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Chronic obstructive disease in over 16s: diagnosis and management

[H] Economic model report

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Evidence reviews

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These evidence reviews were developed by the NICE Guideline Updates Team

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Introduction

The *de novo* economic model described in this chapter was developed to address the following review question:

In people with stable COPD, what is the clinical and cost effectiveness of a LAMA plus a LABA compared with:

- a LAMA alone
- a LABA alone
- a LABA plus an inhaled corticosteroid (ICS)?

Although previous economic evaluations have addressed this question in part, these analyses generally focus on 2 specific comparators, rather than evaluating the entire decision space. Furthermore, these evaluations use data from a limited number of trials in order to inform the relative effects of treatments, whereas the network meta-analysis (NMA) conducted for the clinical evidence review allows relative effects of treatments to be modelled in a more comprehensive way.

The committee prioritised this review question for economic modelling as there is currently considerable variation in practice relating to long-acting bronchodilator prescribing, uncertainty regarding the most cost-effective regimen, and a potentially significant resource impact associated with any recommendations made.

Methods

Model overview

Population

Adults with COPD whose symptoms are not adequately controlled using short-acting bronchodilators.

Comparators

Four treatment regimens are assessed by the economic model: LABA monotherapy, LAMA monotherapy, LABA+ICS, and LAMA+LABA. However, since the model simulates the long-acting bronchodilator treatment pathway over patients' lifetime rather than just the initial treatment, the decision space is more complex than this. For most treatments, there is only one logical choice of regimen when stepping up (that is, intensifying therapy because of insufficient efficacy) or switching treatment (that is, changing medication because of side effects or lack of treatment benefit). For instance, when switching treatment, it is logical that patients would receive a regimen containing the same number of drugs (e.g. switching from LABA monotherapy to LAMA monotherapy), and when stepping up from dual therapy, triple therapy would ordinarily be the logical choice.

However, there is some ambiguity regarding the choice of treatment when stepping up from monotherapy to dual therapy. For instance, it is unclear whether a patient starting treatment on LABA monotherapy should, if required, be stepped up to LABA+ICS or LAMA+LABA. Accounting for this uncertainty in the number of possible treatment strategies provides a total of 6 mutually exclusive options:

1. **LABA -to- LABA+ICS** – start treatment on LABA, and step up to LABA+ICS if required
2. **LABA -to- LAMA+LABA** – start treatment on LABA, and step up to LAMA+LABA if required
3. **LAMA -to- LABA+ICS** – start treatment on LAMA, and change treatment to LABA+ICS if stepping up is required
4. **LAMA -to- LAMA+LABA** - start treatment on LAMA, and step up to LAMA+LAMA if required
5. **LABA+ICS** – start treatment on LABA+ICS without first prescribing a monotherapy
6. **LAMA+LABA** – start treatment on LAMA+LABA without first prescribing a monotherapy

Type of evaluation, time horizon, perspective, discount rate

As per the NICE Reference Case, this evaluation is a cost–utility analysis (reporting health benefits in terms of QALYs), conducted from the perspective of the NHS/PSS, which assesses costs and health benefits using a lifetime horizon, and uses a discount rate of 3.5% per annum for both costs and health benefits.

Model structure

In order to represent the natural history of COPD over time, the model uses a Markov structure, with states based on GOLD severity stages defined by FEV1 percent predicted (mild COPD = FEV1 ≥ 80% predicted; moderate COPD = 50% ≤ FEV1 < 80%; severe COPD = 30% ≤ FEV1 < 50% predicted; very severe COPD = FEV1 < 30% predicted). The model

structure is shown in Figure 1. In each cycle of the model, patients had a probability of moving to a more severe GOLD stage (defined by the natural rate of FEV1 decline over time), and a probability of death (defined by stage-specific mortality rates). In the first cycle of the model, patients could move to a less severe GOLD stage, in order to reflect the initial FEV1 benefit from initiating long-acting bronchodilator therapy.

In each cycle, patients could also experience a hospitalised or non-hospitalised exacerbation, or an adverse event. The model used a 3-month cycle length, which was deemed an appropriate period of time to capture progression between states, as well as interfacing well with clinical trial data on long-acting bronchodilators, which typically use 3-, 6-, or 12-month endpoints.

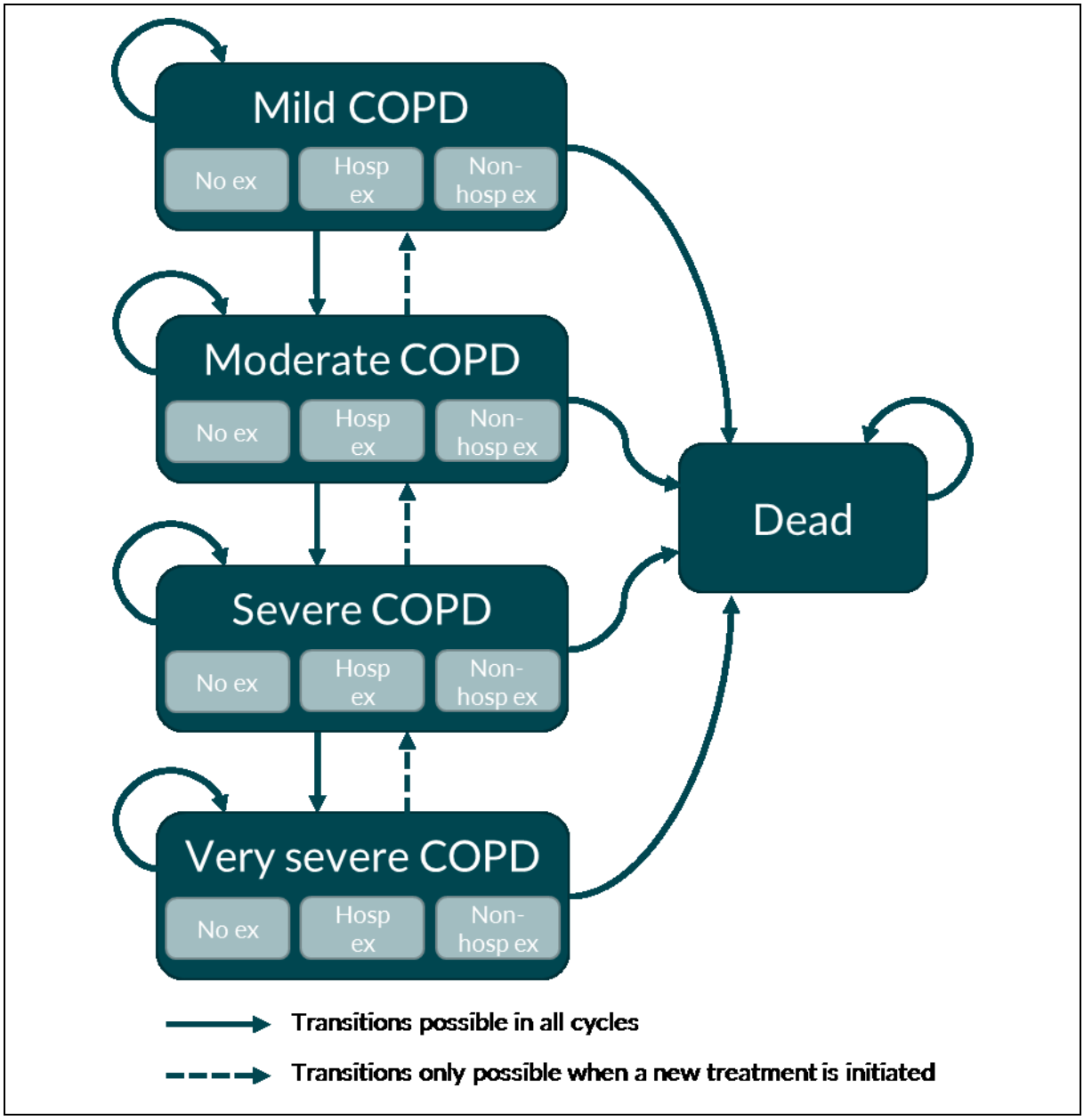

Figure 1 – Overall structure of the model

The model also simulates patients' treatment progression over time. In each cycle, patients have a probability of either stepping up their treatment (adding in another drug) or switching

their treatment (changing to a regimen of the same number of drugs). The pathway for treatment progression is shown in Figure 2. We assumed that patients on dual therapy would, if required, step up to triple therapy (LAMA+LABA+ICS), and that patients receiving this regimen could not make any further treatment changes. The choice of dual therapy regimen was assumed to be a mutually exclusive decision – i.e. when starting with a monotherapy, we modelled stepping up to LABA+ICS or to LAMA+LABA as separate strategies. It should be noted that the transition of LAMA to LABA+ICS was classified as 'stepping up', even though it involves moving to an entirely new regimen rather than adding to a current treatment, as it is a transition from monotherapy to dual therapy.

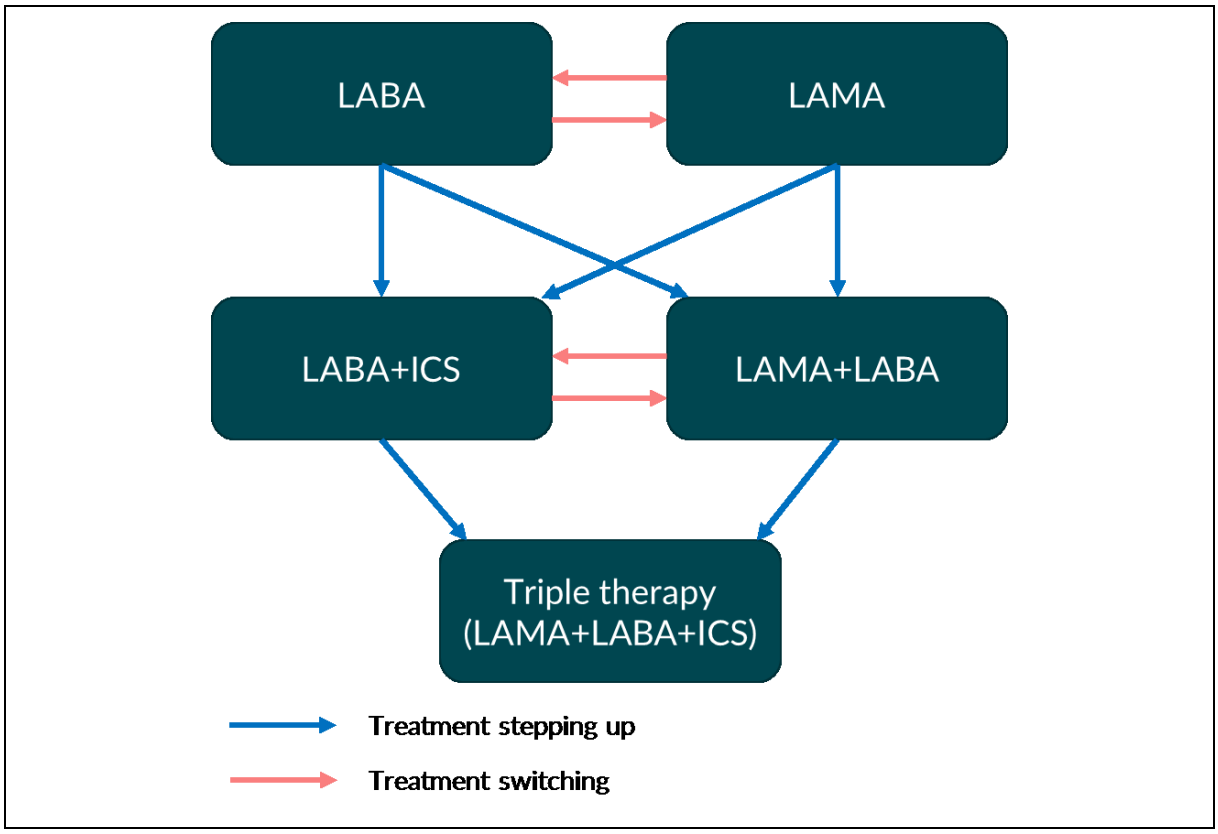

Figure 2 – Treatment progression pathway in the model

Incorporating treatment effects

The network meta-analysis (NMA) conducted for this review question provides a number of outcomes that could be used to model relative treatment benefit: exacerbations, FEV1, breathlessness (TDI), and condition-specific quality of life (SGRQ). However, incorporating all of these outcomes simultaneously in the model would introduce double-counting of benefits. For instance, modelling treatment benefits via relative differences in FEV1 affects patients' stable quality of life by changing the distribution of patients among GOLD stages. Consequently, directly incorporating differences in stable quality of life via the SGRQ outcome would likely overestimate treatment benefits. Therefore, we modelled a number of scenarios, using the following combinations of outcomes from the NMA:

- **Scenario 1: Exacerbations alone**
- **Scenario 2: SGRQ and exacerbations**
- **Scenario 3: FEV1 and exacerbations** – this scenario was modelled by allowing differences in transition probabilities in the first cycle of the model, with more effective

treatments associated with a greater probability of moving to a less severe GOLD stage, as well as including effects of exacerbations on quality of life

- **Scenario 4: TDI and exacerbations** – this scenario was modelled using coefficients from a regression analysis in order to predict the effect of breathlessness on SGRQ score, as well as including effects of exacerbations on quality of life
- **Scenario 5: FEV1, TDI and exacerbations** – as above, this scenario used coefficients from a multiple regression analysis in order to predict the independent effect of FEV1, breathlessness and exacerbations in the previous year on SGRQ, as well as including effects of exacerbations on quality of life

The model also incorporated treatment effects on the probability of stepping up or switching treatment across all scenarios. Due to considerable uncertainty surrounding treatment-specific differences in mortality and adverse events, the impact of including and excluding these treatment effects was explored through three scenarios (referred to as 'options' to distinguish them from treatment benefit scenarios):

- **Option A:** Treatment-specific differences in adverse events and mortality excluded
- **Option B:** Treatment-specific differences in adverse events, but not mortality, included
- **Option C:** Treatment-specific differences in adverse events and mortality included

Uncertainty

In order to explore uncertainty in model results, we conducted both deterministic and probabilistic sensitivity analyses. In deterministic analyses, either alternative point estimates for model parameters were used or different structural assumptions were tested, in order to investigate the impact on results.

For the probabilistic sensitivity analysis, model input parameters were assigned probability distributions reflecting uncertainty surrounding point estimates, defined by standard error/confidence intervals and type of parameter. A random value was drawn from each of these distributions for 1,000 iterations and, for each of these iterations, costs and QALYs for each strategy were recorded. This process allowed uncertainty around model results to be characterised in terms of the proportion of iterations in which each comparator is cost effective at a particular threshold.

The particular distribution assigned to each type of model parameter reflects the nature of the data. Probabilities are parameterised using a beta distribution, to reflect the fact that these values must lie between 0 and 1. Costs are given a gamma distribution, as these values are bound at 0, but theoretically have no upper limit. Mean differences are assigned a normal distribution, as these values are not bound at either end of the number continuum. Relative risks, odds ratios, and hazard ratios are assigned a lognormal distribution, in order to reflect the fact that these parameters are asymmetrically distributed (i.e. values between 0 and 1 favour one comparator, whereas values between 1 and infinity favour the other). Utilities, as with probabilities, are assigned a beta distribution. Treatment effects taken from the NMA conducted for this review question are parameterised by selecting a random iteration from the NMA posterior, rather than assigning distributions to parameters, in order to preserve consistency in outcomes.

For base-case results, structural uncertainty in implementing treatment benefit was also addressed stochastically, using the methodology described by Bojke et al (2009), by randomly selecting 1 of the 5 treatment benefit scenarios for each probabilistic iteration. Results for each of these scenarios individually were also explored in sensitivity analysis.

Baseline population and natural history

Baseline patient population

In order to accurately represent the patient population at its start, the model required data on the following parameters:

- The mean age of the population
- The ratio of males to females in the population
- The distribution of FEV1 scores across the population

While we identified a published source reporting these values for a population of UK COPD patients in general practice (Haughney et al., 2014), the committee agreed that these data were suboptimal for the purposes of the economic model for 2 reasons. First, this study included all patients with a diagnosis of COPD for ≥ 1 year, whereas the population of interest comprises patients who are receiving a long-acting bronchodilator for the first time. Therefore, since the majority of extant COPD patients are treated with long-acting bronchodilators, it is reasonable to expect that the general population of people with COPD would have, on average, more severe symptoms than those initiating treatment for the first time. Second, as well as informing the proportion of patients in each GOLD stage, the initial distribution of FEV1 scores is also used to estimate transition probabilities of moving between GOLD stages in each cycle of the model (see the subsequent section on estimating transition probabilities). In the literature, this distribution is reported with suboptimal granularity to accurately estimate these probabilities.

To address these issues, we obtained data on the population of interest from The Health Improvement Network (THIN) – a dataset of primary care records collected from 562 general practices across the UK. Patients were identified between the period of 1st January 2014 and 31st December 2016, and were selected on the basis of having a clinical diagnosis of COPD and being prescribed one of the regimens of interest for the first time during this period. The COPD and treatment medcodes used to select these patients are reported in full in Appendix A. Data on patients' FEV1 score, sex and age were collected from the GP visit before they were initiated on a long-acting bronchodilator, in order to be certain that the effect of treatment on FEV1 was not captured in the data. In total, records on 4,657 patients were identified. These data are summarised in Table 1, with patient data grouped into 0.1 litre FEV1 bins (scores rounded to the nearest 1 decimal place).

Table 1 – THIN data on the distribution FEV1 scores in people with COPD prior to the first prescription of a long-acting bronchodilator*

FEV1 Score - Litres	Patient count	Male	Female	Mean age
less than 0.64	83	21	62	72.4
0.7	82	22	60	72.5
0.8	140	33	107	71.9
0.9	174	43	131	71.4
1.0	203	65	138	70.5
1.1	255	89	166	70.7
1.2	280	91	189	68.7
1.3	294	110	184	69.6
1.4	292	115	177	68.1
1.5	297	118	179	68.9
1.6	289	112	177	67.4

FEV1 Score - Litres	Patient count	Male	Female	Mean age
1.7	321	165	156	67.0
1.8	260	135	125	66.3
1.9	221	126	95	65.8
2.0	216	132	84	66.2
2.1	195	134	61	64.7
2.2	191	132	59	63.5
2.3	161	117	44	62.7
2.4	118	99	19	63.6
2.5	107	91	16	63.1
2.6	84	76	8	61.7
2.7	88	73	15	63.2
2.8	82	73	9	62.1
2.9	46	43	3	60.6
3.0	41	39	2	61.6
Greater than 3.05	137	131	6	58.0

As the GOLD classification system is based on percent predicted FEV1, rather than absolute FEV1, we had to transform the data in order to calculate the proportion of patients in each GOLD stage at baseline. First, we fitted a parametric distribution to the data. We selected a lognormal distribution as the most appropriate candidate, in order to reflect the skewness of the data, due to the natural lower bound for possible FEV1 scores. For the highest and lowest FEV1 categories (less than 0.64 L and greater than 3.05 L) mean FEV1 scores were unknown. To approximate these values, a measure of the goodness of fit of the lognormal distribution was first calculated, by taking the square root of the sum of squares of differences between the proportion of patients in each FEV1 category and the proportion of patients predicted by the lognormal distribution. We then used numerical optimisation (Microsoft Excel Solver) to minimise this value by adjusting the mean FEV1 score for the top and bottom categories. This produced FEV1 estimates of 4.02 L and 0.62 L for the high and low categories respectively. The resulting lognormal distribution (shown below in Figure 3) was determined to be a good fit by visual inspection.

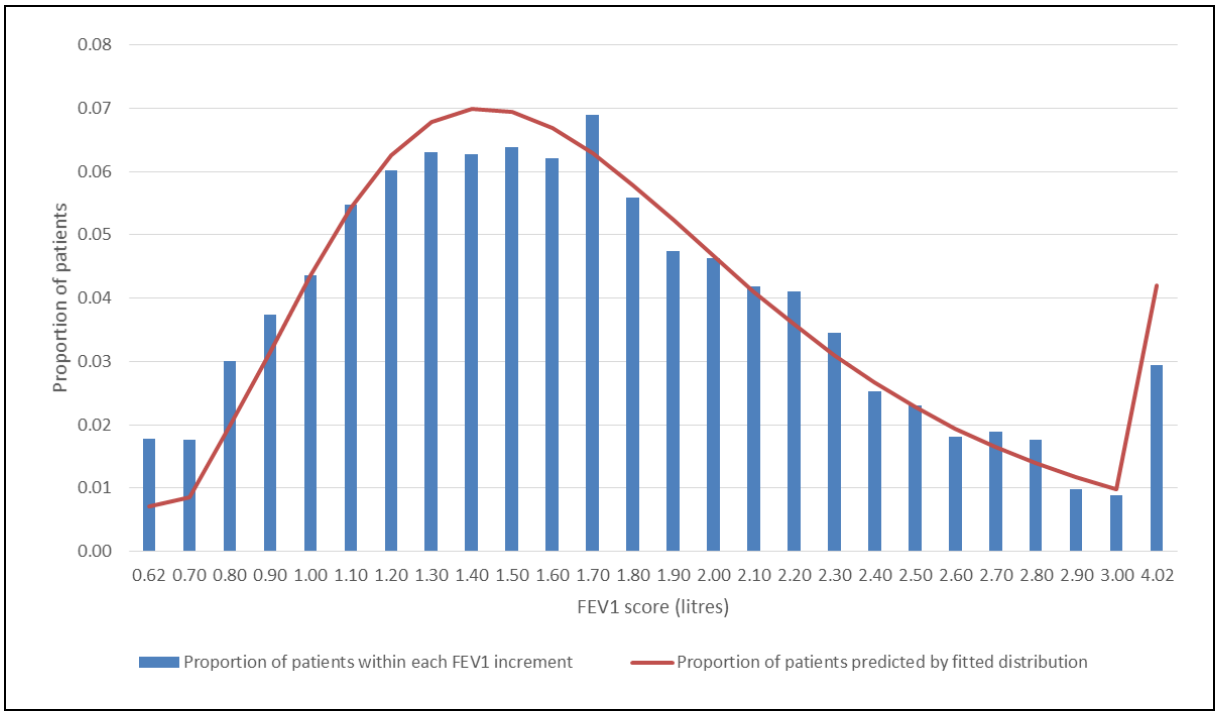

Figure 3 – Lognormal distribution fitted to distribution of FEV1 scores from THIN data

To convert absolute FEV1 scores in litres into FEV1 percent predicted values, we used the following equations (Bellamy et al., 2005):

FEV1 predicted for men (litres) = (0.043 x height) - (0.029 x age) - 2.49

FEV1 predicted for women (litres) = (0.0395 x height) - (0.025 x age) - 2.60

We weighted the coefficients in these equations by the gender split in the THIN population in order to derive 1 equation for the modelled cohort.

Inspection of the THIN data showed that patients' gender and age were not independent of their FEV1 score. Therefore, rather than using average sex and age values for the cohort to estimate FEV1 predicted, we derived regression equations from the THIN data in order to predict these variables based on FEV1 score:

Age = 75.72 + (FEV1 (L) x -5.08)

Logit(proportion male) = -2.76 + (FEV1 (L) x 1.74)

As the THIN data did not report height, we used a mean height for the population taken from the TORCH study of 168.7 cm (Briggs et al. 2017). This source was selected as mean age at baseline in the TORCH cohort (65.0 years) was comparable to that of the THIN population (67.0 years). To calculate the proportion of patients in each GOLD stage, we calculated the proportion of patients falling into each 10-ml FEV1 increment ranging from 0 ml to 5,000 ml, using the previously specified distribution of FEV1 scores. For each of these increments, we also calculated the corresponding FEV1 predicted score in litres and FEV1 percent predicted. Since both the proportion of patients within each increment and the GOLD stage associated with each increment were known, this allowed the overall proportion of patients within each GOLD stage to be estimated. Via this method, we also calculated the mean baseline FEV1 (in litres) and FEV1 % predicted associated with each GOLD stage. These values are displayed below in Table 2.

Table 2 – Proportion of patients, mean FEV1 % predicted, and mean absolute FEV1 for each GOLD stage

GOLD stage	Proportion of patients (SE)*	Mean FEV1 % predicted (SE)	mean FEV1 - litres (SE)
Mild	27.21% (0.007)	96.6% (0.005)	2.602 (0.016)
Moderate	54.80% (0.007)	64.7% (0.003)	1.546 (0.008)
Severe	17.19% (0.006)	42.9% (0.004)	9.49 (0.011)
Very severe	0.80% (0.001)	26.8% (0.044)	5.68 (0.092)
Overall population	100%	69.3% (0.003)	1.719 (0.010)

* Standard errors for the proportion of patients in each GOLD stage were estimated using the total number of patients in the THIN dataset via the formula SE = $\sqrt{(p(1-p)/n)}$

This distribution indicates that patients' disease is, on average, less severe than the source identified from the published literature (Haughney et al., 2014), with very few patients in the very severe GOLD stage. The committee confirmed that this discrepancy is logical, given that patients newly initiated on a long-acting bronchodilator are expected to be, on average, at a less severe disease stage than the general COPD population, the majority of whom are already treated with long-acting bronchodilators. Moreover, one would expect a very small proportion of patients to occupy the very severe GOLD stage, since it is unlikely that their condition would be allowed to reach this stage without escalating treatment to long-acting bronchodilator therapy.

Calculating transition probabilities

The model uses 2 sets of baseline probabilities for transitions between GOLD stages. In the first cycle, transition probabilities reflect the initial FEV1 benefit from long-acting bronchodilator treatment. In subsequent cycles, probabilities reflect the natural decline in FEV1 over time. We took the initial treatment effect from the LABA+ICS arm of the unpublished trial SCO100470 (data taken from the NMA conducted for the clinical review), shown in Table 3. We selected this study because the committee felt that LABA+ICS is the most commonly prescribed treatment in the decision space, and therefore should be used as the reference regimen. SCO100470 was the largest trial with a LABA+ICS arm included in the NMA. We took data on the natural decline in FEV1 over time, stratified by GOLD stage, from the TORCH study (Celli et al., 2008).

Table 3 – Initial change in FEV1 from treatment, and annual decline in FEV1 by GOLD stage

Parameter	Change in FEV1 – litres (SD)	Source
Initial treatment effect - 3 months	0.047 (0.273)	SCO100470 (see clinical review)
Mild COPD - annual FEV1 decline	-0.047 (0.110)	Assumed equivalent to moderate COPD
Moderate COPD - annual FEV1 decline	-0.047 (0.110)	Celli et al. 2008
Severe COPD - annual FEV1 decline	-0.0472 (0.113)	Celli et al. 2008
Very severe COPD - annual FEV1 decline	-0.0284 (0.112)	Celli et al. 2008

To calculate transition probabilities in the first cycle of the model, we calculated the proportion of patients falling into each 10-ml increment of FEV1, ranging from 0 ml to 5,000 ml, as well as the corresponding FEV1 percent predicted for each increment, as described in the baseline patient population section above. We then calculated the absolute FEV1 threshold representing the border between both a less severe and more severe GOLD

stage for each increment. For instance, a patient with an absolute FEV1 score of 1.805 L might have a corresponding FEV1 percent predicted of 73%, which would place the patient in the moderate GOLD stage. The FEV1 percent predicted threshold for a less and more severe GOLD stage would be 80% (for the mild stage) and 50% (for the severe stage), which might correspond to absolute FEV1 scores of 1.970 L and 1.230 L respectively. Next, we assigned a normal distribution to the treatment effect on FEV1 (according to its mean and standard deviation), and used this to estimate the proportion of patients within each 10-ml increment who crossed the threshold into a more or less severe GOLD stage. This distribution was selected as, in the absence of empirical evidence, a symmetrical distribution was deemed to be an appropriate choice for change in a continuous variable over time. Previous analyses (such as Hertel et al, 2012 and the de novo model developed for the 2010 update of this guideline) also implicitly assumed symmetry in the distribution of FEV1 change over time, by simply using mean FEV1 change to estimate transition probabilities.

These data, along with the proportion of patients starting within each increment, were used to calculate the probabilities of both increasing and decreasing in severity in the first cycle of the model for each GOLD stage. The resulting probabilities are shown in Table 4.

Table 4 – Baseline transition probabilities for the first cycle of the model

Transition	Probability
Mild to moderate	13.9%
Moderate to severe	12.5%
Severe to very severe	12.5%
Moderate to mild	14.1%
Severe to moderate	33.0%
Very severe to severe	45.7%

One limitation of this method is that it introduces both a ‘floor’ and ‘ceiling’ effect of treatment – patients in the mild and very severe GOLD stages cannot move to a less or more severe stage, respectively, as a result of treatment. This issue becomes more pertinent in scenarios where differential effects of treatment on FEV1 are implemented in the model (see later section on incorporating treatment effects) and may result in benefits of treatment being somewhat underestimated in those scenarios.

The model makes the assumption that patients may only move to adjacent GOLD stages within 1 cycle. For example, a patient cannot move from the very severe stage to the moderate stage within the space of three months. The committee agreed that this assumption is valid as, despite the wide variability in the initial treatment effect on FEV1, it is unlikely that many patients will experience such a precipitous change in lung function over a short period of time. An exploratory analysis confirmed that, if such transitions were allowed, less than 0.1% of the modelled cohort would transition through 2 or more GOLD stages as a result of initial treatment.

In order to calculate transition probabilities for the second cycle of the model onwards, the model recalculates the distribution of patients within each 10-ml FEV1 increment following the initial treatment effect in the first cycle. This was achieved in the same way as for the initial distribution at baseline, but adding the mean treatment effect at 3 months to the mean FEV1 score at baseline when specifying the distribution. In effect, this shifted the entire baseline distribution up by the FEV1 treatment benefit at 3 months. We calculated transition probabilities by assuming a normal distribution around the annual FEV1 decline for each GOLD stage, and estimated the proportion of patients within each 10-ml increment who crossed the threshold to a more severe GOLD stage. As described above, these probabilities, combined with the proportion of patients in each increment at the start of the

cycle, were used to calculate probabilities per cycle of increasing and decreasing severity for each GOLD stage. These values are shown in Table 5. Unlike the first cycle, the model assumes that patients cannot move to a less severe GOLD stage. This was consistent with the committee's experience – that patients' COPD spirometry readings do not spontaneously improve over time.

Table 5 – Baseline transition probabilities following the first cycle of the model

Transition	Probability
Mild to moderate	3.63%
Moderate to severe	2.37%
Severe to very severe	1.25%
Moderate to mild	-
Severe to moderate	-
Very severe to severe	-

Baseline exacerbation rate

We took data on baseline non-hospitalised and hospitalised exacerbation rate (i.e. rates for the reference regimen, to which treatment effects are applied), stratified by GOLD stage, from a study of the natural history of exacerbations in COPD patients identified through the UK Clinical Practice Research Datalink (CPRD; Rothnie et al., 2018). This source was selected as it reports data on real-world COPD patients (as opposed to those in a clinical trial) in a UK setting, and has a large sample size (n = 37,787). These data are shown in Table 6. These data show that exacerbation rates for mild and moderate COPD are broadly similar. This was consistent with the committee's experience, that differences in disease symptoms are more pronounced between moderate and severe stages, with relatively small differences between patients with mild and moderate COPD.

Table 6 – Baseline exacerbation rates per cycle stratified by GOLD stage

GOLD stage	Non-hospitalised exacerbations	Hospitalised exacerbations
Mild	0.382 (0.371 to 0.390)	0.030 (0.028 to 0.030)
Moderate	0.387 (0.382 to 0.397)	0.024 (0.022 to 0.026)
Severe	0.497 (0.489 to 0.508)	0.051 (0.049 to 0.054)
Very severe	0.60 (0.579 to 0.623)	0.081 (0.075 to 0.088)

Baseline mortality rate

We derived standardised mortality ratios (SMRs) stratified by GOLD stage from a large Norwegian observational study of COPD patients (Leivseth et al., 2013). This source was selected as it has a large sample size (n = 1,540) and reports data on real-world patients. While some unpublished data were identified for UK patients, this source did not report SMRs relative to the general population, meaning that sizeable assumptions would be required to incorporate these data in the model. Since the study reported SMRs separately for men and women, we weighted these values by the gender split in the modelled population in order to calculate overall SMRs. These values are shown in Table 7.

Table 7 – Baseline mortality rate, stratified by GOLD stage

GOLD stage	Males (95% CI)	Females (95% CI)	Overall population
Mild	0.91 (0.76-1.08)	0.75 (0.59-0.95)	0.83
Moderate	1.33 (1.2-1.47)	1.7 (1.46-1.99)	1.51

GOLD stage	Males (95% CI)	Females (95% CI)	Overall population
Severe	1.77 (1.47-2.12)	4.72 (3.62-6.08)	3.21
Very severe	3.47 (2.7-4.39)	5.15 (2.45-9.92)	4.29

Overall, the committee indicated that these values were consistent with their experience; the largest difference in mortality risk occurs between moderate and severe stages. It was not entirely clear why mild COPD is associated with a slightly lower mortality risk than the general population, but this finding is not unprecedented. For example, Shavelle et al. (2009) reports a mortality relative risk of 0.9 for patients with mild COPD compared to the reference population.

The model applies the SMRs to mortality rates for the general population, stratified by year of age, from the Office for National Statistics national life tables for England and Wales, 2014–16. Since these data are also stratified by sex, we use a weighted mean mortality rate calculated using the gender split of the modelled population.

Implementing mortality via this method allows the model to account for differential mortality rates according to both disease severity and age of the cohort.

Adverse event rate

In order to determine which adverse events should be included in the model, the committee reviewed outcomes from a study assessing the safety of long-acting bronchodilators in COPD patients identified through the THIN database (Jara et al., 2012). The committee selected which events to include based on 2 factors: first, events had to be of sufficient importance and occur with sufficient frequency to merit inclusion. Second, there had to be a plausible mechanism of action through which long-acting bronchodilator regimens could differentially affect adverse event rates. Of the outcomes reported, the committee indicated that cardiac arrest, syncope, ventricular tachycardia, myocardial infarction, atrial fibrillation/flutter, angina, stroke, heart failure, pneumonia, constipation, dry mouth, and urinary retention should be included in the model. The committee agreed that, although not included in Jara et al. (2012), diarrhoea and glaucoma should also be included. Therefore, we identified data on these events from alternative sources (Calverley et al., 2007; Miller et al. 2011). Table 8 shows baseline annual rates for each adverse event included in the model. These values relate to patients treated with a LABA, as this was the arm with the highest number of patients (n = 6,073) in Jara et al. (2012).

Table 8 – Annual incidence rate for individual adverse events

Adverse event	Category	Annual rate (95% CIs)	Source
Cardiac arrest	Cardiac acute	0.0017 (0.0005-0.0038)	Jara et al. (2012)
Syncope	Cardiac acute	0.0153 (0.0107-0.0208)	Jara et al. (2012)
Ventricular tachycardia	Cardiac acute	0.0004 (0.0000-0.0016)	Jara et al. (2012)
Myocardial infarction	Cardiac acute	0.01 (0.0063-0.0145)	Jara et al. (2012)
Atrial fibrillation/flutter	Cardiac acute	0.0335 (0.0264-0.0414)	Jara et al. (2012)
Angina	Cardiac chronic	0.0167 (0.0118-0.0224)	Jara et al. (2012)
Stroke	Cardiac chronic	0.0122 (0.0081-0.0171)	Jara et al. (2012)
Heart failure	Cardiac chronic	0.0464 (0.0379-0.0556)	Jara et al. (2012)
Pneumonia	Pneumonia	0.0148 (0.0103-0.0202)	Jara et al. (2012)
Constipation	Other acute	0.0551 (0.0458-0.0652)	Jara et al. (2012)
Diarrhoea	Other acute	0.0266 (0.0162-0.0394)	Calverley et al. (2007)
Dry mouth	Other acute	0.003 (0.0012-0.0057)	Jara et al. (2012)

Adverse event	Category	Annual rate (95% CIs)	Source
Urinary retention	Other acute	0.0109 (0.0071-0.0156)	Jara et al. (2012)
Glaucoma	Other chronic	0.0015 (0.0053-0.0066)	Miller et al. (2011)

To interface with the relative treatment effect outcomes from the NMA (see later section on adverse event treatment effects), we categorised adverse events as cardiac, pneumonia or 'other' events. We also stratified cardiac and 'other' events according to whether they are 'acute' (associated with a one-off cost and QALY loss) or 'chronic' (lasting for the remainder of a patient's life, with a disutility and cost applied for each cycle of the model). Incidence rates for each event category are shown in Table 9.

The model tracks the proportion of patients with a chronic cardiac or chronic 'other' adverse event over time. In order to avoid double-counting of chronic events, the model assumes that patients cannot have more than 1 chronic cardiac or chronic 'other' event at a time. A substantial number of patients will already have cardiovascular comorbidities at the onset of treatment, so the model assumes that the proportion of people with existing chronic cardiac conditions at baseline is 45.8% (SE = 0.005; Haughney et al., 2014).

Table 9 – Incidence rate per cycle of the model for adverse events by category

Adverse event category	Incidence rate
Cardiac acute	0.0152
Cardiac chronic	0.0188
Pneumonia	0.0037
Other acute	0.0239
Other chronic	0.0004

Treatment progression

We take patients' baseline probabilities of stepping-up (changing to a regimen with more drugs) and switching (changing to a regimen with the same number of drugs) from the LABA+ICS arm of a study of treatment evolution in UK COPD patients identified through the CRPD (Wurst et al., 2014). We converted these values to 3 month probabilities, as shown in Table 10.

Table 10 – Baseline probabilities of stepping up and switching treatment

Parameter	Two year probability (95% CIs)	Probability per 3-month cycle
Probability of stepping up treatment	7.4% (6.1%-8.8%)	0.96%
Probability of switching treatment	24.4% (22.2%-26.7%)	3.44%

Costs

Five cost categories were included in the model:

1. **Drug costs** – acquisition costs of long-acting bronchodilators
2. **Maintenance costs** – routine healthcare resource use for each GOLD severity stage
3. **Exacerbation costs** – resource use associated with a hospitalised or non-hospitalised exacerbation
4. **Adverse event costs** – costs associated with treating acute and chronic adverse events

5. **Treatment progression costs** – healthcare costs associated with switching or stepping up treatment

Drug costs

To calculate the cost of each regimen, we used Prescription Cost Analysis (PCA) data for January 2018 to inform the relative frequency of prescribing of individual products within each class. We calculated a cost per cycle for each product using unit costs from the NHS Drug Tariff, and dosage data from each product's summary of product characteristics (SPC). For some LABA products, the SPC specified 2 possible dosages. In these cases, we made the assumption that an equal split of patients used low and high doses. To obtain the overall cost of each regimen, we weighted the cost per cycle of each product by the number of times it was prescribed.

The base case assumes that all patients on dual therapy use a single combination inhaler. We relaxed this assumption in a scenario analysis where 25% of patients on dual therapy were assumed to use 2 separate inhaler devices. To implement this scenario, we used PCA data on individual ICS inhalers. Due to the number of ICS products on the market, and ambiguity in matching less frequently prescribed inhalers to costs in the Drug Tariff, only products with more than 10,000 prescriptions nationally were included. As ICS inhalers alone are not licensed for COPD, we made the assumption that the daily dosage of ICS is equivalent to the dosage when delivered in a LABA+ICS combination inhaler.

To calculate the cost of triple therapy, we made the assumption that 90% of patients use a LABA+ICS combination inhaler plus a LAMA inhaler, and 10% of patients use a LAMA+LABA combination inhaler plus an ICS inhaler. This split was consistent with the committee's experience. We also conducted a sensitivity analysis in which we used the cost of a triple fixed-dose combination inhaler rather than the cost of 2 separate inhalers.

To reflect the fact that patient adherence is not perfect, drug costs were weighted by the proportion of prescribed doses taken from the TORCH study (88.5%; Calverley et al., 2007). It is likely that this is an optimistic estimate of adherence in practice, since participants in clinical trials are generally substantially more likely to take their medication as prescribed. However, it should be noted that treatment effectiveness outcomes from the NMA are also based on clinical trial data. Therefore, using an adherence estimate from a real-world population could unfairly benefit more expensive and more effective regimens, if treatment effects are based on a highly adherent population but costs are reflective of a lower adherence rate.

Table 11 shows data on the relative prescribing frequency, dosage and cost of each individual product. Table 12 gives the calculated mean costs per cycle for each treatment.

Table 11 – Prescribing and cost data for each long-acting bronchodilator

Chemical name	Drug name (as listed in PCA data)	Items dispensed	Cost per pack	Doses	Average daily dosage	Cost per cycle
LABAs						
Formoterol Fumarate	Atimos Modulite_Inh 12mcg (100D)	3053	£30.06	100	3	£82.29
Formoterol Fumarate	Foradil_Inh Cap 12mcg + Inha	569	£28.06	60	2	£85.35
Formoterol Fumarate	Formoterol Easyhaler_12mcg (120 D)	4357	£23.75	120	2	£36.12
Formoterol Fumarate	Oxis 12_Turbohaler 12mcg (60 D)	2858	£24.80	60	1.5	£56.58
Formoterol Fumarate	Oxis 6_Turbohaler 6mcg (60 D)	1167	£24.80	60	3	£113.15
Indacaterol Maleate	Onbrez Breezhaler_Pdr Inh Cap 150mcg+Dev	1934	£32.19	30	1	£97.91
Indacaterol Maleate	Onbrez Breezhaler_Pdr Inh Cap 300mcg+Dev	346	£32.19	30	1	£97.91
Olodaterol	Striverdi Respimat_Inha 2.5mcg (60D)+Dev	203	£26.35	60	2	£80.15
Salmeterol	Neovent_Inha 25mcg (120 D) CFF	19	£29.26	120	4	£89.00
Salmeterol	Salmeterol_Inha 25mcg (120 D) CFF	22770	£29.26	120	4	£89.00
Salmeterol	Serevent_Accuhaler 50mcg (60 D)	6789	£35.11	60	2	£106.79
Salmeterol	Serevent_Evohaler 25mcg (120 D)	5217	£29.26	120	4	£89.00
Salmeterol	Soltel_Inha 25mcg (120D) CFF	1717	£19.95	120	4	£60.68
Salmeterol	Vertine_Inha 25mcg (120 D) CFF	107	£23.40	120	4	£71.18
LAMAs						
Aclidinium Bromide	Aclidinium Brom_Pdr For Inh 375mcg (60D)	9299	£28.60	60	2	£86.99
Aclidinium Bromide	Eklira_Inh 322mcg (60D) (Genuair)	20459	£28.60	60	2	£86.99
Glycopyrronium Bromide	Glycopyrronium Brom_Inh Cap 55mcg + Dev	7666	£27.50	30	1	£83.65
Glycopyrronium Bromide	Seebri_Breezhaler Inh Cap 55mcg + Dev	30740	£27.50	30	1	£83.65
Tiotropium	Braltus_Pdr For Inh Cap 10mcg+Zonda Inh	129290	£25.80	30	1	£78.48
Tiotropium	Spiriva Respimat_Inha 2.5mcg (60D) + Dev	37923	£23.00	60	2	£69.96
Tiotropium	Spiriva_Pdr For Inh Cap 18mcg	132864	£33.50	30	1	£101.90

Chemical name	Drug name (as listed in PCA data)	Items dispensed	Cost per pack	Doses	Average daily dosage	Cost per cycle
Tiotropium	Spiriva_Pdr For Inh Cap 18mcg+HandiHaler	27834	£34.87	30	1	£106.06
Tiotropium	Tiotropium_Inha 2.5mcg (60D) CFF + Dev	28890	£23.00	60	2	£69.96
Umeclidinium Brom	Incruse Ellipta_Inh 55mcg (30D)	52853	£27.50	30	1	£83.65
LABA+ICS						
Beclometasone Dipropionate	Fostair NEXThaler_Inh 100mcg/6mcg (120D)	34631	£29.32	120	4	£89.18
Beclometasone Dipropionate	Fostair_Inh 100mcg/6mcg (120D) CFF	273879	£29.32	120	4	£89.18
Budesonide	DuoResp Spiromax_Inh 160mcg/4.5mcg(120D)	58767	£27.97	120	4	£85.08
Budesonide	DuoResp Spiromax_Inh 320mcg/9mcg (60 D)	44425	£27.97	60	2	£85.08
Budesonide	Symbicort_Inh Pressurised 200/6mcg(120D)	4666	£28.00	120	4	£85.17
Budesonide	Symbicort_Turbohaler 200mcg/6mcg (120 D)	104097	£28.00	120	4	£85.17
Budesonide	Symbicort_Turbohaler 400mcg/12mcg (60 D)	54982	£28.00	60	2	£85.17
Fluticasone Fuorate (Inh)	Fluticasone/Vilanterol_Inha 92/22mcg 30D	9688	£22.00	30	1	£66.92
Fluticasone Fuorate (Inh)	Relvar Ellipta_Inha 92mcg/22mcg (30 D)	55507	£22.00	30	1	£66.92
Fluticasone Propionate (Inh)	Aerivio Spiromax_Inh 500/50mcg (60D)	1388	£29.97	60	2	£91.16
Fluticasone Propionate (Inh)	AirFluSal Forspiro_Inh 500/50mcg (60D)	5509	£29.97	60	2	£91.16
Fluticasone Propionate (Inh)	Fluticasone/Salmeterol_Inh 500/50mcg 60D	20309	£40.92	60	2	£124.47
Fluticasone Propionate (Inh)	Seretide 500_Accuhaler 500mcg/50mcg(60D)	56039	£40.92	60	2	£124.47
LAMA+LABA						
Aclidinium Brom/Formoterol	Aclid/Formot_PdrFor Inh 396/11.8mcg(60D)	1880	£32.50	60	2	£98.85
Aclidinium Brom/Formoterol	Duaklir Genuair_340mcg/12mcg (60D)	11257	£32.50	60	2	£98.85
Indacaterol/Glycopyrronium	Ultibro Breezhaler_Pdr Inh Cap + Dev	16580	£32.50	30	1	£98.85
Tiotropium Brom/Olodaterol	Spiolto Respimat_Inha2.5/2.5mcg(60D)+Dev	7902	£32.50	60	2	£98.85
Tiotropium Brom/Olodaterol	Tiotropium/Olodaterol_Inha2.5/2.5mcg 60D	1814	£32.50	60	2	£98.85
Umeclidinium Brom/Vilanterol	Anoro Ellipta_Inha 55mcg/22mcg (30D)	29900	£32.50	30	1	£98.85

Chemical name	Drug name (as listed in PCA data)	Items dispensed	Cost per pack	Doses	Average daily dosage	Cost per cycle
Umeclidinium Brom/Vilanterol	Umeclidinium/Vilanterol_Inha 65/22mcg30D	3734	£32.50	30	1	£98.85
ICS						
Beclometasone Dipropionate	Clenil Modulite_Inha 100mcg (200D)	252855	£7.42	200	4	£13.54
Beclometasone Dipropionate	Clenil Modulite_Inha 200mcg (200D)	56711	£16.17	200	2	£14.76
Beclometasone Dipropionate	Clenil Modulite_Inha 250mcg (200D)	10342	£16.29	200	2	£14.86
Beclometasone Dipropionate	Clenil Modulite_Inha 50mcg (200D)	70291	£3.70	200	8	£13.51
Beclometasone Dipropionate	Qvar 100 E-Breathe_Inha 100mcg (200 D)	10701	£16.95	200	4	£30.93
Beclometasone Dipropionate	Qvar 100_Inha 100mcg (200 D)	47829	£17.21	200	4	£31.41
Beclometasone Dipropionate	Qvar 50_Inha 50mcg (200 D)	25223	£7.87	200	8	£28.73
Budesonide	Pulmicort_Turbohaler 200mcg (100 D)	10904	£14.25	100	4	£52.01
Triple therapy - combined inhaler (for sensitivity analysis)						
BeclometDiprop/Formoterol/Glycopyrronium	Trimbow_Inh 87mcg/5mcg/9mcg (120 D)	549	£44.50	120	4	£135.35
Fluticasone/Umeclidinium/Vilanterol	Trelegy Ellipta_Inha 92/55/22mcg (30 D)	369	£44.50	30	1	£135.35

Table 12 – Cost per cycle for each long-acting bronchodilator regimen*

Treatment	Cost per cycle
LABA	£74.80
LAMA	£76.93
LABA+ICS	£79.14
LAMA+LABA	£87.49
Triple therapy	£150.76

*Please note that these costs are weighted to capture 11.5% non-adherence

Maintenance costs

Table 13 shows annual resource use inputs for each GOLD stage. We did not identify empirical data on GP visits, respiratory team visits, outpatient visits, spirometry tests and CT scans in the literature, so the committee estimated them. Table 14 shows corresponding unit costs. We inflated values from sources published in previous years to current value using the Hospital and Community Health Services Index (Curtis et al. 2017).

Table 15 shows the total costs for each GOLD stage per cycle of the model calculated from these values.

Table 13 – Annual maintenance resource use inputs

Resource category	Mild COPD	Moderate COPD	Severe COPD	Very severe COPD	Source
GP visit	1	1	1.5	2	Committee consensus
Respiratory team visit	0	0	2	4	Committee consensus
Outpatient visit	0	0	1	2	Committee consensus
Spirometry	1	1	2	3	Committee consensus
Pulmonary rehabilitation	0.02	0.03	0.06	0.09	Price et al. (2013)
Home oxygen therapy – proportion of patients	0	0	0.05	0.4	Price et al. (2013)
Influenza vaccine – proportion of patients	0.73	0.73	0.73	0.73	Price et al. (2013)
SABA (scripts)	3.74	4.65	6.87	9.78	Price et al. (2013)
SAMA (scripts)	0.59	0.65	0.91	1.19	Price et al. (2013)
Theophylline (days)	122.06	122.06	161.77	159.07	Rutten van Mölken et al. (2007)
Mucolytics (days)	39.74	39.74	48.31	80.6	Rutten van Mölken et al. (2007)
Oral corticosteroids (scripts)	0.88	0.96	1.7	2.7	Price et al. (2013)
CT scan	0	0	0.05	0.1	Committee consensus

Table 14 – Unit costs for maintenance resource use

Resource category	Unit cost	Source
GP visit	£36	PSSRU Unit Costs of Health and Social Care 2017
Respiratory team - cost per episode	£189	PSSRU Unit Costs of Health and Social Care 2017 - Episode assumed to comprise six 40 minute visits from either a band 6 (75%) or band 7 (25%) hospital nurse
Outpatient visit	£155	NHS Reference Costs 2015–16 - mean of respiratory medicine outpatient procedures
Spirometry - adjusted to current value	£30	NHS Reference costs 2010–2011*
Pulmonary rehabilitation per patient - adjusted to current value	£788	Griffiths et al. (2001)

Resource category	Unit cost	Source
Home oxygen therapy – cost per day - adjusted to current value	£16	Hertel et al. (2012)
Influenza vaccine - adjusted to current value	£6.67	Department of Health 2011
SABA - Salbutamol 100mcg - 200 D	£1.50	NHS Drug Tariff 2017
SAMA - Ipratropium bromide 20mcg - 200D	£5.56	NHS Drug Tariff 2017
Theophylline - cost per day	£0.05	NHS Drug Tariff 2017 - 200 mg modified-release tablets
Mucolytics - cost per day	£0.04	NHS Drug Tariff 2017 - carbocisteine 375 mg capsules
Oral corticosteroids - prednisolone 5mg tables (28)	£0.66	NHS Drug Tariff 2017
CT scan	£562	NHS Reference costs 2015–16 - Positron Emission Tomography with Computed Tomography (PET-CT) of one area, 19 years and over

*Reference cost from 2010-2011 (inflated to current value) used for the cost of spirometry, as this is the latest publication that explicitly reports this value

Table 15 – Cost per cycle for each GOLD stage

GOLD stage	Cost per cycle
Mild COPD	£26
Moderate COPD	£28
Severe COPD	£189
V. severe COPD	£350

Exacerbation costs

Table 16 shows inputs for resource use associated with non-hospitalised and hospitalised exacerbations. We did not identify empirical data on these values in the literature, so the committee estimated them. Table 17 shows unit costs for each resource. We used these values to calculate the overall cost per non-hospitalised and hospitalised exacerbation: £78 and £2,111 respectively.

Table 16 – Resource use associated with non-hospitalised and hospitalised exacerbations

Resource category	Resource use
Non-hospitalised exacerbation	
A&E visit without admission	0.3
Respiratory team visit	0.1
GP visit	0.6
Oral corticosteroids	1
Antibiotics	2
Hospitalised exacerbation	
Ambulance journey to A&E	0.7
Hospital stay	1
Oral corticosteroids	1
Antibiotics	2

Table 17 – Unit costs associated with exacerbations

Resource category	Unit cost	Source
A&E visit - not admitted	£118	NHS Reference Costs 2015-16 - weighted average of all non-admitted emergency medicine entries
Respiratory team - cost per episode	£189	PSSRU Unit Costs of Health and Social Care 2017 - Episode assumed to comprise six 40 minute visits from either a band 6 (75%) or band 7 (25%) hospital nurse
GP visit	£36	PSSRU Unit Costs of Health and Social Care 2017
Oral corticosteroids - prednisolone 5mg tables (28)	£0.66	NHS Drug Tariff 2017
Antibiotics - amoxicillin 500mg - 15 capsules	£0.73	NHS Drug Tariff 2017
Ambulance journey to A&E	£236	NHS Reference Costs 2015–16
Hospital stay	£1,944	NHS Reference Costs 2015–16 - weighted average COPD non-elective long stay, excluding one day or less category

Adverse event costs

Table 18 shows costs for each type of adverse event included in the model. Costs of acute events represent a one-off cost, whereas chronic event costs are expressed as values per cycle, which reoccur for the remainder of a patient's lifetime.

Table 18 – Costs associated with acute and chronic adverse events

Adverse event	Cost	Source
Acute events		
Cardiac arrest	£1,647	NHS Reference Costs 2015–16 - weighted average of cardiac arrest costs
Syncope	£118	NHS Reference Costs 2015–16 - weighted average of all non-admitted emergency medicine entries
Ventricular tachycardia	£169	Assumed that all patients would visit a GP and half would visit a cardiology specialist (NHS Reference Costs 2015–16). Also

Adverse event	Cost	Source
		assumed that half of patients receive adenosine treatment (Adenocor 6mg/2ml solution for injection vials – BNF 2017), which also requires a cardiology specialist visit
Myocardial infarction	£1,755	NHS Reference Costs 2015–16 - weighted average of myocardial infarction costs plus cost of rehabilitation for myocardial infarction
Atrial fibrillation/flutter	£429	NICE CG180 - costing template - cost per patient over one year, excluding cost of stroke
Pneumonia	£1,909	NHS Reference costs 2015–16 - weighted average of all pneumonia costs
Constipation	£27	Assumed that half of patients visit a GP (PSSRU Unit Costs of Health and Social Care 2017), half of patients are prescribed a laxative (Methylcellulose 500mg tablets - Drug Tariff 2017) and 5% of patients require emergency admission (NHS Reference Costs 2015–16 - weighted average of all emergency medicine costs)
Diarrhoea	£18	Assumed that half of patients visit a GP (PSSRU Unit Costs of Health and Social Care 2017) and are prescribed loperamide 2mg capsules (Drug Tariff 2017)
Dry mouth	£18	Assumed that half of patients visit a GP (PSSRU Unit Costs of Health and Social Care 2017)
Urinary retention	£2,756	NHS Reference Costs 2015–16 - weighted average of ureteric or bladder disorders
Chronic events - cost per model cycle		
Angina	£416	Stewart et al. (2003)
Stroke	£1,064	Youman et al. (2003)
Heart failure	£416	Stewart et al. (2002)
Glaucoma	£119	Rahman et al. (2013)

Treatment progression costs

The model assumes that switching or stepping up treatment is associated with 2 GP visits (Curtis et al., 2017) – 1 visit at which the new treatment is initiated, plus a further follow-up visit. This produces a cost of £72 per change of treatment.

Utilities

The model implements health-related quality of life as a stable utility value for each GOLD stage, to which disutilities are applied in each cycle for patients who experience exacerbations and adverse events.

Stable utilities

In determining a source for stable utilities, the committee reviewed EQ-5D scores stratified by GOLD stage for patients in the UPLIFT study (Rutten van Mölken 2006). Since this study does not include patients with mild COPD, we used EQ-5D scores from a smaller study of Swedish patients with COPD (Stahl 2005) to estimate a utility score for this severity stage. We did this by calculating the proportional difference between mild and moderate utilities in the Stahl study, and then applying this difference to the utility score for moderate COPD from the UPLIFT study. Table 19 shows the resulting values.

Table 19 – EQ-5D scores associated with each GOLD stage from Rutten van Mölken et al. (2006) and Stahl et al. (2005)

GOLD stage	Utility score (95% CIs)
Rutten van Mölken et al. (2006) utility scores	
Mild (calculated from Stahl 2005)	0.91
Moderate	0.79 (0.77 to 0.80)
Severe	0.75 (0.73 to 0.77)
Very severe	0.65 (0.60 to 0.70)
Stahl et al. (2005) utility scores - used to calculate mild utility score above	
Mild	0.84 (0.78 to 0.90)
Moderate	0.73 (0.68 to 0.78)

On inspection, the committee agreed that these values did not adequately capture differences in quality of life between GOLD stages. In particular, the data show a relatively small utility difference between moderate and severe COPD. In the committee's experience, differences in patients' quality of life are generally much more pronounced between these stages.

Therefore, we identified alternative quality of life data from a large pan-European study of SGRQ scores for COPD patients in primary care (Jones et al., 2011), shown in Table 20. The model converts these values to EQ-5D scores using the following mapping algorithm, developed using data from the TORCH trial (Starkie et al., 2011):

$$EQ\text{-}5D\ utility = 0.9617 + 0.0013\ SGRQ\ Total + 0.0001\ SGRQ\ Total^2 + 0.0231\ Male$$

The authors did not include estimates of uncertainty around the intercept and coefficients for the mapping algorithm, so these values were not implemented probabilistically in the model.

Table 20 – SGRQ-derived utility scores by GOLD stage from Jones et al. (2011)

GOLD stage	SGRQ score (95% CIs)	Corresponding EQ-5D score
Mild	38.5 (36.0 to 41.0)	0.78
Moderate	40.4 (39.2 to 41.6)	0.76
Severe	50.2 (48.6 to 51.8)	0.66
Very severe	58.6 (55.4 to 61.8)	0.55

The committee agreed that these values are a more accurate reflection of differences in quality of life across COPD severity stages. Therefore, the model base case uses the SGRQ-derived utilities, with the UPLIFT values used in a sensitivity analysis.

In order to reflect the decline in quality of life as people age, we calculated the difference between the stable utility for each GOLD stage and the mean general population utility score for people of an equivalent age (sourced from Kind et al., 1999). For each cycle of the model, these differences were added to the general population utility score corresponding to the age of the modelled cohort.

Exacerbation and adverse event disutilities

We derived QALY losses associated with hospitalised and non-hospitalised exacerbations from a study of 'holistic' health preferences for COPD (Rutten van Mölken et al., 2009). In this study, healthy people valued a number of COPD health profiles, developed from patient-level clinical data, using the time trade-off method. The investigators used random effects

regression analysis to disaggregate the QALY loss associated non-hospitalised and hospitalised exacerbations. Table 21 shows the resulting values.

While some directly measured utilities for patients experiencing exacerbations are available in the literature, these scores represent utilities at a particular moment in time, meaning that sizeable assumptions are required regarding the way in which utility changes over time during an exacerbation in order to estimate QALY loss. For this reason, the committee preferred the values derived using the time trade-off method.

Table 21 shows disutility values for adverse events. For acute adverse events, these values represent a one-off QALY loss. For chronic adverse events, the values are constant disutilities, which the model applies for the remainder of a patient's lifetime.

Table 21 – Disutilities associated with exacerbations and adverse events

Event	Disutility (95% CIs)	Source
Exacerbations - QALY loss		
Non-hospitalised exacerbation	0.01 (0.00 to 0.02)	Rutten van Mölken et al. (2009)
Hospitalised exacerbation	0.04 (0.02 to 0.06)	Rutten van Mölken et al. (2009)
Acute adverse events - QALY loss		
Cardiac arrest	0.13 (0.04 to 0.08)	Davies et al. (2015)
Syncope	0.0014 (0.0007 to 0.0021)	Assumed disutility of 0.5 for a period of 1 day
Ventricular tachycardia	0.032 (0.022 to 0.050)	Assumed to be equivalent to the QALY loss for atrial fibrilation/flutter
Myocardial infarction	0.13 (0.04 to 0.08)	Davies et al. (2015)
Atrial fibrillation/flutter	0.032 (0.022 to 0.050)	QoL disutility taken from Steg et al. (2011), with the assumption that this disutility lasts for 0.5 years
Pneumonia	0.130 (0.09 to 0.16)	Mangen et al. (2017)
Constipation	0.0014 (-0.0001 to 0.0037)	Disutility derived from Christensen et al. (2016), with the assumption that this disutility lasts for 7 days
Diarrhoea	0.41 (0.16 to 0.65)	QoL disutility taken from Lloyd et al. (2006), with an assumed duration of 4 days
Dry mouth	0.001 (0.0005 to 0.0014)	Assumed disutility of 0.05 for a period of 7 days
Urinary retention	0.012 (0.007 to 0.017)	QoL disutility taken from Ackerman et al. (2000), with an assumed duration of 30 days
Chronic adverse events - disutility		
Angina	0.18 (0.06 to 0.12)	Davies et al. (2015)
Stroke	0.18 (0.16 to 0.2)	Xie et al. (2006)
Heart failure	0.2 (0.11 to 0.18)	Davies et al. (2015)
Glaucoma	0.056 (0.026 to 0.100)	Taken from economic analysis for NICE guideline NG81 (glaucoma diagnosis and management)

Incorporating treatment effects

In the clinical evidence review, separate NMAs were conducted for patients at high and low risk of exacerbations – defined as patients with 1 or more exacerbations in the year before

trial entry, versus patients with no exacerbations or with unspecified exacerbation status. For the purposes of the economic model, we combined these 2 subgroups, and conducted NMAs to produce outcomes for the overall population, using the methods described in Chapter F.

To test whether results varied significantly between the two populations, we conducted another NMA for each outcome, in which a covariate was added to the model which took a value of 0 for studies with a low-risk population and 1 for studies with a high-risk population. If the estimated value of that coefficient were meaningfully different from 0, this would indicate that there is an interaction between treatment effect and risk status.

Table 22 shows NMA outcomes for the combined population, and for the analysis with a covariate indicating participants' risk group. Credible intervals around the risk status coefficients show that, in the large majority of cases, there are no significant differences between the 2 subgroups (intervals cross 0). Therefore, the base-case analysis of the model focuses on the overall population, rather than stratifying patients by risk status. We assess results for separate high- and low-risk populations in subgroup analyses.

For TDI outcomes, only data pertaining to a low-risk population were available. Therefore, the model also uses outcomes for this group to inform results for the overall population and for the high-risk population.

Table 22 – Treatment effect outcomes for the overall population and for low- and high-risk subgroups*

Comparison	Treatment effect - overall population (95% CrI)	Treatment effect - low risk subgroup (95% CrI)†	Coefficient - high versus low risk (95% CrI)	Treatment effect - high risk subgroup (95% CrI)‡
Moderate exacerbations - hazard ratios				
LAMA versus LABA	0.83 (0.77 to 0.90)	0.9 (0.79 to 1.02)	-0.11 (-0.27 to 0.04)	0.8 (0.73 to 0.87)
LABA+ICS versus LABA	0.83 (0.78 to 0.87)	0.87 (0.78 to 0.95)	-0.07 (-0.19 to 0.05)	0.81 (0.75 to 0.86)
LAMA+LABA versus LABA	0.73 (0.67 to 0.80)	0.78 (0.68 to 0.89)	-0.11 (-0.28 to 0.07)	0.70 (0.62 to 0.78)
Severe exacerbations - hazard ratios				
LAMA versus LABA	0.77 (0.69 to 0.85)	0.83 (0.67 to 1.01)	-0.13 (-0.37 to 0.12)	0.72 (0.64 to 0.82)
LABA+ICS versus LABA	0.94 (0.85 to 1.04)	1.03 (0.89 to 1.17)	-0.21 (-0.42 to -0.01)	0.83 (0.71 to 0.96)
LAMA+LABA versus LABA	0.71 (0.59 to 0.84)	0.76 (0.57 to 1.00)	-0.17 (-0.47 to 0.13)	0.64 (0.51 to 0.78)
FEV1 - 3 months - mean difference – litres				
LAMA versus LABA	0.021 (-0.016 to 0.058)	0.016 (-0.022 to 0.057)	0.030 (-0.018 to 0.077)	0.047 (-0.009 to 0.102)
LABA+ICS versus LABA	0.038 (0.015 to 0.062)	0.037 (0.011 to 0.064)	0.009 (-0.024 to 0.043)	0.046 (0.014 to 0.08)
LAMA+LABA versus LABA	0.090 (0.062 to 0.117)	0.087 (0.058 to 0.116)	0.010 (-0.046 to 0.063)	0.097 (0.04 to 0.15)
FEV1 - 6 months - mean difference – litres				
LAMA versus LABA	0.029 (0.004 to 0.061)	0.020 (-0.007 to 0.049)	0.058 (0.017 to 0.101)	0.078 (0.035 to 0.124)
LABA+ICS versus LABA	0.035 (0.008 to 0.067)	0.023 (-0.03 to 0.073)	0.025 (-0.014 to 0.068)	0.048 (0.006 to 0.1)
LAMA+LABA versus LABA	0.085 (0.051 to 0.119)	0.077 (0.048 to 0.108)	0.034 (-0.013 to 0.084)	0.111 (0.059 to 0.164)
FEV1 - 12 months - mean difference – litres				
LAMA versus LABA	0.050 (0.01 to 0.103)	0.020 (0.001 to 0.039)	0.058 (0.012 to 0.105)	0.078 (0.036 to 0.121)
LABA+ICS versus LABA	0.059 (0.03 to 0.104)	N/A (no trials included LABA+ICS in for this outcome in the low-risk population)	0.049 (0.03 to 0.069)	0.049 (0.03 to 0.069)
LAMA+LABA versus LABA	0.1 (0.044 to 0.166)	0.078 (0.059 to 0.096)	0.041 (-0.002 to 0.085)	0.119 (0.08 to 0.158)
SGRQ - 3 months - mean difference				
LAMA versus LABA	0.20 (-0.48 to 0.89)	1.01 (-0.2 to 2.15)	-0.90 (-2.35 to 0.56)	0.11 (-0.76 to 0.96)

Comparison	Treatment effect - overall population (95% CrI)	Treatment effect - low risk subgroup (95% CrI)†	Coefficient - high versus low risk (95% CrI)	Treatment effect - high risk subgroup (95% CrI)‡
LABA+ICS versus LABA	-1.21 (-1.95 to -0.49)	-0.68 (-1.85 to 0.49)	-1.15 (-2.7 to 0.39)	-1.82 (-2.87 to -0.8)
LAMA+LABA versus LABA	-1.66 (-2.41 to -0.89)	-0.64 (-1.85 to 0.55)	-2.58 (-4.33 to -0.81)	-3.21 (-4.52 to -1.91)
SGRQ - 6 months - mean difference				
LAMA versus LABA	-0.35 (-0.91 to 0.20)	-0.18 (-0.92 to 0.55)	-0.22 (-1.37 to 0.95)	-0.39 (-1.27 to 0.48)
LABA+ICS versus LABA	-1.25 (-1.73 to -0.76)	-1.13 (-1.88 to -0.35)	-0.47 (-1.49 to 0.54)	-1.60 (-2.28 to -0.93)
LAMA+LABA versus LABA	-1.77 (-2.38 to -1.16)	-1.36 (-2.13 to -0.59)	-1.52 (-2.89 to -0.12)	-2.88 (-4.03 to -1.75)
SGRQ - 12 months - mean difference				
LAMA versus LABA	-0.37 (-1.26 to 0.54)	0.13 (-1.26 to 1.50)	-0.95 (-2.84 to 1.08)	-0.82 (-2.14 to 0.61)
LABA+ICS versus LABA	-1.45 (-2.17 to -0.78)	-1.78 (-3.70 to 0.20)	0.17 (-2.00 to 2.31)	-1.60 (-2.46 to -0.74)
LAMA+LABA versus LABA	-1.43 (-2.4 to -0.45)	-0.64 (-2.07 to 0.86)	-1.64 (-3.86 to 0.4)	-2.28 (-3.88 to -0.79)
TDI - 3 months (low risk subgroup only) - mean difference				
LAMA versus LABA	-0.10 (-0.35 to 0.13)	-0.10 (-0.35 to 0.13)	-	-
LABA+ICS versus LABA	0.09 (-0.17 to 0.35)	0.09 (-0.17 to 0.35)	-	-
LAMA+LABA versus LABA	0.44 (0.2 to 0.67)	0.44 (0.2 to 0.67)	-	-
TDI - 6 months (low risk subgroup only) - mean difference				
LAMA versus LABA	0.04 (-0.12 to 0.21)	0.04 (-0.12 to 0.21)	-	-
LABA+ICS versus LABA	0.22 (-0.02 to 0.46)	0.22 (-0.02 to 0.46)	-	-
LAMA+LABA versus LABA	0.37 (0.21 to 0.52)	0.37 (0.21 to 0.52)	-	-
Mortality - odds ratios				
LAMA versus LABA	1.07 (0.86 to 1.32)	1.31 (0.83 to 1.99)	-0.25 (-0.76 to 0.26)	1.00 (0.78 to 1.28)
LABA+ICS versus LABA	0.91 (0.78 to 1.05)	0.93 (0.76 to 1.14)	-0.06 (-0.37 to 0.24)	0.88 (0.69 to 1.09)
LAMA+LABA versus LABA	1.04 (0.78 to 1.37)	1.2 (0.76 to 1.81)	-0.18 (-0.78 to 0.42)	1.00 (0.65 to 1.47)
Cardiac adverse events - odds ratios				
LAMA versus LABA	1.17 (0.94 to 1.45)	1.22 (0.89 to 1.65)	-0.06 (-0.51 to 0.41)	1.15 (0.82 to 1.62)
LABA+ICS versus LABA	0.99 (0.82 to 1.19)	1.02 (0.73 to 1.43)	-0.06 (-0.47 to 0.34)	0.95 (0.73 to 1.23)
LAMA+LABA versus LABA	1.11 (0.85 to 1.43)	1.27 (0.90 to 1.72)	-0.37 (-0.95 to 0.23)	0.89 (0.54 to 1.41)

Comparison	Treatment effect - overall population (95% CrI)	Treatment effect - low risk subgroup (95% CrI)†	Coefficient - high versus low risk (95% CrI)	Treatment effect - high risk subgroup (95% CrI)‡
Pneumonia - odds ratios				
LAMA versus LABA	0.95 (0.46 to 1.68)	1.00 (0.41 to 1.86)	-0.07 (-0.73 to 0.58)	0.92 (0.42 to 1.75)
LABA+ICS versus LABA	1.61 (0.99 to 2.39)	1.88 (1.03 to 3.25)	-0.17 (-0.75 to 0.38)	1.57 (0.97 to 2.47)
LAMA+LABA versus LABA	1.24 (0.77 to 2.01)	1.29 (0.66 to 2.27)	0.12 (-0.81 to 1.18)	1.58 (0.58 to 3.95)
Total serious adverse events - odds ratios				
LAMA versus LABA	0.93 (0.86 to 1.00)	0.99 (0.88 to 1.11)	-0.11 (-0.26 to 0.03)	0.89 (0.81 to 0.97)
LABA+ICS versus LABA	1.06 (0.99 to 1.13)	1.13 (1.01 to 1.27)	-0.12 (-0.26 to 0.03)	1.01 (0.92 to 1.10)
LAMA+LABA versus LABA	0.96 (0.88 to 1.05)	1.02 (0.91 to 1.15)	-0.14 (-0.33 to 0.06)	0.89 (0.77 to 1.04)
Discontinuation due to adverse events – hazard ratios				
LAMA versus LABA	0.86 (0.78 to 0.95)	0.84 (0.72 to 0.97)	0.05 (-0.15 to 0.25)	0.88 (0.77 to 1.00)
LABA+ICS versus LABA	0.91 (0.84 to 1.00)	0.93 (0.80 to 1.06)	-0.03 (-0.22 to 0.15)	0.90 (0.79 to 1.01)
LAMA+LABA versus LABA	0.90 (0.80 to 1.01)	0.91 (0.79 to 1.06)	-0.09 (-0.36 to 0.17)	0.83 (0.67 to 1.03)

*Please note that treatment effects in this table are expressed relative to LABA, for ease of interpretation and for consistency with NMA results in the clinical evidence review. Contrastingly, treatment effects in the model executable file are expressed relative to the reference regimen.
†Treatment effects for the low-risk subgroup are simply the base treatment effect outcomes from the NMAs in which a covariate was added to denote risk status
‡Treatment effects for the high-risk subgroup were calculated by adding the coefficient for the high- versus low-risk population to the treatment effect for the low-risk population (for continuous outcomes) or to the natural logarithm of the treatment effect for the low-risk population (for hazard ratios or odds ratios). Note that the mean of the resulting distribution may not be identical to the sum of the means of the 2 coefficients, owing to asymmetries and within-sample correlations.

Since triple therapy was not included in the NMA, we obtained treatment effects for this regimen from alternative sources. Where possible, we took outcomes from a Cochrane review comparing triple therapy with LAMA monotherapy (Rojas-Reyes et al., 2016). Where the Cochrane review did not report outcomes of interest, we took data directly from the RCTs included in the review. Only one study (Aaron et al., 2007) reported most of these outcomes, so we took these directly from this source. However, 2 studies reported treatment effect on pneumonia (Aaron et al., 2007; Jung et al., 2012), so we meta-analysed these data. Table 23 shows treatment effects for triple therapy versus LAMA.

Table 23 – Treatment effects for triple therapy compared with LAMA

Parameter	Treatment effect (95%CrI)
Moderate exacerbations - hazard ratio	0.85 (0.65 to 1.11)
Severe exacerbations - hazard ratio	0.53 (0.33 to 0.86)
FEV1 - mean difference - ml	60 (40 to 80)
SGRQ - mean difference	-3.46 (-5.05 to -1.87)
TDI - mean difference	0.06 (-0.84 to 0.96)
Mortality - odds ratio	0.92 (0.75 to 1.13)
Cardiac adverse events - odds ratio	1.08 (0.15 to 7.82)
Pneumonia - odds ratio	1.76 (0.25 to 15.18)
Total serious adverse events - odds ratio	0.86 (0.57 to 1.3)

Treatment effect scenarios

As discussed in the model overview section, we modelled 5 different scenarios for implementing treatment effects. Each of these scenarios was associated with its own advantages and disadvantages, which are listed in Table 24. Since the committee did not express an explicit preference for any one method, we made the decision to incorporate these scenarios in the model stochastically. That is to say, base-case results are probabilistic means, in which one of the 5 scenarios is selected at random in each iteration of the model. Results of the each of the 5 scenarios are also presented individually as sensitivity analyses.

The committee indicated that scenario 1 is likely to underestimate treatment benefits, since long-acting bronchodilators demonstrably produce benefits beyond a reduction in exacerbations. However, we opted to keep this scenario in the base case, as it provides a conservative lower bound for treatment effect, and it is the only scenario in which we can be certain that there is no double-counting of benefits. Scenario 2, because it implements treatment effects through both exacerbations and SGRQ, may somewhat overestimate treatment effects if patients were experiencing exacerbations while SGRQ was measured. Similarly, scenario 3 implements treatment effects through exacerbations and FEV1, and may somewhat overestimate benefits, since treatment-specific differences in FEV1 also indirectly affect exacerbation rate, as this outcome affects the distribution of patients among GOLD stages. In order to investigate the effects of these assumptions, we conducted a highly conservative sensitivity analysis in which disutilities associated with exacerbations were omitted.

Table 24 – Advantages and disadvantages of each treatment effect scenario

Scenario	Advantages	Disadvantages
Scenario 1: Exacerbations alone	Is the most conservative scenario, so avoids any potential overestimation of treatment effects.	The committee indicated that this scenario is likely to underestimate treatment benefits, since evidence shows beneficial effects of treatment beyond a reduction in exacerbations.
Scenario 2: SGRQ and exacerbations	Directly implements treatment effect on quality of life, so requires fewer assumptions than other scenarios.	SGRQ outcomes are less precise than other measures of treatment benefit. May provide an estimate of treatment benefit if patients were experiencing exacerbations when SGRQ was measured.
Scenario 3: FEV1 and exacerbations	Allows differences in maintenance costs and mortality to be modelled through differences in GOLD stage distributions. Is most closely aligned to previous economic analyses in the literature.	The committee indicated that FEV1 is a less consistent predictor of costs and quality of life than breathlessness. Potentially overestimates treatment benefits, since changing patients' GOLD stage affects exacerbation rate.
Scenario 4: TDI and exacerbations	The committee indicated that breathlessness is the primary determinant of treatment benefits, so TDI is the most appropriate outcome to use *a priori*.	Requires the intermediate step of approximating odds ratios from TDI mean differences, and is therefore less direct than other scenarios (see 'treatment effect on TDI' section).
Scenario 5: FEV1, TDI and exacerbations	Implements the independent effects of FEV1, TDI, and previous exacerbations through coefficients from a multiple regression analysis, so avoids potential double-counting.	Requires the intermediate step of approximating odds ratios from TDI mean differences, and is therefore less direct than other scenarios.

Treatment effect on exacerbations

Since the NMA expressed treatment effects on non-hospitalised and hospitalised exacerbations as hazard ratios, the model applied these outcomes directly to baseline exacerbation rates for each GOLD stage, with LABA+ICS as the reference comparator. Table 25 shows the resulting exacerbation rates for each treatment.

Table 25 – Exacerbation rate per cycle stratified by treatment and GOLD stage

GOLD stage	Non-hospitalised exacerbation rate	Hospitalised exacerbation rate
LABA		
Mild	0.460	0.031
Moderate	0.473	0.026
Severe	0.605	0.055
Very severe	0.728	0.088
LAMA		

GOLD stage	Non-hospitalised exacerbation rate	Hospitalised exacerbation rate
Mild	0.383	0.024
Moderate	0.394	0.020
Severe	0.503	0.042
Very severe	0.606	0.067
LABA+ICS		
Mild	0.380	0.029
Moderate	0.390	0.024
Severe	0.499	0.052
Very severe	0.601	0.082
LAMA+LABA		
Mild	0.335	0.022
Moderate	0.344	0.018
Severe	0.440	0.039
Very severe	0.530	0.062
Triple therapy		
Mild	0.325	0.013
Moderate	0.335	0.011
Severe	0.428	0.023
Very severe	0.515	0.036

The model made the assumption that patients' exacerbation rate relates to the treatment they are currently receiving, rather than the regimen they started treatment on. That is to say – we assumed that exacerbation rate is not affected by treatment history.

Treatment effect on SGRQ

In Scenario 2 (treatment effect on SGRQ and exacerbations incorporated in the model), the model applied treatment effects on SGRQ directly to QoL scores from Jones et al. (2011), before mapping scores to EQ-5D values, using Starkie et al.'s algorithm (2011). This produced stable utilities stratified by both GOLD stage and treatment regimen, which are shown in Table 26.

Table 26 – Stable EQ-5D scores, stratified by treatment and GOLD stage

Treatment	Mild COPD	Moderate COPD	Severe COPD	Very severe COPD
LABA	0.764	0.746	0.642	0.538
LAMA	0.762	0.744	0.640	0.535
LABA+ICS	0.775	0.758	0.656	0.554
LAMA+LABA	0.779	0.762	0.661	0.560
Triple therapy	0.817	0.801	0.709	0.615

The model base case used only the SGRQ effect at 3 months, with the assumption that this effect persisted for as long as the patient remained on treatment, as the largest number of studies in the NMA used this time point. We also conducted sensitivity analyses using SGRQ effect at 6 and 12 months. These analyses initially used the relevant SGRQ outcome for each cycle of the model – i.e. the first cycle used data for the 3-month endpoint, the second cycle used data for the 6-month endpoint, and so on. The model determined treatment effect going into the future by the last time point used. For example, in the sensitivity analysis using

SGRQ outcomes at 3 and 6 months, relative treatment effects subsequent to the second cycle were informed by the 6 month outcome.

As with treatment effect on exacerbations, the model assumed that patients' stable QoL relates to the current treatment, and is not affected by treatment history.

In the scenario analysis using EQ-5D scores from Rutten van Mölken et al. (2006), rather than the SGRQ scores from Jones et al. (2011), the model first converts EQ-5D scores to SGRQ scores, using an algebraic rearrangement of the mapping algorithm. It then applies the treatment effects on SGRQ to these values, and converts back into EQ-5D scores using the original algorithm.

Treatment effect on FEV1

In Scenario 3 and Scenario 5, the model incorporates treatment effects on FEV1 through differences in transition probabilities in its first cycle. We achieved this by adding the treatment effect on FEV1 relative to LABA+ICS to the baseline treatment effect at 3 months when calculating the probability of transitioning to a different GOLD stage for each 10 ml FEV1 increment (see previous section 'calculating transition probabilities' for a full description of the method). Table 27 shows these transition probabilities for each regimen.

Table 27 – Transition probabilities in the first cycle of the model for cycles in which treatment effect on FEV1 is incorporated

Treatment	Mild to moderate	Moderate to severe	Severe to v. severe	Moderate to mild	Severe to moderate	V. severe to severe
LABA	16.4%	14.9%	15.2%	11.8%	28.5%	40.4%
LAMA	15.0%	13.6%	13.7%	13.0%	30.9%	43.3%
LABA+ICS	13.9%	12.5%	12.5%	14.1%	33.0%	45.7%
LAMA+LABA	10.8%	9.6%	9.3%	17.7%	39.5%	53.1%
Triple therapy	11.3%	10.1%	9.8%	17.1%	38.3%	51.8%

The base case makes the assumption that transition probabilities are equivalent between treatments after the first cycle of the model.

We considered 3 potential options for how to model FEV1 change when patients switch or step up treatment:

1. No treatment benefit: Transition probabilities are unaffected by treatment changes, and simply reflect the natural decline in FEV1 over time for the cycle in which the change occurs.
2. Residual treatment benefit: Transition probabilities reflect the difference in initial FEV1 benefit between the original regimen and the regimen changed to. The model calculates probabilities by adding the difference in treatment effects to the natural decline in FEV1 for the cycle. For instance, if a patient steps up from LAMA to LAMA+LABA, the model adds a value of 69.4 ml (the difference in FEV1 effect between the 2 treatments) to the natural decline in FEV1 over 3 months (dependent on GOLD stage) in calculating transition probabilities for that cycle. Patients may move to a less severe GOLD stage for the cycle in which the change occurs.
3. Full treatment benefit: Transition probabilities are equivalent to those in the first cycle of the model for the new treatment regimen. For example, stepping up from LAMA to LAMA+LABA is associated with the same set of transition probabilities as for a patient starting treatment on a LAMA+LABA.

For patients stepping up treatment, the model base case uses the 'residual treatment benefit' option, as it seems logical that patients would receive an additional FEV1 benefit if they are stepped up to a more effective regimen, but assuming a full treatment benefit would unfairly favour strategies which involve more treatment changes (i.e. ones in which patients start on a monotherapy). For patients switching treatment, the model base case uses the 'no treatment benefit' option, as treatment switching occurs primarily because of adverse effects associated with a regimen, rather than due to lack of effectiveness in managing disease symptoms. We explore the impact of changing these assumptions through sensitivity analysis.

We also conducted sensitivity analyses using FEV1 outcomes from the NMA at 6 and 12 months. In these scenarios, the model calculates transition probabilities for its second cycle by adding the difference in FEV1 effect at 3 and 6 months to the natural 3-month FEV1 decline. Similarly, in the scenario using 12-month outcomes, we calculated transition probabilities for the third and fourth cycle using the difference in FEV1 effect at 6 and 12 months. For the fifth cycle onwards, as in the base case, transition probabilities reflected only the natural decline in FEV1 over time.

Treatment effect on TDI

Scenario 4 and Scenario 5 incorporated the treatment effect on TDI into the model via change in SGRQ score. To achieve this, we identified coefficients predicting the independent effect of breathlessness on SGRQ from a multivariable analysis of patients in the ECLIPSE study (Exuzides et al., 2017). These values are shown in Table 28. The authors did not report uncertainty around these estimates, so they were not implemented probabilistically in the model.

Table 28 – Regression coefficients for categories of breathlessness symptoms

Explanatory variable	Change in SGRQ total score
Breathlessness symptoms – most days versus none	17.5914
Breathlessness symptoms – several days versus none	9.6256

As these coefficients relate to 3 discrete categories of breathlessness symptoms (most days, several days or none), we had to transform the continuous TDI outcome into an odds ratio. To accomplish this, we converted the relative TDI effect for each treatment compared with LABA+ICS into a standardised mean difference (SMD), by dividing treatment effect by standard deviation. Since standard deviations were not available as an output of the NMA, we used a value of 2.697 from the study with the largest number of patients for this outcome – the unpublished study SCO100470. We then approximated odds ratios from these SMDs, using the formula described in Chinn (2000):

$$\ln(odds\ ratio) = -\frac{\pi . SMD}{\sqrt{3}}$$

We then converted the odds ratios to relative risks using the following formula:

$$RR = OR/(1 - p + (p.OR))$$

, where *p* is the baseline proportion of patients who experience breathlessness symptoms on most/several days. We sourced these values from the baseline patient characteristics in the ECLIPSE study (Briggs et al., 2017), as shown in Table 29.

Table 29 – Baseline proportion of patients within each category of breathlessness symptoms

Breathlessness status at baseline	Proportion of patients (95% CIs)
Breathlessness symptoms most days per week	60.8% (58.6% to 62.9%)
Breathlessness symptoms several days per week	28.7% (26.7% to 46.0%)
Breathlessness symptoms - none	10.6% (9.2% to 11.9%)

For each treatment, the model calculates the difference in proportion of patients experiencing breathlessness symptoms most days per week compared with the reference regimen by multiplying the baseline proportion of patients with breathlessness most days by the corresponding relative risk, and then subtracting the original baseline proportion of patients with breathlessness symptoms most days. The difference in patients experiencing several symptoms several days per week is calculated in the same way, but also subtracting the difference in the proportion of patients with symptoms most day from the previous step. This accounts for the fact that a less effective treatment will result in patients moving into the 'several days' state from the 'no symptoms' state, but also from the 'several days' state into the 'most days' state.

To calculate the SGRQ score associated with each treatment, the model multiplies the difference between the proportion of patients in the 'most days' and 'several days' state and the reference population by the corresponding regression coefficient. The model then adds these values to the stable SGRQ score for each GOLD stage, and maps to EQ-5D scores, as described previously. Table 30 shows the resulting utilities, stratified by treatment and disease severity.

Table 30 - Stable utilities for each treatment implemented through differences in TDI

Treatment	Mild COPD	Moderate COPD	Severe COPD	Very severe COPD
LABA	0.773	0.756	0.654	0.551
LAMA	0.771	0.753	0.651	0.547
LABA+ICS	0.775	0.758	0.656	0.554
LAMA+LABA	0.783	0.766	0.666	0.565
Triple therapy	0.772	0.755	0.652	0.549

As with the other continuous treatment effects, we conducted sensitivity analyses in which the model incorporated outcomes at 6 and 12 months. In these analyses, patients' utility going into the future was determined by the latest observed time point.

Independent effect of FEV1 and exacerbations in the previous year on SGRQ

As well as including the effect of TDI on SGRQ, Scenario 5 also incorporates the independent effect of FEV1 and exacerbations in the previous year on SGRQ. To achieve this, the model uses regression coefficients from Briggs et al. (2017); see Table 31. As with coefficients for breathlessness, uncertainty around these values was not reported, so they were not implemented in the model probabilistically.

Table 31 – Regression coefficients predicting effect of FEV1 % predicted and exacerbation history on SGRQ

Explanatory variable	Change in SGRQ total score
FEV1 % predicted	-0.006
Moderate exacerbations in the previous year	0.8524
Severe exacerbations in the previous year	1.9092

This scenario, as with Scenario 2, includes relative treatment effects on FEV1 as differential treatment probabilities in the first cycle of the model. However, unlike in Scenario 2, this approach calculates patients' stable QoL purely as a function of TDI, FEV1 % predicted, and exacerbations in the previous year, using the regression equations above. This approach does not use different baseline SGRQ scores for each GOLD stage, since this would introduce double-counting, as GOLD stage is a function of FEV1 % predicted.

To implement the regression equations, we calculated an average 'baseline' SGRQ score, by weighting the score for each GOLD stage by the proportion of patients in each stage at baseline. We then calculated differences in SGRQ scores according to GOLD stage and treatment, and used methods described in the previous section to incorporate treatment effects on TDI. The mean FEV1 % predicted for each GOLD stage was applied to the corresponding coefficient to implement the effect of lung function on QoL. The model then adds these differences to the baseline SGRQ value to produce scores stratified by GOLD stage and treatment.

In order to incorporate the effect of previous exacerbations on SGRQ, the model calculates the average cohort SGRQ score for each cycle of the model, by weighting the proportion of patients in each state (defined by treatment and disease severity) by the appropriate SGRQ score. It also tracks the number of non-hospitalised and hospitalised exacerbations in the previous year for each cycle. For the first four cycles of the model, we made the assumption that patients' exacerbation history prior to initiation of long-acting bronchodilator treatment was equivalent to the baseline exacerbation rate. We used exacerbation history to approximate the proportion of patients experiencing a non-hospitalised and hospitalised exacerbation in the previous year, using the following formula:

$$\%\ patients\ experiencing\ exacerbation = 1 - \exp(-exacerbation\ rate)$$

The model applies these values to the corresponding regression coefficients and adds the mean SGRQ score per cycle, to produce a QoL value that accounts for TDI, FEV1 and exacerbation history. These values are mapped to EQ-5D scores, and disutilities for adverse events and exacerbation occurring within the cycle are applied, as in other scenarios.

Treatment effect on switching and stepping up

As treatment progression outcomes were not available from the NMA, we used other outcomes as a proxy for treatment differences in stepping up and switching probabilities.

Treatment stepping up primarily occurs due to suboptimal control of COPD symptoms, so the committee agreed that treatment effect on TDI would serve as the best proxy for relative differences in this probability. Contrastingly, treatment switching generally occurs due to adverse events or intolerance, so the committee agreed that treatment effect on discontinuation due to adverse events would be the most appropriate proxy outcome.

The model implements treatment effect on the probability of stepping up using methods similar to those described in the 'treatment effect on TDI' section. It converts treatment effect on TDI into an SMD for each treatment effect, with LABA+ICS as the reference regimen. It then uses these values to approximate odds ratios, and applies these to the baseline odds of treatment switching, with the resulting value converted into a probability of stepping up for each regimen.

The model implements treatment effect on switching by simply applying the odds ratio for treatment discontinuation to the baseline odds of switching, and converting the resulting value into a probability. Table 32 shows probabilities of stepping up and switching treatment per cycle of the model for each regimen.

Table 32 – Probability of stepping up and switching per cycle of the model according to treatment

Treatment	Probability of stepping up	Probability of switching
LABA	3.62%	1.05%
LAMA	3.83%	0.91%
LABA+ICS	3.44%	0.96%
LAMA+LABA	2.81%	0.94%

Treatment effect on adverse events

In order to implement adverse event effects (for Options B and C), the model converts the baseline incidence rate of each adverse event category (cardiac acute events, cardiac chronic events, pneumonia, 'other' acute events, and 'other' chronic events) to an odds value (since treatment effects outcomes are expressed as odds ratios). It then applies the relevant treatment effect to each value (expressed relative to LABA, since baseline adverse event rates relate to this treatment), and converts the resulting value back into a rate.

Since the NMA did not include an outcome which specifically related to 'other' adverse events, the relative treatment effect on total serious adverse events was used as a proxy. This outcome also included other categories of adverse event (cardiac and pneumonia) as well as COPD exacerbations, but the committee agreed that this was the best available representation of treatment effect on adverse events in the 'other' category. Moreover, events in this category have a relatively small effect on QALYs compared with cardiac events, so this choice of treatment effect is unlikely to materially affect results. Table 33 shows rates for each category of adverse event, stratified by treatment regimen.

Table 33 – Incidence rates for each category of adverse event per cycle of the model, stratified by treatment regimen, for scenarios which include treatment-specific adverse event differences

Treatment	Cardiac acute	Cardiac chronic	Pneumonia	Other acute	Other chronic
LABA	0.0156	0.0194	0.0037	0.0248	0.0004
LAMA	0.0182	0.0225	0.0035	0.0231	0.0003
LABA+ICS	0.0154	0.0192	0.0060	0.0262	0.0004
LAMA+LABA	0.0173	0.0214	0.0046	0.0240	0.0004
Triple therapy	0.0195	0.0206	0.0062	0.0200	0.0003

Treatment effect on mortality

To implement treatment-specific mortality differences (for Option C), the model first converts mortality odds ratios to relative risks. To achieve this, we sourced a baseline mortality rate for patients with COPD from Leivseth et al. (2013) for both males and females, shown in Table 34. We weighted these values by the gender split for the modelled population in order to produce an overall mortality rate.

Table 34 – Overall baseline mortality rates used to convert mortality odds ratios to relative risks

Parameter	Value (95% CIs)
Baseline mortality rate - men	0.052 (0.048 to 0.057)
Baseline mortality rate - women	0.037 (0.033 to 0.042)

Parameter	Value (95% CIs)
Overall mortality rate	0.045

The model then applies relative risks to the baseline SMRs for each GOLD stage, in order to produce SMRs stratified by both treatment and disease severity. Table 35 shows these values.

Table 35 – Mortality SMRs stratified by GOLD stage and treatment, for scenarios which include treatment-specific mortality differences

Treatment	Mild COPD	Moderate COPD	Severe COPD	Very severe COPD
LABA	0.91	1.66	3.53	4.71
LAMA	0.98	1.78	3.77	5.04
LABA+ICS	0.83	1.51	3.21	4.29
LAMA+LABA	0.96	1.74	3.70	4.94
Triple therapy	0.90	1.64	3.48	4.66

Subgroup analyses

We conducted subgroup analyses for patients at high and low risk of exacerbations separately. These analyses differed from the base case analysis in 2 ways. First, they used treatment effect outcomes from the NMA model which included a covariate for risk status, rather than outcomes for the overall population. Second, the subgroup analyses stratified the baseline exacerbation rate according to patients who had experienced 1 or more exacerbations in the previous year (for the high-risk group) and those who had experienced no exacerbations in the previous year (for the low-risk group). Table 36 shows these values.

Table 36 – Baseline exacerbation rates for high- and low-risk subgroups

GOLD stage	Non-hospitalised exacerbations	Hospitalised exacerbations
High risk subgroup		
Mild	0.557	0.041
Moderate	0.556	0.032
Severe	0.666	0.067
Very severe	0.788	0.102
Low risk subgroup		
Mild	0.233	0.020
Moderate	0.245	0.018
Severe	0.310	0.035
Very severe	0.350	0.055

Results

For all scenarios, we express the costs and health benefits associated with each strategy as means of 1,000 probabilistic iterations, alongside the probability that each strategy is cost effective at a threshold of £20,000 per QALY.

Base-case results

For 'base-case' results, the model addresses structural uncertainty in implementing treatment benefit stochastically, by randomly selecting 1 of the 5 treatment effect scenarios in each probabilistic iteration. These results relate to the overall population, not stratified by exacerbation risk status, and progression to triple therapy is allowed in the model.

Option A – treatment-specific differences in adverse events and mortality excluded

Table 37 shows results for Option A, in which treatment-specific differences in mortality and adverse events are not included. These results show that the strategy of starting patients on a LAMA+LABA is associated with a relatively low incremental cost-effectiveness ratio (ICER) of £3,428 per QALY, compared with a strategy of starting patients on a LAMA and stepping up to a LAMA+LABA, meaning that LAMA+LABA is the optimal strategy if QALYs are valued at £20,000 each. This is because this regimen shows a favourable treatment effect on exacerbations, SGRQ, FEV1, and TDI in the NMA, and therefore generates the highest number of QALYs, as well as achieving cost savings through reduced numbers of exacerbations. Probabilistic results also show that this strategy is cost effective in 86.3% of iterations at a threshold of £20,000 per QALY, indicating a relatively high degree of certainty in this conclusion.

The strategy LAMA -to- LAMA+LABA is the least expensive option overall, and is also associated with a non-trivial probability (11.7%) of being cost effective. This result occurs because LAMA is a less costly regimen than LAMA+LABA, and also achieves cost savings compared with other strategies due to a lower exacerbation rate than LABA or LABA+ICS.

Table 37 – Base case results for Option A: treatment-specific differences in adverse events and mortality excluded

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,554	5.44	-	-	-	11.7%
LAMA - to - LABA+ICS	£27,747	5.41	£192	-0.029	dominated	0.0%
LAMA+LABA	£27,825	5.52	£271	0.079	£3,428	86.3%
LABA - to - LAMA+LABA	£27,912	5.42	£86	-0.100	dominated	0.1%
LABA - to - LABA+ICS	£28,102	5.39	£276	-0.128	dominated	0.0%
LABA+ICS	£28,113	5.48	£287	-0.039	dominated	1.9%

Figure 4 displays probabilistic results as a cost-effectiveness acceptability curve, where the probability of each strategy being cost effective is shown over a range of thresholds. These results show that, at low thresholds, the strategy of LAMA -to- LAMA+LABA has a high probability of being the most cost-effective, confirming that LAMA is likely to be the least costly treatment overall. As the threshold increases, LAMA+LABA becomes the strategy with the highest probability of being cost-effective, again demonstrating that LAMA+LABA is likely to produce the highest number of QALYs.

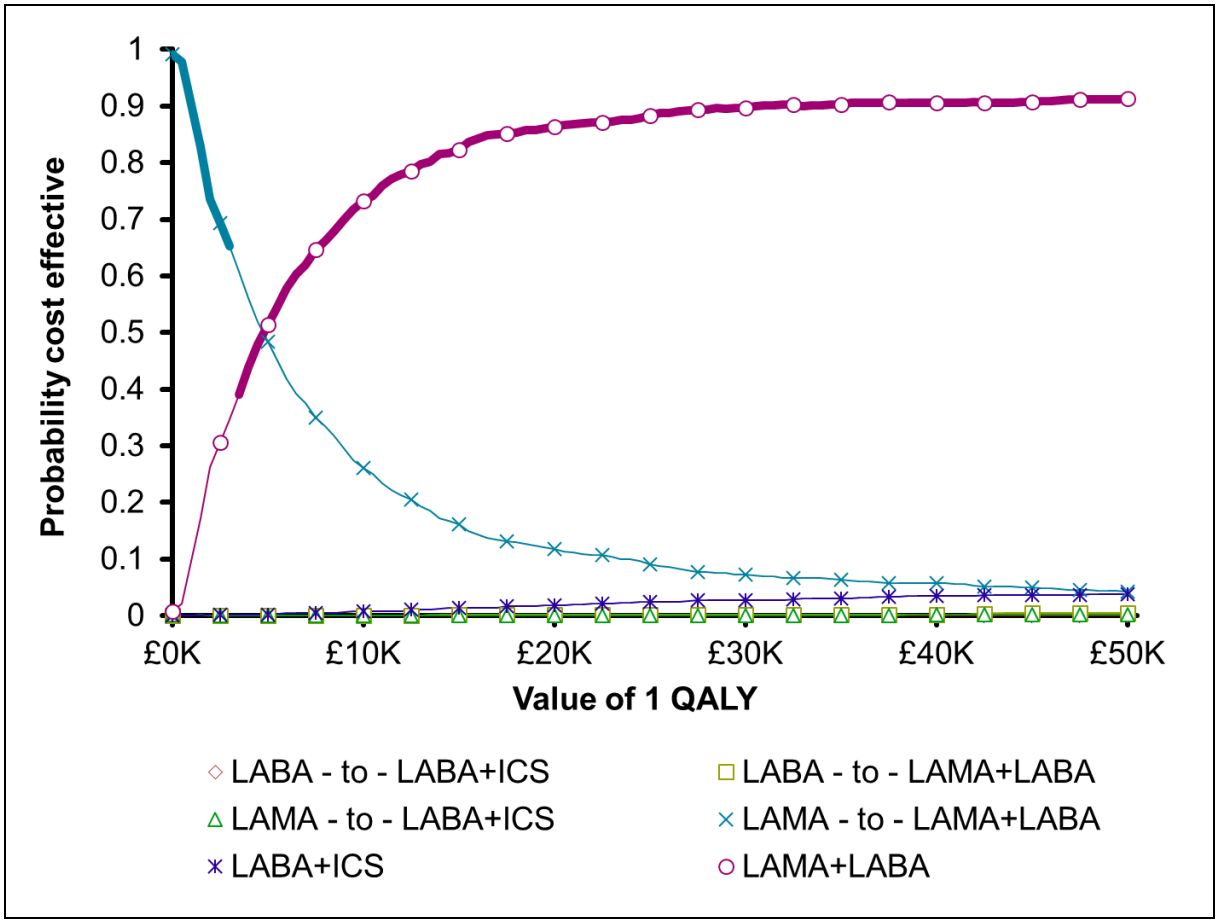

Figure 4 – Cost effectiveness acceptability curve for Option A: treatment-specific differences in adverse events and mortality excluded

Option B – treatment-specific differences in adverse events but not mortality included

Table 38 shows results for Option B, in which treatment-specific differences in adverse events but not mortality are included. Mean cost-effectiveness estimates show that LAMA+LABA remains the optimal strategy if QALYs are valued at £20,000 each, although the ICER is higher than in the previous scenario. This is primarily due to point estimates for treatment effects on cardiac adverse events favouring LABA+ICS and LABA. While treatment effects for pneumonia and all serious adverse events are more favourable towards LAMA+LABA, cardiac adverse events have a more pronounced effect on health outcomes, as they occur more frequently, are typically associated with a large disutility, and are often chronic in nature.

Results of this scenario show a universal QALY reduction across all strategies, compared with Option A. This finding is due to point estimates for adverse event treatment effects generally favouring LABA – the reference regimen – which results in a QALY loss for all other treatments due to additional adverse events. Strategies in which patients start on a LABA also produce fewer QALYs than in Option A, since a proportion of patients progress to other treatments. Probabilistic results show that there is now a larger degree of uncertainty around outcomes. Although LAMA+LABA still shows the highest probability of being cost-effective by a considerable margin, the number of iterations in which LAMA+LABA is the optimal strategy is reduced to 57.2%. This is primarily due to the wide confidence intervals

around adverse event treatment effects. In particular, this is driven by adverse event rates for triple therapy, which are associated with a large degree of uncertainty, due to being informed by a much smaller evidence base than monotherapy and dual therapy regimens.

Table 38 – Base case results for Option B: treatment-specific differences in adverse events but not mortality included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£28,170	5.40	-	-	-	21.7%
LABA - to - LAMA+LABA	£28,306	5.39	£136	-0.009	dominated	7.3%
LAMA - to - LABA+ICS	£28,341	5.37	£171	-0.029	dominated	0.2%
LABA - to - LABA+ICS	£28,472	5.36	£302	-0.038	dominated	0.1%
LAMA+LABA	£28,577	5.47	£407	0.073	£5,546	57.2%
LABA+ICS	£28,765	5.44	£188	-0.037	dominated	13.5%

Figure 5 shows the cost-effectiveness acceptability curve for this scenario. At low thresholds, LABA -to- LAMA+LABA has the highest probability of being cost-effective, indicating that it is likely to be the cheapest strategy. As the threshold increases, LAMA+LABA becomes the strategy with the highest probability of being cost-effective.

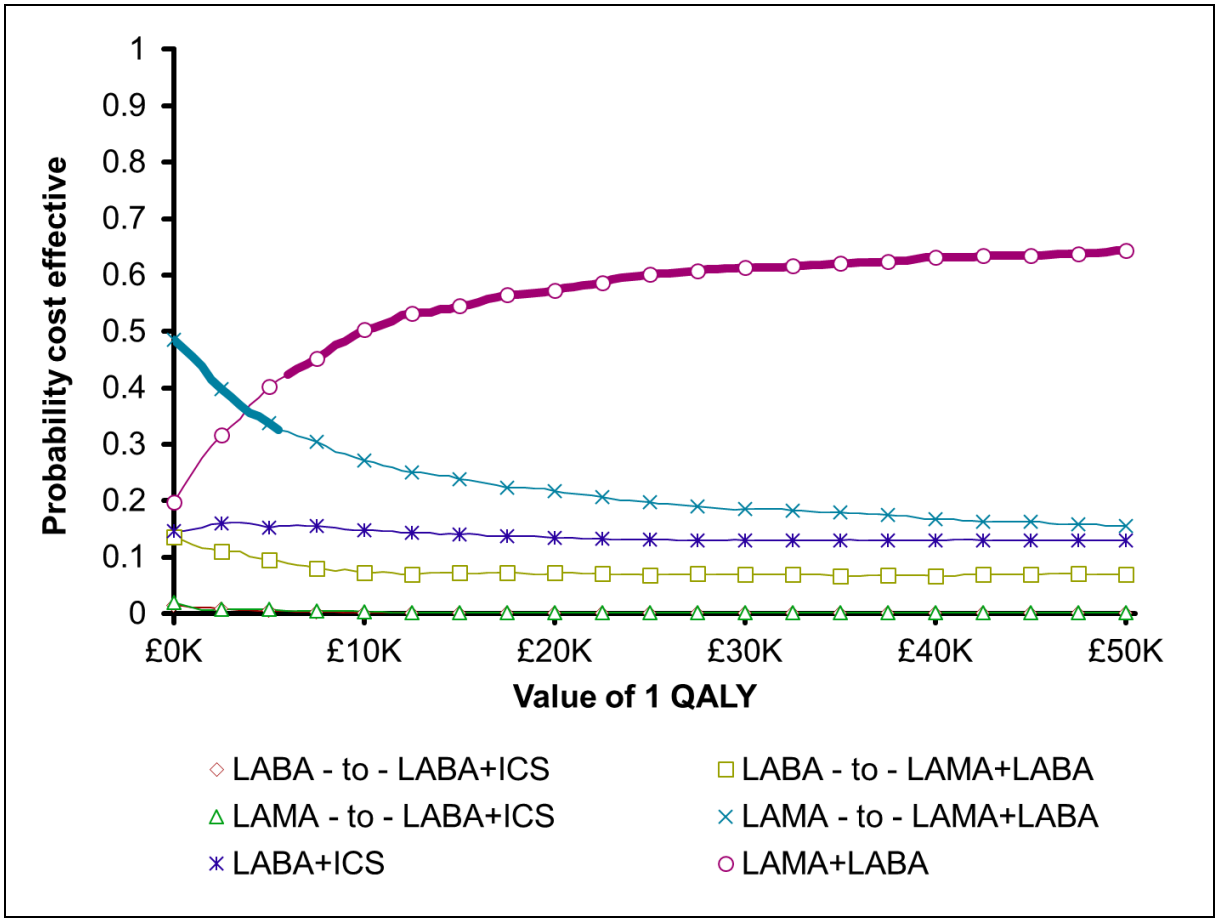

Figure 5 – Cost-effectiveness acceptability curve for Option B: treatment effects on adverse events but not mortality included

Option C – treatment effect on adverse events and mortality included

Table 39 shows results for Option C, in which treatment effects on both adverse events and mortality are included. Mean results now show that LABA+ICS is the strategy which produces the highest number of QALYs, with an ICER of £24,432 compared with LAMA+LABA. This is due to point estimates for treatment effect on mortality favouring LABA+ICS. Since mortality rate is an important determinant of health benefits, this leads to a higher overall number of QALYs for LABA+ICS, despite the treatment benefits associated with LAMA+LABA for other outcomes. Probabilistic results show that, due to the wide confidence intervals associated with both mortality and, to a lesser extent, adverse events, there is now a large amount of uncertainty in outcomes. While LAMA+LABA still shows the highest probability of being optimal if QALYs are valued at £20,000 each, this regimen is only the optimal strategy in 37.8% of iterations. This result is also reflected by the cost-effectiveness acceptability curve, shown in Figure 6.

Results of this scenario show a universal reduction in QALYs across all strategies, compared to Option B. This is because point estimates for treatment-specific differences in mortality favour LABA+ICS (the reference regimen for this outcome), which results in a QALY reduction for all other regimens. The strategy in which patients start treatment on LABA+ICS also produces fewer QALYs than in Option B, since a proportion of patients progress to other treatments.

Table 39 – Base case results for Option C: treatment-specific differences in adverse events and mortality included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£26,712	5.22	-	-	-	9.9%
LABA - to - LAMA+LABA	£27,034	5.24	£322	0.018	ext. dom.	7.5%
LAMA - to - LABA+ICS	£27,209	5.24	£497	0.015	dominated	2.6%
LAMA+LABA	£27,388	5.33	£675	0.108	£6,256	37.8%
LABA - to - LABA+ICS	£27,526	5.25	£139	-0.075	dominated	5.5%
LABA+ICS	£28,004	5.35	£617	0.025	£24,432	36.7%

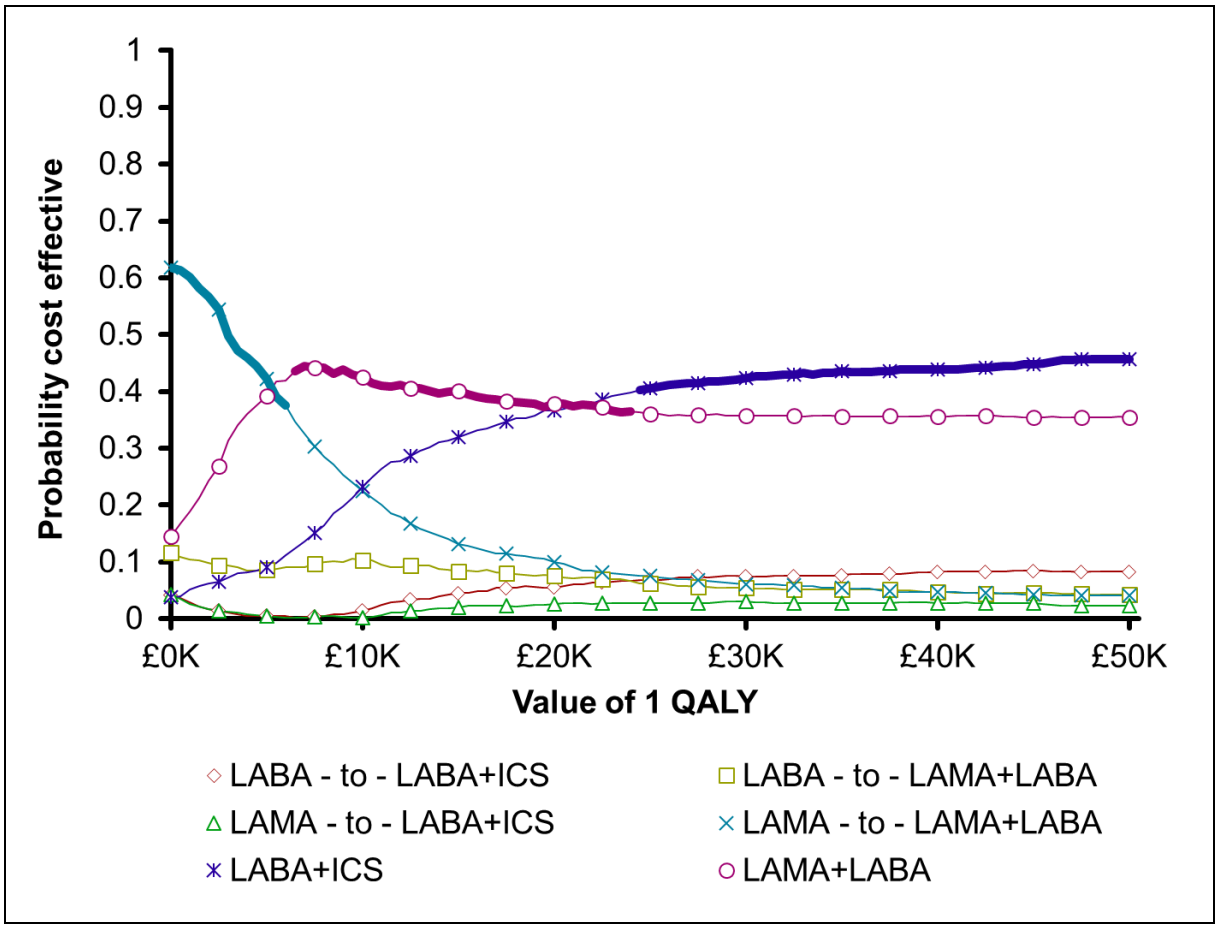

Figure 6 – Cost-effectiveness acceptability curve for Option C: treatment-specific differences in adverse events and mortality included

In order to further explore the high level of uncertainty in Option C, an 'inverse' cost-effectiveness acceptability curve was produced, which shows the probability that each strategy is the **least** cost-effective (i.e. producing the lowest net monetary benefit) at a range of thresholds. These results are displayed in Figure 7, and show that all strategies are associated with non-trivial probabilities of being the least cost-effective option at a threshold of £20,000 per QALY, further demonstrating the uncertainty introduced by including treatment-specific differences in adverse events and mortality.

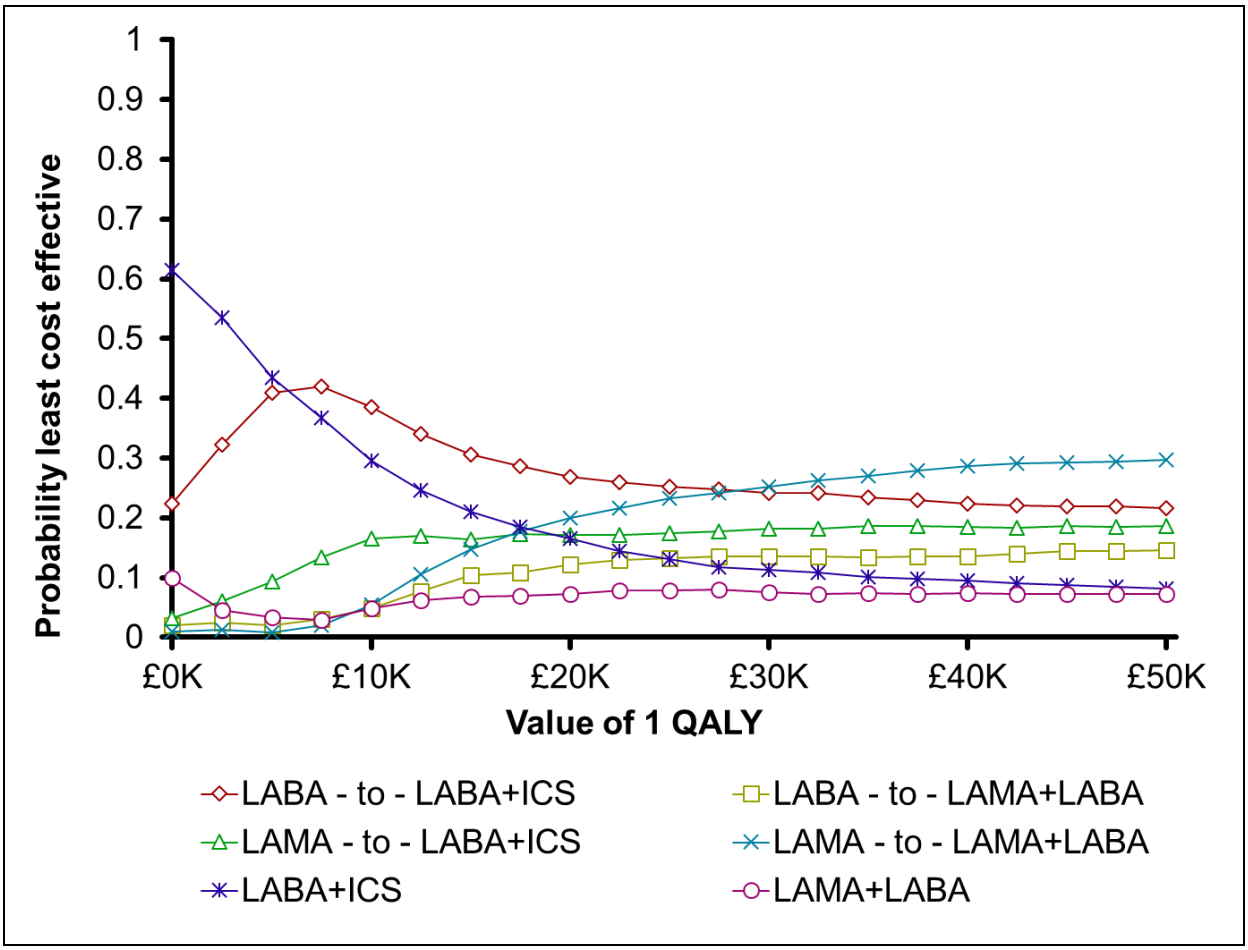

Figure 7 – 'Inverse' cost-effectiveness acceptability curve, showing the probability that each strategy is the least cost effective for Option C: treatment-specific differences in adverse events and mortality included

Results when progression to triple therapy is not permitted

Table 40 to Table 42 show model results when patients cannot progress beyond dual therapy for Options A, B and C. In general, these scenarios show lower mean ICERs for LAMA+LABA, and a higher probability that LAMA+LABA is the optimal strategy. This is for 2 key reasons. First, based on the model setup and input parameters, triple therapy is not, of itself, a cost-effective option for this population. This means that including triple therapy in the pathway reduces the cost effectiveness of strategies in which patients start on dual therapy, as fewer step-ups are required to reach triple therapy. Second, the confidence intervals for the relative incidence of adverse events associated with triple therapy are very wide, relative to outcomes from the NMA. This propagates a considerable degree of uncertainty through probabilistic results for scenarios in which treatment effects on adverse events are included.

Table 40 – Results when progression to triple therapy is not permitted. Option A: treatment-specific differences in adverse events and mortality excluded

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA+LABA	£27,270	5.47	-	-	-	96.4%
LAMA - to - LAMA+LABA	£27,280	5.42	£10	-0.053	dominated	3.5%
LAMA - to - LABA+ICS	£27,558	5.37	£288	-0.105	dominated	0.0%
LABA - to - LAMA+LABA	£27,646	5.40	£376	-0.073	dominated	0.0%
LABA+ICS	£27,710	5.39	£440	-0.080	dominated	0.1%
LABA - to - LABA+ICS	£27,919	5.35	£649	-0.124	dominated	0.0%

Table 41 – Results when progression to triple therapy is not permitted. Option B: treatment-specific differences in adverse events, but not mortality, included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA+LABA	£27,607	5.45	-	-	-	83.7%
LAMA - to - LAMA+LABA	£27,679	5.39	£72	-0.054	dominated	7.4%
LABA - to - LAMA+LABA	£27,813	5.39	£206	-0.063	dominated	1.4%
LABA+ICS	£27,860	5.37	£254	-0.076	dominated	6.7%
LAMA - to - LABA+ICS	£27,899	5.34	£293	-0.107	dominated	0.4%
LABA - to - LABA+ICS	£28,025	5.33	£419	-0.115	dominated	0.4%

Table 42 – Results when progression to triple therapy is not permitted. Option C: treatment effect on adverse events and mortality included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£26,261	5.21	-	-	-	2.2%
LAMA+LABA	£26,453	5.30	£192	0.091	£2,120	53.4%
LABA - to - LAMA+LABA	£26,598	5.23	£145	-0.071	dominated	1.0%
LAMA - to - LABA+ICS	£27,050	5.23	£597	-0.069	dominated	1.2%
LABA - to - LABA+ICS	£27,374	5.25	£921	-0.049	dominated	0.9%
LABA+ICS	£27,546	5.33	£1,093	0.037	£29,411	41.3%

Results for individual treatment benefit scenarios

Table 45 to Table 59 in Appendix B show results for individual treatment effect Scenarios 1 to 5 for Options A, B and C. These results show that the broad pattern of results for the base case remains the same across all treatment benefit scenarios. When treatment-specific differences in adverse events and mortality are excluded, LAMA+LABA shows a high probability of being cost effective, with progressively more uncertainty introduced as adverse event and mortality treatment effects are introduced.

The outlier in this pattern is Scenario 1. For this scenario, when treatment-specific differences in adverse events and mortality are excluded, the strategy LAMA -to-LAMA+LABA has substantially higher probability of being cost-effective than in the other 4 scenarios (35.3%), although LAMA+LABA remains the strategy with the highest probability of being cost-effective. This is because this scenario only mediates treatment benefits through exacerbations, whereas the other 4 scenarios model treatment benefits through SGRQ,

FEV1, or TDI as well, meaning that the QALY benefit of LAMA+LABA is not as high in relation to its incremental cost.

Subgroup results

Results for the high- and low-risk subgroups are presented for Options A, B C. As in the base case, these results are probabilistic means, where 1 of the 5 treatment benefit scenarios is selected at random in each iteration.

High-risk subgroup

Table 60 to Table 62 in Appendix B give results for the high-risk subgroup. These results show that LAMA+LABA is more cost effective, and is associated with a higher probability of being cost effective, compared with corresponding base-case scenarios. This is largely due to a higher baseline exacerbation rate, which means that more effective treatments achieve a larger absolute reduction in exacerbations, and therefore greater QALY gains and cost savings.

Low-risk subgroup

Table 63 to Table 65 in Appendix B give results for the low-risk subgroup. These results show the opposite trend to the high-risk subgroup: LAMA+LABA is generally less cost effective in mean results, and is associated with a lower probability of being cost-effective compared with the corresponding base-case scenarios. This is largely due to a lower baseline exacerbation rate, which means that more effective treatments produce a smaller absolute reduction in exacerbations.

Results for other sensitivity analyses

Table 66 to Table 75 show scenario analyses exploring a range of key assumptions made throughout the model methods for Option A. The majority of these analyses show a relatively small change in results compared with the base case, and the overall conclusion remains the same across all scenarios.

The analysis in which exacerbation disutilities are omitted (Table 75) shows that, while the probability that LAMA+LABA is the most cost-effective strategy is lower than in the base case (62.4%), this strategy still retains the highest probability of being cost effective, even under the extremely conservative assumption that all QoL reductions associated with exacerbations are fully captured by other outcomes.

Discussion

Discussion of model results

For the overall population, results show that, when treatment-specific differences in mortality and adverse events are excluded, the strategy of starting patients on a LAMA+LABA has a high probability of being the optimal option, and is associated with a relatively low mean ICER of £3,428 per QALY. This is because LAMA+LABA shows a favourable treatment effect on exacerbations, SGRQ, FEV1, and TD, and therefore generates the highest number of QALYs across all 5 treatment effect scenarios. Results show that the strategy LAMA -to- LAMA+LABA is the least costly regimen overall, primarily due to the effectiveness of LAMA and LAMA+LABA in reducing hospitalised and non-hospitalised exacerbations, as well as the relatively low acquisition cost of LAMA.

Introducing treatment-specific differences in adverse events produces a higher degree of uncertainty in results. This is largely due to differences in the incidence of cardiac adverse events, a high proportion of which are chronic in nature, and are therefore associated with substantial costs and QALY losses. Odds ratios for cardiac adverse events are associated with wide confidence intervals, with point estimates favouring LABA+ICS and LABA. These factors reduce the certainty that LAMA+LABA is the best option, although this regimen retains the highest probability of being cost-effective by a considerable margin. The inclusion of triple therapy in the treatment pathway is also responsible for a considerable proportion of uncertainty in results, due to extremely wide confidence intervals surrounding adverse event odds ratios for this regimen.

Including treatment-specific differences in mortality as well as adverse events produces an even higher degree of uncertainty in model results, to such an extent that there is no clear choice of optimal strategy. As with adverse event outcomes, the reason for this increase in uncertainty is the wide confidence intervals around mortality odds ratios, as well as point estimates favouring LABA+ICS (although this effect is non-significant). Differences in mortality rate have an especially pronounced impact on results due to the strong association between survival and total QALYs. It should be noted that the favourable mortality effect for LABA+ICS is almost exclusively driven by a single study comparing LABA+ICS with LAMA monotherapy (Wedzicha et al., 2008). Since this result provides indirect evidence in the NMA, LABA+ICS also shows a favourable mortality effect compared with other regimens. The implications of this are captured fully through the committee's discussion of the evidence in Chapter F.

Results of the individual treatment benefit scenarios are largely consistent, and generally produce the same conclusion as the results combining all 5 scenarios. The exception to this is Scenario 1, in which LAMA -to- LAMA+LABA shows a relatively high probability of being cost-effective compared to the other 4 scenarios when treatment-specific differences in adverse events and mortality are excluded (35.3%), although LAMA+LABA still has the highest probability of being cost-effective (64.6%). This is because this scenario is the most conservative in terms of modelling treatment benefits, and only incorporates exacerbation effects, whereas other scenarios also include benefits in terms of SGRQ scores, FEV1, or TDI.

Subgroup analyses show that, for the high-risk population, LAMA+LABA is associated with a lower ICER and a higher probability of being cost effective than in the overall population. This is primarily due to a higher baseline exacerbation rate, rather than differences in treatment effects, which results in more effective treatments achieving a larger absolute reduction in exacerbations, and therefore larger QALY gains and cost reductions. For the low-risk

subgroup, the opposite is true: a lower baseline exacerbation rate results in higher ICERs and more uncertainty that LAMA+LABA is the most cost-effective treatment.

Model strengths

Our analysis was associated with a number of strengths. Firstly, we were able to use outcomes from a large network meta-analysis to inform treatment effects. This approach allowed us to assess the cost effectiveness of all options within the decision space simultaneously, rather than making a limited number of pairwise comparisons, as in the majority of published analyses. It also meant that we were able to base our model on a much larger and more robust evidence base than most published analyses, which generally use data from a limited number of clinical trials.

Secondly, our analysis explores various scenarios for implementing treatment effects. The fact that the results of these scenarios are generally consistent serves to strengthen the conclusions of the analysis.

Thirdly, our analysis modelled the entire treatment pathway, by allowing patients to step-up or switch to different regimens, whereas most published analyses assume that patients remain on the same long-acting bronchodilator for the duration of the model. Consequently, most evaluations in the literature also used a limited time horizon, since a substantial proportion of patients will change treatment within a few years, making modelling a lifetime horizon unrealistic. Since our analysis was not subject to this limitation, we were able to use a lifetime horizon.

Finally, we used primary care records (from the THIN database) to inform the baseline patient population in the model. This method is preferable to using one of the arms from a clinical trial, as generalisability of trial participants to 'real-world' patients is not assured. Furthermore, using the THIN database allowed selection of a patient population directly relevant to our decision problem (i.e. using records of patients immediately prior to first prescription of a long-acting bronchodilator), rather than using data for the COPD population as a whole.

Model limitations

As with all economic models, this evaluation is subject to a number of limitations. Firstly, there was uncertainty in the most appropriate scenario with which to model treatment benefits. The committee's initial preference was to use TDI and exacerbation outcomes from the NMA (Scenario 4), as they expressed the view that breathlessness is the primary determinant of the experience of people with COPD. However, implementing this scenario required the intermediate step of approximating odds ratios from mean changes in TDI score in order to predict the effect of treatment on SGRQ score. The inherent indirectness of this method reduced the intrinsic appeal of the scenario. Using SGRQ and exacerbations outcomes (Scenario 2) was also an appealing choice, as it allowed a measure of quality of life to be directly implemented in the model. However, this outcome is a relatively insensitive measure of treatment benefit compared with TDI or FEV1, and is associated with wider confidence intervals. Moreover, there appears to be some inconsistency between SGRQ results and other measures of treatment benefit: point estimates for LABA+ICS and LAMA+LABA are far closer together for this outcome than for TDI or FEV1. The scenario using FEV1 and exacerbation outcomes (Scenario 3) had intrinsic appeal as it was most closely aligned to previous models in the literature, and also allowed differences in maintenance costs and mortality rates to be modelled through differential distributions of patients among GOLD stages. However, the committee felt that FEV1 was generally a less consistent predictor of costs and quality of life than TDI. Scenario 5, which used regression

coefficients to model TDI, FEV1, and exacerbation history was appealing as it was able to model the independent effect of 3 separate outcomes. However, this scenario had the same limitation as Scenario 4, in that it used a somewhat indirect method of approximating effect of TDI on QoL. Finally, the committee felt that modelling treatment benefits through exacerbations alone (Scenario 1) is likely to underestimate the benefit of treatment, as long-acting bronchodilators demonstrably produce benefits beyond simply reducing the number of exacerbations, although the simplicity of this scenario ensures that double-counting is not an issue. Despite the additional complexity of using 5 different treatment effect scenarios, the fact that LAMA+LABA consistently shows a high probability of being cost effective (when treatment-specific differences in mortality and adverse events are excluded) strengthens, rather than weakens, the conclusions of the analysis; it demonstrates that the cost effectiveness of this regimen persists across a range of different outcomes.

Another key limitation of the model is the inclusion of triple therapy as a downstream option in the pathway. This regimen was not included in the scope of this guideline update, so was not included in the NMA. Instead, it was modelled via pairwise data using LAMA as a comparison. With these outcomes, triple therapy produced only a small incremental QALY benefit in relation to its additional acquisition cost, meaning that starting patients on this regimen would not be a cost-effective option if it was included in the decision space. This resulted in a reduction in the cost effectiveness of strategies in which patients begin treatment on dual therapy, since these regimens require fewer step-ups to reach triple therapy. Limited evidence on the effectiveness of triple therapy also meant that effect estimates were associated with wide confidence intervals, particularly for adverse events. This resulted in a greater degree of uncertainty in results. Fortunately, as demonstrated by scenario analyses, excluding triple therapy from the treatment pathway does not affect overall conclusions. In most cases, LAMA+LABA is associated with the highest probability of being cost effective, and removing triple therapy from the pathway only serves to increase confidence in this result. Further work is required to explicitly assess the cost effectiveness of triple therapy as a treatment option.

A further limitation of the model was measures of uncertainty were not available for the constant and coefficients of the mapping algorithm for conversion of SGRQ values into EQ-5D scores, and for the regression coefficients describing the effect of breathlessness, FEV1, and previous exacerbations on SGRQ. This meant that these parameters could not be implemented probabilistically in the model, and therefore results for relevant scenarios may somewhat underestimate overall uncertainty. However, it is unlikely that this limitation could affect conclusions, since results for scenarios which do not rely on these parameters do not materially differ from those that do.

Finally, it was not possible for this analysis to evaluate all subpopulations of interest. Specifically, the committee felt that stratifying the patient population by current smokers, ex-smokers and non-smokers would be a worthwhile extension. However, due to limited clinical evidence, conducting separate analyses for these two groups was not possible. Similarly, conducting an analysis in COPD patients with asthmatic features would likely have been beneficial, as patients with asthma generally respond to inhaled corticosteroids, meaning that a different conclusion may well be reached for this population. However, as before, limited clinical evidence meant that this analysis was not feasible.

Comparison with other cost–utility analyses

The results of our analysis are broadly consistent with the results of other cost–utility analyses of long-acting bronchodilators conducted from an NHS perspective. The 1 study identified by the economic literature review which evaluated the cost effectiveness of all treatments within the decision space (Hertel et al., 2012) found that LAMA+LABA is the most

cost-effective option (when other treatments not relevant to the decision problem were excluded), with an ICER of £10,950 compared with LABA+ICS. This value is qualitatively the same as – though quantitatively somewhat higher than – the base-case ICER in our analysis (when treatment-specific differences in adverse events and mortality are excluded), most likely due to treatment effects only being implemented through exacerbations in this evaluation.

Two analyses identified in the literature (Punekar et al., 2005 and Ramos et al., 2016) compared a LAMA+LABA with a LAMA. Both evaluations found that the LAMA+LABA was associated with a low ICER (<£3,000 per QALY) and had a high probability of being cost effective. Again, these findings are consistent with the results of our analysis.

Two analyses compared a LAMA with a LABA. The first (Gani et al. 2010; funded by a LAMA manufacturer) found that the LAMA dominated the LABA, and was therefore consistent with our base-case results. However, the second study (Price et al., 2013; funded by a LABA manufacturer) reported the opposite: that the LABA dominated the LAMA. This result is largely due to point estimates for exacerbations and FEV1 favouring the LABA in the clinical trial that informed the analysis. Conversely, the NMA which informed our analysis (which relied on a much larger evidence base) favoured LAMA over LABA for these outcomes.

Conclusions

In base-case results, when treatment effects on adverse events and mortality are excluded, a strategy of starting patients on a LAMA+LABA shows a high probability of being the most cost-effective strategy. This is due to favourable treatment effects on exacerbations, SGRQ, FEV1, and TDI. This finding is robust to assumptions regarding inclusion of triple therapy in the treatment pathway, cost of drugs, treatment effect time points used, utility sources, and method of implementing FEV1 benefit.

Including treatment-specific differences in adverse events and mortality produces progressively more uncertainty that LAMA+LABA is the most cost-effective option. This is primarily due to the wide confidence intervals associated with these outcomes. When adverse event effects are included, LAMA+LABA remains cost effective in the majority of probabilistic iterations, but including mortality effects produces a degree of uncertainty such that there is no clear choice of optimal strategy.

In the subgroup of patients at high risk of exacerbations, LAMA+LABA shows a higher probability of being the optimal option than in the overall population, primarily due to a higher baseline exacerbation rate. In patients at low risk of exacerbations the converse is true, although LAMA+LABA still shows the highest probability of being cost effective when adverse event and mortality effects are not included.

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Appendix A – Coding terms used to select THIN data

Table 43 – List of medcodes used to select people with COPD from THIN dataset

Medcode	Description
H3...00	Chronic obstructive pulmonary disease
H3...11	Chronic obstructive airways disease
H31..00	Chronic bronchitis
H310.00	Simple chronic bronchitis
H310000	Chronic catarrhal bronchitis
H310z00	Simple chronic bronchitis NOS
H311.00	Mucopurulent chronic bronchitis
H311000	Purulent chronic bronchitis
H311100	Fetid chronic bronchitis
H311z00	Mucopurulent chronic bronchitis NOS
H312.00	Obstructive chronic bronchitis
H312000	Chronic asthmatic bronchitis
H312011	Chronic wheezy bronchitis
H312100	Emphysematous bronchitis
H312300	Bronchiolitis obliterans
H312z00	Obstructive chronic bronchitis NOS
H313.00	Mixed simple and mucopurulent chronic bronchitis
H31y.00	Other chronic bronchitis
H31y100	Chronic tracheobronchitis
H31yz00	Other chronic bronchitis NOS
H31z.00	Chronic bronchitis NOS
H32..00	Emphysema
H320.00	Chronic bullous emphysema
H320000	Segmental bullous emphysema
H320100	Zonal bullous emphysema
H320200	Giant bullous emphysema
H320300	Bullous emphysema with collapse
H320311	Tension pneumatocoele
H320z00	Chronic bullous emphysema NOS
H321.00	Panlobular emphysema
H322.00	Centrilobular emphysema
H32y.00	Other emphysema
H32y000	Acute vesicular emphysema
H32y100	Atrophic (senile) emphysema
H32y111	Acute interstitial emphysema
H32y200	MacLeod's unilateral emphysema
H32yz00	Other emphysema NOS
H32yz11	Sawyer - Jones syndrome

Medcode	Description
H32z.00	Emphysema NOS
H36..00	Mild chronic obstructive pulmonary disease
H37..00	Moderate chronic obstructive pulmonary disease
H38..00	Severe chronic obstructive pulmonary disease
H39..00	Very severe chronic obstructive pulmonary disease
H3A..00	End stage chronic obstructive airways disease
H3B..00	Asthma-chronic obstructive pulmonary disease overlap syndrom
H3y..00	Other specified chronic obstructive airways disease
H3y..11	Other specified chronic obstructive pulmonary disease
H3z..00	Chronic obstructive airways disease NOS
H3z..11	Chronic obstructive pulmonary disease NOS
H464000	Chronic emphysema due to chemical fumes
H464100	Obliterative bronchiolitis due to chemical fumes
H583200	Eosinophilic bronchitis
Hyu3000	[X]Other emphysema
Hyu3100	[X]Other specified chronic obstructive pulmonary disease

Table 44 – List of codes used to select patients being initiated on a long-acting bronchodilator from THIN dataset

Code	Description	Therapy class
55814978	Aclidinium bromide 396micrograms/dose / Formoterol 11.8micrograms/dose dry powder inhaler	LAMA+LABA
55815978	Aclidinium bromide 396micrograms/dose / Formoterol 11.8micrograms/dose dry powder inhaler	LAMA+LABA
56923978	Indacaterol 85micrograms/dose / Glycopyrronium bromide 54micrograms/dose inhalation powder capsules with device	LAMA+LABA
56924978	Indacaterol 85micrograms/dose / Glycopyrronium bromide 54micrograms/dose inhalation powder capsules with device	LAMA+LABA
94757998	Neostigmine 2.5mg/1ml / Glycopyrronium bromide 500micrograms/1ml solution for injection ampoules	LAMA+LABA
46811978	Tiotropium bromide 2.5micrograms/dose / Olodaterol 2.5micrograms/dose solution for inhalation cartridge with device CFC	LAMA+LABA
46812978	Tiotropium bromide 2.5micrograms/dose / Olodaterol 2.5micrograms/dose solution for inhalation cartridge with device CFC	LAMA+LABA
73013978	Umeclidinium bromide 65micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler	LAMA+LABA
73014978	Umeclidinium bromide 65micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler	LAMA+LABA
78414979	Tiotropium bromide 18microgram inhalation powder capsules with device	LAMA
78416979	Tiotropium bromide 18microgram inhalation powder capsules with device	LAMA
78417979	Tiotropium bromide 18microgram inhalation powder capsules with device	LAMA

Code	Description	Therapy class
78419979	Tiotropium bromide 18microgram inhalation powder capsules with device	LAMA
78420979	Tiotropium bromide 18microgram inhalation powder capsules with device	LAMA
84357998	Tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device CFC free	LAMA
84358998	Tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device CFC free	LAMA
85051998	Tiotropium bromide 18microgram inhalation powder capsules with device	LAMA
85052998	Tiotropium bromide 18microgram inhalation powder capsules with device	LAMA
85053998	Tiotropium bromide 18microgram inhalation powder capsules with device	LAMA
85054998	Tiotropium bromide 18microgram inhalation powder capsules with device	LAMA
89235998	Tiotropium bromide 18microgram inhalation powder capsules with device	LAMA
93457998	Tiotropium bromide 18microgram inhalation powder capsules with device	LAMA
55228978	Aclidinium bromide 375micrograms/dose dry powder inhaler	LAMA
55864979	Aclidinium bromide 375 micrograms (aclidinium 322 micrograms)	LAMA
55865979	Aclidinium bromide 375micrograms/dose dry powder inhaler	LAMA
53811979	Glycopyrronium bromide 55microgram inhalation powder capsules with device	LAMA
53812979	Glycopyrronium bromide 55microgram inhalation powder capsules with device	LAMA
56209979	Glycopyrronium bromide 2% solution	LAMA
63476979	Glycopyrronium bromide 1% solution	LAMA
63477979	Glycopyrronium bromide 1% solution	LAMA
63479979	Glycopyrronium bromide 0.1% solution	LAMA
64139979	Glycopyrronium bromide 0.5% solution	LAMA
64882979	Glycopyrronium bromide 1.8mg/5ml oral suspension	LAMA
73138978	Glycopyrronium bromide 2mg tablets	LAMA
73172978	Glycopyrronium bromide 1mg tablets	LAMA
79334978	Glycopyrronium bromide 2.5mg/5ml oral suspension	LAMA
79971979	Glycopyrronium bromide 750micrograms/5ml oral solution	LAMA
79973979	Glycopyrronium bromide 600micrograms/5ml oral suspension	LAMA
79976979	Glycopyrronium bromide 5mg/5ml oral suspension	LAMA
79977979	Glycopyrronium bromide 5mg/5ml oral suspension	LAMA
79979979	Glycopyrronium bromide 5mg/5ml oral solution	LAMA
79981979	Glycopyrronium bromide 500micrograms/5ml oral suspension	LAMA
79983979	Glycopyrronium bromide 500micrograms/5ml oral solution	LAMA
79987979	Glycopyrronium bromide 400micrograms/5ml oral solution	LAMA
79993979	Glycopyrronium bromide 250micrograms/5ml oral solution	LAMA
79995979	Glycopyrronium bromide 200micrograms/5ml oral suspension	LAMA

Code	Description	Therapy class
79997979	Glycopyrronium bromide 200micrograms/5ml oral solution	LAMA
81116998	Glycopyrronium bromide 1mg/5ml oral suspension	LAMA
81567998	Glycopyrronium bromide 5mg/5ml oral solution	LAMA
81820979	Glycopyrronium bromide 1mg tablets	LAMA
84118998	Glycopyrronium bromide 2mg/5ml oral suspension	LAMA
84119998	Glycopyrronium bromide 2mg/5ml oral solution	LAMA
85268978	Glycopyrronium bromide 300micrograms/5ml oral suspension	LAMA
85528998	Glycopyrronium bromide oral solution	LAMA
86004998	Glycopyrronium bromide 200micrograms/1ml solution for injection ampoules	LAMA
86005998	Glycopyrronium bromide 600micrograms/3ml solution for injection ampoules	LAMA
86006998	Glycopyrronium bromide 200micrograms/1ml solution for injection ampoules	LAMA
86007998	Glycopyrronium bromide 600micrograms/3ml solution for injection ampoules	LAMA
86083998	Glycopyrronium bromide 1mg/5ml oral solution	LAMA
87610998	Glycopyrronium bromide 0.05% solution	LAMA
87611998	Glycopyrronium bromide 0.05% solution	LAMA
87727998	Glycopyrronium bromide 1mg tablets	LAMA
87728998	Glycopyrronium bromide 1mg tablets	LAMA
93496990	Glycopyrronium bromide 200micrograms/1ml solution for injection ampoules	LAMA
94758998	Glycopyrronium bromide 200micrograms/1ml solution for injection ampoules	LAMA
94901998	Glycopyrronium bromide 600micrograms/3ml solution for injection ampoules	LAMA
96265998	Glycopyrronium bromide 2mg tablets	LAMA
96266998	Glycopyrronium bromide powder for solution for iontophoresis	LAMA
97823998	Glycopyrronium bromide powder for solution for iontophoresis	LAMA
98132990	Glycopyrronium bromide 600micrograms/3ml solution for injection ampoules	LAMA
99172998	Glycopyrronium bromide 2mg tablets	LAMA
59425978	Umeclidinium bromide 65micrograms/dose dry powder inhaler	LAMA
59426978	Umeclidinium bromide 65micrograms/dose dry powder inhaler	LAMA
67601979	Formoterol 12microgram inhalation powder capsules with device	LABA
84989998	Formoterol 12micrograms/dose dry powder inhaler	LABA
86529998	Formoterol 12micrograms/dose inhaler CFC free	LABA
86530998	Formoterol 12micrograms/dose inhaler CFC free	LABA
88487998	Formoterol 12micrograms/dose dry powder inhaler	LABA
88488998	Formoterol 6micrograms/dose dry powder inhaler	LABA
88490997	Formoterol 12micrograms/dose dry powder inhaler	LABA
88490998	Formoterol 6micrograms/dose dry powder inhaler	LABA
90942998	Formoterol 12microgram inhalation powder capsules with device	LABA
90943998	Formoterol 12microgram inhalation powder capsules with device	LABA

Code	Description	Therapy class
97276979	Formoterol 12micrograms/dose dry powder inhaler	LABA
97279979	Formoterol 6micrograms/dose dry powder inhaler	LABA
97281979	Formoterol 6micrograms/dose dry powder inhaler	LABA
97285979	Formoterol 6micrograms/dose dry powder inhaler	LABA
62630979	Indacaterol 300microgram inhalation powder capsules with device	LABA
82082998	Indacaterol 300microgram inhalation powder capsules with device	LABA
82083998	Indacaterol 150microgram inhalation powder capsules with device	LABA
82122998	Indacaterol 300microgram inhalation powder capsules with device	LABA
82124998	Indacaterol 150microgram inhalation powder capsules with device	LABA
58009979	Salmeterol 25micrograms/dose inhaler CFC free	LABA
78113979	Salmeterol 25micrograms/dose inhaler CFC free	LABA
78116979	Salmeterol 25micrograms/dose inhaler CFC free	LABA
81136998	Salmeterol 25micrograms/dose inhaler CFC free	LABA
83070978	Salmeterol 25micrograms/dose inhaler CFC free	LABA
84908998	Salmeterol xinafoate 50mcg disks refill	LABA
84911998	Salmeterol xinafoate 50mcg disks plus disk inhaler	LABA
84912998	Salmeterol 50microgram inhalation powder blisters	LABA
84915998	Salmeterol 50microgram inhalation powder blisters with device	LABA
86320998	Salmeterol 25micrograms/dose inhaler CFC free	LABA
86321998	Salmeterol 25micrograms/dose inhaler CFC free	LABA
93181996	Salmeterol 50micrograms/dose dry powder inhaler	LABA
93181997	Salmeterol xinafoate 50mcg disks refill	LABA
93181998	Salmeterol xinafoate 25mcg inhaler	LABA
93182996	Salmeterol 50micrograms/dose dry powder inhaler	LABA
93182997	Salmeterol 50micrograms disc	LABA
93182998	Salmeterol 25micrograms/dose inhaler	LABA
97297979	Salmeterol 50micrograms/dose dry powder inhaler	LABA
97298979	Salmeterol xinafoate 50mcg disks refill	LABA
97299979	Salmeterol 50microgram inhalation powder blisters with device	LABA
97300979	Salmeterol xinafoate 50mcg disks plus disk inhaler	LABA
97687998	Tulobuterol hydrochloride 2mg tablets	LABA
98403998	Tulobuterol 2mg	LABA
72854978	Olodaterol 2.5micrograms/dose solution for inhalation cartridge with device CFC free	LABA
72855978	Olodaterol 2.5micrograms/dose solution for inhalation cartridge with device CFC free	LABA
48014978	Beclometasone 200micrograms/dose inhaler CFC free	ICS
61236979	Beclometasone 250micrograms/dose inhaler CFC free	ICS
61237979	Beclometasone 200micrograms/dose inhaler CFC free	ICS
61396979	Beclometasone 100micrograms/dose inhaler CFC free	ICS
61397979	Beclometasone 50micrograms/dose inhaler CFC free	ICS
72959978	Beclometasone 100micrograms/dose inhaler cfc free	ICS
83447998	Beclometasone dipropionate 250mcg inhaler	ICS

Code	Description	Therapy class
84869998	Beclometasone dipropionate 400mcg disks refill	ICS
84871998	Beclometasone dipropionate 400mcg disks plus disk inhaler	ICS
84872998	Beclometasone 400microgram inhalation powder blisters	ICS
84873998	Beclometasone 400microgram inhalation powder blisters with device	ICS
84874998	Beclometasone dipropionate 200mcg disks refill	ICS
84875998	Beclometasone dipropionate 200mcg disks plus disk inhaler	ICS
84876998	Beclometasone 200microgram inhalation powder blisters	ICS
84877998	Beclometasone 200microgram inhalation powder blisters with device	ICS
84878998	Beclometasone dipropionate 100mcg disks refill	ICS
84879998	Beclometasone dipropionate 100mcg disks plus disk inhaler	ICS
84880998	Beclometasone 100microgram inhalation powder blisters	ICS
84881998	Beclometasone 100microgram inhalation powder blisters with device	ICS
85823998	Beclometasone 250micrograms/dose inhaler CFC free	ICS
85824998	Beclometasone 200micrograms/dose inhaler CFC free	ICS
85825998	Beclometasone 100micrograms/dose inhaler CFC free	ICS
85826998	Beclometasone 50micrograms/dose inhaler CFC free	ICS
85827998	Beclometasone 250micrograms/dose inhaler CFC free	ICS
85828998	Beclometasone 200micrograms/dose inhaler CFC free	ICS
85829998	Beclometasone 100micrograms/dose inhaler CFC free	ICS
85830998	Beclometasone 50micrograms/dose inhaler CFC free	ICS
86569998	Beclometasone 200micrograms/dose dry powder inhaler	ICS
87173998	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	ICS
87174998	Beclometasone 50micrograms/dose breath actuated inhaler CFC free	ICS
87986997	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	ICS
87986998	Beclometasone 50micrograms/dose breath actuated inhaler CFC free	ICS
87988997	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	ICS
87988998	Beclometasone 50micrograms/dose breath actuated inhaler CFC free	ICS
87990997	Beclometasone 100micrograms/dose inhaler CFC free	ICS
87990998	Beclometasone 50micrograms/dose inhaler CFC free	ICS
87991997	Beclometasone 100micrograms/actuation extrafine particle cfc free inhaler	ICS
88434996	Beclometasone dipropionate 250mcg breath-actuated dry powder inhaler	ICS
88434997	Beclometasone 100micrograms/dose dry powder inhaler	ICS
88434998	Beclometasone dipropionate 50mcg breath-actuated dry powder inhaler	ICS
88469996	Beclometasone dipropionate 250mcg vortex metered dose inhaler	ICS
88469997	Beclometasone dipropionate 100mcg vortex metered dose inhaler	ICS
88469998	Beclometasone dipropionate 50mcg vortex metered dose inhaler	ICS
88832998	Beclometasone 250micrograms/dose breath actuated inhaler	ICS
88833997	Beclometasone 100micrograms/dose breath actuated inhaler	ICS

Code	Description	Therapy class
88833998	Beclometasone 50micrograms/dose breath actuated inhaler	ICS
89262979	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	ICS
89263979	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	ICS
89264979	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	ICS
89265979	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	ICS
89267979	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	ICS
89268979	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	ICS
89270979	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	ICS
89271979	Beclometasone 100micrograms/dose inhaler CFC free	ICS
89273979	Beclometasone 100micrograms/dose inhaler CFC free	ICS
89274979	Beclometasone 100micrograms/dose inhaler CFC free	ICS
89276979	Beclometasone 50micrograms/dose breath actuated inhaler CFC free	ICS
89276996	Beclometasone dipropionate 250mcg vortex metered dose inhaler	ICS
89276997	Beclometasone dipropionate 100mcg vortex metered dose inhaler	ICS
89276998	Beclometasone dipropionate 50mcg vortex metered dose inhaler	ICS
89278979	Beclometasone 50micrograms/dose inhaler CFC free	ICS
89279979	Beclometasone 50micrograms/dose inhaler CFC free	ICS
89862996	Beclometasone dipropionate 250mcg inhaler	ICS
89862997	Beclometasone dipropionate 100mcg inhaler	ICS
89862998	Beclometasone dipropionate 50mcg inhaler	ICS
90416996	Beclometasone dipropionate 250mcg vortex metered dose inhaler	ICS
90416997	Beclometasone dipropionate 100mcg vortex metered dose inhaler	ICS
90416998	Beclometasone dipropionate 50mcg vortex metered dose inhaler	ICS
90417996	Beclometasone 250micrograms/actuation vortex inhaler	ICS
90417997	Beclometasone 100 micrograms/actuation vortex inhaler	ICS
90588998	Beclometasone dipropionate 200mcg inhaler	ICS
91088996	Beclometasone dipropionate 400mcg breath-actuated dry powder inhaler	ICS
91088997	Beclometasone 200micrograms/dose dry powder inhaler	ICS
91088998	Beclometasone 100micrograms/dose dry powder inhaler	ICS
91363996	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	ICS
91363997	Beclometasone 50micrograms/dose dry powder inhaler	ICS
91363998	Beclometasone 250micrograms/actuation inhaler and compact spacer	ICS
91387998	Beclometasone dipropionate 250mcg refill	ICS
91403996	Beclometasone dipropionate 250mcg inhaler	ICS
91403997	Beclometasone dipropionate 100mcg inhaler	ICS

Code	Description	Therapy class
91403998	Beclometasone dipropionate 50mcg inhaler	ICS
92285996	Beclometasone 400micrograms/dose dry powder inhaler	ICS
92285997	Beclometasone 200micrograms/dose dry powder inhaler	ICS
92285998	Beclometasone 250micrograms/dose dry powder inhaler	ICS
93066996	Beclometasone 250micrograms/dose breath actuated inhaler	ICS
93066997	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	ICS
93066998	Beclometasone 50micrograms/dose breath actuated inhaler CFC free	ICS
94456996	Beclometasone 400microgram disc	ICS
94456997	Beclometasone 200micrograms disc	ICS
94456998	Beclometasone 100micrograms disc	ICS
94557996	Beclometasone 400micrograms/actuation inhaler	ICS
94557997	Beclometasone 200micrograms/dose inhaler	ICS
94558996	Beclometasone 400microgram inhalation powder capsules	ICS
94558997	Beclometasone 200microgram inhalation powder capsules	ICS
94558998	Beclometasone 100microgram inhalation powder capsules	ICS
94559996	Beclometasone 100micrograms/dose inhaler	ICS
94559998	Beclometasone 250micrograms/dose inhaler	ICS
94847996	Beclometasone dipropionate 400mcg disks plus disk inhaler	ICS
94847997	Beclometasone dipropionate 200mcg disks plus disk inhaler	ICS
94847998	Beclometasone dipropionate 100mcg disks plus disk inhaler	ICS
95111998	Beclometasone dipropionate 200mcg inhaler	ICS
95162990	Beclometasone 250micrograms/dose inhaler	ICS
95163990	Beclometasone 100micrograms/dose inhaler	ICS
95536990	Beclometasone 200micrograms/dose inhaler	ICS
96027990	Beclometasone dipropionate 400mcg inhalation capsules	ICS
96028990	Beclometasone dipropionate 200mcg inhalation capsules	ICS
96029990	Beclometasone dipropionate 100mcg inhalation capsules	ICS
96130990	Beclometasone 250micrograms/dose inhaler	ICS
96131990	Beclometasone 100micrograms/dose inhaler	ICS
96626988	Beclometasone 250micrograms/dose inhaler	ICS
96626989	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	ICS
96626990	Beclometasone 50micrograms/dose inhaler	ICS
96935988	Beclometasone 250micrograms/dose inhaler	ICS
96935989	Beclometasone 100micrograms/dose inhaler	ICS
97006988	Beclometasone 250micrograms/dose inhaler	ICS
97006989	Beclometasone 100micrograms/dose inhaler	ICS
97154979	Beclometasone dipropionate 100mcg inhaler	ICS
97168979	Beclometasone dipropionate 250mcg inhaler	ICS
97169979	Beclometasone dipropionate 250mcg inhaler	ICS
97172979	Beclometasone dipropionate 200mcg disks plus disk inhaler	ICS
97173979	Beclometasone dipropionate 200mcg disks refill	ICS

Code	Description	Therapy class
97174979	Beclometasone dipropionate 200mcg disks refill	ICS
97181979	Beclometasone dipropionate 400mcg disks plus disk inhaler	ICS
97255988	Beclometasone 100micrograms/dose inhaler	ICS
97255990	Beclometasone 250micrograms/dose inhaler	ICS
97517997	Beclometasone 400microgram inhalation powder blisters	ICS
97517998	Beclometasone dipropionate 400mcg disks plus disk inhaler	ICS
97698998	Beclometasone dipropionate 100mcg inhaler	ICS
97872996	Beclometasone dipropionate 250mcg inhaler	ICS
97872997	Beclometasone dipropionate 100mcg inhaler	ICS
97872998	Beclometasone dipropionate 50mcg inhaler	ICS
98288998	Beclometasone dipropionate 250mcg inhaler	ICS
98332996	Beclometasone dipropionate 100mcg inhaler	ICS
98332997	Beclometasone dipropionate 250mcg inhaler	ICS
98332998	Beclometasone dipropionate 50mcg inhaler	ICS
98590996	Beclometasone dipropionate 400mcg inhalation capsules	ICS
98590997	Beclometasone dipropionate 200mcg inhalation capsules	ICS
98590998	Beclometasone dipropionate 100mcg inhalation capsules	ICS
99914997	Beclometasone 250micrograms/dose inhaler	ICS
99914998	Beclometasone dipropionate 250mcg inhaler	ICS
99965997	Beclometasone dipropionate 100mcg inhaler	ICS
94176998	Betamethasone 4mg/1ml solution for injection ampoules	ICS
95964996	Betamethasone valerate 100micrograms/actuation inhaler	ICS
98395998	Betamethasone 4mg/1ml solution for injection ampoules	ICS
99887998	Betamethasone 100mcg inhaler	ICS
83268998	Budesonide 200mcg/dose CFC-free inhaler	ICS
83269998	Budesonide 100mcg/dose CFC-free inhaler	ICS
83306998	Budesonide 200micrograms/dose inhaler cfc free	ICS
83307998	Budesonide 100micrograms/dose inhaler cfc free	ICS
85036998	Budesonide 200micrograms/dose dry powder inhalation cartridge	ICS
85037998	Budesonide 200micrograms/dose dry powder inhalation cartridge with device	ICS
85041998	Budesonide 200micrograms/dose dry powder inhalation cartridge	ICS
85045998	Budesonide 200micrograms/dose dry powder inhalation cartridge with device	ICS
86195998	Budesonide 400micrograms/dose dry powder inhaler	ICS
86196998	Budesonide 200micrograms/dose dry powder inhaler	ICS
86197998	Budesonide 100micrograms/dose dry powder inhaler	ICS
87438998	Budesonide 200micrograms/dose dry powder inhalation cartridge	ICS
87439998	Budesonide 200micrograms/dose dry powder inhaler	ICS
88156998	Budesonide 200microgram inhalation powder capsules	ICS
89121998	Budesonide 400microgram inhalation powder capsules	ICS
93302996	Budesonide 50micrograms/actuation refill canister	ICS
93302997	Budesonide 200micrograms/actuation refill canister	ICS

Code	Description	Therapy class
93302998	Budesonide 400micrograms/dose dry powder inhaler	ICS
93303996	Budesonide 100micrograms/dose dry powder inhaler	ICS
93303997	Budesonide 400micrograms/dose dry powder inhaler	ICS
93303998	Budesonide 200micrograms/dose dry powder inhaler	ICS
95526992	Budesonide 50mcg inhaler	ICS
95527992	Budesonide 50mcg inhaler refill	ICS
95528992	Budesonide 200mcg inhaler	ICS
95938996	Budesonide 100micrograms/dose dry powder inhaler	ICS
95938997	Budesonide 50micrograms/dose inhaler	ICS
95938998	Budesonide 200micrograms/dose inhaler	ICS
97123979	Budesonide 200mcg inhaler	ICS
97125979	Budesonide 400micrograms/dose dry powder inhaler	ICS
97128979	Budesonide 400micrograms/dose dry powder inhaler	ICS
97129979	Budesonide 400micrograms/dose dry powder inhaler	ICS
97130979	Budesonide 400micrograms/dose dry powder inhaler	ICS
97132979	Budesonide 400micrograms/dose dry powder inhaler	ICS
97133979	Budesonide 400micrograms/dose dry powder inhaler	ICS
97134979	Budesonide 200micrograms/dose dry powder inhaler	ICS
97136979	Budesonide 200micrograms/dose dry powder inhaler	ICS
97138979	Budesonide 200micrograms/dose dry powder inhaler	ICS
97139979	Budesonide 200micrograms/dose dry powder inhaler	ICS
97140979	Budesonide 200micrograms/dose dry powder inhaler	ICS
97141979	Budesonide 200micrograms/dose dry powder inhaler	ICS
97143979	Budesonide 100micrograms/dose dry powder inhaler	ICS
97146979	Budesonide 100micrograms/dose dry powder inhaler	ICS
97147979	Budesonide 100micrograms/dose dry powder inhaler	ICS
97149979	Budesonide 100micrograms/dose dry powder inhaler	ICS
98595997	Budesonide 50mcg inhaler refill	ICS
98595998	Budesonide 50mcg inhaler	ICS
98596997	Budesonide 200micrograms/actuation refill canister	ICS
98596998	Budesonide 200mcg/dose inhaler	ICS
98887996	Budesonide 100micrograms/dose dry powder inhaler	ICS
98887997	Budesonide 400micrograms/dose dry powder inhaler	ICS
98887998	Budesonide 200micrograms/dose dry powder inhaler	ICS
82254998	Fluticasone propionate 500micrograms/dose dry powder inhaler	ICS
82255998	Fluticasone propionate 250micrograms/dose dry powder inhaler	ICS
82257998	Fluticasone propionate 100micrograms/dose dry powder inhaler	ICS
82258998	Fluticasone propionate 50micrograms/dose dry powder inhaler	ICS
84750998	Fluticasone propionate 500mcg disks refill	ICS
84751998	Fluticasone propionate 500mcg disks plus disk inhaler	ICS
84752998	Fluticasone propionate 500microgram inhalation powder blisters	ICS
84753998	Fluticasone propionate 500microgram inhalation powder blisters with device	ICS

Code	Description	Therapy class
84754998	Fluticasone propionate 250mcg disks refill	ICS
84755998	Fluticasone propionate 250mcg disks plus disk inhaler	ICS
84756998	Fluticasone propionate 250microgram inhalation powder blisters	ICS
84757998	Fluticasone propionate 250microgram inhalation powder blisters with device	ICS
84759998	Fluticasone propionate 100mcg disks refill	ICS
84760998	Fluticasone propionate 100mcg disks plus disk inhaler	ICS
84762998	Fluticasone propionate 100microgram inhalation powder blisters	ICS
84763998	Fluticasone propionate 100microgram inhalation powder blisters with device	ICS
84767998	Fluticasone propionate 50mcg disks refill	ICS
84768998	Fluticasone propionate 50mcg disks plus disk inhaler	ICS
84770998	Fluticasone propionate 50microgram inhalation powder blisters	ICS
84771998	Fluticasone propionate 50microgram inhalation powder blisters with device	ICS
91322997	Fluticasone propionate 500micrograms/dose dry powder inhaler	ICS
91322998	Fluticasone propionate 250micrograms/dose dry powder inhaler	ICS
91334997	Fluticasone propionate 500micrograms/dose dry powder inhaler	ICS
91334998	Fluticasone propionate 250micrograms/dose dry powder inhaler	ICS
91619996	Fluticasone 50micrograms/dose inhaler CFC free	ICS
91619997	Fluticasone 250micrograms/dose inhaler CFC free	ICS
91619998	Fluticasone 125micrograms/dose inhaler CFC free	ICS
92473996	Fluticasone 50micrograms/dose inhaler CFC free	ICS
92473997	Fluticasone 250micrograms/dose inhaler CFC free	ICS
92473998	Fluticasone 125micrograms/dose inhaler CFC free	ICS
92842996	Fluticasone propionate 100micrograms/dose dry powder inhaler	ICS
92842997	Fluticasone propionate 50micrograms/dose dry powder inhaler	ICS
92842998	Fluticasone propionate 250mcg inhaler	ICS
92843998	Fluticasone propionate 500mcg disks plus disk inhaler	ICS
92844998	Fluticasone 500microgram disc	ICS
92845996	Fluticasone propionate 100micrograms/dose dry powder inhaler	ICS
92845997	Fluticasone propionate 50micrograms/dose dry powder inhaler	ICS
92845998	Fluticasone 250microgram/actuation pressurised inhalation	ICS
92899996	Fluticasone 125microgram/actuation pressurised inhalation	ICS
92899997	Fluticasone 50microgram/actuation pressurised inhalation	ICS
92899998	Fluticasone 25micrograms/dose inhaler	ICS
92900996	Fluticasone propionate 125mcg inhaler	ICS
92900997	Fluticasone propionate 50mcg inhaler	ICS
92900998	Fluticasone propionate 25mcg inhaler	ICS
93056996	Fluticasone 250microgram disc	ICS
93056997	Fluticasone 100microgram disc	ICS
93056998	Fluticasone 50microgram disc	ICS
93057996	Fluticasone propionate 250mcg disks plus disk inhaler	ICS

Code	Description	Therapy class
93057997	Fluticasone propionate 100mcg disks refill	ICS
93057998	Fluticasone propionate 50mcg disks plus disk inhaler	ICS
96041992	Fluticasone propionate 50mcg disks plus disk inhaler	ICS
96884992	Fluticasone propionate 250mcg disks plus disk inhaler	ICS
96885992	Fluticasone propionate 100mcg disks plus disk inhaler	ICS
97048979	Fluticasone 50micrograms/dose inhaler CFC free	ICS
97050979	Fluticasone 50micrograms/dose inhaler CFC free	ICS
97055979	Fluticasone 250micrograms/dose inhaler CFC free	ICS
97056979	Fluticasone 250micrograms/dose inhaler CFC free	ICS
97058979	Fluticasone 250micrograms/dose inhaler CFC free	ICS
97061979	Fluticasone 250micrograms/dose inhaler CFC free	ICS
97065979	Fluticasone 125micrograms/dose inhaler CFC free	ICS
97069979	Fluticasone 125micrograms/dose inhaler CFC free	ICS
97070979	Fluticasone 125micrograms/dose inhaler CFC free	ICS
97085979	Fluticasone propionate 500micrograms/dose dry powder inhaler	ICS
97087979	Fluticasone propionate 500micrograms/dose dry powder inhaler	ICS
97088979	Fluticasone propionate 250micrograms/dose dry powder inhaler	ICS
97089979	Fluticasone propionate 250micrograms/dose dry powder inhaler	ICS
97090979	Fluticasone propionate 250micrograms/dose dry powder inhaler	ICS
97093979	Fluticasone propionate 250micrograms/dose dry powder inhaler	ICS
97095979	Fluticasone propionate 250micrograms/dose dry powder inhaler	ICS
97096979	Fluticasone propionate 100micrograms/dose dry powder inhaler	ICS
97099979	Fluticasone propionate 100micrograms/dose dry powder inhaler	ICS
97101979	Fluticasone propionate 100micrograms/dose dry powder inhaler	ICS
97102979	Fluticasone propionate 50micrograms/dose dry powder inhaler	ICS
97103979	Fluticasone propionate 50micrograms/dose dry powder inhaler	ICS
97104979	Fluticasone propionate 50micrograms/dose dry powder inhaler	ICS
94324992	Pulmicort refil 200 mcg inh	ICS

Appendix B – Additional sensitivity analysis results

Results for individual treatment benefit scenarios

Scenario 1

Table 45 – Results for Scenario 1 (treatment effect on exacerbations); Option A (treatment effects on adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,478	5.37	-	-	-	35.3%
LAMA - to - LABA+ICS	£27,651	5.37	£173	-0.007	dominated	0.0%
LAMA+LABA	£27,751	5.39	£272	0.019	£14,165	64.6%
LABA - to - LAMA+LABA	£27,828	5.36	£77	-0.038	dominated	0.0%
LABA - to - LABA+ICS	£27,998	5.35	£247	-0.045	dominated	0.0%
LABA+ICS	£28,029	5.38	£278	-0.012	dominated	0.1%

Table 46 – Results for Scenario 1 (treatment effect on exacerbations); Option B (treatment effects on adverse events, but not mortality, included)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,993	5.35	-	-	-	34.4%
LABA - to - LAMA+LABA	£28,115	5.34	£123	-0.007	dominated	12.1%
LAMA - to - LABA+ICS	£28,145	5.34	£152	-0.008	dominated	1.4%
LABA - to - LABA+ICS	£28,262	5.33	£269	-0.014	dominated	1.6%
LAMA+LABA	£28,410	5.36	£417	0.012	£35,369	30.5%
LABA+ICS	£28,588	5.35	£179	-0.009	dominated	20.0%

Table 47 – Results for Scenario 1 (treatment effect on exacerbations); Option C (treatment effects on adverse events and mortality included)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£26,862	5.18	-	-	-	9.8%
LABA - to - LAMA+LABA	£27,159	5.20	£297	0.017	ext. dom.	9.2%
LAMA - to - LABA+ICS	£27,336	5.22	£473	0.033	ext. dom.	7.7%
LAMA+LABA	£27,582	5.23	£720	0.046	ext. dom.	18.7%
LABA - to - LABA+ICS	£27,627	5.24	£764	0.051	ext. dom.	15.5%
LABA+ICS	£28,184	5.28	£1,322	0.095	£13,927	39.1%

Scenario 2

Table 48 – Results for Scenario 2 (treatment effect on SGRQ and exacerbations); Option A (treatment-specific differences in adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,474	5.43	-	-	-	0.0%
LAMA - to - LABA+ICS	£27,644	5.42	£170	-0.008	dominated	0.0%
LAMA+LABA	£27,747	5.63	£273	0.206	£1,328	92.1%
LABA - to - LAMA+LABA	£27,824	5.41	£77	-0.222	dominated	0.0%
LABA - to - LABA+ICS	£27,991	5.40	£244	-0.230	dominated	0.0%
LABA+ICS	£28,020	5.62	£272	-0.012	dominated	7.9%

Table 49 – Results for Scenario 2 (treatment effect on SGRQ and exacerbations); Option B (treatment-specific differences in adverse events, but not mortality, included)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£28,084	5.39	-	-	-	1.6%
LABA - to - LAMA+LABA	£28,216	5.39	£132	-0.004	dominated	1.3%
LAMA - to - LABA+ICS	£28,246	5.39	£162	-0.008	dominated	0.0%
LABA - to - LABA+ICS	£28,373	5.38	£289	-0.011	dominated	0.0%
LAMA+LABA	£28,529	5.59	£445	0.197	£2,257	65.5%
LABA+ICS	£28,729	5.58	£200	-0.008	dominated	31.6%

Table 50 – Results for Scenario 2 (treatment effect on SGRQ and exacerbations); Option C (treatment-specific differences in adverse events and mortality included)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£26,777	5.21	-	-	-	1.0%
LABA - to - LAMA+LABA	£27,082	5.23	£305	0.022	ext. dom.	1.0%
LAMA - to - LABA+ICS	£27,265	5.25	£488	0.038	ext. dom.	0.3%
LAMA+LABA	£27,514	5.44	£737	0.230	£3,200	31.6%
LABA - to - LABA+ICS	£27,563	5.27	£49	-0.170	dominated	1.2%
LABA+ICS	£28,129	5.50	£615	0.057	£10,783	64.9%

Scenario 3

Table 51 – Results for Scenario 3 (treatment effect on FEV1 and exacerbations); Option A (treatment-specific differences in adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,613	5.39	-	-	-	6.3%
LAMA - to - LABA+ICS	£27,836	5.34	£223	-0.046	dominated	0.0%
LAMA+LABA	£27,878	5.43	£265	0.040	£6,542	93.7%
LABA - to - LAMA+LABA	£27,990	5.35	£112	-0.077	dominated	0.0%
LABA+ICS	£28,185	5.38	£307	-0.050	dominated	0.0%
LABA - to - LABA+ICS	£28,211	5.30	£333	-0.125	dominated	0.0%

Table 52 – Results for Scenario 3 (treatment effect on FEV1 and exacerbations); Option B (treatment-specific differences in adverse events, but not mortality, included)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£28,197	5.35	-	-	-	36.7%
LABA - to - LAMA+LABA	£28,352	5.32	£155	-0.025	dominated	3.6%
LAMA - to - LABA+ICS	£28,398	5.30	£200	-0.047	dominated	0.0%
LABA - to - LABA+ICS	£28,550	5.28	£352	-0.072	dominated	0.0%
LAMA+LABA	£28,636	5.38	£439	0.032	£13,604	52.6%
LABA+ICS	£28,846	5.33	£210	-0.046	dominated	7.1%

Table 53 – Results for Scenario 3 (treatment effect on FEV1 and exacerbations); Option C (treatment-specific differences in adverse events and mortality included)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£26,935	5.20	-	-	-	16.5%
LABA - to - LAMA+LABA	£27,248	5.20	£313	0.000	ext. dom.	9.3%
LAMA - to - LABA+ICS	£27,450	5.20	£515	-0.003	dominated	2.0%
LAMA+LABA	£27,661	5.27	£726	0.073	£9,986	40.2%
LABA - to - LABA+ICS	£27,757	5.19	£96	-0.077	dominated	1.6%
LABA+ICS	£28,278	5.28	£617	0.013	£46,430	30.4%

Scenario 4

Table 54 – Results for Scenario 4 (treatment effect on TDI and exacerbations); Option A (treatment-specific differences in adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,420	5.37	-	-	-	10.9%
LAMA - to - LABA+ICS	£27,593	5.34	£174	-0.029	dominated	0.0%
LAMA+LABA	£27,692	5.42	£272	0.052	£5,286	88.4%
LABA - to - LAMA+LABA	£27,774	5.36	£82	-0.062	dominated	0.7%
LABA - to - LABA+ICS	£27,945	5.33	£253	-0.091	dominated	0.0%
LABA+ICS	£27,971	5.37	£279	-0.050	dominated	0.0%

Table 55 – Results for Scenario 4 (treatment effect on TDI and exacerbations); Option B (treatment-specific differences in adverse events, but not mortality, included)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£28,115	5.33	-	-	-	21.5%
LABA - to - LAMA+LABA	£28,241	5.33	£125	0.001	ext. dom.	18.1%
LAMA - to - LABA+ICS	£28,280	5.30	£165	-0.031	dominated	0.0%
LABA - to - LABA+ICS	£28,400	5.30	£285	-0.029	dominated	0.0%
LAMA+LABA	£28,587	5.37	£472	0.041	£11,563	55.1%
LABA+ICS	£28,795	5.32	£207	-0.049	dominated	5.3%

Table 56 – Results for Scenario 4 (treatment effect on TDI and exacerbations); Option C (treatment-specific differences in adverse events and mortality included)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£26,869	5.18	-	-	-	10.3%
LABA - to - LAMA+LABA	£27,160	5.20	£291	0.027	ext. dom.	13.3%
LAMA - to - LABA+ICS	£27,318	5.19	£449	0.009	dominated	1.4%
LAMA+LABA	£27,598	5.26	£729	0.081	£9,035	39.7%
LABA - to - LABA+ICS	£27,603	5.21	£6	-0.044	dominated	9.5%
LABA+ICS	£28,164	5.26	£566	0.007	£80,155	25.8%

Scenario 5

Table 57 – Results for Scenario 5 (independent effect of FEV1, TDI, and exacerbations on SGRQ); Option A (treatment-specific differences in adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,640	5.63	-	-	-	4.1%
LAMA - to - LABA+ICS	£27,864	5.58	£225	-0.055	dominated	0.0%
LAMA+LABA	£27,905	5.70	£265	0.071	£3,747	95.8%
LABA - to - LAMA+LABA	£28,013	5.61	£109	-0.095	dominated	0.1%
LABA+ICS	£28,212	5.63	£307	-0.077	dominated	0.0%
LABA - to - LABA+ICS	£28,237	5.55	£332	-0.150	dominated	0.0%

Table 58 – Results for Scenario 5 (independent effect of FEV1, TDI, and exacerbations on SGRQ); Option B (treatment-specific differences in adverse events, but not mortality, included)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£28,204	5.60	-	-	-	24.3%
LABA - to - LAMA+LABA	£28,360	5.58	£155	-0.014	dominated	5.6%
LAMA - to - LABA+ICS	£28,403	5.54	£199	-0.055	dominated	0.0%
LABA - to - LABA+ICS	£28,555	5.53	£351	-0.069	dominated	0.0%
LAMA+LABA	£28,626	5.66	£422	0.062	£6,856	68.6%
LABA+ICS	£28,837	5.58	£211	-0.074	dominated	1.5%

Table 59 – Results for Scenario 5 (independent effect of FEV1, TDI, and exacerbations on SGRQ); Option C (treatment-specific differences in adverse events and mortality included)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£26,855	5.41	-	-	-	8.4%
LABA - to - LAMA+LABA	£27,200	5.42	£345	0.018	ext. dom.	11.8%
LAMA - to - LABA+ICS	£27,371	5.40	£516	-0.005	dominated	1.2%
LAMA+LABA	£27,562	5.51	£707	0.106	£6,661	51.4%
LABA - to - LABA+ICS	£27,710	5.42	£149	-0.093	dominated	3.6%
LABA+ICS	£28,188	5.51	£626	-0.006	dominated	23.6%

Subgroup results

High-risk subgroup

Table 60 – Results for high-risk subgroup; Option A: treatment effects on adverse events and mortality excluded

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£28,922	5.36	-	-	-	6.0%
LAMA+LABA	£28,959	5.45	£37	0.091	£404	93.6%
LAMA - to - LABA+ICS	£29,173	5.32	£214	-0.128	dominated	0.0%
LABA+ICS	£29,341	5.40	£382	-0.050	dominated	0.4%
LABA - to - LAMA+LABA	£29,581	5.31	£622	-0.132	dominated	0.0%
LABA - to - LABA+ICS	£29,830	5.28	£871	-0.169	dominated	0.0%

Table 61 – Results for high-risk subgroup; Option B: treatment effects on adverse events, but not mortality, included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA+LABA	£29,332	5.46	-	-	-	75.0%
LAMA - to - LAMA+LABA	£29,337	5.36	£5	-0.098	dominated	19.2%
LAMA - to - LABA+ICS	£29,658	5.31	£326	-0.141	dominated	0.3%
LABA - to - LAMA+LABA	£29,819	5.33	£487	-0.130	dominated	2.0%
LABA+ICS	£29,873	5.39	£541	-0.064	dominated	3.4%
LABA - to - LABA+ICS	£30,136	5.28	£804	-0.173	dominated	0.1%

Table 62 – Results for high-risk subgroup; Option C: treatment effects on adverse events and mortality included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£28,255	5.20	-	-	-	11.2%
LAMA+LABA	£28,527	5.33	£272	0.133	£2,047	64.1%
LABA - to - LAMA+LABA	£28,687	5.16	£159	-0.171	dominated	1.5%
LAMA - to - LABA+ICS	£28,854	5.19	£327	-0.140	dominated	2.6%
LABA - to - LABA+ICS	£29,278	5.15	£751	-0.178	dominated	0.4%
LABA+ICS	£29,448	5.32	£921	-0.014	dominated	20.2%

Low-risk subgroup

Table 63 – Results for low-risk subgroup; Option A: treatment effects on adverse events and mortality excluded

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£26,222	5.52	-	-	-	23.4%
LABA - to - LAMA+LABA	£26,356	5.52	£134	0.000	ext. dom.	3.4%
LAMA - to - LABA+ICS	£26,356	5.49	£134	-0.024	dominated	0.4%
LABA - to - LABA+ICS	£26,489	5.49	£267	-0.024	dominated	0.0%
LAMA+LABA	£26,647	5.59	£425	0.073	£5,865	60.3%
LABA+ICS	£26,845	5.56	£197	-0.030	dominated	12.5%

Table 64 – Results for low-risk subgroup; Option B: treatment effects on adverse events, but not mortality, included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LABA - to - LAMA+LABA	£26,869	5.48	-	-	-	29.2%
LABA - to - LABA+ICS	£26,924	5.46	£55	-0.021	dominated	4.8%
LAMA - to - LAMA+LABA	£27,037	5.46	£168	-0.018	dominated	13.3%
LAMA - to - LABA+ICS	£27,101	5.44	£232	-0.040	dominated	0.8%
LABA+ICS	£27,654	5.50	£785	0.021	ext. dom.	27.6%
LAMA+LABA	£27,712	5.52	£843	0.038	£22,348	24.3%

Table 65 – Results for low-risk subgroup; Option C: treatment effects on adverse events and mortality included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£24,355	5.07	-	-	-	2.3%
LAMA - to - LABA+ICS	£24,914	5.12	£559	0.053	ext. dom.	0.6%
LABA - to - LAMA+LABA	£24,957	5.21	£602	0.140	£4,293	17.9%
LAMA+LABA	£25,349	5.17	£391	-0.034	dominated	10.7%
LABA - to - LABA+ICS	£25,528	5.26	£571	0.055	£10,317	35.9%
LABA+ICS	£25,976	5.26	£448	0.002	£256,979	32.6%

Results for other sensitivity analyses

Table 66 – Results for scenario in which 25% of patients receiving dual therapy are assumed to use 2 separate inhalers when calculating acquisition costs.

Option A (treatment-specific differences in adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,773	5.44	-	-	-	19.2%
LAMA - to - LABA+ICS	£27,844	5.41	£71	-0.030	dominated	0.3%
LABA - to - LAMA+LABA	£28,127	5.42	£354	-0.022	dominated	0.4%
LABA - to - LABA+ICS	£28,198	5.39	£425	-0.052	dominated	0.0%
LAMA+LABA	£28,205	5.52	£432	0.077	£5,618	76.8%
LABA+ICS	£28,277	5.48	£72	-0.041	dominated	3.3%

Table 67 – Results for scenario in which the cost of a single fixed-dose combination inhaler is used for triple therapy. Option A (treatment-specific differences in adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA+LABA	£27,249	5.52	-	-	-	95.2%
LAMA - to - LAMA+LABA	£27,262	5.44	£13	-0.082	dominated	2.5%
LAMA - to - LABA+ICS	£27,429	5.41	£180	-0.109	dominated	0.0%
LABA+ICS	£27,489	5.48	£240	-0.039	dominated	2.2%
LABA - to - LAMA+LABA	£27,626	5.42	£377	-0.102	dominated	0.1%
LABA - to - LABA+ICS	£27,791	5.39	£542	-0.130	dominated	0.0%

Table 68 – Results for scenario in which the cost of the cheapest product is used for every regimen. Option A (treatment-specific differences in adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LABA - to - LABA+ICS	£26,837	5.39	-	-	-	0.8%
LABA - to - LAMA+LABA	£26,838	5.41	£1	0.029	£47	3.3%
LAMA - to - LABA+ICS	£26,884	5.41	£46	-0.008	dominated	0.6%
LAMA - to - LAMA+LABA	£26,887	5.43	£49	0.021	£2,355	12.8%
LABA+ICS	£27,131	5.47	£244	0.035	ext. dom.	9.9%
LAMA+LABA	£27,193	5.51	£306	0.074	£4,110	72.6%

Table 69 – Results for scenario in which drug costs are not adjusted by adherence. Option A (treatment-specific differences in adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£28,020	5.46	-	-	-	17.6%
LAMA - to - LABA+ICS	£28,210	5.43	£190	-0.030	dominated	0.0%
LABA - to - LAMA+LABA	£28,375	5.44	£355	-0.021	dominated	0.6%
LAMA+LABA	£28,398	5.53	£378	0.072	£5,283	80.4%
LABA - to - LABA+ICS	£28,563	5.41	£165	-0.122	dominated	0.0%
LABA+ICS	£28,683	5.49	£285	-0.041	dominated	1.4%

Table 70 – Results for scenario in which stable utilities from Rutten van Mölken (2006) are used, rather than values from Jones et al. (2011). Option A (treatment-specific differences in adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,500	5.99	-	-	-	13.3%
LAMA - to - LABA+ICS	£27,692	5.96	£191	-0.029	dominated	0.0%
LAMA+LABA	£27,775	6.06	£274	0.069	£3,966	84.9%
LABA - to - LAMA+LABA	£27,861	5.97	£86	-0.091	dominated	0.4%
LABA - to - LABA+ICS	£28,050	5.94	£275	-0.120	dominated	0.0%
LABA+ICS	£28,062	6.02	£288	-0.040	dominated	1.4%

Table 71 – Results for scenario in which treatment effects for continuous outcomes at 3 and 6 months are used, as opposed to only 3 months. Option A (treatment-specific differences in adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,498	5.44	-	-	-	19.9%
LAMA - to - LABA+ICS	£27,690	5.41	£191	-0.025	dominated	0.0%
LAMA+LABA	£27,774	5.50	£275	0.064	£4,327	78.6%
LABA - to - LAMA+LABA	£27,862	5.41	£89	-0.095	dominated	0.0%
LABA - to - LABA+ICS	£28,052	5.38	£278	-0.120	dominated	0.0%
LABA+ICS	£28,055	5.47	£282	-0.031	dominated	1.5%

Table 72 – Results for scenario in which treatment effects for continuous outcomes at 3, 6, and 12 months are used, as opposed to only 3 months. Option A (treatment-specific differences in adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,516	5.43	-	-	-	20.4%
LAMA - to - LABA+ICS	£27,710	5.41	£194	-0.024	dominated	0.1%
LAMA+LABA	£27,793	5.49	£277	0.061	£4,554	72.6%
LABA - to - LAMA+LABA	£27,890	5.39	£97	-0.101	dominated	0.0%
LABA+ICS	£28,074	5.47	£281	-0.024	dominated	6.9%
LABA - to - LABA+ICS	£28,082	5.37	£289	-0.125	dominated	0.0%

Table 73 – Results for scenario in which there is no FEV1 benefit from stepping up or

switching treatment. Option A (treatment-specific differences in adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,558	5.39	-	-	-	11.2%
LAMA - to - LABA+ICS	£27,732	5.38	£174	-0.016	dominated	0.0%
LAMA+LABA	£27,794	5.50	£235	0.105	£2,234	86.3%
LABA - to - LAMA+LABA	£27,932	5.37	£138	-0.133	dominated	0.3%
LABA+ICS	£28,095	5.45	£302	-0.053	dominated	2.2%
LABA - to - LABA+ICS	£28,103	5.35	£309	-0.149	dominated	0.0%

Table 74 – Results for scenario in which patients receive full FEV1 benefit from stepping up or switching treatment. Option A (treatment-specific differences in adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,572	5.46	-	-	-	11.4%
LAMA - to - LABA+ICS	£27,746	5.43	£175	-0.030	dominated	0.1%
LAMA+LABA	£27,803	5.54	£231	0.076	£3,031	87.2%
LABA - to - LAMA+LABA	£27,942	5.43	£139	-0.104	dominated	0.1%
LABA+ICS	£28,095	5.49	£293	-0.051	dominated	1.2%
LABA - to - LABA+ICS	£28,114	5.40	£311	-0.133	dominated	0.0%

Table 75 – Results for scenario in which exacerbation disutilities are omitted. Option A (treatment-specific differences in adverse events and mortality excluded)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,506	5.65	-	-	-	30.8%
LAMA - to - LABA+ICS	£27,697	5.63	£190	-0.022	dominated	0.0%
LAMA+LABA	£27,782	5.71	£275	0.057	£4,825	62.4%
LABA - to - LAMA+LABA	£27,867	5.65	£85	-0.059	dominated	3.0%
LABA - to - LABA+ICS	£28,054	5.63	£273	-0.080	dominated	0.0%
LABA+ICS	£28,068	5.68	£286	-0.028	dominated	3.8%

Appendix C – Full list of model parameters

Table 76 – Full list of model input parameters (except for THIN data and relative treatment effects, which are displayed in subsequent tables)

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Baseline patient characteristics				
Starting age	67.0	0.148	THIN data	Gamma
Sex (% male)	51.2%	0.007	THIN data	Beta
Height (cm)	168.7	0.194	Briggs 2017	Gamma
Starting distribution of patients among GOLD stages				
Mild COPD	19.3%	0.006	Calculated from THIN data	Dirichlet
Moderate COPD	55.6%	0.007	Calculated from THIN data	Dirichlet
Severe COPD	23.6%	0.006	Calculated from THIN data	Dirichlet
Very severe COPD	1.5%	0.002	Calculated from THIN data	Dirichlet
Mean baseline FEV1 % predicted by GOLD stage				
Mild COPD	95.3%	0.005	Calculated from THIN data	Gamma
Moderate COPD	63.7%	0.003	Calculated from THIN data	Gamma
Severe COPD	42.4%	0.004	Calculated from THIN data	Gamma
Very severe COPD	26.6%	0.032	Calculated from THIN data	Gamma
Overall population	64.3%	0.003	Calculated from THIN data	Gamma
Mean baseline FEV1 by GOLD stage (ml)				
Mild COPD	2798	18.7	Calculated from THIN data	Gamma
Moderate COPD	1674	8.4	Calculated from THIN data	Gamma
Severe COPD	1028	9.8	Calculated from THIN data	Gamma

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Very severe COPD	616	73.5	Calculated from THIN data	Gamma
Overall population	1719	10.0	Calculated from THIN data	Gamma
Change in FEV1 (ml)				
Treatment effect at 3 months	47	12.0	SCO100470	Normal
Annual FEV1 decline - mild COPD	47.0	2.5	Assumed same as moderate COPD	Normal
Annual FEV1 decline - moderate COPD	47.0	2.5	Celli 2008	Normal
Annual FEV1 decline - severe COPD	47.2	2.2	Celli 2008	Normal
Annual FEV1 decline - v. severe COPD	28.4	4.3	Celli 2008	Normal
Existing cardiovascular comorbidities				
Proportion of patients with existing cardiovascular comorbidities	0.46	0.005	SCO100470	Beta
Non-hospitalised exacerbations - grouped by exacerbations in previous year				
Mild COPD - no exacerbations in previous year	0.93	0.018	Rothnie 2018	Gamma
Mild COPD - 1 moderate exacerbation in previous year	1.40	0.031	Rothnie 2018	Gamma
Mild COPD - 2 moderate exacerbations in previous year	1.98	0.051	Rothnie 2018	Gamma
Mild COPD - 3 moderate exacerbations in previous year	2.55	0.082	Rothnie 2018	Gamma
Mild COPD - 4 moderate exacerbations in previous year	3.29	0.133	Rothnie 2018	Gamma
Mild COPD - 5+ moderate exacerbations in previous year	4.81	0.143	Rothnie 2018	Gamma

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Mild COPD - 1+ severe exacerbations in previous year	2.96	0.135	Rothnie 2018	Gamma
Moderate COPD - no exacerbations in previous year	0.98	0.015	Rothnie 2018	Gamma
Moderate COPD - 1 moderate exacerbation in previous year	1.50	0.023	Rothnie 2018	Gamma
Moderate COPD - 2 moderate exacerbations in previous year	2.01	0.038	Rothnie 2018	Gamma
Moderate COPD - 3 moderate exacerbations in previous year	2.55	0.059	Rothnie 2018	Gamma
Moderate COPD - 4 moderate exacerbations in previous year	3.22	0.092	Rothnie 2018	Gamma
Moderate COPD - 5+ moderate exacerbations in previous year	4.67	0.099	Rothnie 2018	Gamma
Moderate COPD - 1+ severe exacerbations in previous year	2.80	0.117	Rothnie 2018	Gamma
Severe COPD - no exacerbations in previous year	1.24	0.023	Rothnie 2018	Gamma
Severe COPD - 1 moderate exacerbation in previous year	1.73	0.033	Rothnie 2018	Gamma
Severe COPD - 2 moderate exacerbations in previous year	2.40	0.054	Rothnie 2018	Gamma
Severe COPD - 3 moderate exacerbations in previous year	3.06	0.079	Rothnie 2018	Gamma
Severe COPD - 4 moderate exacerbations in previous year	3.60	0.117	Rothnie 2018	Gamma

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Severe COPD - 5+ moderate exacerbations in previous year	5.04	0.112	Rothnie 2018	Gamma
Severe COPD - 1+ severe exacerbations in previous year	3.01	0.110	Rothnie 2018	Gamma
Very severe COPD - no exacerbations in previous year	1.40	0.054	Rothnie 2018	Gamma
Very severe COPD - 1 moderate exacerbation in previous year	1.90	0.077	Rothnie 2018	Gamma
Very severe COPD - 2 moderate exacerbations in previous year	2.55	0.089	Rothnie 2018	Gamma
Very severe COPD - 3 moderate exacerbations in previous year	3.65	0.181	Rothnie 2018	Gamma
Very severe COPD - 4 moderate exacerbations in previous year	3.68	0.199	Rothnie 2018	Gamma
Very severe COPD - 5+ moderate exacerbations in previous year	5.61	0.209	Rothnie 2018	Gamma
Very severe COPD - 1+ severe exacerbations in previous year	3.44	0.184	Rothnie 2018	Gamma
Hospitalised exacerbations - grouped by exacerbations in previous year				
Mild COPD - no exacerbations in previous year	0.08	0.003	Rothnie 2018	Gamma
Mild COPD - 1 moderate exacerbation in previous year	0.09	0.005	Rothnie 2018	Gamma
Mild COPD - 2 moderate exacerbations in previous year	0.12	0.010	Rothnie 2018	Gamma
Mild COPD - 3 moderate exacerbations in previous year	0.19	0.020	Rothnie 2018	Gamma

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Mild COPD - 4 moderate exacerbations in previous year	0.20	0.026	Rothnie 2018	Gamma
Mild COPD - 5+ moderate exacerbations in previous year	0.25	0.026	Rothnie 2018	Gamma
Mild COPD - 1+ severe exacerbations in previous year	0.53	0.048	Rothnie 2018	Gamma
Moderate COPD - no exacerbations in previous year	0.07	0.005	Rothnie 2018	Gamma
Moderate COPD - 1 moderate exacerbation in previous year	0.09	0.003	Rothnie 2018	Gamma
Moderate COPD - 2 moderate exacerbations in previous year	0.11	0.005	Rothnie 2018	Gamma
Moderate COPD - 3 moderate exacerbations in previous year	0.14	0.010	Rothnie 2018	Gamma
Moderate COPD - 4 moderate exacerbations in previous year	0.15	0.013	Rothnie 2018	Gamma
Moderate COPD - 5+ moderate exacerbations in previous year	0.21	0.028	Rothnie 2018	Gamma
Moderate COPD - 1+ severe exacerbations in previous year	0.31	0.020	Rothnie 2018	Gamma
Severe COPD - no exacerbations in previous year	0.14	0.005	Rothnie 2018	Gamma
Severe COPD - 1 moderate exacerbation in previous year	0.17	0.008	Rothnie 2018	Gamma
Severe COPD - 2 moderate exacerbations in previous year	0.22	0.013	Rothnie 2018	Gamma

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Severe COPD - 3 moderate exacerbations in previous year	0.27	0.018	Rothnie 2018	Gamma
Severe COPD - 4 moderate exacerbations in previous year	0.28	0.020	Rothnie 2018	Gamma
Severe COPD - 5+ moderate exacerbations in previous year	0.39	0.026	Rothnie 2018	Gamma
Severe COPD - 1+ severe exacerbations in previous year	0.57	0.031	Rothnie 2018	Gamma
Very severe COPD - no exacerbations in previous year	0.22	0.013	Rothnie 2018	Gamma
Very severe COPD - 1 moderate exacerbation in previous year	0.27	0.026	Rothnie 2018	Gamma
Very severe COPD - 2 moderate exacerbations in previous year	0.31	0.023	Rothnie 2018	Gamma
Very severe COPD - 3 moderate exacerbations in previous year	0.42	0.043	Rothnie 2018	Gamma
Very severe COPD - 4 moderate exacerbations in previous year	0.46	0.084	Rothnie 2018	Gamma
Very severe COPD - 5+ moderate exacerbations in previous year	0.52	0.046	Rothnie 2018	Gamma
Very severe COPD - 1+ severe exacerbations in previous year	0.65	0.051	Rothnie 2018	Gamma
Exacerbations - proportion of patients within each severity stage				
Mild COPD - no exacerbations in previous year	0.55	0.005	Rothnie 2018	Dirichlet
Mild COPD - 1 moderate exacerbation in previous year	0.19	0.004	Rothnie 2018	Dirichlet

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Mild COPD - 2 moderate exacerbations in previous year	0.10	0.003	Rothnie 2018	Dirichlet
Mild COPD - 3 moderate exacerbations in previous year	0.05	0.002	Rothnie 2018	Dirichlet
Mild COPD - 4 moderate exacerbations in previous year	0.03	0.002	Rothnie 2018	Dirichlet
Mild COPD - 5+ moderate exacerbations in previous year	0.04	0.002	Rothnie 2018	Dirichlet
Mild COPD - 1+ severe exacerbations in previous year	0.03	0.002	Rothnie 2018	Dirichlet
Moderate COPD - no exacerbations in previous year	0.53	0.003	Rothnie 2018	Dirichlet
Moderate COPD - 1 moderate exacerbation in previous year	0.20	0.003	Rothnie 2018	Dirichlet
Moderate COPD - 2 moderate exacerbations in previous year	0.11	0.002	Rothnie 2018	Dirichlet
Moderate COPD - 3 moderate exacerbations in previous year	0.05	0.002	Rothnie 2018	Dirichlet
Moderate COPD - 4 moderate exacerbations in previous year	0.03	0.001	Rothnie 2018	Dirichlet
Moderate COPD - 5+ moderate exacerbations in previous year	0.04	0.001	Rothnie 2018	Dirichlet
Moderate COPD - 1+ severe exacerbations in previous year	0.03	0.001	Rothnie 2018	Dirichlet
Severe COPD - no exacerbations in previous year	0.47	0.004	Rothnie 2018	Dirichlet

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Severe COPD - 1 moderate exacerbation in previous year	0.20	0.004	Rothnie 2018	Dirichlet
Severe COPD - 2 moderate exacerbations in previous year	0.11	0.003	Rothnie 2018	Dirichlet
Severe COPD - 3 moderate exacerbations in previous year	0.07	0.002	Rothnie 2018	Dirichlet
Severe COPD - 4 moderate exacerbations in previous year	0.04	0.002	Rothnie 2018	Dirichlet
Severe COPD - 5+ moderate exacerbations in previous year	0.06	0.002	Rothnie 2018	Dirichlet
Severe COPD - 1+ severe exacerbations in previous year	0.06	0.002	Rothnie 2018	Dirichlet
Very severe COPD - no exacerbations in previous year	0.43	0.009	Rothnie 2018	Dirichlet
Very severe COPD - 1 moderate exacerbation in previous year	0.18	0.007	Rothnie 2018	Dirichlet
Very severe COPD - 2 moderate exacerbations in previous year	0.12	0.006	Rothnie 2018	Dirichlet
Very severe COPD - 3 moderate exacerbations in previous year	0.06	0.004	Rothnie 2018	Dirichlet
Very severe COPD - 4 moderate exacerbations in previous year	0.04	0.004	Rothnie 2018	Dirichlet
Very severe COPD - 5+ moderate exacerbations in previous year	0.08	0.005	Rothnie 2018	Dirichlet
Very severe COPD - 1+ severe exacerbations in previous year	0.09	0.005	Rothnie 2018	Dirichlet
Mortality				

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
SMR - mild COPD - males	0.91	0.090	Leviseth 2013	Lognormal
SMR - moderate COPD - males	1.33	0.052	Leviseth 2013	Lognormal
SMR - severe COPD - males	1.77	0.093	Leviseth 2013	Lognormal
SMR - v. severe COPD - males	3.47	0.124	Leviseth 2013	Lognormal
SMR - mild COPD - females	0.75	0.122	Leviseth 2013	Lognormal
SMR - moderate COPD - females	1.70	0.079	Leviseth 2013	Lognormal
SMR - severe COPD - females	4.72	0.132	Leviseth 2013	Lognormal
SMR - v. severe COPD - females	5.15	0.357	Leviseth 2013	Lognormal
Baseline mortality - males (for calculation of treatment effect RRs)	0.05	0.002	Leviseth 2013	Beta
Baseline mortality - females (for calculation of treatment effect RRs)	0.04	0.002	Leviseth 2013	Beta
Adverse events (annual rates unless stated otherwise; reference treatment LABA)				
Atrial fibrillation/flutter	0.033	0.004	Jara 2012	Gamma
Cardiac arrest	0.002	0.001	Jara 2012	Gamma
Angina	0.017	0.003	Jara 2012	Gamma
Myocardial infarction	0.010	0.002	Jara 2012	Gamma
Heart failure	0.046	0.005	Jara 2012	Gamma
Stroke	0.012	0.002	Jara 2012	Gamma
Syncope	0.015	0.003	Jara 2012	Gamma
Ventricular tachycardia	0.000	0.000	Jara 2012	Gamma
Pneumonia	0.015	0.003	Jara 2012	Gamma
Constipation	0.055	0.005	Jara 2012	Gamma
Dry mouth	0.003	0.001	Jara 2012	Gamma

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Urinary retention	0.011	0.002	Jara 2012	Gamma
Diarrhoea	0.027	0.006	Calverley 2007	Gamma
Glaucoma - 4 year rate	0.006	0.000	Miller 2011	Gamma
Stepping up and switching (reference treatment LABA+ICS)				
Two year probability of switching	0.074	0.007	Wurst 2014	Beta
Two year probability of stepping up	0.244	0.012	Wurst 2014	Beta
Unit costs				
GP visit	£36.00	-	Unit costs of Health and Social Care 2017	-
Respiratory team - cost per visit - band 6 nurse	£30.00	-	Unit Costs of Health and Social Care 2017 - cost for 40 minutes of hospital nurse time	-
Respiratory team - cost per visit - band 7 nurse	£36.00	-	Unit Costs of Health and Social Care 2017 - cost for 40 minutes of hospital nurse time	-
Respiratory team - proportion of visits from a band 6 nurse	0.75	0.08	Committee's opinion	Gamma
Respiratory team - vists per episode	6	1.02	Committee's opinion	Gamma
Respiratory team - cost per episode	£189.00	-	Calculated	-
Outpatient visit	£154.77	-	Reference costs 2015-2016 - respiratory medicine outpatient procedures	-
Spirometry	£28.00	-	Reference costs 2010-2011 - spirometry test and broncho dilator response test	-
Spirometry - adjusted to current value	£30.05	-	Calculated	-
Pulmonary rehabilitation - course for 17 patients	£12,120.00	-	Griffiths 2001	-
Pulmonary rehabilitation per patient - adjusted to current value	£788.32	-	Calculated	-

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Home oxygen therapy	£14.70	-	Hertel 2012	-
Home oxygen therapy - adjusted to current value	£16.25	-	Calculated	-
Influenza vaccine	£6.21	-	Department of Health 2011	-
Influenza vaccine - adjusted to current value	£6.67	-	Calculated	-
SABA - Salbutamol 100mcg - 200 D	£1.50	-	Drug Tariff 2017	-
SAMA - Ipratropium bromide 20mcg - 200D	£5.56	-	Drug Tariff 2017	-
Theophylline - 200mg modified-release tablets - 56 tablets	£2.96	-	Drug Tariff 2017	-
Theophylline - cost per day	£0.05	-	Calculated	-
Mucolytics - carbocisteine 375mg capsules - 120 capsules	£4.81	-	Drug Tariff 2017	-
Mucolytics - cost per day	£0.04	-	Calculated	-
Oral corticosteroids - prednisolone 5mg tables (28)	£0.66	-	Drug Tariff 2017	-
CT scan	£562.12	-	Reference costs 2015-16 - Positron Emission Tomography with Computed Tomography (PET-CT) of one area, 19 years and over	-
Antibiotics - amoxicillin 500mg - 15 capsules	£0.73	-	Drug Tariff 2017	-
Ambulance journey to A&E	£236.00	-	Reference costs 2015-16 - see, treat and convey	-
Hospital stay	£1,944.00	-	Reference costs 2015-2016 - weighted average COPD non-elective long stay, excluding one day or less category	-
A&E visit - not admitted	£118.00	-	Reference costs 2015-16 - weighted average of all non-admitted emergency medicine entries	-
Atrial fibrillation/flutter - annual cost	£420.00	-	Costing template for Atrial Fibrillation (2014) - cost per patient in future costs scenario excluding cost of stroke	-

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Atrial fibrillation - annual cost - adjusted to current value	£429.40	-	Calculated	-
Cardiac arrest	£1,647.00	-	Reference costs 2015-16 - Cardiac arrest weighted average - all HRGs	-
Myocardial infarction	£1,497.00	-	Reference costs 2015-16 weighted average of all myocardial infarction	-
Myocardial infarction - rehabilitation	£258.00	-	Reference costs 2015-16	-
Pneumonia	£1,909.00	-	Reference costs 2015-16 weighted average of all pneumonia	-
Stroke - five year cost	£15,306.00	-	Youman 2003	-
Stroke - adjusted to current value - annual cost	£4,254.45	-	Calculated	-
Angina - annual cost	£1,055.00	-	Stewart 2003	-
Angina - annual cost - adjusted to current value	£1,662.25	-	Calculated	-
Heart failure - annual cost	£760.00	-	Stewart 2002	-
Heart failure - annual cost - adjusted to current value	£1,414.29	-	Calculated	-
Syncope	£118.00	-	Reference costs 2015-16 - weighted average of all non-admitted emergency medicine entries	-
Ventricular tachycardia - cardiac specialist visit	£156.00	-	Reference costs 2015-16 - cardiology consulstant outpatient visit - face-to-face, first visit	-
Ventricular tachycardia - healthcare visit for administration of adenosine injection	£103.00	-	Reference costs 2015-16 - cardiology non-consultant led outpatient visit	-
Ventricular tachycardia - adenosine - Adenocor 6mg/2ml solution for injection vials	£6.45	-	BNF - Dec 2017	-

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Constipation - emergency admission	£138.00	-	Reference costs 2015-16 - weighted average of all emergency medicine costs	-
Constipation - laxative - Methylcellulose 500mg tablets - 112	£5.13	-	Drug Tariff Feb 2018	-
Urinary retention - surgical procedure	£2,756.00	-	Reference costs 2015-16 - weighted average of ureteric or bladder disorders	-
Diarrhoea - loperamide 2mg capsules - 30	£0.86	-	Drug Tariff Feb 2018	-
Glaucoma - annual cost	£475.00	-	Rahman 2013	-
Drug usage				
Proportion of patients on high LABA dose	0.5	-	Assumption	-
Adherence	0.885	-	Calverley 2007	-
Proportion of patients using LABA+ICS with LAMA inhaler for triple therapy	0.9	-	Assumption	-
Maintenance resource use - mild COPD (annual)				
GP visit	1	0.13	Committee's opinion	Gamma
Respiratory team visit	0	-	Committee's opinion	-
Outpatient visit	0	-	Committee's opinion	-
Spirometry	1	0.15	Committee's opinion	Gamma
Pulmonary rehabilitation	0.02	0.01	OPCRD 2012	Gamma
Home oxygen therapy	0	-	Assumption	-
Influenza vaccine	0.73	0.10	Department of Health 2011	Beta
SABA	3.74	0.57	OPCRD 2012	Gamma
SAMA	0.59	0.09	OPCRD 2012	Gamma
Theophylline	122.06	24.41	Rutten van Molken 2007	Gamma

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Mucolytics	39.74	7.95	Rutten van Molken 2007	Gamma
Oral corticosteroids	0.88	0.14	OPCRD 2012	Gamma
CT scan	0		Committee's opinion	-
Maintenance resource use - moderate COPD (annual)				
GP visit	1	0.13	Committee's opinion	Gamma
Respiratory team visit	0	-	Committee's opinion	-
Outpatient visit	0	-	Committee's opinion	-
Spirometry	1	0.13	Committee's opinion	Gamma
Pulmonary rehabilitation	0.03	0.01	OPCRD 2012	Gamma
Home oxygen therapy	0	-	Assumption	-
Influenza vaccine	0.73	0.10	Department of Health 2011	Beta
SABA	4.65	0.71	OPCRD 2012	Gamma
SAMA	0.65	0.10	OPCRD 2012	Gamma
Theophylline	122.06	24.41	Rutten van Molken 2007	Gamma
Mucolytics	39.74	7.95	Rutten van Molken 2007	Gamma
Oral corticosteroids	0.96	0.15	OPCRD 2012	Gamma
CT scan	0	-	Committee's opinion	-
Maintenance resource use - severe COPD (annual)				
GP visit	1.5	0.13	Committee's opinion	Gamma
Respiratory team visit	2	0.13	Committee's opinion	Gamma
Outpatient visit	1	0.13	Committee's opinion	Gamma
Spirometry	2	0.13	Committee's opinion	Gamma
Pulmonary rehabilitation	0.06	0.01	OPCRD 2012	Gamma

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Home oxygen therapy	0.05	0.01	Assumption	Gamma
Influenza vaccine	0.73	0.10	Department of Health 2011	Beta
SABA	6.87	1.05	OPCRD 2012	Gamma
SAMA	0.91	0.14	OPCRD 2012	Gamma
Theophylline	161.77	32.35	Rutten van Molken 2007	Gamma
Mucolytics	48.31	9.66	Rutten van Molken 2007	Gamma
Oral corticosteroids	1.7	0.26	OPCRD 2012	Gamma
CT scan	0.05	0.01	Committee's opinion	Gamma
Maintenance resource use - very severe COPD (annual)				
GP visit	2	0.13	Committee's opinion	Gamma
Respiratory team visit	4	0.26	Committee's opinion	Gamma
Outpatient visit	2	0.13	Committee's opinion	Gamma
Spirometry	3	0.26	Committee's opinion	Gamma
Pulmonary rehabilitation	0.09	0.01	OPCRD 2012	Gamma
Home oxygen therapy	0.4	0.06	Assumption	Gamma
Influenza vaccine	0.73	0.10	Department of Health 2011	Beta
SABA	9.78	1.49	OPCRD 2012	Gamma
SAMA	1.19	0.18	OPCRD 2012	Gamma
Theophylline	159.07	31.81	Rutten van Molken 2007	Gamma
Mucolytics	80.6	16.12	Rutten van Molken 2007	Gamma
Oral corticosteroids	2.7	0.42	OPCRD 2012	Gamma
CT scan	0.1	0.10	Committee's opinion	Gamma
Resource use - non-hospitalised exacerbation				

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
A&E visit without admission	0.3	0.051	Committee's opinion	Beta
Respiratory team visit	0.1	0.013	Committee's opinion	Beta
GP visit	0.6	-	Calculated	-
Oral corticosteroids	1	0.128	Committee's opinion	Gamma
Antibiotics	2	0.255	Committee's opinion	Gamma
Resource use - hospitalised exacerbation				
Ambulance journey to A&E	0.7	0.05	Committee's opinion	Gamma
Hospital stay	1	-	Committee's opinion	-
Oral corticosteroids	1	0.05	Committee's opinion	Gamma
Antibiotics	2	0.05	Committee's opinion	Gamma
Resource use - adverse events				
Proportion of patients requiring surgery for aneurysm	0.85	0.01	Powell 2007	Beta
Proportion of patients with ventricular tachycardia visiting a cardiology specialist	0.5	0.13	Assumption	Beta
Proportion of patients with ventricular tachycardia requiring adenosine injection	0.5	0.13	Assumption	Beta
Proportion of patients with constipation who see a GP	0.5	0.13	Assumption	Beta
Proportion of patients with constipation with emergency admission	0.05	0.01	Assumption	Beta
Proportion of patients with constipation prescribed a laxative	0.5	0.13	Assumption	Beta
Proportion of patients with dry mouth who see a GP	0.5	0.13	Assumption	Beta

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Proportion of patients with diarrhoea who see a GP	0.5	0.13	Assumption	Beta
Proportion of patients with diarrhoea prescribed loperamide	0.5	0.13	Assumption	Beta
Treatment changing costs				
Number of GP visits associated with treatment change	2	0.26	Committee's opinion	Gamma
Cost of changing treatment	72	-	Calculated	-
Steady state utilities - Jones 2011 (SGRQ scores)				
Mild COPD	38.5	1.29	Jones 2011	Beta
Moderate COPD	40.4	0.61	Jones 2011	Beta
Severe COPD	50.2	0.79	Jones 2011	Beta
Very severe COPD	58.6	1.62	Jones 2011	Beta
Steady state utilities - Stahl 2005				
Mild COPD	0.84	0.029	Stahl 2005	Beta
Moderate COPD	0.73	0.024	Stahl 2005	Beta
Severe COPD	0.74	0.044	Stahl 2005	Beta
Very severe COPD	0.52	0.087	Stahl 2005	Beta
Steady state utilities - Rutten van Molken 2006				
Mild COPD - input	0.9056	-	Calculated	-
Moderate COPD	0.787	0.008	Rutten van Molken 2006	Beta
Severe COPD	0.75	0.009	Rutten van Molken 2006	Beta
V. severe COPD	0.647	0.025	Rutten van Molken 2006	Beta
Exacerbation disutilities				

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Non-hospitalised exacerbation	0.01	0.007	Rutten van Molken 2009	Normal
Hospitalised exacerbation	0.042	0.009	Rutten van Molken 2009	Normal
Individual adverse event utilities				
Atrial fibrillation disutility	0.063	0.005	Economic analysis from NICE CG180	Beta
Atrial fibrillation duration of disutility (years)	0.500	0.128	Assumption	Gamma
Atrial fibrillation QALY loss	0.032	-	Calculated	-
Cardiac arrest QALY loss	0.060	0.011	Davies 2015	Beta
Angina QALY loss	0.090	0.016	Davies 2015	Beta
Myocardial infarction QALY loss	0.060	0.011	Davies 2015	Beta
Heart failure disutility 1 year	0.140	0.017	Davies 2015	Beta
Stroke utility	0.690	0.010	Jipan 2006	Beta
Nonstroke utility	0.870	0.003	Jipan 2006	Beta
Stroke disutility	0.180	-	Calculated	-
Syncope disutility	0.500	0.128	Assumption	Beta
Syncope duration of disutility (days)	1	0.128	Assumption	Gamma
Syncope QALY loss	0.001	-	Calculated	-
Ventricular tachycardia - QALY loss	0.032	-	Assumed equivalent to atrial fibrillation disutility	-
Pneumonia utility at 1 year	0.680	0.010	Mangen 2017	Beta
Non-pneumonia utility at 1 year	0.810	0.010	Mangen 2017	Beta
Pneumonia QALY loss	0.130	-	Calculated	-
Constipation - QoL in patients currently constipated	0.555	0.029	Christensen 2016	Beta
Constipation in patients not currently constipated	0.629	0.026	Christensen 2016	Beta

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Constipation disutility	0.074	-	Calculated	-
Constipation duration (days)	7	2.041	Assumption	Gamma
Constipation QALY loss	0.001	-	Calculated	-
Dry mouth disutility	0.050	0.010	Assumption	Normal
Dry mouth duration (days)	7	1.020	Assumption	Gamma
Dry mouth QALY loss	0.001	-	Calculated	-
Urinary retention disutility	0.140	0.014	Ackerman 2000	Beta
Urinary retention duration (days)	30	5.102	Assumption	Gamma
Urinary retention QALY loss	0.012	-	Calculated	-
Diarrhoea disutility	0.103	0.010	Lloyd 2006	Beta
Diarrhoea duration	4	1.020	Assumption	Gamma
Diarrhoea QALY loss	0.412	-	Calculated	-
Glaucoma disutility	0.056	0.019	Economic analysis from NICE NG81	Normal
SGRQ to EQ-5D mapping algorithm				
Intercept	0.962	-	Starkie 2011	-
Coefficient - SGRQ	-0.001	-	Starkie 2011	-
Coefficient - SGRQ2^2	0.000	-	Starkie 2011	-
Coefficient - male	0.023	-	Starkie 2011	-
Regression coefficients for effect of disease symptoms on SGRQ				
Dyspnea symptoms - most days versus none	17.59	-	Exuzides 2017	-
Dyspnea symptoms - several days versus none	9.63	-	Exuzides 2017	-
FEV1 % predicted	-0.01	-	Exuzides 2017	-
Recent moderate exacerbations	0.85	-	Exuzides 2017	-

Parameter	Point estimate	Standard error	Source	Distribution used in probabilistic sensitivity analysis
Recent severe exacerbations	1.91	-	Exuzides 2017	-
Age (years)	-0.37	-	Exuzides 2017	-
FEV1 predicted equations - in litres				
Intercept - men	-2.49	-	BTS spirometry in practice	-
Height coefficient - men	0.04	-	BTS spirometry in practice	-
Age coefficient - men	-0.03	-	BTS spirometry in practice	-
Intercept - women	-2.60	-	BTS spirometry in practice	-
Height coefficient - women	0.04	-	BTS spirometry in practice	-
Age coefficient - women	-0.03	-	BTS spirometry in practice	-
Intercept - both genders weighted	-2.54	-	BTS spirometry in practice	-
Height coefficient - both genders weighted	0.04	-	BTS spirometry in practice	-
Age coefficient - both genders weighted	-0.03	-	BTS spirometry in practice	-
Baseline TDI - for calculation of SGRQ and stepping up effects				
Baseline TDI - for calculation of RR from OR	1.9	0.12	SCO100470	Normal
SD of TDI - for calculation of SMD	2.70	-	SCO100470	-

Table 77 – THIN data on the distribution FEV1 scores in people with COPD prior to the first prescription of a long-acting bronchodilator*

FEV1 Score - Litres	Patient count	Male	Female	Mean age
less than 0.64	83	21	62	72.4
0.7	82	22	60	72.5
0.8	140	33	107	71.9
0.9	174	43	131	71.4
1.0	203	65	138	70.5
1.1	255	89	166	70.7

FEV1 Score - Litres	Patient count	Male	Female	Mean age
1.2	280	91	189	68.7
1.3	294	110	184	69.6
1.4	292	115	177	68.1
1.5	297	118	179	68.9
1.6	289	112	177	67.4
1.7	321	165	156	67.0
1.8	260	135	125	66.3
1.9	221	126	95	65.8
2.0	216	132	84	66.2
2.1	195	134	61	64.7
2.2	191	132	59	63.5
2.3	161	117	44	62.7
2.4	118	99	19	63.6
2.5	107	91	16	63.1
2.6	84	76	8	61.7
2.7	88	73	15	63.2
2.8	82	73	9	62.1
2.9	46	43	3	60.6
3.0	41	39	2	61.6
Greater than 3.05	137	131	6	58.0

Table 78 – Treatment effect outcomes for the overall population and for low- and high-risk subgroups*

Comparison	Treatment effect - overall population (95% CrI)	Treatment effect - low risk subgroup (95% CrI)†	Coefficient - high versus low risk (95% CrI)	Treatment effect - high risk subgroup (95% CrI)‡
Moderate exacerbations - hazard ratios				
LAMA versus LABA	0.83 (0.77 to 0.90)	0.9 (0.79 to 1.02)	-0.11 (-0.27 to 0.04)	0.8 (0.73 to 0.87)

Comparison	Treatment effect - overall population (95% CrI)	Treatment effect - low risk subgroup (95% CrI)†	Coefficient - high versus low risk (95% CrI)	Treatment effect - high risk subgroup (95% CrI)‡
LABA+ICS versus LABA	0.83 (0.78 to 0.87)	0.87 (0.78 to 0.95)	-0.07 (-0.19 to 0.05)	0.81 (0.75 to 0.86)
LAMA+LABA versus LABA	0.73 (0.67 to 0.80)	0.78 (0.68 to 0.89)	-0.11 (-0.28 to 0.07)	0.7 (0.62 to 0.78)
Severe exacerbations - hazard ratios				
LAMA versus LABA	0.77 (0.69 to 0.85)	0.83 (0.67 to 1.01)	-0.13 (-0.37 to 0.12)	0.72 (0.64 to 0.82)
LABA+ICS versus LABA	0.94 (0.85 to 1.04)	1.03 (0.89 to 1.17)	-0.21 (-0.42 to -0.01)	0.83 (0.71 to 0.96)
LAMA+LABA versus LABA	0.71 (0.59 to 0.84)	0.76 (0.57 to 1.00)	-0.17 (-0.47 to 0.13)	0.64 (0.51 to 0.78)
FEV1 - 3 months - mean difference – litres				
LAMA versus LABA	0.021 (-0.016 to 0.058)	0.016 (-0.022 to 0.057)	0.030 (-0.018 to 0.077)	0.047 (-0.009 to 0.102)
LABA+ICS versus LABA	0.038 (0.015 to 0.062)	0.037 (0.011 to 0.064)	0.009 (-0.024 to 0.043)	0.046 (0.014 to 0.08)
LAMA+LABA versus LABA	0.090 (0.062 to 0.117)	0.087 (0.058 to 0.116)	0.010 (-0.046 to 0.063)	0.097 (0.04 to 0.15)
FEV1 - 6 months - mean difference – litres				
LAMA versus LABA	0.029 (0.004 to 0.061)	0.020 (-0.007 to 0.049)	0.058 (0.017 to 0.101)	0.078 (0.035 to 0.124)
LABA+ICS versus LABA	0.035 (0.008 to 0.067)	0.023 (-0.03 to 0.073)	0.025 (-0.014 to 0.068)	0.048 (0.006 to 0.1)
LAMA+LABA versus LABA	0.085 (0.051 to 0.119)	0.077 (0.048 to 0.108)	0.034 (-0.013 to 0.084)	0.111 (0.059 to 0.164)
FEV1 - 12 months - mean difference – litres				
LAMA versus LABA	0.050 (0.01 to 0.103)	0.020 (0.001 to 0.039)	0.058 (0.012 to 0.105)	0.078 (0.036 to 0.121)
LABA+ICS versus LABA	0.059 (0.03 to 0.104)	N/A (no trials included LABA+ICS in for this outcome in the low-risk population)	0.049 (0.03 to 0.069)	0.049 (0.03 to 0.069)
LAMA+LABA versus LABA	0.1 (0.044 to 0.166)	0.078 (0.059 to 0.096)	0.041 (-0.002 to 0.085)	0.119 (0.08 to 0.158)
SGRQ - 3 months - mean difference				
LAMA versus LABA	0.20 (-0.48 to 0.89)	1.01 (-0.2 to 2.15)	-0.90 (-2.35 to 0.56)	0.11 (-0.76 to 0.96)
LABA+ICS versus LABA	-1.21 (-1.95 to -0.49)	-0.68 (-1.85 to 0.49)	-1.15 (-2.7 to 0.39)	-1.82 (-2.87 to -0.8)
LAMA+LABA versus LABA	-1.66 (-2.41 to -0.89)	-0.64 (-1.85 to 0.55)	-2.58 (-4.33 to -0.81)	-3.21 (-4.52 to -1.91)
SGRQ - 6 months - mean difference				

Comparison	Treatment effect - overall population (95% CrI)	Treatment effect - low risk subgroup (95% CrI)†	Coefficient - high versus low risk (95% CrI)	Treatment effect - high risk subgroup (95% CrI)‡
LAMA versus LABA	-0.35 (-0.91 to 0.20)	-0.18 (-0.92 to 0.55)	-0.22 (-1.37 to 0.95)	-0.39 (-1.27 to 0.48)
LABA+ICS versus LABA	-1.25 (-1.73 to -0.76)	-1.13 (-1.88 to -0.35)	-0.47 (-1.49 to 0.54)	-1.60 (-2.28 to -0.93)
LAMA+LABA versus LABA	-1.77 (-2.38 to -1.16)	-1.36 (-2.13 to -0.59)	-1.52 (-2.89 to -0.12)	-2.88 (-4.03 to -1.75)
SGRQ - 12 months - mean difference				
LAMA versus LABA	-0.37 (-1.26 to 0.54)	0.13 (-1.26 to 1.50)	-0.95 (-2.84 to 1.08)	-0.82 (-2.14 to 0.61)
LABA+ICS versus LABA	-1.45 (-2.17 to -0.78)	-1.78 (-3.70 to 0.20)	0.17 (-2.00 to 2.31)	-1.60 (-2.46 to -0.74)
LAMA+LABA versus LABA	-1.43 (-2.4 to -0.45)	-0.64 (-2.07 to 0.86)	-1.64 (-3.86 to 0.4)	-2.28 (-3.88 to -0.79)
TDI - 3 months (low risk subgroup only) - mean difference				
LAMA versus LABA	-0.10 (-0.35 to 0.13)	-0.10 (-0.35 to 0.13)	-	-
LABA+ICS versus LABA	0.09 (-0.17 to 0.35)	0.09 (-0.17 to 0.35)	-	-
LAMA+LABA versus LABA	0.44 (0.2 to 0.67)	0.44 (0.2 to 0.67)	-	-
TDI - 6 months (low risk subgroup only) - mean difference				
LAMA versus LABA	0.04 (-0.12 to 0.21)	0.04 (-0.12 to 0.21)	-	-
LABA+ICS versus LABA	0.22 (-0.02 to 0.46)	0.22 (-0.02 to 0.46)	-	-
LAMA+LABA versus LABA	0.37 (0.21 to 0.52)	0.37 (0.21 to 0.52)	-	-
Mortality - odds ratios				
LAMA versus LABA	1.07 (0.86 to 1.32)	1.31 (0.83 to 1.99)	-0.25 (-0.76 to 0.26)	1.00 (0.78 to 1.28)
LABA+ICS versus LABA	0.91 (0.78 to 1.05)	0.93 (0.76 to 1.14)	-0.06 (-0.37 to 0.24)	0.88 (0.69 to 1.09)
LAMA+LABA versus LABA	1.04 (0.78 to 1.37)	1.2 (0.76 to 1.81)	-0.18 (-0.78 to 0.42)	1.00 (0.65 to 1.47)
Cardiac adverse events - odds ratios				
LAMA versus LABA	1.17 (0.94 to 1.45)	1.22 (0.89 to 1.65)	-0.06 (-0.51 to 0.41)	1.15 (0.82 to 1.62)
LABA+ICS versus LABA	0.99 (0.82 to 1.19)	1.02 (0.73 to 1.43)	-0.06 (-0.47 to 0.34)	0.95 (0.73 to 1.23)
LAMA+LABA versus LABA	1.11 (0.85 to 1.43)	1.27 (0.90 to 1.72)	-0.37 (-0.95 to 0.23)	0.89 (0.54 to 1.41)
Pneumonia - odds ratios				
LAMA versus LABA	0.95 (0.46 to 1.68)	1.00 (0.41 to 1.86)	-0.07 (-0.73 to 0.58)	0.92 (0.42 to 1.75)
LABA+ICS versus LABA	1.61 (0.99 to 2.39)	1.88 (1.03 to 3.25)	-0.17 (-0.75 to 0.38)	1.57 (0.97 to 2.47)

Comparison	Treatment effect - overall population (95% CrI)	Treatment effect - low risk subgroup (95% CrI)†	Coefficient - high versus low risk (95% CrI)	Treatment effect - high risk subgroup (95% CrI)‡
LAMA+LABA versus LABA	1.24 (0.77 to 2.01)	1.29 (0.66 to 2.27)	0.12 (-0.81 to 1.18)	1.58 (0.58 to 3.95)
Total serious adverse events - odds ratios				
LAMA versus LABA	0.93 (0.86 to 1.00)	0.99 (0.88 to 1.11)	-0.11 (-0.26 to 0.03)	0.89 (0.81 to 0.97)
LABA+ICS versus LABA	1.06 (0.99 to 1.13)	1.13 (1.01 to 1.27)	-0.12 (-0.26 to 0.03)	1.01 (0.92 to 1.10)
LAMA+LABA versus LABA	0.96 (0.88 to 1.05)	1.02 (0.91 to 1.15)	-0.14 (-0.33 to 0.06)	0.89 (0.77 to 1.04)
Discontinuation due to adverse events – hazard ratios				
LAMA versus LABA	0.86 (0.78 to 0.95)	0.84 (0.72 to 0.97)	0.05 (-0.15 to 0.25)	0.88 (0.77 to 1.00)
LABA+ICS versus LABA	0.91 (0.84 to 1.00)	0.93 (0.80 to 1.06)	-0.03 (-0.22 to 0.15)	0.90 (0.79 to 1.01)
LAMA+LABA versus LABA	0.90 (0.80 to 1.01)	0.91 (0.79 to 1.06)	-0.09 (-0.36 to 0.17)	0.83 (0.67 to 1.03)

*Please note that treatment effects in this table are expressed relative to LABA, for ease of interpretation and for consistency with NMA results in the clinical evidence review. Contrastingly, treatment effects in the model executable file are expressed relative to the reference regimen.
†Treatment effects for the low-risk subgroup are simply the base treatment effect outcomes from the NMAs in which a covariate was added to denote risk status
‡Treatment effects for the high-risk subgroup were calculated by adding the coefficient for the high- versus low-risk population to the treatment effect for the low-risk population (for continuous outcomes) or to the natural logarithm of the treatment effect for the low-risk population (for hazard ratios or odds ratios). Note that the mean of the resulting distribution may not be identical to the sum of the means of the 2 coefficients, owing to asymmetries and within-sample correlations.