National Institute for Health and Care Excellence

FINAL

Chronic obstructive disease in over 16s: diagnosis and management

[K] Economic model report for inhaled triple therapy

NICE guideline NG115

Evidence review

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Final

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 LAMA plus a LABA plus ICS compared with:

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

The committee prioritised this review question for economic modelling as there is currently considerable variation in practice relating to triple therapy, uncertainty regarding its cost effectiveness, and a potentially large resource impact associated with recommendations.

The economic model described in this chapter is based on the analysis used to assess the cost effectiveness of mono and dual long-acting bronchodilator regimens in the previous update of this guideline. Therefore, only aspects which differ from the original model are described here. For full methods, please refer to the economic model report for the 2018 guideline update.

Methods

Model overview

Population

Adults diagnosed with COPD who continue to experience breathlessness or exacerbations, despite treatment with a dual long-acting bronchodilator regimen (LAMA+LABA or LABA+ICS).

Comparators

Three treatment regimens are included in the analysis:

1. Triple therapy (LAMA+LABA+ICS)
2. LAMA+LABA
3. LABA+ICS

Since the review question focuses on the clinical and cost effectiveness of triple therapy compared with dual therapy (rather than on dual therapy regimens compared with each other), the model assesses 2 separate decision problems:

1. Triple therapy versus LAMA+LABA
2. Triple therapy versus LABA+ICS

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. It 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 1-4, 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 have 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 can move to a less severe GOLD stage, in order to reflect the initial FEV1 benefit for patients stepping up from dual therapy to triple therapy.

In each cycle, patients can also experience a hospitalised or non-hospitalised exacerbation, or an adverse event. The model uses 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.

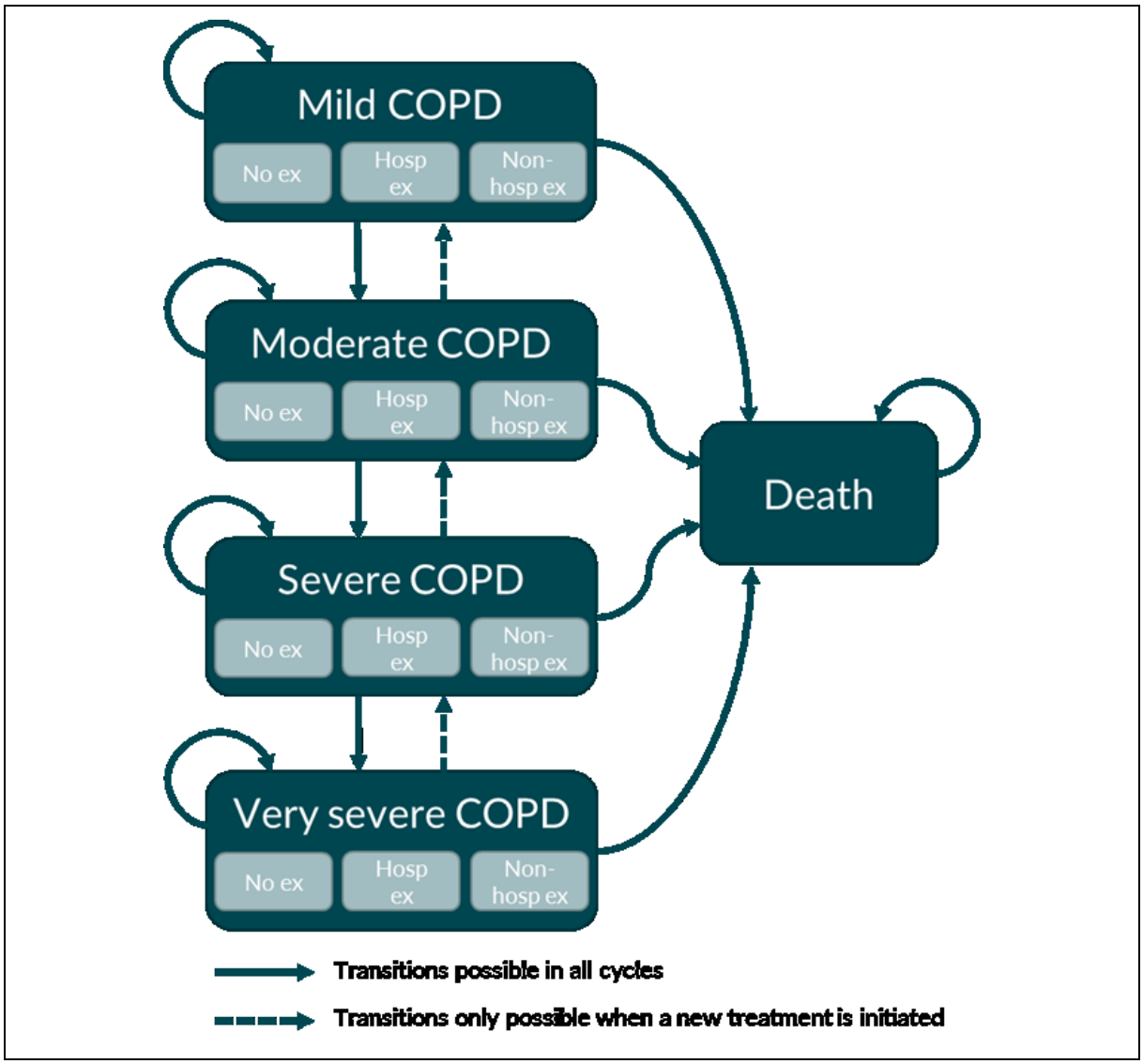


Figure 1 – Overall structure of the model

The model also simulates patients' treatment progression over time. In each cycle, patients treated with dual therapy regimen (LAMA+LABA or LABA+ICS) have a probability of either stepping up to triple therapy, or switching to an alternative dual therapy regimen (patients on a LAMA+LABA switch to a LABA+ICS, and vice versa). The pathway for treatment progression is shown in Figure 2. We made the assumption that no further stepping up or switching occurs once patients are initiated onto triple therapy.

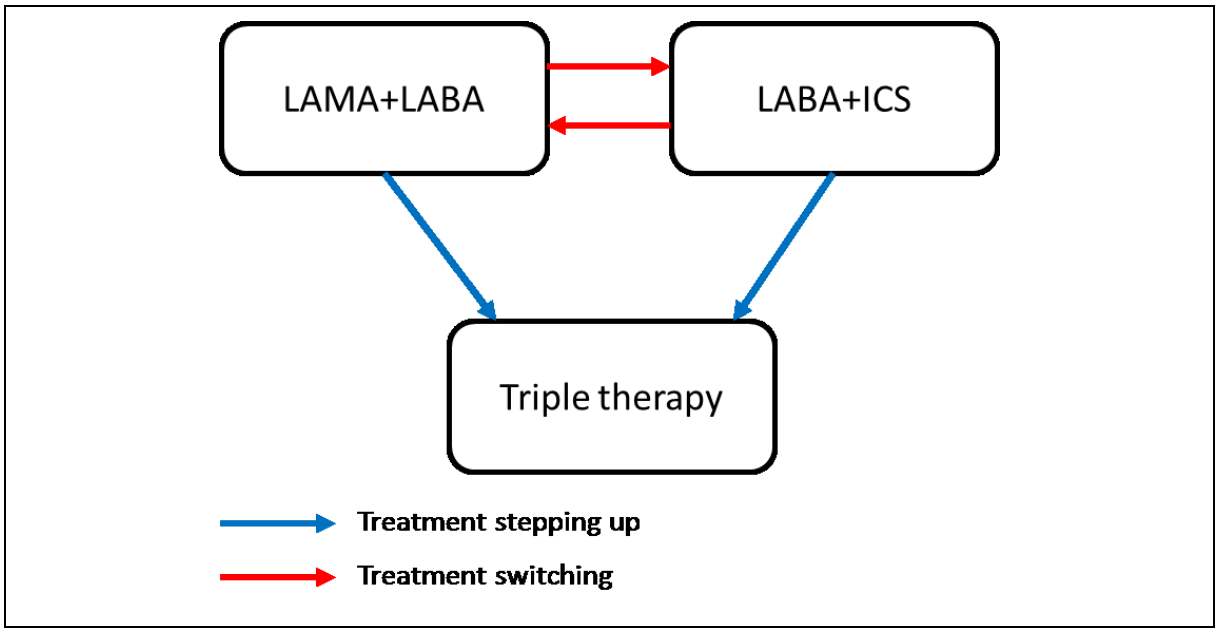


Figure 2 – Treatment progression pathway in the model

Incorporating treatment effects

The model uses pairwise meta-analyses conducted for the clinical evidence review for this question comparing triple therapy with LAMA+LABA, and triple therapy with LABA+ICS to inform treatment effects in the model. These provide a number of outcomes which 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. Therefore, we modelled a number of scenarios, using the following combinations of outcomes:

- **Scenario 1: Exacerbations alone**
- **Scenario 2: SGRQ and exacerbations**
- **Scenario 3: FEV1 and exacerbations** – this scenario allows 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 uses 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 uses 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 applies treatment effects to 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 model explores the impact of including and excluding these treatment effects through 3 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, we assigned probability distributions to model input parameters 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 5,000 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 rate 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.

For base-case results, we also addressed structural uncertainty in implementing treatment benefit stochastically, using the method 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

We used the same data as in the 2018 model to inform the majority of natural history parameters (decline in FEV1 over time, exacerbation rate according to GOLD stage, mortality according to GOLD stage, and adverse events). However, we used a different source to inform patients' FEV1 distribution at baseline. This is because patients who continue to experience exacerbations or breathlessness despite treatment with a dual long-acting bronchodilator regimen are expected, on average, to have more advanced disease than patients starting a long-acting bronchodilator for the first time. In turn, the choice of baseline FEV1 distribution informs the key aspects of disease natural history, since exacerbation rate, quality of life, mortality, and maintenance costs are all stratified by GOLD stage, and are therefore dependent on patients' FEV1.

We considered 2 sources to inform baseline FEV1 distribution. The first was the mean FEV1 of patients identified in the Clinical Practice Research Datalink (CPRD)[a] who:

[a] Thanks to Jennifer Quint of Imperial College London for CPRD data analysis

- Had a diagnosis of COPD
- Received treatment with a dual long-acting bronchodilator regimen
- Were coded as having breathlessness or exacerbations in primary care records in the year after starting a dual long-acting bronchodilator regimen

The second was the mean baseline FEV1 of patients in a phase IIIB trial of a fixed-dose triple therapy inhaler (fluticasone furoate / umeclidinium bromide / vilanterol; GSK 2017; clinical trial NCT02729051). For inclusion into the trial, participants had to have a post-bronchodilator FEV1 of <50% predicted and a history of at least 1 exacerbation in the previous year, or a post-bronchodilator FEV1 of ≥50% and <80% and a history of at least 2 moderate or at least 1 severe exacerbation in the previous year. As might be expected from these more stringent criteria, the mean FEV1 of the trial population is lower than that of the CPRD population, as shown in Table 1.

Table 1 – Mean FEV1 scores in patients selected from the CPRD, and in trial NCT02729051

Source	mean FEV1 (SD) - L	Sample size
CPRD	1.52 (0.68)	6545
Trial NCT02729051	1.174 (0.448)	983

To estimate the proportion of patients falling into each GOLD stage at baseline, we assigned a lognormal distribution to mean FEV1 (since this was shown to be a good fit in the 2018 evaluation). Using conversion formulae and regression equations predicting age and gender based on FEV1 (described in 2018 model methods), we converted the absolute FEV1 distribution into a FEV1 % predicted distribution, from which we calculated the proportion of patients in each GOLD stage. These values are shown in Table 2, compared with the baseline distribution in the 2018 model. Continuous FEV1 % predicted density functions for the 3 populations are also shown in Figure 3, for illustrative purposes. Both sources produce a more severe distribution than that in the 2018 model, but the distribution provided by the trial data contains a higher proportion of patients in the severe and very severe stages.

Table 2 – Distribution of patients among GOLD stages at baseline, calculated using CPRD data, triple therapy phase IIIB trial data, compared to the distribution in the 2018 model

GOLD stage	CPRD	Trial NCT02729051	Population in 2018 model
Mild	13.4%	2.8%	19.3%
Moderate	47.3%	34.6%	55.6%
Severe	34.0%	51.8%	23.6%
Very severe	5.3%	10.8%	1.5%

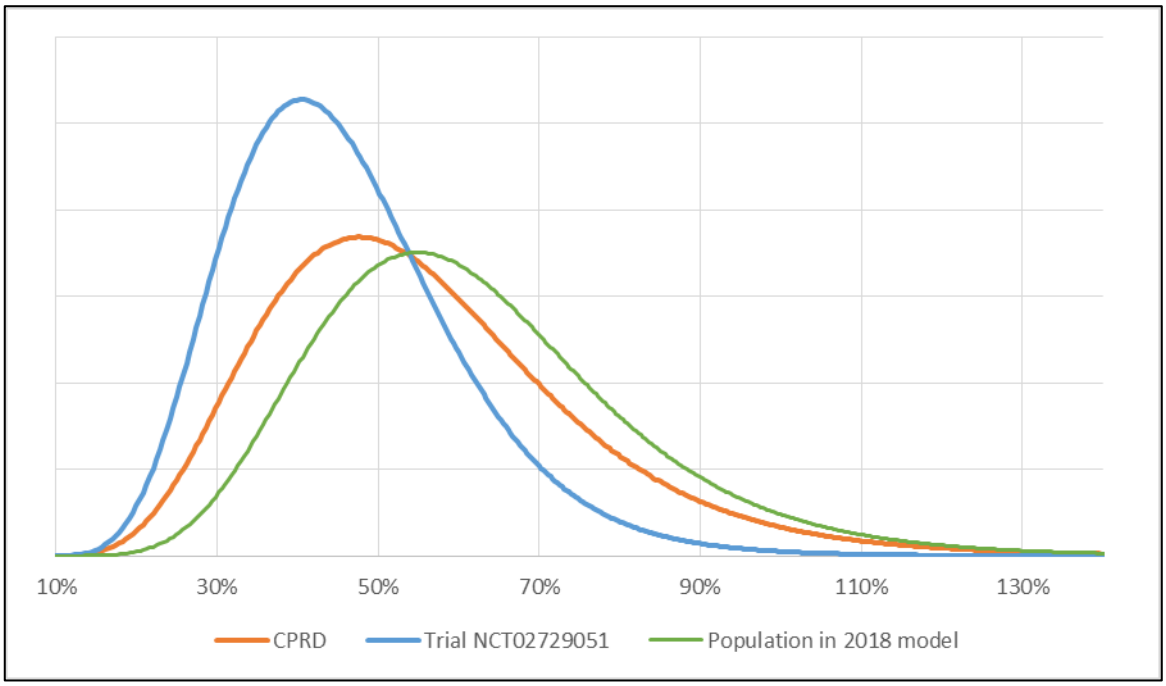


Figure 3 – FEV1 % predicted density functions specified using data from the CPRD and trial NCT02729051, compared to the population in the 2018 model

Since the NCT02729051 trial report also provided the actual proportion of patients in each GOLD stage, we used these data to test the accuracy of estimating the distribution using mean FEV1. The predicted and actual proportion of patients in each GOLD stage are shown in Table 3. These results confirm that the lognormal distribution generally provides a reasonable estimation of the proportion of patients in each GOLD stage, although the proportion of patients in the mild and very severe stages are somewhat over- and under-estimated, respectively. This is to be expected, since patients in the mild stage were explicitly excluded from the trial, whereas the lognormal distribution is continuous, without a hard cut-off.

Table 3 – Comparison of predicted and actual distribution of patients among GOLD stages at baseline in trial NCT02729051

GOLD stage	Distribution predicted using mean FEV1	Actual distribution from trial
Mild	2.8%	0.1%
Moderate	34.6%	35.3%
Severe	51.8%	49.1%
Very severe	10.8%	15.5%

We made the decision to use the CPRD data in the model base case, since it reflects the population of interest in a real-world setting, rather than a population based on the inclusion and exclusion criteria of the clinical trial. We explored using the triple therapy trial data to define patients' FEV1 at baseline in sensitivity analysis.

Calculating transition probabilities

In the 2018 model, we estimated transition probabilities for the reference regimen (LABA+ICS) in the first cycle by using the FEV1 distribution at baseline to calculate the probability of patients in each GOLD stage moving to a more or less severe stage, after applying the initial effect of treatment on FEV1 at 3 months. In subsequent cycles, the model used data on the annual decline in FEV1 (stratified by GOLD stage) to estimate the probability of moving to a more severe stage each cycle. We made the assumption that patients could not move to a less severe stage unless switching or stepping up treatment.

In the 2018 model, an initial effect of long-acting bronchodilator treatment on FEV1 was used to inform transition probabilities in the first cycle of the model. However, this was not appropriate for the purposes of this decision problem, since patients on a LABA+ICS or a LAMA+LABA are continuing an existing treatment, rather than initiating a new therapy. Therefore, as with subsequent cycles, the annual decline in FEV1 was used to calculate transition probabilities in the first cycle for the reference regimen. However, unlike in subsequent cycles, transitions to less severe GOLD stages were still allowed in the first cycle, based on the distribution of the natural decline in FEV1. This was to allow parity with triple therapy, since stepping up to this regimen does produce an initial FEV1 improvement, and therefore allowing patients to move to less severe GOLD stages in the first cycle is appropriate for this regimen.

Table 4 – Transition probabilities in the first cycle of the model

Transition	Probability
Mild to moderate	3.82%
Moderate to severe	3.10%
Severe to very severe	2.24%
Moderate to mild	0.38%
Severe to moderate	1.67%
Very severe to severe	6.01%

Costs

As with the 2018 model, the model included 5 cost categories:

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

Cost categories 2–5 were identical to those in the 2018 model. For drug costs, to calculate the cost of each regimen, we used Prescription Cost Analysis (PCA) data for July 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 (or using the NHS indicative price from the BNF if unit costs were unavailable), and dosage data from each product's summary of product characteristics.

In the base case, we assume that all regimens are delivered as a single combination inhaler when calculating costs. We relax this assumption in a scenario analysis where triple therapy is delivered via 2 separate inhaler devices. To do this, we assume that triple therapy is delivered as a LABA+ICS combination inhaler plus a LAMA inhaler.

To reflect the fact that patient adherence is not perfect, drug costs are 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 more likely to take their medication as prescribed. However, it should be noted that data on treatment effectiveness 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 5 shows data on the relative prescribing frequency, dosage and cost of each individual product. Table 6 gives the calculated mean costs per cycle for each treatment.

Table 5 – Cost and prescribing data for each long-acting bronchodilator product

Chemical name	Drug name (as listed in PCA data)	Items dispensed	Cost per pack	Doses	Daily dosage	Cost per day	Cost per cycle
LABA+ICS							
Beclometasone Dipropionate	Fostair_Inh 100mcg/6mcg (120D) CFF	278951	£29.32	120	4	£0.98	£89.18
Beclometasone Dipropionate	Fostair NEXThaler_Inh 100mcg/6mcg (120D)	36178	£29.32	120	4	£0.98	£89.18
Budesonide	Symbicort_Turbohaler 200mcg/6mcg (120 D)	98918	£28.00	120	4	£0.93	£85.17
Budesonide	Symbicort_Turbohaler 400mcg/12mcg (60 D)	49842	£28.00	60	2	£0.93	£85.17
Budesonide	Symbicort_Inh Pressurised 200/6mcg(120D)	5261	£28.00	120	4	£0.93	£85.17
Budesonide	DuoResp Spiromax_Inh 160mcg/4.5mcg(120D)	55298	£27.97	120	4	£0.93	£85.08
Budesonide	DuoResp Spiromax_Inh 320mcg/9mcg (60 D)	40913	£27.97	60	2	£0.93	£85.08
Fluticasone Propionate (Inh)	Fluticasone/Salmeterol_Inh 500/50mcg 60D	14605	£32.74	60	2	£1.09	£99.58
Fluticasone Propionate (Inh)	Seretide 500_Accuhaler 500mcg/50mcg(60D)	46093	£32.74	60	2	£1.09	£99.58
Fluticasone Propionate (Inh)	AirFluSal Forspiro_Inh 500/50mcg (60D)	6011	£29.97	60	2	£1.00	£91.16
Fluticasone Propionate (Inh)	Aerivio Spiromax_Inh 500/50mcg (60D)	1503	£29.97	60	2	£1.00	£91.16
Fluticasone Fuorate (Inh)	Fluticasone/Vilanterol_Inha 92/22mcg 30D	9022	£22.00	30	1	£0.73	£66.92

Chemical name	Drug name (as listed in PCA data)	Items dispensed	Cost per pack	Doses	Daily dosage	Cost per day	Cost per cycle
Fluticasone Fuorate (Inh)	Relvar Ellipta_Inha 92mcg/22mcg (30 D)	56908	£22.00	30	1	£0.73	£66.92
LAMA+LABA							
Aclidinium Brom/Formoterol	Aclid/Formot_PdrFor Inh 396/11.8mcg(60D)	1690	£32.50	60	2	£1.08	£98.85
Aclidinium Brom/Formoterol	Duaklir Genuair_340mcg/12mcg (60D)	11953	£32.50	60	2	£1.08	£98.85
Umeclidinium Brom/Vilanterol	Umeclidinium/Vilanterol_Inha 65/22mcg30D	3811	£32.50	30	1	£1.08	£98.85
Umeclidinium Brom/Vilanterol	Anoro Ellipta_Inha 55mcg/22mcg (30D)	35375	£32.50	30	1	£1.08	£98.85
Tiotropium Brom/Olodaterol	Spiolto Respimat_Inha2.5/2.5mcg(60D)+Dev	12654	£32.50	60	2	£1.08	£98.85
Indacaterol/Glycopyrronium	Ultibro Breezhaler_Pdr Inh Cap + Dev	19165	£32.50	30	1	£1.08	£98.85
Triple therapy							
Beclometasone Dipropionate/ Formoterol/Glycopyrronium	Trimbow_Inh 87mcg/5mcg/9mcg (120 D)	15522	£44.50	120	4	£1.48	£135.35
Fluticasone/Umeclidinium/ Vilanterol	Trelegy Ellipta_Inha 92/55/22mcg (30 D)	12342	£44.50	30	1	£1.48	£135.35
LAMA							
Tiotropium	Tiotropium_Inha 2.5mcg (60D) CFF + Dev	28107	£23.00	60	2	£0.77	£69.96
Tiotropium	Spiriva_Pdr For Inh Cap 18mcg+HandiHaler	22715	£34.87	30	1	£1.16	£106.06
Tiotropium	Spiriva_Pdr For Inh Cap 18mcg	100068	£33.50	30	1	£1.12	£101.90

Chemical name	Drug name (as listed in PCA data)	Items dispensed	Cost per pack	Doses	Daily dosage	Cost per day	Cost per cycle
Tiotropium	Spiriva Respimat_Inha 2.5mcg (60D) + Dev	44423	£23.00	60	2	£0.77	£69.96
Tiotropium	Braltus_Pdr For Inh Cap 10mcg+Zonda Inh	138206	£25.80	30	1	£0.86	£78.48
Aclidinium Bromide	Aclidinium Brom_Pdr For Inh 375mcg (60D)	7949	£28.60	60	2	£0.95	£86.99
Aclidinium Bromide	Eklira_Inh 322mcg (60D) (Genuair)	19654	£28.60	60	2	£0.95	£86.99
Glycopyrronium Bromide	Glycopyrronium Brom_Inh Cap 55mcg + Dev	6648	£27.50	30	1	£0.92	£83.65
Glycopyrronium Bromide	Seebri_Breezhaler Inh Cap 55mcg + Dev	31970	£27.50	30	1	£0.92	£83.65
Umeclidinium Brom	Incruse Ellipta_Inh 55mcg (30D)	54439	£27.50	30	1	£0.92	£83.65

Table 6 – Cost per cycle for each regimen*

Treatment	Cost per cycle
LABA+ICS	£76.60
LAMA+LABA	£87.49
Triple therapy – delivered as a single inhaler (base case)	£119.79
Triple therapy – delivered as 2 devices (sensitivity analysis)	£152.03

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

Incorporating treatment effects

We used the meta-analyses conducted for the clinical evidence review for this review question to inform treatment effects on exacerbations, SGRQ, FEV1, TDI, mortality, cardiac adverse events, total serious adverse events, and discontinuation due to adverse events. For details, see Chapter I (inhaled triple therapy evidence review; appendix G – GRADE tables). The model inputs are shown in Table 7.

Table 7 – Treatment effects used in the model

Outcome	LAMA+LABA versus triple therapy	LABA+ICS versus triple therapy
Non-hospitalised exacerbations (rate ratio)	1.17 (1.11 to 1.23)	1.18 (1.12 to 1.24)
Hospitalised exacerbations (rate ratio)	1.22 (1.11 to 1.34)	1.51 (1.28 to 1.78)
FEV1 (mean difference; ml)		
change from baseline to 3 months	-	-111.4 (-122.5 to -100.2)
change from baseline to 6 months	-22.0 (-40.2 to -3.8)	-122.4 (-217.5 to -27.4)
change from baseline to 12 months	-54.0 (-68.4 to -39.6)	-134.6 (-214.7 to -54.5)
SGRQ change from baseline (mean difference)		
change from baseline to 3 months	-	1.71 (1.07 to 2.35)
change from baseline to 6 months	-	1.41 (-0.45 to 3.27)
change from baseline to 12 months	1.2 (-0.1 to 2.5)	1.85 (1.22 to 2.47)
TDI change from baseline (mean difference)		
change from baseline to 6 months	-0.18 (-0.43 to 0.07)	-0.35 (-0.52 to -0.19)
change from baseline to 12 months	-0.44 (-1.34 to 0.46)	-0.25 (-0.52 to 0.03)
Mortality (risk ratio)	1.43 (1.00 to 2.04)	1.01 (0.73 to 1.40)
Cardiac adverse events (risk ratio)	1.16 (0.39 to 3.44)	1.15 (0.34 to 3.89)
Pneumonia (risk ratio)	0.65 (0.5 to 0.84)	0.83 (0.68 to 1.01)
Total serious adverse events (risk ratio)	1.07 (0.99 to 1.17)	1.16 (0.82 to 1.65)

For continuous outcomes, in cases where outcomes were reported at multiple time points, we use the earliest observation in the model base case. We explored this in sensitivity analysis, in a scenario where all available time points were used.

As per the 2018 evaluation, we model 5 different treatment scenarios for implementing treatment effects. Since the committee did not express an explicit preference for any one method, we 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. Results of each of the 5 scenarios are also presented individually as sensitivity analyses.

The model applies the majority of treatment effects using LABA+ICS as the reference regimen, as described in the methods of the 2018 evaluation. Since no direct evidence of treatment effects between LABA+ICS and LAMA+LABA were available from the meta analyses, indirect treatment effects were calculated using comparisons of triple therapy to LABA+ICS, and triple therapy to LAMA+LABA. These values were used to inform absolute exacerbation rates, transition probabilities, quality of life scores, adverse event rates, and

mortality rates for LAMA+LABA. For example, to calculate the hospitalised exacerbation rate for LAMA+LABA, the rate ratio for LAMA+LABA versus triple therapy (1.22) was divided by the rate ratio for LABA+ICS versus triple therapy (1.51), providing a rate ratio of 0.81 for LAMA+LABA versus LABA+ICS. This ratio was then applied to hospitalised exacerbation rates for LABA+ICS to produce absolute rates for LAMA+LABA.

For cardiac adverse events, pneumonia and total adverse events, the model uses the same baseline event rates adopted in the 2018 model, which relate to patients receiving LABA monotherapy. Therefore, to obtain event rates for LABA+ICS, we applied the treatment effect for LABA+ICS versus LABA from the 2018 model to these values. The model then calculates adverse event rates for triple therapy and LAMA+LABA as described above.

In the 2018 model, treatment discontinuation effects were used to inform probabilities of treatment switching. However, since the assumption was made that patients treated with triple therapy do not switch to other regimens, relative risks of discontinuation for triple therapy compared to other regimens were not required in the model. Therefore, the treatment discontinuation effect for LAMA+LABA versus LABA+ICS from the 2018 model was used to inform probabilities of treatment switching for the dual therapy regimens.

Since evidence from the previous guideline update showed that LAMA+LABA produces a greater FEV1 benefit than LABA+ICS, which persists over time, it is likely that patients treated with LAMA+LABA at baseline would have a higher mean FEV1. To account for this, when calculating the GOLD distribution at baseline for the comparison of triple therapy with LAMA+LABA in scenarios where treatment effect on FEV1 was included, we added the indirect FEV1 treatment effect for LAMA+LABA versus LABA+ICS to the mean FEV1 score at baseline. This produced a slightly less severe GOLD distribution, shown in Table 8. However, it is also plausible that the difference in baseline FEV1 between LAMA+LABA and LABA+ICS could be less pronounced in reality, since treatment with a LAMA+LABA may simply delay the point at which patients' symptoms become sufficiently severe for triple therapy to be considered. If this is the case, it may be reasonable to expect mean FEV1 would be broadly comparable between patients treated with LAMA+LABA and patients treated with LABA+ICS. Therefore, we also conducted a sensitivity analysis in which the initial GOLD distribution for the comparison of triple therapy versus LAMA+LABA was the same as the distribution for triple therapy versus LABA+ICS.

Table 8 – Proportion of patients in each GOLD stage at baseline for the comparison of triple therapy with LAMA+LABA, in scenarios including treatment effect on FEV1

GOLD stage	Proportion of patients
Mild	15.8%
Moderate	51.6%
Severe	29.5%
Very severe	3.1%

Results

For all scenarios, we express the costs and health benefits associated with each strategy as means of 5,000 probabilistic iterations, alongside the probability that each strategy is cost effective at a threshold of £20,000 per QALY. In 'base-case' results, the model addresses structural uncertainty by randomly selecting 1 of the 5 treatment effect scenarios in each probabilistic iteration.

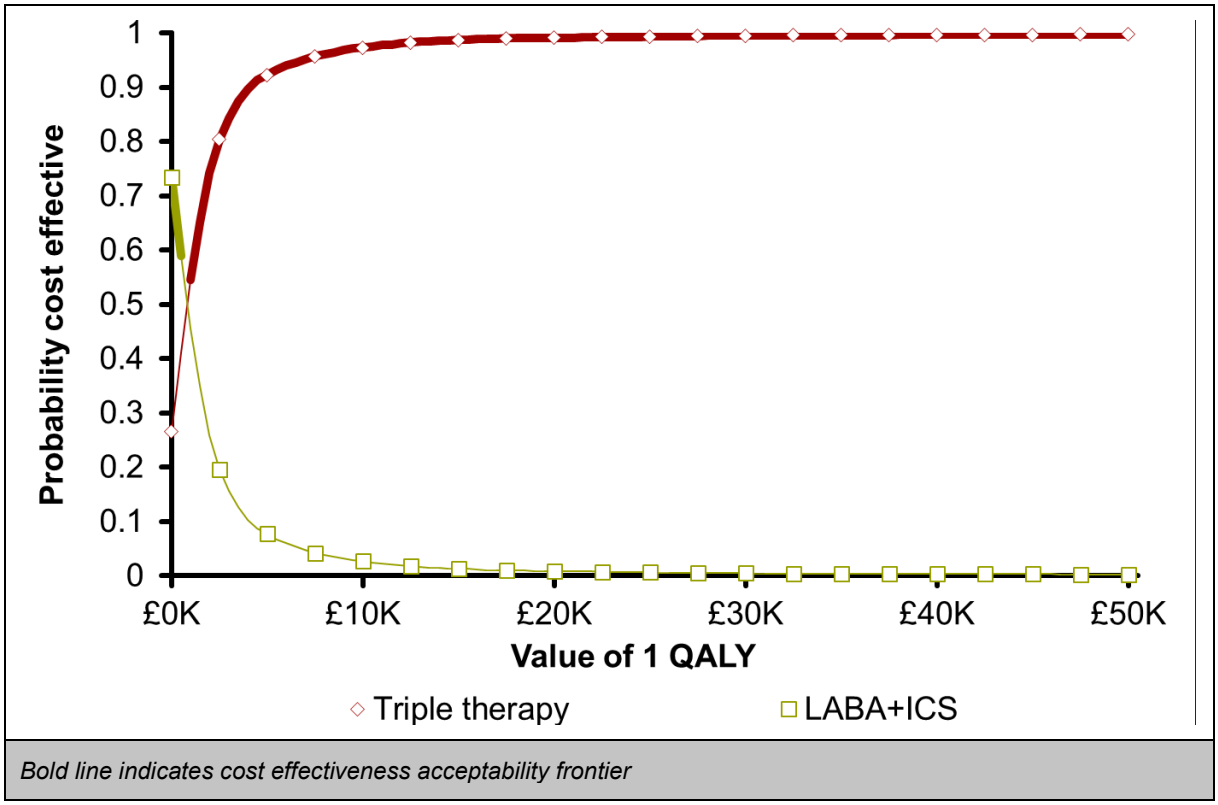
Triple therapy versus LAMA+LABA

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

Table 9 shows base-case results for the comparison of triple therapy with LAMA+LABA when treatment-specific differences in mortality and adverse events are not included. These results show that triple therapy has an ICER of £5,182 per QALY compared with LAMA+LABA. 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 triple therapy has a high probability of being cost effective (89.6%) if QALYs are valued at £20,000 each.

Table 9 – Base-case results for triple therapy versus LAMA+LABA. Option A (treatment-specific differences in adverse events and mortality excluded)

	Absolute		Incremental			Prob CE at
Strategy	Costs	QALYs	Costs	QALYs	ICER	£20k/QALY
LAMA+LABA	£28,438	4.97	-	-	-	10.4%
Triple therapy	£28,637	5.01	£199	0.038	£5,182	89.6%



Bold line indicates cost effectiveness acceptability frontier

Figure 4 – Cost effectiveness acceptability curve for comparison of triple therapy versus LAMA+LABA. Option A (treatment-specific differences in adverse events and mortality excluded)

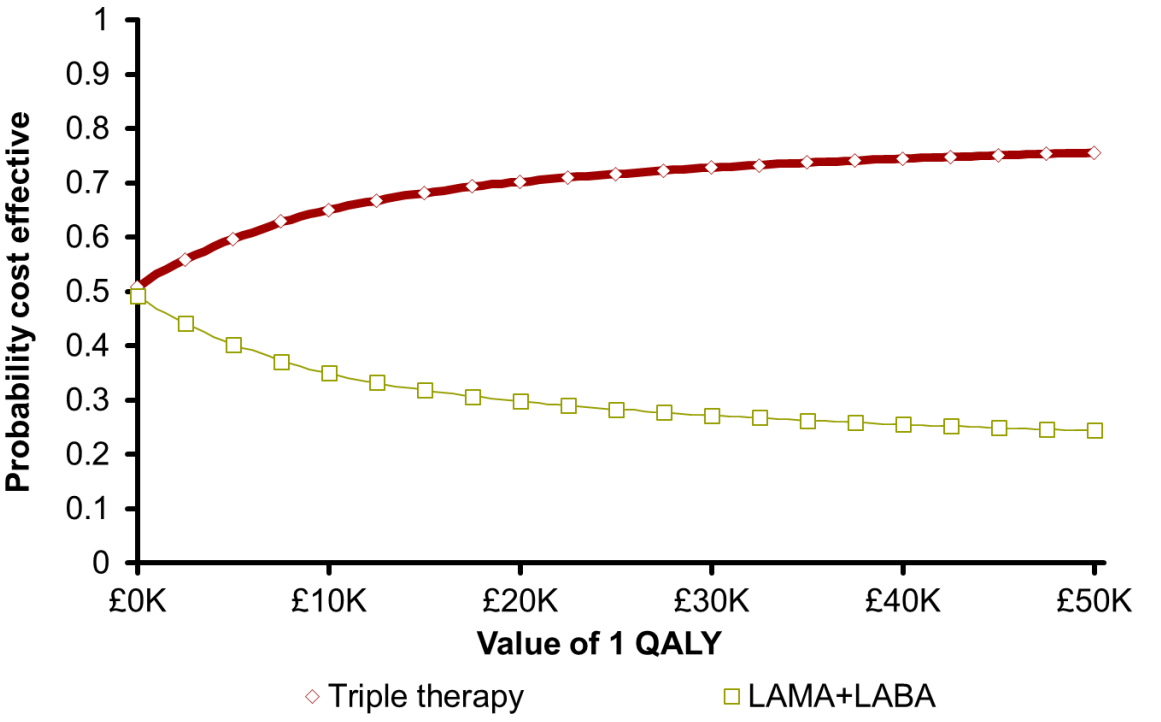
Results for individual treatment benefit scenarios are summarised in Table 10. These results show that triple therapy retains an ICER of below £20,000 per QALY across all scenarios, and has a high probability (>83%) of being cost effective at this threshold.

Table 10 – Results for individual treatment benefit scenarios – triple therapy versus LAMA+LABA. Option A (treatment-specific differences in adverse events and mortality excluded)

Scenario	Triple therapy versus LAMA+LABA			Prob triple therapy CE at £20k/QALY
	Incremental cost	Incremental QALYs	ICER	
Scenario 1	£185	0.02	£9,280	83.70%
Scenario 2	£187	0.054	£3,489	88.4%
Scenario 3	£211	0.022	£9,467	81.50%
Scenario 4	£186	0.047	£3,932	98.00%
Scenario 5	£208	0.051	£4,070	98.60%

Option B: treatment-specific differences in adverse events (but not mortality) included

Table 11 shows base-case results for the comparison of triple therapy with LAMA+LABA when treatment-specific differences in adverse events, but not mortality, are included. These results show that triple therapy dominates LAMA+LABA (is more effective and less costly). However, as shown by the cost-effectiveness acceptability curve in

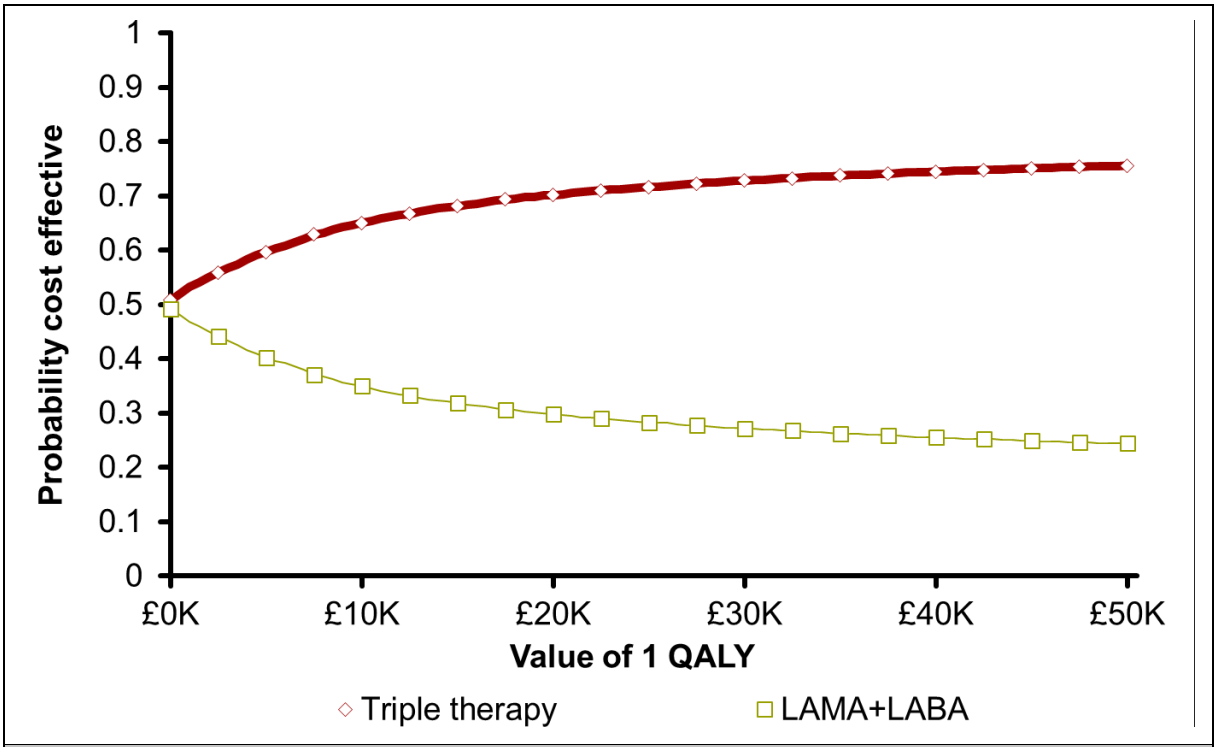


Bold line indicates cost effectiveness acceptability frontier

Figure 5, there is less certainty in these results compared with Option A; triple therapy has a 70.1% probability of being cost effective if QALYs are valued at £20,000.

Table 11 – Base-case results for triple therapy versus LAMA+LABA. 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	
Triple therapy	£28,735	5.01	-	-	-	70.1%
LAMA+LABA	£29,064	4.94	£329	-0.075	dominated	29.9%



Bold line indicates cost effectiveness acceptability frontier

Figure 5 – Cost effectiveness acceptability curve for comparison of triple therapy versus LAMA+LABA. Option B (treatment-specific differences in adverse events, but not mortality, included)

Results for individual treatment benefit scenarios are summarised in Table 12. These results show that triple therapy retains an ICER of below £20,000 per QALY across all scenarios, and has a probability of >63% of being cost effective at this threshold.

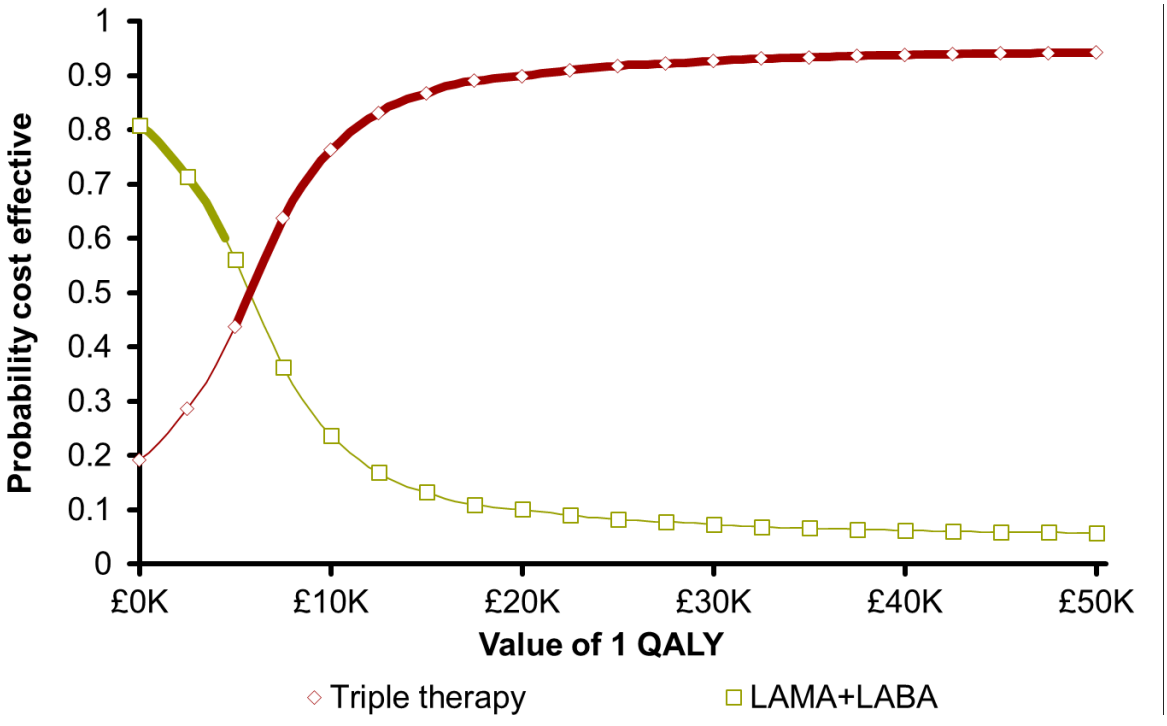
Table 12 – Results for individual treatment benefit scenarios – triple therapy versus LAMA+LABA. Option B (treatment-specific differences in adverse events, but not mortality, included)

Scenario	Triple therapy versus LAMA+LABA			Prob triple therapy CE at £20k/QALY
	Incremental cost	Incremental QALYs	ICER	
Scenario 1	-£286	0.053	Triple therapy dominant	65.30%
Scenario 2	-£300	0.087	Triple therapy dominant	73.90%
Scenario 3	-£245	0.054	Triple therapy dominant	63.70%
Scenario 4	-£251	0.077	Triple therapy dominant	73.40%
Scenario 5	-£285	0.085	Triple therapy dominant	75.30%

Option C: treatment-specific differences in adverse events and mortality included

Table 13 shows base-case results for the comparison of triple therapy with LAMA+LABA when treatment-specific differences in mortality and adverse events are included. These

results show that triple therapy has an ICER of £4,979 per QALY compared with LAMA+LABA. Probabilistic results shown in

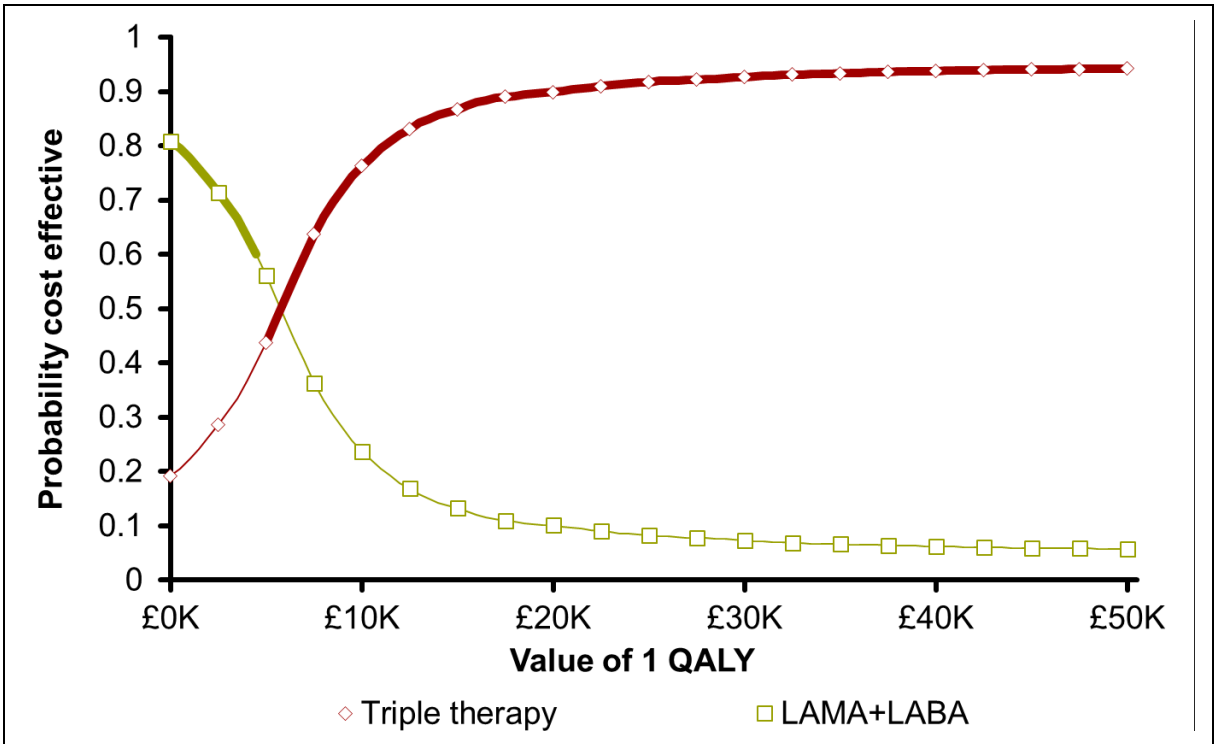


Bold line indicates cost effectiveness acceptability frontier

Figure 6 demonstrate that there is a relatively high degree of certainty behind this finding: triple therapy has an 89.9% probability of being cost effective if QALYs are valued at £20,000.

Table 13 – Base-case results for triple therapy versus LAMA+LABA. 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+LABA	£27,279	4.69	-	-	-	10.1%
Triple therapy	£28,911	5.02	£1,632	0.328	£4,979	89.9%



Bold line indicates cost effectiveness acceptability frontier

Figure 6 – Cost effectiveness acceptability curve for comparison of triple therapy versus LAMA+LABA. Option C (treatment-specific differences in adverse events and mortality included)

Results for individual treatment benefit scenarios are summarised in Table 14. These results show that triple therapy retains an ICER of below £20,000 per QALY across all scenarios, and has a relatively high probability (>88%) of being cost effective at this threshold.

Table 14 – Results for individual treatment benefit scenarios – triple therapy versus LAMA+LABA. Option C (treatment-specific differences in adverse events and mortality included)

Scenario	Triple therapy versus LAMA+LABA			Prob triple therapy CE at £20k/QALY
	Incremental cost	Incremental QALYs	ICER	
Scenario 1	£1,625	0.294	£5,526	88.90%
Scenario 2	£1,628	0.332	£4,904	91.50%
Scenario 3	£1,551	0.294	£5,270	88.80%
Scenario 4	£1,615	0.323	£4,996	91.60%
Scenario 5	£1,592	0.365	£4,364	92.30%

Other sensitivity analyses

Table 15 summarises results for other scenario analyses which test key model assumptions for Option A. These results are based on the model 'base-case' – i.e. 1 of the 5 treatment

benefit scenarios is selected stochastically in each probabilistic iteration. Results show that using the acquisition cost of triple therapy delivered as 2 separate inhalers, rather than 1 combination product, produces an ICER of above £20,000 per QALY (£22,313 per QALY). Probabilistic results show that triple therapy has a relatively low probability (38.6%) of being cost effective at a threshold of £20,000 per QALY for this scenario. However, using acquisition costs for both triple therapy and LAMA+LABA delivered as 2 separate inhalers has the opposite effect on results: triple therapy dominates LAMA+LABA (is less expensive and generates more QALYs), and has a very high probability of being cost effective when QALYs are valued at £20,000 each (99.1%). Triple therapy remains cost effective across all other scenarios.

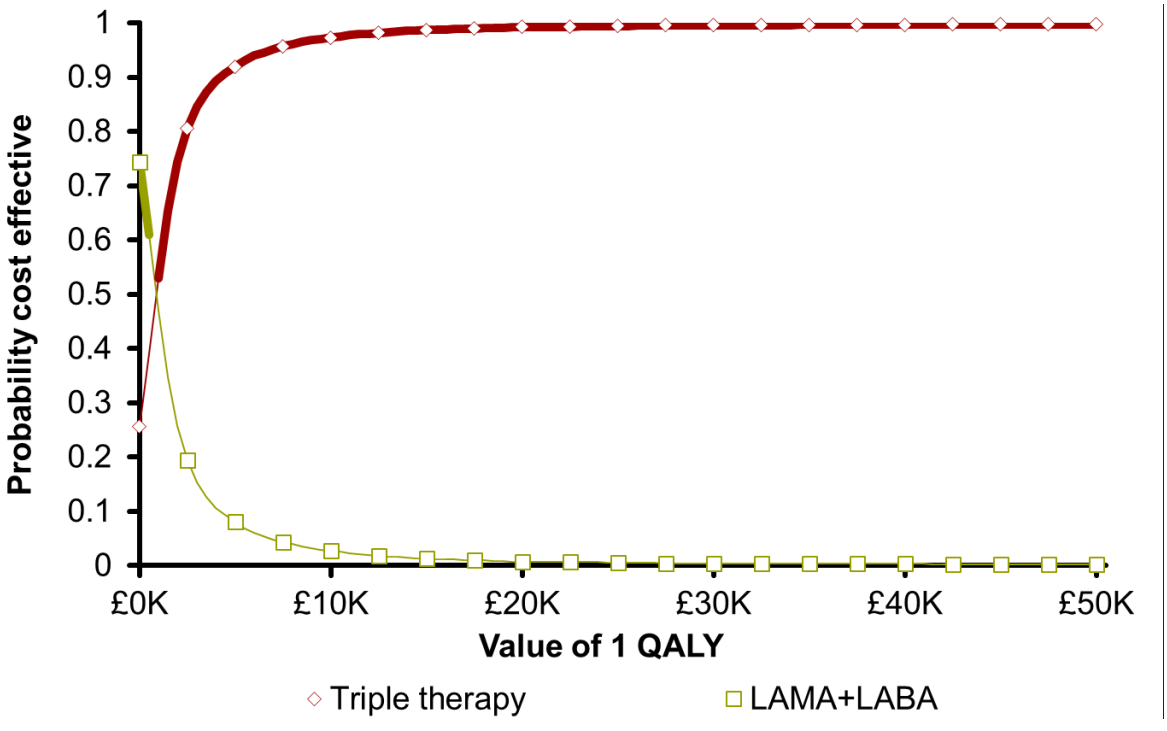
Table 15 – Results for other scenario analyses testing key model assumptions – triple therapy versus LAMA+LABA. Option A (treatment-specific differences in adverse events and mortality excluded)

Scenario	Incremental: triple therapy versus LAMA+LABA			Prob triple therapy CE at £20k/QALY
	Cost	QALYs	ICER	
Triple therapy delivered as 2 separate inhalers	£847	0.038	£22,313	38.6%
Triple therapy and dual therapy regimens delivered as 2 separate inhalers	-£291	0.039	dominant	99.1%
Drug costs not adjusted for adherence	£288	0.039	£7,379	83.7%
Continuous treatment effect at 3, 6 and 12 mo	£181	0.054	£3,330	92.3%
No FEV1 benefit when switching and stepping up	£173	0.051	£3,434	93.6%
Trelegy trial data for baseline FEV1 distribution	£125	0.040	£3,151	92.9%
Cheapest product used for every regimen	£237	0.039	£6,107	87.7%
More severe values for baseline breathlessness	£198	0.036	£5,451	89.6%
Baseline GOLD distribution for comparison of triple therapy versus LABA+ICS used	£188	0.040	£4,698	91.4%

Triple therapy versus LABA+ICS

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

Table 16 shows base-case results for the comparison of triple therapy with LABA+ICS when treatment-specific differences in mortality and adverse events are not included. These results show that triple therapy has an ICER of £881 per QALY compared with LABA+ICS.

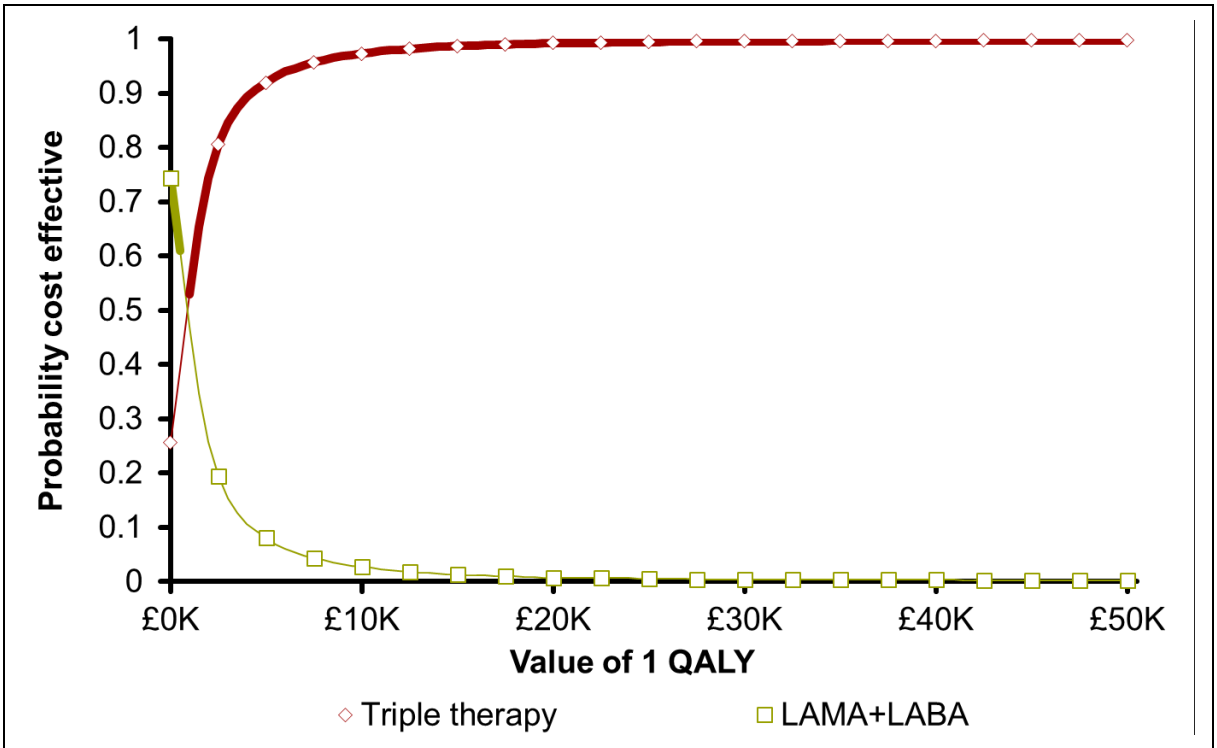


Bold line indicates cost effectiveness acceptability frontier

Figure 7 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 triple therapy has a high probability of being cost effective (99.2%) if QALYs are valued at £20,000 each.

Table 16 – Base-case results for triple therapy versus LABA+ICS. 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+ICS	£28,567	4.90	-	-	-	0.8%
Triple therapy	£28,631	4.98	£64	0.073	£881	99.2%



Bold line indicates cost effectiveness acceptability frontier

Figure 7 – Cost effectiveness acceptability curve for comparison of triple therapy versus LABA+ICS. Option A (treatment-specific differences in adverse events and mortality excluded)

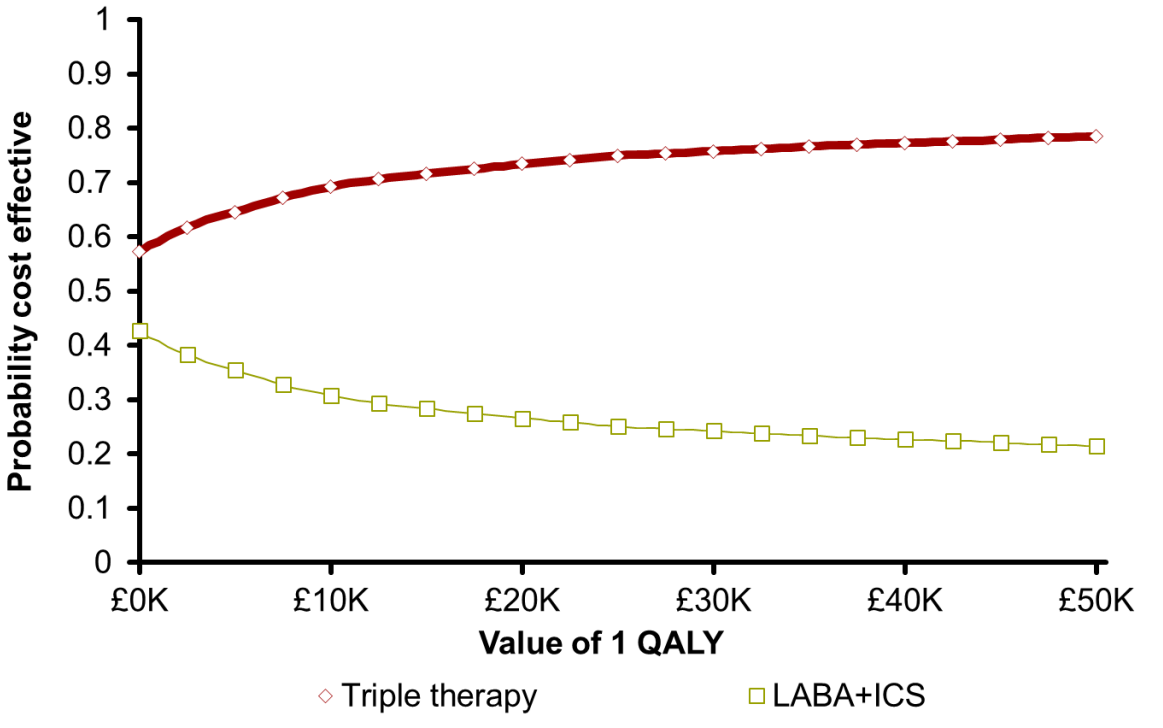
Results for individual treatment benefit scenarios are summarised in Table 17. These results show that triple therapy retains an ICER of below £20,000 per QALY across all scenarios, and has a high probability (>96%) of being cost effective at this threshold.

Table 17 – Results for individual treatment benefit scenarios – triple therapy versus LABA+ICS. Option A (treatment-specific differences in adverse events and mortality excluded)

Scenario	Triple therapy versus LABA+ICS			Prob triple therapy CE at £20k/QALY
	Incremental cost	Incremental QALYs	ICER	
Scenario 1	£82	0.025	£3,339	96.4%
Scenario 2	£84	0.11	£768	100.0%
Scenario 3	£28	0.066	£432	100.0%
Scenario 4	£83	0.068	£1,234	100.0%
Scenario 5	£31	0.096	£320	100.0%

Option B: treatment-specific differences in adverse events (but not mortality) included

Table 18 shows base-case results for the comparison of triple therapy with LABA+ICS when treatment-specific differences in adverse events, but not mortality, are included. These results show that triple therapy has an ICER of £138 per QALY compared with LABA+ICS. However, as shown by the cost-effectiveness acceptability curve in

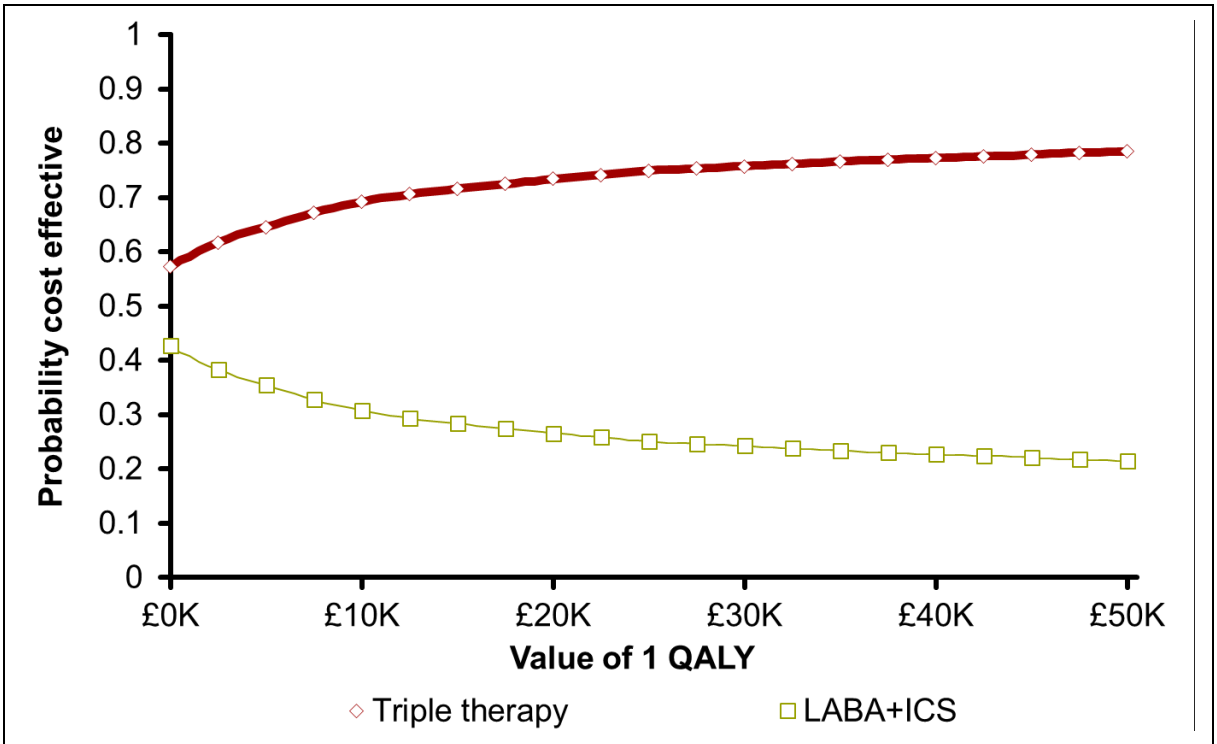


Bold line indicates cost effectiveness acceptability frontier

Figure 8, there is less certainty in these results compared with Option A; triple therapy has a 74.6% probability of being cost effective if QALYs are valued at £20,000.

Table 18 – Base-case results for LABA+ICS. Option B (treatment-specific differences in adverse events, but not mortality, included)

	Absolute		Incremental			Prob CE at
Strategy	Costs	QALYs	Costs	QALYs	ICER	£20k/QALY
LABA+ICS	£28,261	4.92	-	-	-	25.4%
Triple therapy	£28,273	5.01	£11	0.083	£138	74.6%



Bold line indicates cost effectiveness acceptability frontier

Figure 8 – Cost effectiveness acceptability curve for comparison of triple therapy versus LABA+ICS. Option B (treatment-specific differences in adverse events, but not mortality, included)

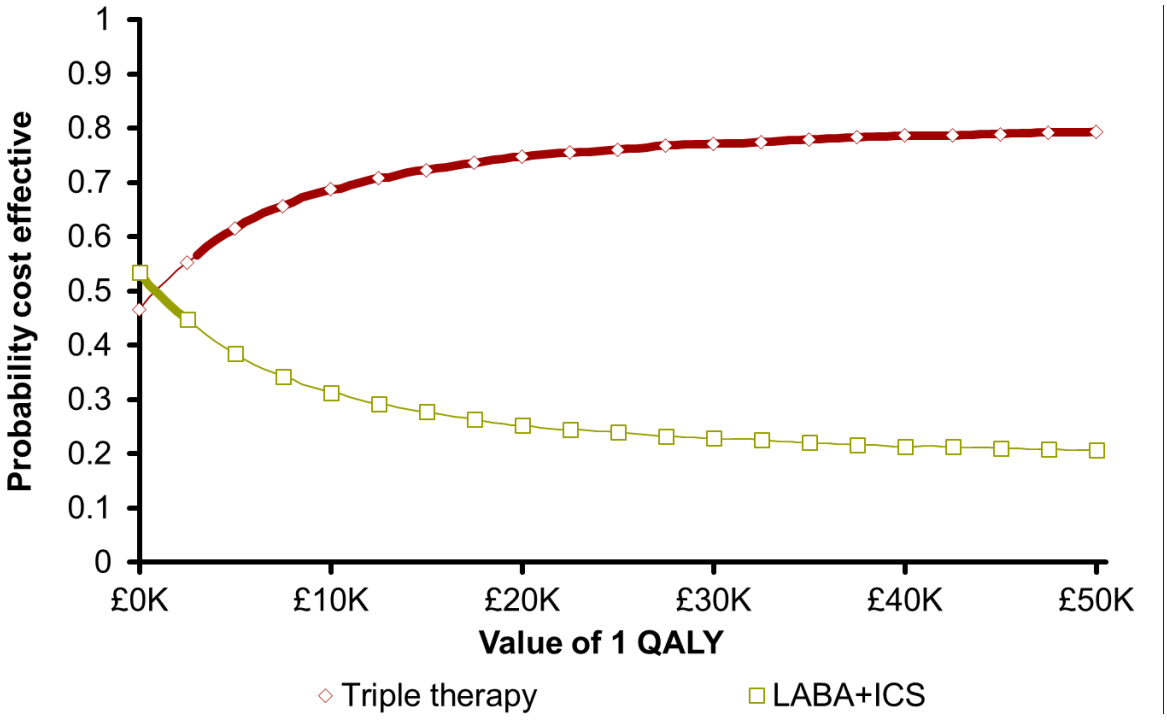
Results for individual treatment benefit scenarios are summarised in Table 19. These results show that triple therapy retains an ICER of below £20,000 per QALY across all scenarios, and has a probability of ≥65% of being cost effective at this threshold.

Table 19 – Results for individual treatment benefit scenarios – triple therapy versus LABA+ICS. Option B (treatment-specific differences in adverse events, but not mortality, included)

Scenario	Triple therapy versus LABA+ICS			Prob triple therapy CE at £20k/QALY
	Incremental cost	Incremental QALYs	ICER	
Scenario 1	£19	0.035	£542	65.0%
Scenario 2	£43	0.119	£363	80.5%
Scenario 3	£49	0.077	Triple therapy dominant	74.6%
Scenario 4	£29	0.077	£379	80.3%
Scenario 5	£53	0.108	Triple therapy dominant	79.3%

Option C: treatment-specific differences in adverse events and mortality included

Table 20 shows base-case results for the comparison of triple therapy with LABA+ICS when treatment-specific differences in mortality and adverse events are included. These results show that triple therapy has an ICER of £3,437 per QALY compared with LABA+ICS. Probabilistic results shown in

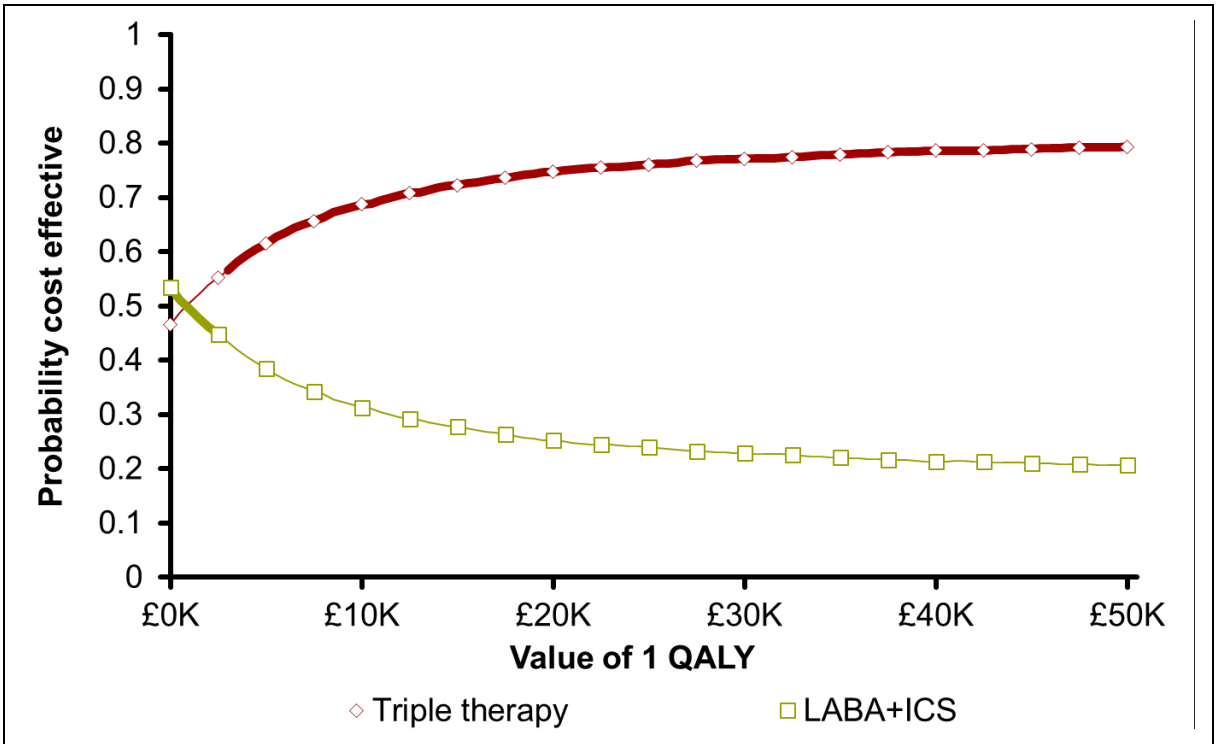


Bold line indicates cost effectiveness acceptability frontier

Figure 9 show that there is a relatively high degree of certainty behind this finding: triple therapy has a 75.7% probability of being cost effective if QALYs are valued at £20,000.

Table 20 – Results for triple therapy versus LABA+ICS. Option C (treatment-specific differences in adverse events and mortality included)

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LABA+ICS	£28,094	4.90	-	-	-	24.3%
Triple therapy	£28,517	5.02	£423	0.123	£3,437	75.7%



Bold line indicates cost effectiveness acceptability frontier

Figure 9 – Cost effectiveness acceptability curve for comparison of triple therapy versus LABA+ICS. Option C (treatment-specific differences in adverse events and mortality included)

Results for individual treatment benefit scenarios are summarised in Table 21. These results show that triple therapy retains an ICER of below £20,000 per QALY across all scenarios.

Table 21 – Results for individual treatment benefit scenarios – triple therapy versus LABA+ICS. Option C (treatment-specific differences in adverse events and mortality included)

Scenario	Triple therapy versus LABA+ICS			Prob triple therapy CE at £20k/QALY
	Incremental cost	Incremental QALYs	ICER	
Scenario 1	£386	0.077	£5,026	68.0%
Scenario 2	£411	0.164	£2,502	83.2%
Scenario 3	£350	0.116	£3,026	75.7%
Scenario 4	£391	0.120	£3,262	75.9%
Scenario 5	£328	0.152	£2,153	80.5%

Other sensitivity analyses

Table 22 summarises results for other scenario analyses which test key model assumptions for Option A. These results are based on the model 'base-case' – i.e. 1 of the 5 treatment benefit scenarios is selected stochastically in each probabilistic iteration. These results show

that using an acquisition cost for triple therapy that reflects use of two separate inhalers, rather than 1 combination product, increases the ICER to £9,493 per QALY; substantially higher than the base case ICER. Triple therapy retains a relatively low ICER across all other scenarios.

Table 22 – Results for other scenario analyses testing key model assumptions – triple therapy versus LABA+ICS. Option A (treatment-specific differences in adverse events and mortality excluded)

Scenario	Incremental: triple therapy versus LAMA+ICS			Prob triple therapy CE at £20k/QALY
	Cost	QALYs	ICER	
Triple therapy delivered as 2 separate inhalers	£683	0.072	£9,493	82.5%
Drug costs not adjusted for adherence	£168	0.073	£2,308	98.3%
Continuous treatment effect at 3, 6 and 12 months	£75	0.068	£1,091	93.8%
No FEV1 benefit when switching and stepping up	-£51	0.124	Dominant	99.3%
Trelegy trial data for baseline FEV1 distribution	-£74	0.075	Dominant	99.8%
Cheapest product used for every regimen	£358	0.073	£4,918	93.5%
More severe values for baseline breathlessness	£61	0.069	£892	99.4%

Discussion

Results show that triple therapy is likely to be cost effective compared with both LAMA+LABA and LABA+ICS in patients who continue to exacerbate or remain breathless on dual therapy if QALYs are valued at £20,000. This finding is primarily due to favourable treatment effects of triple therapy on exacerbations, FEV1, TDI, and SGRQ (even though, in some cases, the data are consistent with no effect at a 95% confidence level). While the acquisition cost of triple therapy is higher than that of either dual therapy regimen, this difference is relatively modest in relation to the health benefits; assuming full adherence, triple therapy costs an additional £16.04 per 30 days of treatment versus LABA+ICS (£44.50 versus £28.46), and an additional £12 per 30 days of treatment versus LAMA+LABA (£44.50 versus £32.50). Furthermore, this cost is at least partially offset by savings from prevented exacerbations.

Probabilistic sensitivity analysis shows a high degree of certainty that triple therapy is cost effective compared with both LAMA+LABA and LABA+ICS when treatment-specific differences in adverse events and mortality are excluded. However, including treatment effects on adverse events and mortality produces a higher degree of uncertainty in results, although triple therapy still retains a >70% probability of being cost effective at a threshold of £20,000 per QALY compared to both LAMA+LABA and LABA+ICS. This is due to the relatively wide confidence intervals around these effects, in particular the treatment effect on cardiovascular events. Scenario analyses also show that triple therapy remains cost effective across individual treatment benefit scenarios. The consistency of these results adds strength to the conclusions of the analysis.

Other sensitivity analyses testing key model assumptions found that triple therapy generally remains cost effective compared with both LABA+ICS and LAMA+LABA. The exception to this is the scenario in which triple therapy is assumed to be delivered as 2 separate inhalers, which produces a substantial increase in ICERs, particularly for the comparison of triple therapy with LAMA+LABA, for which the ICER exceeds £20,000 per QALY. This is because delivering triple therapy as 2 inhalers is more costly than using a single combination inhaler: £56.48 versus £44.50 per 30 days of treatment. While this difference may not appear excessive, it constitutes a considerable proportional increase in the incremental cost of triple therapy compared with dual therapies. Contrastingly, using the cost of 2 separate inhalers for both triple therapy and dual therapy for the comparison of triple therapy with LAMA+LABA produces a very high probability that triple therapy is cost effective (99.1%). This is because the acquisition cost of triple therapy delivered as a LABA+ICS and a LAMA is similar to the cost of LAMA+LABA delivered as its individual components (£56.48 versus £56.07). We did not conduct an analysis using the cost of a LABA+ICS delivered as 2 inhalers, since ICS alone is not licensed for the treatment of COPD, and triple therapy remains cost effective even under the conservative assumption that triple therapy is delivered as 2 devices while LABA+ICS is delivered as a single inhaler.

Our analysis has a number of strengths. First, treatment effects were informed by meta-analyses of randomised controlled trials identified through a systematic literature review, rather than relying on single trials. Second, 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. Third, we used primary care records (from the CPRD) to inform the baseline patient population of the model in the base case. This method is preferable to using data from one of the arms of a clinical trial, as generalisability of trial participants to “real-world” patients is not assured. Furthermore, using the CPRD allowed selection of a data directly relevant to our population of interest (i.e. using

records of patients who remained breathless or had exacerbations despite treatment with long-acting bronchodilator dual therapy).

As with all economic models, this evaluation is subject to a number of limitations. First, there was uncertainty in the most appropriate scenario with which to model treatment benefits. As noted in the 2018 model report, each of these scenarios was associated with weaknesses as well as strengths. Second, 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, as with the 2018 model, it was not possible to evaluate all subpopulations of interest in this analysis. Specifically, it would have been beneficial to conduct an analysis in COPD patients with asthmatic features, as these patients generally respond to inhaled corticosteroids. However, this analysis was not feasible due to limited clinical evidence.

Comparison with other cost-utility analyses

The results of our evaluation are broadly consistent with results of the 1 analysis identified by the economic literature review for this review question (Hertel et al. 2012; summarised in Chapter A). This study found that triple therapy has an ICER of £4,300 per QALY compared to LAMA+LABA and an ICER of £6,960 per QALY compared to LABA+ICS, and is therefore cost effective compared to both dual therapy regimens if QALYs are valued at £20,000 each.

However, an economic analysis conducted for the 2010 update of this guideline found that triple therapy is unlikely to be cost effective at a threshold of £20,000 per QALY, with a base case ICER of between £59,000 and £161,000 per QALY compared to LABA+ICS. There are a few key reasons for the discrepancy between these results and ours. First, the 2010 evaluation was conducted prior to the launch of combined triple therapy inhalers, so the cost of triple therapy reflects the price of a LABA+ICS dual inhaler plus a LAMA monotherapy inhaler. As demonstrated by our analysis, using this cost rather than the cost of a single combined inhaler produces a substantially higher ICER. Second, the 2010 analysis relied on a smaller evidence base, which is less favourable toward triple therapy than more recently published evidence. For example, the 2010 analysis used a hospitalised exacerbation rate ratio of 1.18 for LABA+ICS versus triple therapy, whereas our analysis used a rate ratio of 1.51. Third, the 2010 evaluation implemented treatment benefits through exacerbations alone in the base case, whereas our analysis modelled treatment effects through at least 2 outcomes in the majority of scenarios (exacerbations plus SGRQ, FEV1, or TDI). The authors of the 2010 analysis also conducted a sensitivity analysis in which treatment effects were modelled through both SGRQ mean difference and exacerbations, which produced a substantially lower base case ICER of between £7,337 and £14,606 per QALY.

Conclusion

Triple therapy (delivered as single combination inhaler) has a high probability of being cost effective in patients who remain breathless or continue to have exacerbations despite treatment with LAMA+LABA or LABA+ICS, if QALYs are valued at £20,000 or more. This result is generally robust to sensitivity analysis, although delivering triple therapy as

2 separate inhalers, as opposed to 1 combination inhaler, produces a substantial increase in ICERs.

References

Bojke, L., Claxton, K., Sculpher, M. and Palmer, S., 2009. Characterizing structural uncertainty in decision analytic models: a review and application of methods. Value in Health, 12(5), pp.739-749.

Calverley, P.M., Anderson, J.A., Celli, B., Ferguson, G.T., Jenkins, C., Jones, P.W., Yates, J.C. and Vestbo, J., 2007. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. New England Journal of Medicine, 356(8), pp.775-789.

Hertel, N., Kotchie, R.W., Samyshkin, Y., Radford, M., Humphreys, S. and Jameson, K., 2012. Cost-effectiveness of available treatment options for patients suffering from severe COPD in the UK: a fully incremental analysis. International journal of chronic obstructive pulmonary disease, 7, p.183.

GSK – NCT02729051. 2017. A Phase IIIB, 24-week randomized, double-blind study to compare 'closed' triple therapy (FF/UMEC/VI) with 'open triple' therapy (FF/VI+UMEC), in subjects with Chronic Obstructive Pulmonary Disease (COPD). [Accessed 16th November 2018]. Available from: https://www.gsk-studyregister.com/study/5213

NHS Prescription Services – Drug Tariff. NHS Business Services Authority. [Accessed 16th November 2018]. Available from: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff

Prescription Cost Analysis (PCA) data. NHS Business Services Authority. [Accessed 16th November 2018]. Available from: https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data