonary Rehabilitation (PR) should be completed before considering inhaled therapy. Less than 10% of patients	Thank you for your comment. Pulmonary rehabilitation and SAMA treatment were not within the scope of this update and therefore we are unable to make changes to those areas. However, in the algorithm the offer of pulmonary rehabilitation is not intended to be read as a barrier to treatment with inhaled therapies but is included as a reminder to the clinician to offer this treatment (if relevant for the individual) as part of general COPD care. The algorithm

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				engage with PR even when resources are available. 1) Patients with mild limitation: such patients are not currently enrolled in formal PR, and are not well represented in the evidence base (thus similar gains cannot be assumed especially the reduction in hospital bed days). Inclusion will stretch current services, outcompeting access for those more likely to benefit. Exercise is the most important element and in the era of realistic medicine a more flexible approach, separately providing education whilst promoting exercise (and nutrition) may improve engagement, especially for those currently working. 2) Patients with moderate to severe functional limitation (i.e. those typically represented in the clinical trials): the response to PR is better if the patient is on appropriate bronchodilator therapy. With increasing disease severity, selected patients will gain additional benefit from PR with supplementary oxygen, and even NIV. The evidence base favours performing conventional PR on otherwise optimal therapy to enhance gains.	specifically does not say that this has to have been completed, just offered, prior to starting inhaled therapy. The committee agreed that PR should be offered when indicated by clinical need and have included this in a section of the algorithm (the fundamentals of COPD care) with instructions to revisit these treatments and plans at every review. This should help to stress that these treatments and plans are not once off interventions but need to be revisited regularly based on individual need. Inhaled therapies The algorithm reflects the recommendations in the guideline and as a result, SAMA is still included as this was not within the scope of this update. The committee agreed that the balance of benefits and harms of triple therapy differ between people on LAMA/LABA who have exacerbations and those with symptoms that adversely impact quality of life (including breathlessness) who do not meet the exacerbation threshold and they have structured their recommendations and the algorithm to reflect this. It now has 3 sections including the aforementioned groups and people taking LABA/ICS who have the specified number and type of exacerbations or symptoms. The committee agreed that improvements in quality of life scores in people with COPD in the KRONOS trial (that did not

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				3) PR appears to be a once off intervention; this is not the case. No indication of the interval between courses, and triggers to re-refer, such as following a severe (hospitalised) exacerbation. INHALED THERAPIES SAMA is rarely used as primary reliever: suggest remove (a footnote may be added to describe occasional use, but is not essential). Maintenance therapy 1) We favour distinguishing patients with breathlessness (optimise bronchodilator therapy – LABA/LAMA) from those who also experience frequent exacerbations in whom there is a greater role for adding ICS. 2) The current algorithm recommends triple therapy for patients without exacerbations but with limiting symptoms. As detailed in comment 7, the benefit of adding ICS to LABA/LAMA is largely in reducing ECOPD. Risk/benefit of ICS in patients not experiencing exacerbations (and particularly those with lower eosinophils) is questionable. Airflow obstruction is largely irreversible; symptoms persist. Review and step-down is unlikely to be consistently	report recent exacerbations as part of the inclusion criteria) suggested that there may still be some benefits in the use of triple therapy for people with less severe COPD symptoms. The committee recommended that a 3 month trial of triple therapy be consider for these people. The committee decided to retain this recommendation following discussion of stakeholder comments, but they included an additional recommendation focusing on the clinical review that should precede the decision to escalate treatment. This includes requirements for the clinician to revisit and optimise non-pharmacological management of COPD, treatment of tobacco dependence and vaccinations where appropriate and to remind the clinician that there may be alternative causes of the symptoms besides COPD. The committee also improved the recommendation for the 3 month trial to make it clear that there should be another clinical review at this point where reversion to LABA + LAMA is the default unless symptom improvement is seen. They also added another new recommendation that the reason for ICS use be recorded and reviewed to help ensure that people are not taking ICS unnecessarily. The committee have adjusted the algorithm in response to stakeholder comments. Due to space constraints, they were unable to include details of the review process, but these are covered in the recommendations, rationale and evidence review discussion section. However, the box for the 3 month trial now states "if no improvement, revert to LABA +LAMA".

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				achieved, thus does not mitigate against initiation of triple therapy in a population less likely to show benefit. Concern that his will drive overuse of ICS. 3) There is only a single reference only to de-escalation / step down from ICS: this guideline appears to drive most if not all patients ultimately towards triple therapy. 4) No direct mention of blood eosinophils. Not consistent with GOLD 2019; GOLD 2019 figure 4.3 limits ICS to patients experiencing exacerbations and uses two different eosinophil thresholds to direct when to use LABA/LAMA or ICS/LABA (300) and when to consider adding ICS to LABA/LAMA (100). This is supported by IMPACT and KRONOS data. Clear de-escalation and stopping ICS when not appropriate/ complications arise is included. We recommend considering a similar approach.	Regarding eosinophil counts, the committee examined the evidence for eosinophil count thresholds and concluded that based on the evidence available within the included studies in this review it was not possible to define a specific threshold or to decide whether single or repeated measurement of eosinophils should be carried out. They noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. KRONOS and IMPACT presented data for exacerbations with an eosinophil threshold of 150 cells/ ul and so it is unclear how these could support a threshold of 100 cells/ul as stated in the GOLD guideline. This review followed the methods outline in the NICE guideline manual based on the highest quality evidence available and we are unable to comment on how other guidelines conduct their reviews or examine how they reach their recommendations. The committee agreed that it is important to establish that the threshold of moderate exacerbations is met prior to escalation to triple therapy. They envisaged that exacerbations, their severity and relation to COPD would be captured at the clinical review stage, as part of a conversation ensuring that "acute episode of worsening symptoms are due to COPD exacerbations and are not caused by another physical or mental health condition" or as part of inquiring about people with COPDs quality of life. However, we have added this point to the discussion section of the triple therapy review.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				5) Confirmation of true moderate exacerbations is critical, particularly with self-management in the community (endorsed by NICE 2018). Moderate ECOPD are typically captured by use of rescue meds, but this is often at patient's discretion and may be for minor symptoms on a single day (leading to over-use of prednisolone). Highlight this concern, and that ECOPD should be confirmed by clinical history. Patients not controlled on maximal inhaled therapy: suggest consider specialist referral. Such patients warrant more detailed assessment and selected specialist investigations. Reassess and confirm the diagnosis and treatment, exclude complications and comorbidities. Consider azithromycin, roflumilast and assessment for lung volume reduction procedures / transplantation in appropriate patients.	The algorithm contains a section below the triple therapy boxes that highlights the need to think about further treatment options if the person is not controlled by the treatment options above. This also refers the reader back to the full guideline where there are sections on the topics you list. The algorithm is not intended to be a summary of the whole guideline and it is expected that readers will refer to this document and due to space constraints we cannot add your list of topics.
The British Thoracic Society	Evidence Review Corticosteroids	General	General	We welcome the revision of the previously outdated guidance on duration of oral corticosteroid for COPD exacerbations; however the advised "change" has already been widely implemented in the UK and internationally. We are concerned that there is considerable overuse of oral corticosteroids in this population	Thank you for your comment. We recognise that this change is already common practice in many places and this update was triggered by stakeholder and committee comments about this point. However, based on our methods as detailed in the NICE

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				with substantial iatrogenic harm. This may be further fuelled by increased use of rescue packs (when treatment is indicated, either antibiotics or steroids alone may suffice, but this distinction is the exception rather than the norm). There is limited advice and consideration around which patients and which exacerbations should receive oral corticosteroids. This is also an important research question. There is RCT evidence of lack of benefit in moderate exacerbations with low blood eosinophils. The key questions here have been dodged, which risks condemning patients to continued overuse of steroids for acute exacerbations. To antibiotic stewardship, we call for steroid stewardship.	guideline manual we are required to review the evidence before altering the recommendations. Based on stakeholder comments, the NICE guideline updates team conducted further subgroup analyses and the committee agreed to recommended oral corticosteroid courses of 5 days, because the evidence showed no benefit from taking corticosteroids for more than 5 days and shorter courses of 5 days are routinely used in clinical practice already. The scope of this update was confined to oral corticosteroid duration (and triple therapy) and we are therefore unable to make any changes to the rest of this section of the guideline. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
The British Thoracic Society	Evidence Review Triple Therapy	General	General	The included studies generally select a population with more severe airflow obstruction and more frequent ECOPD than the general COPD population; typically only 3-7% of the general COPD population were eligible to participate in such trials. This is an important limitation, and the assumption that similar outcomes will be achieved if this is more widely applied is almost certainly incorrect. This likely to bias in favour of excessive use of triple therapy.	Thank you for your comment. The recommendations for accessing triple therapy reflect the inclusion criteria of the trials and the committee's clinical expertise and were deliberately intended to restrict triple therapy to people with more severe COPD who had been shown to benefit in the trials and in whom any risks of adding ICS would be overshadowed by benefits in terms of exacerbations. The committee agreed that there was more uncertainty about whether people taking LAMA/LABA with symptoms that affected their quality of life who did not meet the exacerbation criteria would benefit. They recommended a 3 month trial for these

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					people to ensure that they did not remain on triple therapy if they did not see an improvement in symptoms. NICE conducted sensitivity analyses to test for subgroup differences in populations with severity indicators (higher and lower eosinophil counts, with/without an exacerbation in the last 12 months). If the outcomes differed depending on these subgroups this was reported in the evidence review. In studies comparing LABA + LAMA or LABA+ ICS with triple therapy, no subgroup differences were identified between studies which included patients with an exacerbation in the past 12 months compared to those with either no exacerbation in the past 12 months or which didn't have previous exacerbations in the inclusion criteria. apart from change in FEV1 at 12 months for LABA + ICS versus triple therapy.
The British Thoracic Society	Evidence Review Triple Therapy	General	General	There is an inadequate appraisal and discussion on the need for stratifying patients on their likely risk and benefit of ICS response. Particularly around the use of peripheral eosinophil. Here there is a real concern- the committee use the term 'asthmatic features and identify eosinophils as a facet of this. There appears to be no understanding / recognition that eosinophilic inflammation is a common feature of COPD (40%) and not just an overlap of asthma. Analyses on eosinophilic stratification: the findings and conclusion are at odds with global advice GOLD 2019, and the current wealth of	Thank you for your comment. The committee examined the evidence for eosinophil count thresholds and concluded that based on the evidence available within the included studies in this review it was not possible to define a specific threshold or to decide whether single or repeated measurement of eosinophils should be carried out. They noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. KRONOS and IMPACT presented data for exacerbations with an eosinophil threshold of 150 cells/ ul and so it is unclear how these could support a threshold of 100 cells/ul as stated in the GOLD guideline.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				evidence in the literature including meta-analyses. We would be interested in comments from NICE on the GOLD 2019 analysis and recommendations, and rationale for not supporting this.	**This review followed the methods outline in the NICE guideline manual based on the highest quality evidence available and we are unable to comment on how other guidelines conduct their reviews or examine how they reach their recommendations.**
The British Thoracic Society	Evidence Review Triple Therapy	18	Figure 1	Figure 1 P 18 Transitions model: Death has a transition arrow to itself - this isn't feasible without resurrection.	Thank you for your comment. This is a convention in representing Markov models, and indicates that patients in the "death" state will remain in this state in subsequent cycles of the model.
The British Thoracic Society	Evidence Review Triple Therapy	19	Figure 2	This figure and the overall guidance focuses only on treatment escalation and not on step down or withdrawal of ICS. This is a major omission and needs addressing. There is an array of evidence in this area and whilst the committee highlight the adverse effects of ICS and their overuse they have declined to offer evidence based review of withdrawal in this section.	Thank you for your comment. Stepping down treatment for people who have been taking triple therapy long-term is not covered by these recommendations as this topic was not within the scope of the current update and we did not review any evidence for this process. However, the committee did include a trial period of 3 months for people taking LAMA/LABA who had symptoms that affected their quality of life but did not meet the exacerbation criteria. This included the option to revert to LAMA/LABA if there was no improvement in symptoms after this time. The committee have included an additional recommendation following stakeholder comments to ensure that the reason for continued ICS use is recorded and reviewed at least yearly. The economic model did not include stepping down from triple therapy, since it was informed by overall mean treatment effects on exacerbations, FEV1, SGRQ, and TDI from the clinical review. Based on this evidence, it would not have been possible to adequately model treatment "responders" and "non-

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					responders" and, by extension, to satisfactorily model stepping down from triple therapy.
The British Thoracic Society	Evidence Review Triple Therapy	20 21 23	29-30 Table 7 31-33	The economic analysis of separate inhalers must be based on ICS/LABA + LAMA only, an option which is substantially more expensive than a single triple device. The cost of LABA/LAMA + ICS is roughly equivalent to, with some options being cheaper than, current triple preparations. We appreciate that single agent ICS is not licenced in COPD, however in recognition of the financial argument above and clinical arguments below, some local guidelines and formularies specifically allow ICS provided it is co-prescribed with LABA/LAMA. In common with NICE this assumes equivalent outcomes if the same agents are administered separately or in combination. A similar statement from NICE would be clinically useful and substantially reduce costs, thus would be welcomed. LABA/LAMA + ICS is also justified on clinical grounds: • Adding ICS to LABA/LAMA better reflects expected future practice following implementation of NICE guidance. It will be more common to consider adding ICS	Thank you for your comment. As you say, this sensitivity analysis was based on the cost of triple therapy provided as a LABA+ICS inhaler plus a LAMA inhaler. A sensitivity analysis was not conducted using the cost of a LAMA+LABA plus an ICS inhaler since, as you identify, ICS alone is not licensed for the treatment of COPD. Explicitly modelling using the cost of this combination of devices is also unnecessary, since the analysis shows that triple therapy is cost effective at NICE's threshold of £20,000 per QALY, and using a device cost which is equivalent to or cheaper than the one used in the base case would only result in triple therapy appearing equally or more cost effective. The committee recognised that, in some instances, it may be preferable for triple therapy to be delivered via a particular inhaler or combination of inhalers, and they explicitly highlighted the benefit for initiating and discontinuing triple therapy, as you note. This is why the committee did not explicitly recommend that triple therapy should always be provided as a single inhaler.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				to existing LABA/LAMA therapy, which will also facilitate step down. • Some LABA/LAMA combinations are not currently available in a triple combination; this includes the LAMA with the lowest incidence of systemic anticholinergic side effects such as dry mouth (aclidinium). Furthermore, the assumption that all LABA/LAMAs are equivalent is readily open to challenge. We welcome single triple inhaler options. In common with the NICE committee we recognise that there are clinical situations when separate administration is desirable; this can be achieved whilst maintaining cost-effectiveness by using LABA/LAMA + ICS.	
The British Thoracic Society	Evidence Review Triple Therapy	24	14-29; 36-37	The key comparison is between LABA/LAMA and triple therapy. Lack of a signal by eosinophil phenotype is at odds with GOLD 2019 and other sources, including detailed analysis of the differential rate of moderate to severe exacerbations between the relevant arms by continuous blood eosinophil counts from IMPACT. The latter also identifies the thresholds at which there is no benefit from ICS / adverse outcome, and at which confidence intervals completely separate with substantial benefit.	Thank you for your comment. The committee examined the evidence for eosinophil count thresholds and concluded that based on the evidence available within the included studies in this review it was not possible to define a specific threshold or to decide whether single or repeated measurement of eosinophils should be carried out. They noted that the normal levels of eosinophils vary within the population and that different thresholds are used by different centres. KRONOS and IMPACT presented data for exacerbations with an eosinophil threshold of 150 cells/ ul and so it is unclear how these could support a threshold of 100 cells/ul as stated in the GOLD guideline.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				Similar data from Kronos was presented at the last ERS.	This review followed the methods outline in the NICE guideline manual based on the highest quality evidence available and we are unable to comment on how other guidelines conduct their reviews or examine how they reach their recommendations.
The British Thoracic Society	Evidence Review Triple Therapy	26	40-43	The benefit from adding ICS to LABA/LAMA is largely based on exacerbation reduction. The recommendation to step up to triple therapy in patients without (severe or frequent) exacerbations but with persistent symptoms is at odds with this, particularly when applied to the wider COPD population poorly represented in trials (see comment 2) – the low exacerbation comparator group will include patients with no exacerbations, and those with exceptionally infrequent episodes. In COPD, airflow obstruction is at best only partially reversible and the loss of lung parenchyma irreversible, thus persistent symptoms are to be expected. This will drive excessive use of ICS. Reassessment and de-escalation is unlikely to be robustly and consistently achieved; despite the recommendation to review at 3 months.	Thank you for your comment. The recommendations for accessing triple therapy reflect the inclusion criteria of the trials and the committee's clinical expertise. The recommendations were deliberately intended to restrict triple therapy to people with more severe COPD who had been shown to benefit in the trials and in whom any risks of adding ICS would be overshadowed by benefits in terms of exacerbations. The committee agreed that there was more uncertainty about whether people taking LAMA/LABA with symptoms that affected their quality of life who did not meet the exacerbation criteria would benefit. They recommended a 3 month trial for these people to ensure that they did not remain on triple therapy if they did not see an improvement in symptoms. They also added another new recommendation that the reason for ICS use be recorded and reviewed to help ensure that people are not taking ICS unnecessarily.
The British Thoracic Society	Evidence Review Triple Therapy	27 32	27 37-51	The health economic analyses performed indicate the cost benefit of single device for triple therapy – yet the committee fail to recommend cost saving approach which is strange. This contradiction can be resolved and the committee's recommendation for a role for separate devices supported by comparing	Thank you for your comment. Current guidance already specifies that, in general, the number of inhalers should be minimised as far as possible. For this reason, the committee felt that it would be unnecessary to explicitly recommend that triple therapy is provided as a single inhaler. In addition, the committee agreed that it may be appropriate to provide triple therapy as 2 separate inhalers in some instances - such as

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				LABA/LAMA + ICS to single triple device. To ensure both the clinical and costs benefits detailed in comment 5 are achieved this should be explicit; show both analyses (LABA/LAMA + ICS and ICS/LABA + LAMA).	when trialling triple therapy for patients stepping up from dual therapy, so that they can easily revert to their original treatment if triple therapy is not tolerated. As a result, they did not want to specify that the triple therapy should be administered using a single inhaler, but rather leave this decision to clinician discretion.
The British Thoracic Society	Guideline	General	General	Follow up in primary care. In patients with a secure diagnosis of COPD confirmed by spirometry, we raise serious concerns that the current requirement for repeated annual spirometry places undue burden on primary care, contributes little to the management of most patients, and detracts from other elements that consequently fail to be provided. Recent work from Tom Wilkinson's group estimated that spirometry takes up 70% of time available for review, which could be used for self-management advice and other supportive interventions- this needs review and addition. P 37 table 6. Add assessment of comorbidities, confirm annual flu and once off pneumococcal vaccines, promote activity and nutrition, exacerbation recognition supported by a written management plan. We recommend sending patients the BLF COPD Passport to complete prior to assessment, to help direct their own management.	Thank you for your comment. Follow-up of people with COPD was not within the scope of this update and therefore we are unable to make changes to this section and table 6. However, assessment of comorbidities, flu and pneumococcal vaccines and self-management plans are covered in the algorithms under 'fundamentals of COPD care' with a statement that these treatments and plans should be revisited at every review. In addition, committee has made an additional recommendation to conduct a clinical review before commencing triple therapy. This specifically includes mention of ensuring that exacerbations and symptoms are due to COPD and not other comorbidities and that non-pharmacological management has been optimised and smoking cessation treatments offered where relevant.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
The British Thoracic Society	Guideline	General	General	In response to both the scoping document and draft 2018 guideline, we unsuccessfully recommended considering risk-stratification of severe exacerbations by DECAF, and hospital at home selected by DECAF. This has now been selected as an NIHR Signal, which seeks to identify original research most likely to inform practice. https://discover.dc.nihr.ac.uk/content/signal-000691/hospital-at-home-treatment-for-copd-flare-ups https://www.bmj.com/content/364/bmj.k5339 In severe exacerbations, in-hospital mortality is falling but readmissions have proven a harder nut to crack. The HOT HMV RCT of home ventilation defines the subgroup of patients in whom this therapy substantially reduces the risk of readmission or death.	Thank you for your comment and this information. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
The British Thoracic Society	Guideline	8	General	Additional investigations: the addition of a STABLE STATE full blood count- it is important to exclude anaemia in breathless patients and recording the blood eosinophil count is important for decisions on treatment strategy around ICS. Blood eosinophils fall in the setting of sepsis, severe exacerbations and with administration of oral corticosteroids. This needs to be stated clearly for the generalist.	Thank you for your comment. Diagnosing COPD was not within the scope of this update and therefore we are unable to make changes to this area.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
The British Thoracic Society	Guideline	16	20-24	See comments 7&10 in regard to the recommendation for a trial of ICS (triple therapy) in patients with persistent breathlessness but without exacerbations.	Thank you for your comment. We have addressed these concerns in responses to comments 2 and 39.
The British Thoracic Society	Guideline	24	4	We again strongly urge NICE to reconsider their position and to consider seeking independent clinical and legal advice. Smoking is an addiction and not a choice for patients with COPD; to deny a life preserving treatment from smokers is judgemental and wrong. It impinges on patients human rights. The argument that this is about risk reduction is flawed and is unlikely to stand up to independent scrutiny. The life time risk of burns is very low and can be minimised by risk modification, yet the risk of death from withholding LTOT is quantifiable and substantially greater. This advice is at odds with the BTS guidance and the current national standards of care.	Thank you for your comment. Oxygen therapy was not within the scope of this update and therefore we are unable to make changes to this area.
The British Thoracic Society	Guideline	25	5	Short burst oxygen therapy- there is no rationale to offer SBOT at all – the statement 1.2.71 is unclear/incorrect and at odds with BTS guidance. Suggest simplify to do not offer SBOT. Limit oxygen therapy to LTOT and AOT.	Thank you for your comment. Oxygen therapy was not within the scope of this update and therefore we are unable to make changes to this area.
The British Thoracic Society	Guideline	42	3-4	We agree shorter courses of oral corticosteroids are appropriate; however this is catching up with well embedded current practice and evidence.	Thank you for your comment. The introduction to the evidence review for oral corticosteroid duration acknowledges that the previous recommendations are out of date and current practice is for shorter courses. This is also stated in the impact of the

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				Clear guidance on when oral corticosteroids are, and more importantly are not, required would be helpful. There is RCT evidence lack of benefit in moderate ECOPD if blood eosinophils are low normal. Repeated courses of oral prednisolone cause substantial harm. Not all moderate and severe exacerbations need both drug classes. **To the current call for antibiotic stewardship, we strongly endorse steroid stewardship.**	recommendations on practice section of the rationale. This update was initiated to ensure the guideline reflected the evidence and current practice. Based on our methods as detailed in the NICE guideline manual we are required to review the evidence before altering the recommendations. The scope of this update was confined to oral corticosteroid duration (and triple therapy) and we are therefore unable to make any changes to the rest of this section of the guideline. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
The Royal College of General Practitioners	Algorithm	General	General	1. In line with the above, the recommendation to escalate from LABA/LAMA to LAMA/LABAICS on the basis of persistent symptoms should be reconsidered. 2. When escalating therapy (especially to triple) there should be emphasis on the need for healthcare professionals to stop and think, the committee should consider emphasising this in the algorithm.	Thank you for your comment. The committee agreed that improvements in quality of life scores in people with COPD in the KRONOS trial (that did not report recent exacerbations as part of the inclusion criteria) suggested that there may still be some benefits in the use of triple therapy for people with less severe COPD symptoms. The committee recommended that a 3 month trial of triple therapy be consider for these people. The committee decided to retain this recommendation following discussion of stakeholder comments, but they included an additional recommendation focusing on the clinical review that should precede the decision to escalate treatment. This includes requirements for the clinician to revisit and optimise non-pharmacological management of COPD, treatment of tobacco dependence and vaccinations where appropriate and to remind the clinician that there may be alternative causes of the symptoms besides COPD.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					The committee also improved the recommendation for the 3 month trial to make it clear that there should be another clinical review at this point where reversion to LABA + LAMA is the default unless symptom improvement is seen. They also added another new recommendation that the reason for ICS use be recorded and reviewed to help ensure that people are not taking ICS unnecessarily. The committee have adjusted the algorithm in response to stakeholder comments. Due to space constraints, they were unable to include details of the review process, but these are covered in the recommendations, rationale and evidence review discussion section. However, the box for the 3 month trial now states "if no improvement, revert to LABA +LAMA".
The Royal College of General Practitioners	Guideline	16	11	When escalating therapy (especially to triple) there should be emphasis on the need for healthcare professionals to stop and think, and to consider if the patient has an appropriate inhaler device that they can use properly, that their compliance is checked and that their "exacerbations" or symptoms are not actually caused by an alternative pathology. This needs to be done to prevent overprescribing.	Thank you for your comment. The committee has taken stakeholder comments into account and made a recommendation to conduct a clinical review before commencing triple therapy. This specifically includes mention of ensuring that exacerbations and symptoms are due to COPD and not other comorbidities and that non-pharmacological management has been optimised and smoking cessation treatments offered where relevant. This recommendation aims to help ensure that people are not escalated to triple therapy unnecessarily. In addition, there are existing recommendations directly below those on triple therapy that state that the choice of inhaler should be based on a list of points including the person's preference and ability to use the inhalers and that the clinician should ensure that people receive inhalers they have been trained to use. In addition, the algorithm reiterates this point and states **"**assess inhaler technique and adherence

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					regularly for all inhaled therapies" and that inhaled therapies should only be started if "people have been trained to use inhalers and can demonstrate satisfactory technique".
The Royal College of General Practitioners	Guideline	16	20	The recommendation to escalate from LABA/LAMA to LAMA/LABAICS on the basis of persistent symptoms should be reconsidered. We agree with the recommendation that there should be an escalation from LAMA/LABA to triple therapy if there are continued exacerbations, but the recommendation to escalate therapy on the basis of continued symptoms is problematic: 1. We share the committees' concerns about people being stepped up from LAMA+LABA to triple therapy was that the benefits may not outweigh the harms for people who have less severe symptoms, basing this decision of QOL data from Ferguson (2018) may not be sufficient justification for this. 2. As was found with the NICE 2010 COPD Guidelines the recommendation to escalate therapy to triple therapy on the basis of symptoms leads to higher chance of patients ending up on that therapy. Pharmacotherapy does not abolish symptoms in COPD it merely reduces them i.e. there is a high chance that symptoms will persist despite LAMA/LABA and	Thank you for your comment. The committee agreed that improvements in quality of life scores in people with COPD in the KRONOS trial (that did not report recent exacerbations as part of the inclusion criteria) suggested that there may still be some benefits in the use of triple therapy for people with less severe COPD symptoms. The committee recommended that a 3 month trial of triple therapy be consider for these people. The committee decided to retain this recommendation following discussion of stakeholder comments, but they included an additional recommendation focusing on the clinical review that should precede the decision to escalate treatment. This includes requirements for the clinician to revisit and optimise non-pharmacological management of COPD, treatment of tobacco dependence and vaccinations where appropriate and to remind the clinician that there may be alternative causes of the symptoms besides COPD. The committee also improved the recommendation for the 3 month trial to make it clear that there should be another clinical review at this point where reversion to LABA + LAMA is the default unless symptom improvement is seen. They also added another new recommendation that the reason for ICS use be recorded and reviewed to help ensure that people are not taking ICS unnecessarily.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				triple therapy will be added for questionable symptomatic benefit. 3. We welcome that the recommendation specifies there should be 3 month trial of therapy in terms of symptom relief when escalating from IABA/LAMA to ICS. However, in primary care it is possible that patients will not be reviewed objectively at all or at least until the annual check and so will continue with more expensive and potentially unnecessary triple therapy.	
The Royal College of Nursing	General	General	General	It would be helpful to consider the effect of dual diagnosis of bronchiectasis for duration of overactive bladder (OAB) usage. Overall it would also be good to have some objective measure included.	Thank you for your comment. Diagnosing COPD was not within the scope of this update and therefore we are unable to make changes to this area.
The Royal College of Nursing	Guideline	16	11 to 24 (1.2.14 to 1.2.16)	***Offer LAMA+LABA+ICS to people with COPD with asthmatic features/features suggesting steroid responsiveness who remain breathless or have exacerbations despite taking LABA+ICS.*** We note that this recommendation was replaced following an evidence review of inhaled triple versus dual therapies. Replaced by recommendations: 1.2.14 to 1.2.16	Thank you for your comment. The committee has taken stakeholder comments into account and made a recommendation to conduct a clinical review before commencing triple therapy. This specifically includes mention of ensuring that exacerbations and symptoms are due to COPD and not other comorbidities and that non-pharmacological management has been optimised and smoking cessation treatments offered where relevant. This recommendation aims to help ensure that people are not escalated to triple therapy unnecessarily. The guideline already has recommendations covering inhaler technique and in the algorithm the committee have highlighted the importance of assessing inhaler technique

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				"1.2.14 In people with COPD who are taking LABA+ICS, offer LAMA+LABA+ICS if *- their symptoms continue to interfere with activities of daily living* *- they have a severe exacerbation (requiring hospitalisation)* *- they have 2 moderate exacerbations within a year* *1.2.15 In people with COPD who are taking LAMA+LABA, consider LAMA+LABA+ICS* *- they have a severe exacerbation (requiring hospitalisation)* *- they have 2 moderate exacerbations within a year* *1.2.16 In people with COPD who are taking LAMA+LABA and who have symptoms that continue to interfere with activities of daily living, consider a 2-month trial of LAMA+LABA+ICS and* *- if symptoms improve, continue with LAMA+LABA+ICS* *- if symptoms do not improve, switch back to LAMA+LABA"* Our members feel that NICE should consider all causes of breathlessness before starting triple therapy i.e. adherence, obesity, anxiety. It is very difficult assess as the change of two therapies may not even be directly related to their	and adherence regularly for all inhaled therapies by putting these points in a separate box. Regarding activities of daily living, the committee agreed that the best way to determine the effect of COPD on a person was through a general conversation to identify how breathlessness and other key symptoms are impacting the person's quality of life on a day to day basis, and that this would be more useful than relying solely on an objective measure such as the CAT score. The committee amended the recommendation for a 3 month trial in people with symptoms who did not meet the exacerbation criteria to make it clear that if symptoms fail to improve the healthcare professional should stop triple therapy and switch the person back to LAMA/LABA. They also added another new recommendation that the reason for ICS use be recorded and reviewed to help ensure that people are not taking ICS unnecessarily.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				COPD and the initiation of the ICS – sleep or energy levels could improve but nothing else. Or maybe related to other co-morbidities or recovery from an exacerbation. It is considered that Section 1.2.16 needs to be more specific on how impact on activities of daily living (ADLs) and those that have symptoms that interfere with ADLs are measured i.e. use of COPD Assessment Test (CAT) scoring? Should the guidelines state that an increase in CAT score would suggest an 'improvement in symptoms' What is the objective measure? There needs to be some objective measure if giving an inhaled corticosteroid (ICS) for symptoms (not exacerbations) otherwise one would end up having all patients on ICS. CAT is validated and easy to use and at least an improvement (decrease) of two or more therapies gives support to continue. Do we risk missing pneumonia if the symptoms are masked by the introduction of the ICS?	
The Royal College of Nursing	Guideline	41	5 (1.3.17)	*This recommendation was removed following an evidence review of the duration of systemic corticosteroid courses during an exacerbation. Replaced by recommendation:*	Thank you for your comment and support of this change to the oral corticosteroid recommendations.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				1.3.16 Offer prednisolone 30mg daily for up to 7 days. Be aware that there is no benefit from taking corticosteroids for more than 7 days. *It is recommended that a course of corticosteroid treatment should not be longer than 14 days, as there is no advantage in prolonged therapy.* This seems reasonable. No comments received from members on this recommendation.	
The Royal College of Nursing	Guideline	42	3 (1.3.16)	***Prescribe prednisolone 30 mg orally for 7 to 14 days.*** *This recommendation was replaced following an evidence review of the duration of systemic corticosteroid courses during an exacerbation. Replaced by recommendation:* *1.3.16 Offer prednisolone 30mg daily for up to 7 days. Be aware that there is no benefit from taking corticosteroids for more than 7 days*. Our members feel that in terms of oral corticosteroid use the recommendation does not discuss use and duration in those with overlapping asthma? Who may benefit from a longer duration of steroid, however, if it is purely COPD exacerbation then it is clear.	Thank you for your comment. The committee decided that there was no evidence in the review that could provide a basis for giving people with COPD and overlapping asthma an extended course of treatment. However, based on their clinical experience there would not be any necessary changes in treatment for people with COPD and overlapping asthma compared to COPD only for treatment of a COPD exacerbation. They therefore agree that it was unnecessary to add any additional detail for people with COPD and asthma to this recommendation. They noted in the discussion section that people with COPD and asthma should be treated as detailed in asthma guidelines if they have an asthma exacerbation.
The Society & College of Radiographers	Guideline	40	5	The Society and College of Radiographers believes this should be expanded to include the reason for obtaining the chest x-ray (for example	Thank you for your comment. Investigation of exacerbations in people referred to hospital was not within the scope of this update and therefore we are unable to make changes to this area.

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019 update)

Consultation on draft guideline - Stakeholder comments table
5 February 2019 to 5 March 2019

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

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				to exclude other acute causes) and responsive action required as with the other tests.	
The Society & College of Radiographers	Guideline	43	11-13	The Society and College of Radiographers supports the statement "Pulse oximeters should be available to all healthcare professionals involved in the care of people with exacerbations of COPD, and they should be trained in their use" but feels this should also include a recommendation for good communication between healthcare professionals and a written procedure for transportation of the patient around the hospital. For example, the procedure should indicate those patients who should not be transported unescorted and handover information (such as acceptable oxygen saturation range and an alert level) for those who may be.	Thank you for your comment. We are glad you support our recommendation regarding pulse oximeters. However, oxygen therapy during exacerbations of COPD was not within the scope of this update and therefore we are unable to make your suggested changes to this area.
The Society & College of Radiographers	Guideline	50	8-10	The Society and College of Radiographers welcomes the recommendation for additional research into the diagnosis of COPD as an incidental finding on chest x-ray and CT scans including standardisation of practice and reporting terminology in these cases.	Thank you for your comment. We are glad you agree with this recommendation.